THE REACTIONS OF SOME POLYCYCLIC AROMATIC HYDROCARBONS WITH THIYL RADICALS

A THESIS

PRESENTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN THE

ORGANIC CHEMISTRY DEPARTMENT

OF THE

UNIVERSITY OF ADELAIDE

by

Low Beng See, B.Sc.

1962

11th. February, 1963.

The Registrar,
University of Adelaide,
Adelaide,
Australia.

Dear Sir,

I authorise the University of Adelaide to make available for loan and photocopying my thesis entitled, "The Reactions of Some Polycyclic Aromatic Hydrocarbons with Thiyl Radicals."

Yours faithfully,

(LOW BENG SEE)

ACKNOWLEDGEMENTS

I would like to express my deep appreciation of the invaluable and patient guidance of Dr. A. L. J. Beckwith, to whom this work owes its inception.

I am very grateful to Professor G. M. Badger for his great help and encouragement. I would also like to thank Dr. W. H. F. Sasse and Dr. R. W. L. Kimber for their helpful suggestions, and other members of this Department for their ready co-operation.

This work was carried out during the tenure of a Colombo Plan Fellowship from the Commonwealth Government of Australia, to whom I am grateful.

Microanalyses were carried out by the C.S.I.R.O. Microanalytical Laboratory, Melbourne.

STATEMENT

This thesis contains no data that has been previously submitted for a degree in any university, except where due reference is made.

Low Beng See

1962

CONTENTS

CHAPTER I

Free Radical Reactions of Polycyclic Aromatic Hydrocarbons

The existence of organic free radicals was first experimentally demonstrated by Gomberg[1] in 1900. In his attempts to prepare hexaphenylethane by treatment of triphenylmethylchloride with silver powder or zinc dust, he obtained a yellow solution which reacted with air, iodine or nitric oxide resulting in the formation of triphenyl*methyl*-peroxide, -iodide or *triphenyl*-nitrosomethane respectively. To account for this unusual behaviour, he postulated the dissociation of hexaphenylethane into triphenylmethyl radicals, that is,

$$Ph_3C - CPh_3 \rightleftharpoons 2Ph_3C.$$

The idea was not favourably received at the time, but with the increase in number and variety of stable free radicals prepared and studied, the concept of free radicals was firmly established.

The next step in the development of the chemistry of free radicals was the recognition of the significance

of these entities as transient intermediates in chemical reactions. As early as 1925, suggestions for the existence of free radical intermediates in gas-phase reactions were put forward[2], and four years later experimental evidence was obtained by Paneth and Hofeditz[3] in their studies on the pyrolysis of tetramethyl lead whereby methyl radicals were formed. Their findings were soon supported by further experimental data which opened up the field of gas-phase radical reactions.

The recognition of the existence of free radical intermediates in liquid-phase reactions is often traced back to 1937. In that year Hey and Waters[4] published a review in which they postulated free radical mechanisms for a number of reactions which could not be explained by the then accepted electronic theory of reaction mechanisms. These included the reactions of aromatic compounds with benzoyl peroxide, aryl azo and diazo compounds, to give diaryls, and the addition of hydrogen bromide to olefins in a manner which does not follow Markownikoff's rule. At the same time Kharasch[5] proposed for the "abnormal addition" a free radical chain mechanism

which is still accepted today; and Flory[6] presented the kinetics of vinyl polymerisation, based on the process being a free radical chain reaction. Since then extensive investigations have been directed to this field of chemistry, resulting in a clearer understanding of the characteristics and mechanisms of free radical reactions which has enabled the application of these reactions to synthetic work in the laboratory as well as in industry.

Studies of free radical attack on benzene derivatives have provided interesting information on the effect of substituents on the rate of reaction and the orientation of products. Unlike heterolytic processes, all substituents, whether electron-donating or electron-withdrawing, are ortho-para directing in homolytic substitution in benzene derivatives. The rates generally follow the order o > p > m, but when large substituents are present the extent of ortho-substitution is lowered by steric hindrance. Thus, extremely low yields of ortho-substituted products are obtained in the homolytic arylation of benzotrichloride, which possesses the bulky CCl_3 group[7]. Another characteristic of these reactions is that all substituents activate aromatic nuclei towards

free radical attack. The effect increases with the degree of conjugation between the substituent and the nucleus. This is borne out in the relative rates of phenylation of substituted benzene derivatives which reveal that nitrobenzene[8], diphenyl[9] and benzonitrile[10] are more activated towards attack by phenyl radicals than are alkyl-[11] or halogeno-benzenes[10].

Free radicals, though carrying no charge, possess polar characteristics of varying degree. For example, aryl radicals containing electron-withdrawing groups are electrophilic in character and those with electron-donating groups are nucleophilic, compared with the phenyl radical which is regarded as neutral. The effect of the polarisation of aryl radicals by substituents is evident in the relative rates of arylation of benzene derivatives given in Table 1.1. The deactivated nuclei in nitro-, chloro- and bromo-benzene render these substrates more favourable towards attack by nucleophilic radicals than by electrophilic radicals. Thus, it may be seen that the rate of arylation of these compounds by the nucleophilic p-tolyl radical is greater than by p-nitro-, p-chloro- and p-bromo-phenyl

Table 1.1.

Relative Rates of Arylation with Substituted Phenyl Radicals at 80°.[12]

Radical	$\frac{NO_2\ K}{H}$	$\frac{Cl\ K}{H}$	$\frac{Br\ K}{H}$	$\frac{CH_3\ K}{H}$
p-$NO_2C_6H_4$·	0.94	1.17	1.7	2.6
p-ClC_6H_4·	1.5	1.02	-	1.3
p-BrC_6H_4·	1.8	-	-	-
C_6H_5·	4.0	1.5	1.7	1.7
p-MeC_6H_4·	5.1	2.0	-	1.03

radicals.[13-15] Where the substrate is toluene,[15] the order of reaction rates is reversed as the methyl group activates the ring towards electrophilic substitution.

Arylation of toluene results in nuclear substitution as well as hydrogen abstraction from the side-chain, the latter reaction yielding dibenzyl. Theoretically, side-chain attack should be favoured by nucleophilic radicals and this has been shown to be so by Hambling[15] who obtained a 42% yield of dibenzyl from the reaction of toluene with p-tolyl radicals, 10% with

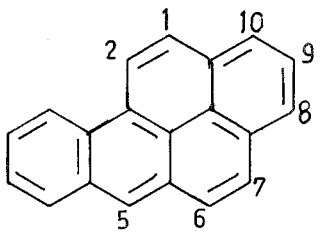
p-chlorophenyl radicals while no dimer was detected with p-nitrophenyl radicals. Thus, it may be seen that the polar nature of free radicals exerts an influence on the rate of reaction as well as on the positions of attack.

Of particular interest to us is the behaviour of polycyclic aromatic hydrocarbons towards free radicals. These condensed systems have been observed to be attacked almost exclusively at one position, that is, there is one position in the molecule which is much more reactive than the others. The relative reactivities of various positions in a polynuclear hydrocarbon may be predicted theoretically on the basis of free valence or atom localisation energy. The concept of free valence was introduced by Coulson[16,17] and is based on the isolated molecule approach. The free valence number represents the difference between the idealised maximum bonding power of an atom and the bonding power in its existing state. It is a measure of the degree of additional bonding of which the atom is capable, and hence is related to the homolytic reactivity of the atom, the highest free valence number corresponding to the most reactive position.

The second line of approach which takes into consideration the transition state is based on the energy difference between the reacting hydrocarbon and the intermediate radical resulting from the addition of the attacking radical to the hydrocarbon[18]. The formation of the new bond in the intermediate complex requires the localisation of an electron at the point of attachment in the substrate, which results in the loss of resonance energy. It follows that the smaller the energy difference between the ground and transition states, the more readily does homolytic attack take place. This energy difference has been termed the atom localisation energy. The validity of these theoretical treatments has been proved experimentally in the observed preferential reaction of free radicals with aromatic hydrocarbons, at the positions of maximum free valence number or minimum atom localisation energy.[19-21]

A quantitative treatment of the relationship between homolytic reactivity and the above theoretical indices reveals that the logarithm of the reaction rate or relative rate at any position should be directly proportional to the free valence number, or inversely proportional to the atom localisation energy. A number

of approaches have been employed to test this hypothesis. Kooyman and Farenhorst[20] observed that the addition of trichloromethyl radicals to n-hexadecene and to styrene was retarded by aromatic hydrocarbons. By measuring the extent of retardation they were able to determine the relative rates of addition of trichloromethyl radicals to hydrocarbons ranging from benzene to 3,4-benzpyrene (I).



(I)

Their results indicate a marked increase in reactivity with increasing size of the ring system, 3,4-benzpyrene being over 100,000 times more reactive than benzene. Further, the logarithms of the relative reactivities were found to bear a roughly linear relationship to maximum free valence numbers as well as to minimum atom localisation energies. Their findings were supported by the work of Dunn, Waters and Roitt[22] on the retardation of the benzoyl peroxide catalysed autoxidation of benzaldehyde by polycyclic hydrocarbons.

From the retarding effects they determined the relative rate constants for the addition of benzoylperoxy radicals to the hydrocarbons and showed that the logarithms of these values were linearly related to free valence numbers.

A different technique was employed by Levy and Szwarc[23] who determined the rate of addition of methyl radicals to an aromatic compound ArH (1) relative to the rate of hydrogen abstraction from the hydrocarbon solvent RH (2) from the difference in the

$$ArH + CH_3\cdot \longrightarrow [ArH\,CH_3]\cdot \quad \ldots\ldots\ldots (1)$$

$$RH + CH_3\cdot \longrightarrow R\cdot + CH_4 \quad \ldots\ldots\ldots (2)$$

amounts of methane formed when acetyl peroxide was allowed to decompose in pure solvent and in the presence of the aromatic compound. Their determinations are based on the assumption that the addition complex $[ArH\,CH_3]\cdot$ does not give rise to methane formation in its subsequent reactions. The values thus obtained for the methyl affinities of some aromatic hydrocarbons are given in Table 1.2. It is obvious from these results that increased conjugation in a molecule enhances

reactivity. Levy and Szwarc showed that linear relationships exist between the logarithm of methyl affinities and of the relative reactivities obtained by Kooyman and Farenhorst[20] and by Dunn, Waters and Roitt.[22] They suggested that the slope of the straight line may be taken as a measure of the ratio of the intrinsic reactivities of the radicals.

Table 1.2.

Methyl Affinities of Aromatic Compounds.[23]

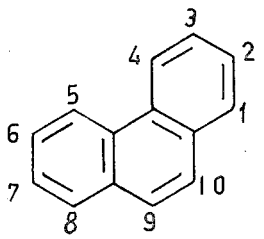
Compound	Methyl Affinity
Benzene	1
Diphenyl ether	2.5
Diphenyl	5
Naphthalene	22
Phenanthrene	27
Chrysene	57.5
Pyrene	125
Benzanthracene	468
Anthracene	820
Naphthacene	9250

Ethyl, n-propyl and iso-propyl affinities of aromatic compounds have been similarly measured by Smid and Szwarc.[24] From the log-log plots of these values against methyl affinity, they concluded that methyl, ethyl, and n-propyl radicals possess the same intrinsic reactivity for an addition reaction. Also, the intrinsic reactivity of iso-propyl radicals is similar to that of the primary alkyl radicals, which is a little surprising.

Coulson[25] has shown that for a series of polynuclear hydrocarbons a plot of the logarithm of methyl affinity against atom localisation energy gives a straight line and he suggested that localisation energy values may be used to determine the methyl affinities of compounds that have not been measured experimentally. A similar relationship has been found to exist between methyl affinity and free valence number.

Most of the evidence in support of the correlation between homolytic reactivity and theoretical indices has resulted from studies of the relative reactivities of various aromatic compounds. Very little work has been devoted to a comparison of

theoretical quantities with reactivities of the different positions in a molecule. An extensive investigation of this nature was recently reported by Beckwith and Thompson[21] who studied the reaction of phenanthrene (II) with phenyl radicals produced by the



(II)

thermal decomposition of diazoaminobenzene. The relative yields of phenylphenanthrenes, determined by chromatographic methods and ultraviolet spectral measurements, indicate that phenylation of the phenanthrene molecule occurred in the order 9>1>3>2, which is in agreement with theoretical calculations of free valence number, atom localisation energy and Dewar's "reactivity numbers". Their results together with the relevant theoretical data are set out in Table 1.3. The marked absence of 4-phenylphenanthrene was ascribed by the authors to steric hindrance.

Table 1.3.

Relative Yields of Phenylation, and Theoretical Indices of Reactivity for Phenanthrene

Position	Relative Yields[21]	$F_{V.B.}$	$F_{M.O.}$	E	R
1-	4.1	0.197	0.450	2.30	1.86
2-	1.0	0.163	0.402	2.50	2.18
3-	1.0	0.172	0.407	2.41	2.04
4-	0	0.184	0.440	2.39	1.96
9-	6.7	0.200	0.451	2.30	1.80

$F_{V.B.}$, free valence number calculated by the valence bond method (Daudel and Daudel, J.Chem.Phys., 1948, 16, 639); $F_{M.O.}$ and E, free valence number, and atom localisation energy respectively calculated by the molecular orbital method (Coulson and Daudel, "Dictionary of Values of Molecular Constants", 1955, Vol. II, p. 20); R, Dewar's "Reactivity Numbers" (Dewar, J.Amer.Chem.Soc., 1952, 74, 3357).

A large variety of free radicals has been used in the investigation of the homolytic reactions of aromatic hydrocarbons. These include aryl, alkyl, aroyloxy, acyloxy, halogen, hydroxyl and amino radicals.

The production of free radicals which involves the homolytic fission of a covalent bond may be accomplished by a number of ways. One of the most frequently employed methods is the thermal decomposition of organic peroxides as this reaction is comparatively clean and peroxides are obtainable in a pure form. The action of the decomposition products of benzoyl peroxide on aromatic nuclei has been studied by several workers. The peroxide, on thermal decomposition, yields benzoyloxy radicals (3) which may break down to phenyl radicals with loss of carbon dioxide (4). It can therefore act

$$PhCO.OO.COPh \longrightarrow 2PhCO_2^{\cdot} \qquad \ldots\ldots\ldots (3)$$

$$PhCO_2^{\cdot} \longrightarrow Ph^{\cdot} + CO_2 \qquad \ldots\ldots\ldots (4)$$

as a benzoyloxylating as well as a phenylating agent. Benzoyloxy radicals, being much less reactive than phenyl radicals, will attack only reactive substrates so that benzoyloxylation becomes more significant with increasing reactivity of the substrate. Thus benzene and its substituted derivatives react predominantly by phenylation to give dienthryls[26]; naphthalene being more reactive is attacked by phenyl and benzoyloxy radicals[27]; anthracene and higher polycyclic hydrocarbons

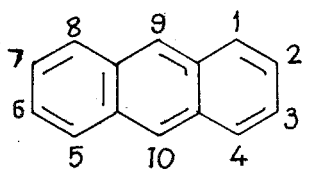
are exclusively benzoyloxylated.[19]

Davies, Hey and Williams[27], in their studies of the decomposition of benzoyl peroxide in dilute solution in naphthalene at 85° and 100°, isolated the isomeric phenylnaphthalenes, naphthylbenzoates and dinaphthyls. While the phenylnaphthalenes obviously resulted from the reaction of naphthalene with phenyl radicals, the authors suggested that the benzoyloxy radicals reacted with the hydrocarbon by hydrogen abstraction to give dinaphthyls and by substitution to yield naphthylbenzoates. Their results indicate that attack by both types of radicals occurred predominantly at the 1-position, in accord with theoretical predictions.[18,28] At the higher temperature, the extent of phenylation increased, presumably due to easier decarboxylation of the benzoyloxy radicals. Increase in the reaction temperature also resulted in slightly larger yields of 2-naphthylbenzoate and 2-phenylnaphthalene. This effect of temperature on isomer distribution has also been observed in other substitution reactions.

The reactions of naphthalene with o- and p-nitro- and o- and p-chloro-benzoyl peroxides were investigated by Davies[29] who found that the greater

electrophilic character of the aroyloxy radicals markedly increased the extent of aroyloxylation and decreased that of arylation. This is not surprising as naphthalene is known to exhibit greater reactivity towards electrophilic reagents than towards free radicals.

The work of Nott and Waters[19] on the action of benzoyl peroxide on polynuclear hydrocarbons has resulted in some interesting observations. Anthracene (III), 1,2-benzanthracene (IV) and 3,4-benzpyrene (I) were readily converted to the 9-, 10- and 5-benzoates respectively; no products of phenylation were detected. 1,2-5,6-Dibenzanthracene (V) was unaffected; but in the presence of air, it was oxidised



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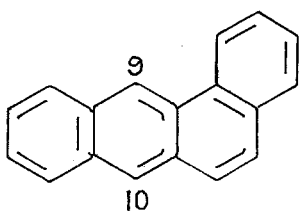

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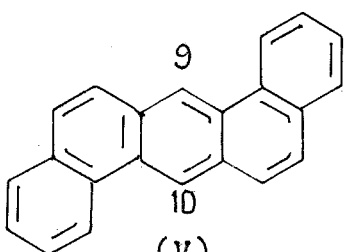
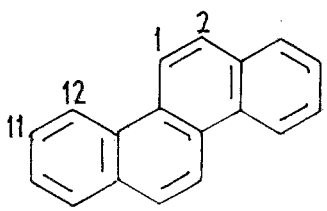


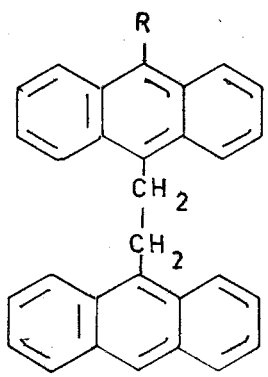
(V)



(VI)

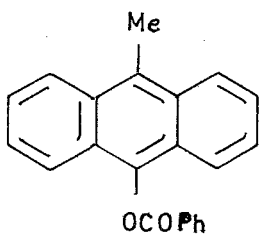
in low yields to the 9,10- and 3,4-quinones, probably by a secondary autoxidation process. Phenanthrene and chrysene (VI) were not attacked at all. The order of reactivity, viz., 3,4-benzpyrene$\gg$ anthracene, 1,2-benzanthracene$>$1,2-5,6-dibenzanthracene$>$chrysene, phenanthrene agrees with the order of the free valence numbers of the reacting positions.[30] The lack of reactivity in dibenzanthracene and at the 9-position of benzanthracene was considered as being possibly due to steric hindrance.

9-Methylanthracene was found to react very readily with benzoyloxy radicals, yielding 1,2-di-(9'-anthranyl)ethane (VII), the substituted dianthryl derivative (VIII), 9-benzoyloxy-10-methylanthracene (IX) and two colourless compounds believed to be polymorphic crystalline modifications of the photodimer of (VII).



(VII), R = H

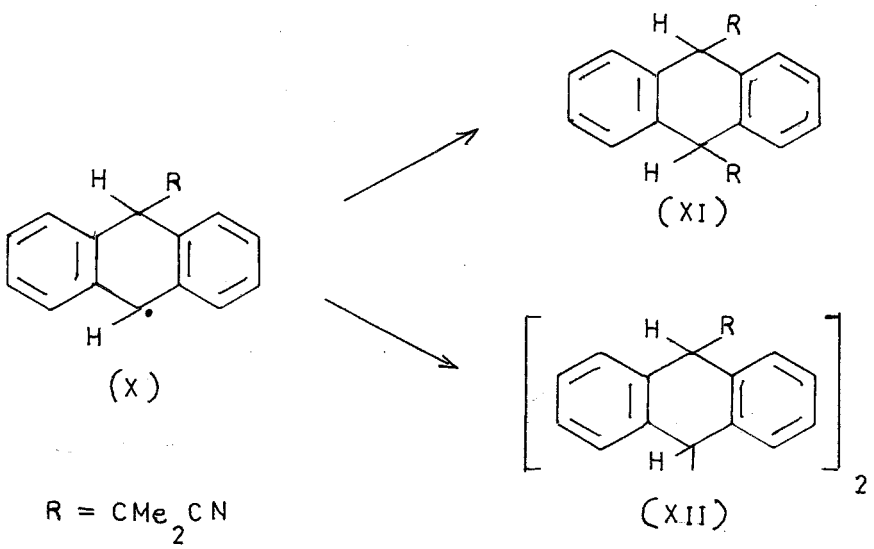
(VIII), R = OCOPh



(IX)

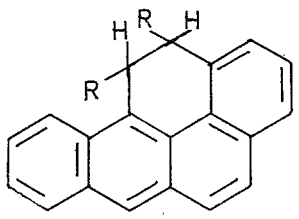
Of interest is the absence of substitution in the side-chain by the benzoyloxy radical, in view of the fact that alkyl side-chains are highly susceptible to free radical attack.

The addition of radicals to polycyclic hydrocarbons was demonstrated by Bickel and Kooyman[31] who isolated from the reaction of anthracene with 2-cyano-2-propyl radicals cis- and trans- 9,10-di(2-cyano-2-propyl)-9,10-dihydroanthracene (XI) and the dimeric product (XII). They postulated the addition of a



cyanopropyl radical to anthracene to give the complex (X) which could then dimerise to (XII) or add on another cyanopropyl radical to give (XI). Dehydrogenation of the complex, which is the third possibility, is

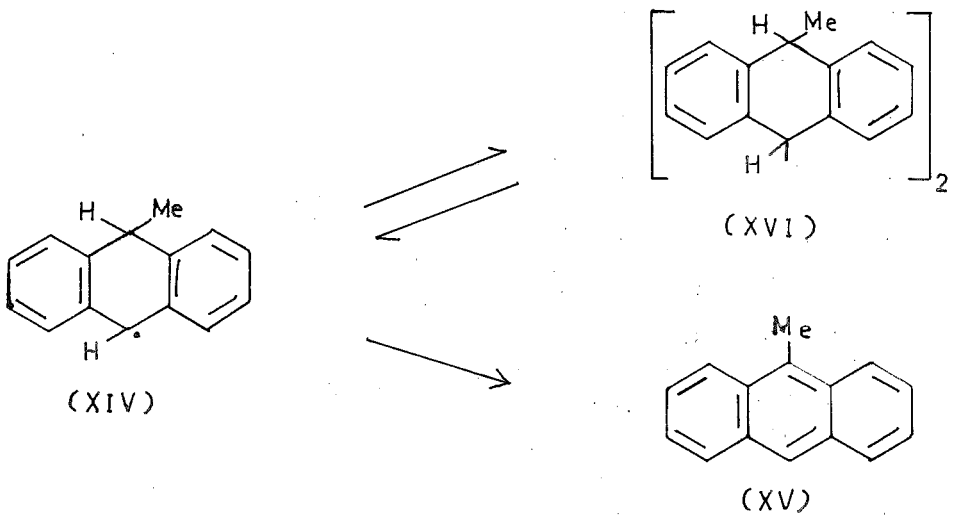
insignificant in this reaction as the cyanopropyl radical is a relatively weak hydrogen-acceptor. Interestingly, Conway and Tarbell[32] isolated two products from the reaction with 3,4-benzpyrene. The major product is believed to be 1,2-di(2-cyano-2-propyl)-1,2-dihydro-3,4-benzpyrene (XIII) and formed in small yield was a monocyanopropyl-benzpyrene which is probably the 5-substituted derivative.



(XIII), $R = CMe_2CN$

The work of Beckwith and Waters has given strong support to the view that homolytic reactions of aromatic compounds proceed by an initial addition step. Employing di-t-butyl peroxide as a source of methyl and t-butoxy radicals, they studied the action of these radicals on polycyclic hydrocarbons.[33] Naphthalene, phensanthrene and pyrene were not appreciably affected, but anthracene yielded 9-methylanthracene (XV), 9,9',10,10'-tetrahydro-10,10'-dimethyl-9,9'-dianthryl (XVI) and anthraquinone. As in the reaction with

cyanopropyl radicals the postulated intermediate is an addition complex (XIV); unlike the former reaction, the intermediate radical does not add another methyl radical but dehydrogenates to the fully aromatic methylanthracene.



This difference is due to the greater reactivity of methyl and t-butoxy radicals compared to cyanopropyl radicals; the methyl radical, in particular, is well known for its ability to abstract hydrogen. It is significant that 9,9'-dianthryl was not formed; it indicates that the direct abstraction of hydrogen from anthracene did not occur. Another interesting observation was that the reaction when performed at a higher temperature gave increased yields of 9-methylanthracene and anthraquinone but no dimeric

product (XVI). From this it was concluded that the coupling of the intermediate radical (XIV) is a reversible step, the formation of the dimer (XVI) being favoured by low temperatures.

9-Methylanthracene was more reactive than anthracene, being attacked in the nucleus to give substitution derivatives and in the side-chain to give dimeric products. It was observed that low temperatures favoured reaction in the substituent while increased temperatures resulted in higher yields of substitution products. The authors suggested that under the former conditions, the reacting species is the t-butoxy radical which is sufficiently reactive to abstract hydrogen from the side-chain; but at higher temperatures, the t-butoxy radicals break down to methyl radicals which readily attack the anthracene nucleus.

Benzyl radicals, produced by the thermal decomposition of di-t-butyl peroxide in toluene, reacted with anthracene in a similar manner, yielding the products (XVIII), (XIX), (XXII) and (XXIII).[34] The suggested routes by which they were formed are indicated in Figure 1.1. The significant feature of the reaction is the simultaneous production of derivatives of anthracene and 9,10-dihydroanthracene. This means that both

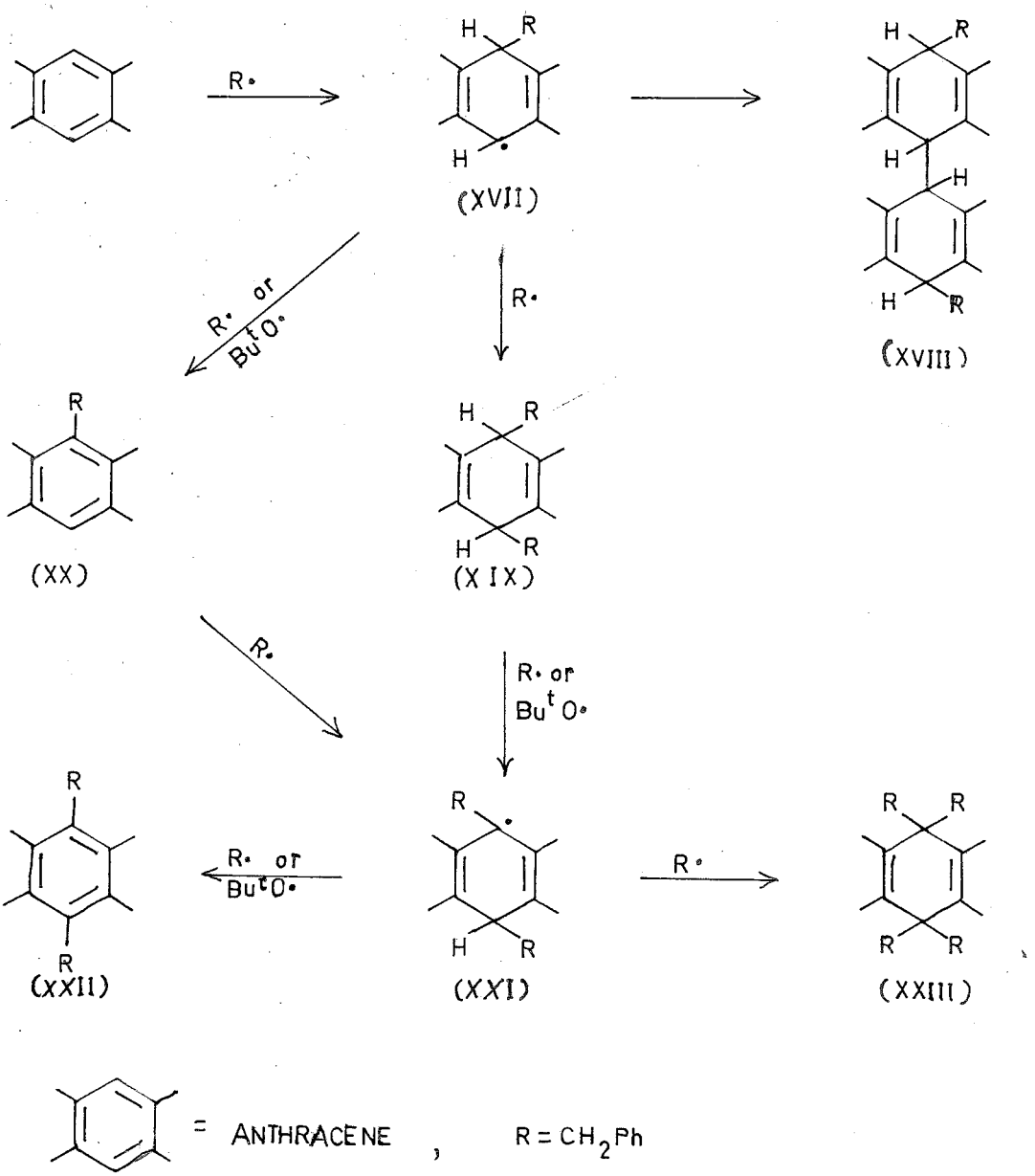


Fig. 1.1. Reaction of Anthracene with Benzyl Radicals.

substitution and addition products are derived from the same intermediate (XVII) formed by addition of a benzyl

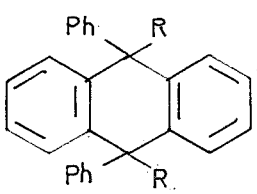
radical to a meso-position of anthracene. Another point of interest is the formation of the trisubstituted compound (XXIII), which is the first of its kind isolated from the reaction of anthracene with free radicals, though a similar compound has been postulated as an intermediate in the lead tetra-acetate oxidation of anthracene.[35] Its formation probably proceeds through the intermediate (XXI) which may be formed by addition of a benzyl radical to 9-benzylanthracene (XX) or by loss of a hydrogen atom from the dihydroanthracene derivative (XIX). The former route is the more likely as compounds such as (XIX) are known to be resistant to the abstraction of hydrogen by free radicals.[36]

Norman and Waters[37] who obtained benzyl radicals by the action of benzyl chloride and cobaltous chloride on benzyl magnesium chloride, also reported radical addition to anthracene yielding dihydroanthracene derivatives. However, no substituted anthracene products were isolated.

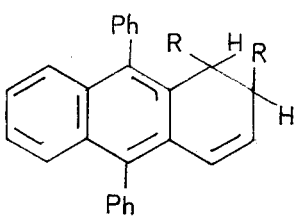
The action of phenyl radicals on anthracene has been reported to yield 9,10-diphenylanthracene and 9,9',10,10'-tetrahydro-10,10'-diphenyl-9,9'-dianthryl.[38] Unlike the reaction with benzyl radicals, there was no dihydroanthracene derivative corresponding to (XIX),

obviously due to the preferred formation of the fully aromatic compound. 9-Methyl- and 9-phenyl-anthracenes were found to be more reactive than the parent hydrocarbon. The enhanced reactivity of meso-substituted anthracenes has been noted in other homolytic reactions.[19,33,39] Of interest is the fact that phenylation of methylanthracene occurred exclusively in the nucleus to give 9-methyl-10-phenylanthracene whereas in the reaction with methyl radicals, the hydrocarbon underwent side-chain as well as nuclear attack.[33] Contrary to expectations, 9,10-dimethylanthracene was unaffected by phenyl radicals.

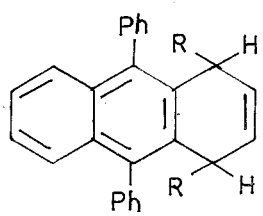
9,10-Diphenylanthracene exhibits unusual behaviour in its reactions with free radicals in that it can react in a terminal ring as well as at its meso-positions. Thus, with benzyl radicals it was converted to the dihydroanthracene derivative (XXIV) and small



(XXIV), R = CH_2Ph



(XXV), R = CH_2Ph



(XXVI), R = CH_2Ph

(XXVII), R = Me

amounts of two isomeric hydrocarbons believed to be 1,2-dibenzyl-1,2-dihydro- and 1,4-dibenzyl-1,4-dihydro-9,10-diphenylanthracenes, (XXV) and (XXVI).[40] The latter compounds clearly resulted from the addition of benzyl radicals to the terminal ring.

The reaction of 9,10-diphenylanthracene with methyl radicals proceeded normally, addition occurring across the meso-positions to give (XXVII), though only in low yield. Phenyl radicals, however, did not attack the meso-positions as the only product from the phenylation of 9,10-diphenylanthracene was 1,4,9,10-tetraphenyl-anthracene. It appears that the phenyl substituents, though not large enough to prevent the addition of methyl and benzyl radicals to the 9,10-positions, do hinder attack by phenyl radicals at these positions.

Though the mechanism of homolytic reactions of aromatic compounds has not been completely elucidated, there is strong evidence to support the widely accepted view that the initial step is the addition of the attacking radical R· to a reactive carbon atom in the aromatic substrate ArH. The resulting intermediate $[R\text{-}Ar\text{-}H]\cdot$ has been considered by Waters[41] as a π-complex, and more recently by Rondestvedt and Blanchard[42] as a σ-complex, in the formation of which a π-complex is an

intermediate. The complex could lose a hydrogen atom to a second radical and so be converted to a substitution product, or add on another radical, resulting in an addition product. The ratio of substitution to addition depends on the nature of both the substrate and the attacking radical. The substitution reaction predominates in the presence of radicals that readily accept hydrogen as in the reaction of anthracene with methyl radicals. On the other hand, addition is preferred with relatively stable radicals such as cyanopropyl or benzyl radicals. The third reaction path is dimerisation of the intermediate radical and this occurs when the complex is stable enough to exist in a concentration sufficient for coupling. Dimeric products have been isolated from most of the homolytic reactions of anthracene. Depending on their reactivity, the primary products may undergo further reaction of similar type. The above mechanism satisfactorily accounts for the various products that have been isolated from free radical reactions of aromatic hydrocarbons.

Reactions of Thiyl Radicals with Olefines and Polycyclic Aromatic Hydrocarbons.

The reaction of thiols with olefines was first reported by Posner[43] who treated a variety of olefines with thiophenol and toluene-ω-thiol at room temperature in the presence of acetic and sulphuric acids. He observed that the orientation of the addition was contrary to Markownikoff's rule, that is,

$$CH_2 = CHR' + RSH \longrightarrow RSCH_2 - CH_2R'.$$

The free radical nature of the reaction was first recognised by Ashworth and Burkhardt[44] who observed that the addition of thiophenol to styrene was accelerated by light and inhibited by traces of piperidine. The effect of peroxides[45] and other radical sources in these additions was later noted, and in 1938 Kharasch[46] proposed the presently accepted mechanism which involves the chain propagating steps (5) and (6). Both the addition (5) and displacement (6) steps are appreciably

$$RS\cdot + CH_2 = CHR' \longrightarrow RSCH_2 - \dot{C}HR' \quad \ldots\ldots (5)$$

$$RSCH_2 - \dot{C}HR' + RSH \longrightarrow RSCH_2 - CH_2R' + RS\cdot \quad \ldots\ldots (6)$$

exothermic making a rapid chain reaction possible.[47(a)]

That the addition of a thiyl radical to an olefine (5) is reversible was suggested by Sivertz and his co-workers[48] who obtained negative over-all activation energies of 8 to 9 kcal. for the photochemical addition of methanethiol to isobutylene, propylene and ethylene in the gas phase. The occurrence of the reversible reaction in solution was demonstrated by Walling and Helmreich[49] who observed that in the addition of methanethiol to cis- and trans-2-butenes at 60°, the unreacted olefine underwent rapid isomerisation. The isomerisation of 2-butene by thiophenol in solution has also been reported.[50]

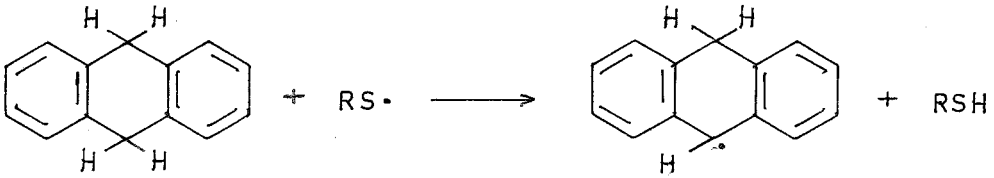
A consideration of the activation energy and the C-H and S-H bond dissociation energies in the chain transfer reaction of styrene indicates that the reverse of the displacement step (6) should occur readily.[47(b)] There has been a number of observations that support this conclusion. Tetralin when refluxed in isoamyl disulphide yielded naphthalene and isoamyl mercaptan, the reaction proceeding more rapidly with peroxide-containing tetralin.[51] Nakasaki[52] reported a similar dehydrogenation of tetralin, 9,10-dihydroanthracene and phenylcyclohexane by phenyl disulphide and 2-benzothiazyl disulphide at

260°. That these dehydrogenations are effected by thiyl radicals is shown by the observation that similar reactions may be induced photochemically at room temperature.[53] Cohen and Wang[54] obtained a 72% yield of 1,1,2,2-tetraphenylethane on irradiation of a dilute solution of phenyldisulphide in diphenylmethane. The photolysis of isobutyl disulphide in cumene at 35° led to the rapid formation of isobutyl mercaptan and 2,3-dimethyl-2,3-diphenylbutane.[55] The thiol-catalysed decarbonylation of aldehydes is believed to involve abstraction of the carbonyl hydrogen by thiyl radicals.[56-58]

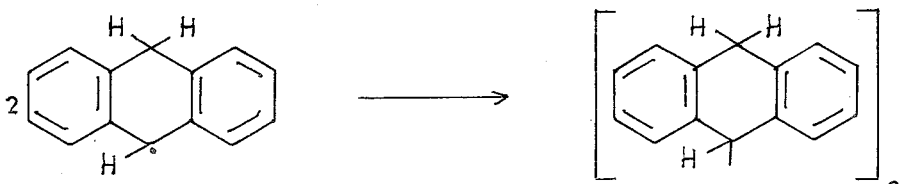
Bickel and Kooyman[59] found that the thermal decomposition of $\alpha\alpha'$-azoethylbenzene in the presence of a thiol and 9,10-dihydroanthracene (XXVIII) resulted in the dehydrogenation of the hydrocarbon to give 9,9',10,10'-tetrahydro-9,9'-dianthryl (XXX). The reaction apparently proceeds by the abstraction of a meso-hydrogen atom from the hydrocarbon by a thiyl

$$PhCHMeN = NCHMePh \longrightarrow 2\,PhC^{\bullet}HMe + N_2$$

$$PhC^{\bullet}HMe + RSH \longrightarrow PhCH_2Me + RS^{\bullet}$$



(XXIX)



(XXX)

radical followed by dimerisation of the resulting radical (XXIX). The thiol acts as a hydrogen transfer agent as only one mole of thiol is used for every four moles of ethylbenzene formed. Other aliphatic azo compounds may be used in place of $\alpha\alpha'$-azoethylbenzene. When 9,10-dibenzyl-9,10-dihydroanthracene was treated with $\alpha\alpha'$-azoisobutyronitrile and mercaptoacetic acid, it was reduced to 9,10-dibenzylanthracene, which means that the substituted radical corresponding to (XXIX) was sterically hindered from dimerising and instead was converted to the fully aromatic compound by the loss of a second hydrogen atom.[34]

The easy reversibility of thiyl addition reactions together with the fact that many enzyme systems

are known to contain -SH groupings has prompted a number of workers to speculate on the significance of thiyl radicals as hydrogen transfer agents in biological systems.[47(c),59]

Recently Jenner and Lindsey, Jr.[60] studied the oxidation of thiols (RSH) in the presence of butadiene (M) as a means of preparing some novel dithio compounds. The reaction gave several types of products: RSSR, RSMH, RSMSR, RSMMSR and RSMOH, the course of the reaction depending largely on the oxidising agent used. Butadiene reacted with mercaptoacetic acid in the presence of hydroxyl radicals or ceric salt to give the additive dimer $(HO_2C.CH_2S.CH_2CH=CHCH_2-)_2$ but when ferric salts were employed as the oxidising agent, the sole product was the simple disulphide $(HO_2C.CH_2S-)_2$. Similarly with thioacetic acid and ethanethiol, formation of the additive dimer occurred only under the oxidising action of hydroxyl radicals or ceric ions. In the presence of the other oxidising agents a variety of products, of the types indicated earlier, was obtained. The formation of additive dimers in other systems has been shown to be free radical in nature[61,62] and Jenner and Lindsey, Jr. propose that thiyl radicals are involved in the production of these

butadiene-thiol adducts. They, however, suggest that thiyl radicals are not formed under those conditions where butadiene was not attacked and only the disulphide was formed.

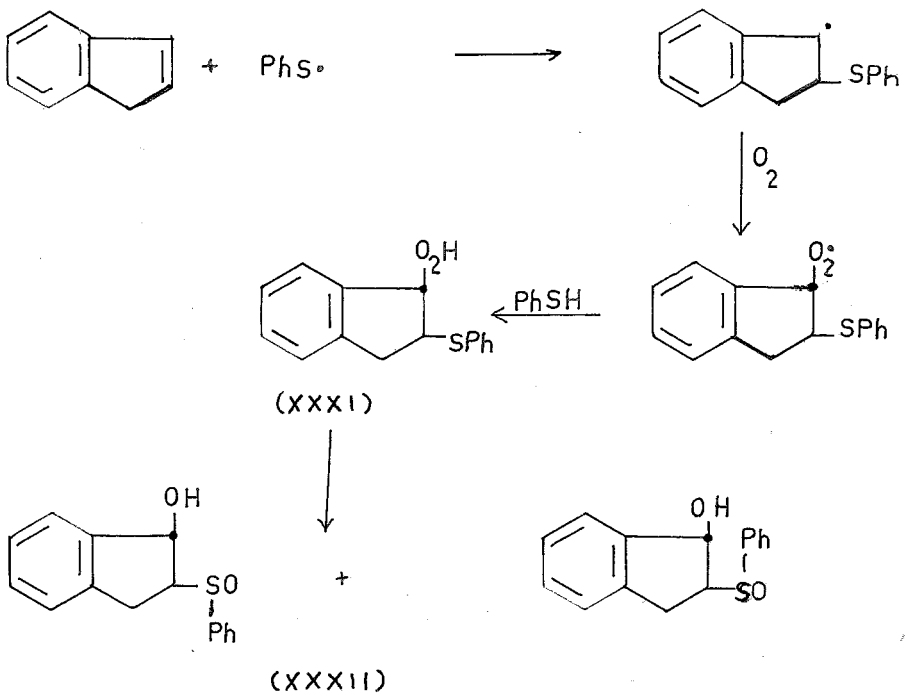
In their studies of the reactions of styrene and other olefines with mercaptans under oxygen, Kharasch and his co-workers[63] obtained sulphoxides instead of the usual free radical addition products. They observed that the amount of oxygen absorbed was

$$PhCH = CH_2 + RSH \xrightarrow{O_2} PhCHOH - CH_2SOR.$$

equivalent to the mercaptan consumed. Further, the rate of oxygen absorption varied directly with the relative reactivity of the olefine and increased with the ease of oxidation of the thiol. The ease of reaction increased in the order $ArSH > HSCH_2CO_2H >> RCH_2SH > RR'CHSH > RR'R''CSH$. Addition of ferrous salt and cumene hydroperoxide was found to catalyse the reaction.

A similar reaction was observed by Ford, Pitkethly and Young[64] in the co-oxidation of indene and thiophenol. The major primary product was the trans-hydroperoxide (XXXI) which spontaneously rearranged to the two racemates of trans-2-phenylsulphinyl-1-indanol (XXXII). The reaction path proposed by the authors is

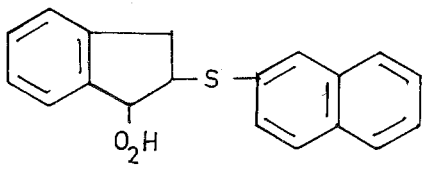
indicated below. The indene molecule is attacked by the



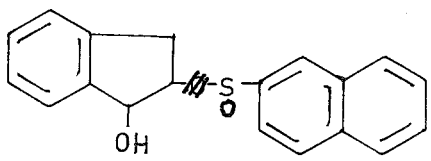
(XXXII)

phenylmercaptyl radical at the 2-position exclusively, to within 5%, and subsequent addition of oxygen to the intermediate 2-phenylmercaptoindanyl radical is, within the same limits, exclusively a trans-addition.

From the reaction of indene with 2-naphthalenethiol in air, Oswald[65] isolated the hydroperoxide (XXXIII) which showed exceptional stability, being stable up to 70°. In benzene solution at 40°, it rearranged to give mainly the hydroxy-sulphoxide (XXXIV).



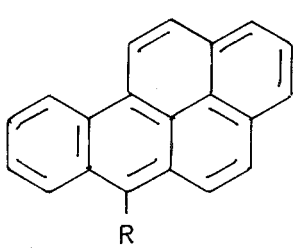
(XXXIII)



(XXXIV)

It has been suggested that the peroxidation and gum formation in untreated petroleum distillate is largely due to the co-oxidation of olefines and thiols to give hydroperoxide intermediates.[65] This reaction is believed to be responsible for the inhibitory effect of oxygen in thiol-induced polymerisations.[63]

Though the addition of thiols to olefines has been extensively investigated, very little is known about the interaction of thiyl radicals with polycyclic aromatic hydrocarbons. Conway and Tarbell[32] recently studied the interaction of 3,4-benzpyrene with thiols under conditions favourable for the production of thiyl radicals. Irradiation of a mixture of the hydrocarbon and mercaptoacetic acid gave 5-(3,4-benzpyrenyl)acetate (XXXV) and a small amount of



(XXXV), R = CH_2CO_2H
(XXXVI), R = SH
(XXXVII), R = SCH_2CO_2Me
(XXXVIII), R = CH_2CO_2Me
(XXXIX), R = SCH_2CO_2H.

5-mercapto-3,4-benzpyrene (XXXVI). This is surprising in view of the fact that mercaptans are known to dissociate to thiyl radicals on irradiation.[66] Of significance in this connection is the observation that methyl-5-(3,4-benzpyrenyl)mercaptoacetate (XXXVII) on irradiation decomposed to the acetate[32] (XXXVIII). This means that in the reaction of 3,4-benzpyrene with mercaptoacetic acid, 5-(carboxymethylthio)-3,4-benzpyrene (XXXIX) may have been actually formed, but decomposed to the observed product (XXXV). However, Conway and Tarbell, on the basis of bond strengths, have suggested that the reaction proceeds by way of dissociation of the thiol into $\cdot CH_2CO_2H$ and $\cdot SH$ radicals which attack the hydrocarbon. That the reaction is free radical in nature is substantiated by the observation that the mixture was unaffected by irradiation in Pyrex vessels.

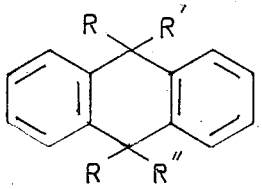
Irradiation of a mixture of benzpyrene and n-hexanethiol gave no substitution product. The difference in behaviour between n-hexanethiol and mercaptoacetic acid is not unexpected as the ethyl ester of the acid is known to be a much more effective chain transfer agent than saturated mercaptans.[67]

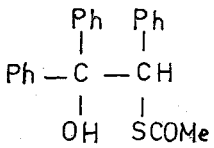
3,4-Benzpyrene was found to be almost unaffected when treated with ethylmercaptoacetate and Fenton's

reagent or with mercaptoacetic acid or thioacetic acid in the presence of oxygen.[32] Failure of the hydrocarbon to react with thiyl radicals is surprising in view of the high reactivity of benzpyrene towards free radicals.[20]

The reaction between anthracene, thioacetic acid, and oxygen was first described by Mikhailov and Blokhina,[68] who observed that approximately one molar equivalent of the gas was rapidly absorbed; two isomeric 9,10-dihydro-9,10-di(acetylthio)anthracenes (XL) were formed and an unidentified yellow substance, m.p. 228-229°. 9,10-Dihydro-9,10-dimethyl-9,10-di(acetylthio) anthracene (XLI) and the ethyl derivative (XLII) were formed from 9,10-dimethyl- and 9,10-diethyl-anthracenes respectively by similar, though less rapid, reactions. In a later study[69] the same authors extended the reaction to 1,2-benzanthracene which yielded 9,10-dihydro-9,10-di(acetylthio)-1,2-benzanthracene and to 9,9'-difluorenylidene and 9-benzylidenefluorene, both of which were converted to di(thiolacetates) by addition of CH_3COS groups across the exocyclic double bonds. Products of somewhat different types were obtained from 1,1,2-triphenylethylene, which yielded S-(2-hydroxy-1,2,2-triphenylethyl)thioacetate (XLIII), and from anthracene and thioacetic acid in ether, which produced

9,10-dihydro-9-acetylthioanthracene (XLIV).





(XLIII)

(XL), R = H, R' = R'' = S.CO.Me
(XLI), R = Me, R' = R'' = S.CO.Me
(XLII), R = Et, R' = R'' = S.CO.Me
(XLIV), R = R' = H, R'' = S.CO.Me.

The structures of these products were not rigorously confirmed. The compounds obtained from anthracene were assigned their structures on the basis of their oxidation to anthraquinone. No additional evidence was presented for the structures proposed for the products formed in reactions of substituted anthracenes.

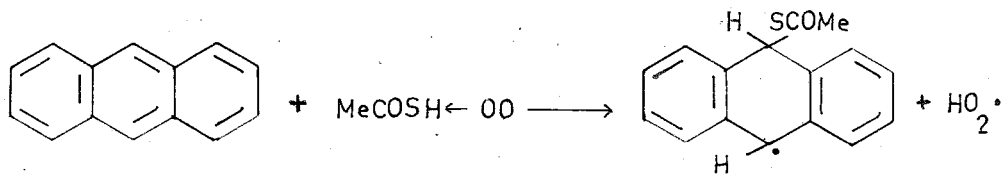
The reaction mechanism originally put forward by Mikhailov and Blokhina[68] involved the addition across the reactive meso-positions of anthracene of two thioacetoxy radicals formed by oxidation of thioacetic acid:

$$MeCOSH + O_2 \longrightarrow MeCOS\cdot + HO_2\cdot$$

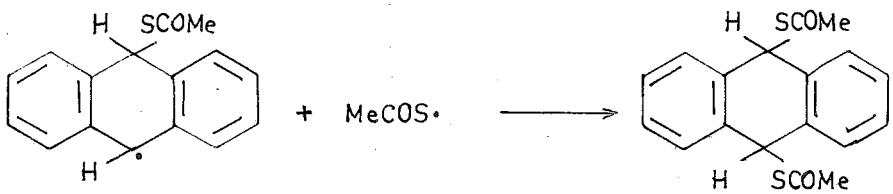
$$MeCOSH + HO_2\cdot \longrightarrow MeCOS\cdot + H_2O_2$$

Later, the same authors,[69] aware that this mechanism accounts neither for the amount of oxygen absorbed nor for its rate of absorption, proposed a modified mechanism:

$$MeCOSH + O_2 \longrightarrow MeCOSH \leftarrow OO$$



$$MeCOSH + HO_2\cdot \longrightarrow MeCOS\cdot + H_2O_2$$



This mechanism is unsatisfactory: it does not account for the formation of the product (XLIV), and it involves an intermediate (Me.COSH←OO) of a type never before described, for whose existence no direct evidence is offered.

These reactions show unusual features when compared with other free radical reactions of anthracene. Thus, no dianthryl derivatives were isolated although

attack of methyl,[33,37] benzyl,[34,37] 2-cyanopropyl,[31] phenyl,[37] and benzoylperoxy radicals[70] on anthracene all lead to products of this type. Secondly, reactions between alkyl-substituted anthracenes and benzoylperoxide[19] and di-t-butylperoxide[33] give products whose formation could be ascribed to abstraction of hydrogen from the substituent but such products were not isolated by the Russian workers. This is surprising in view of the well-known efficiency of thiyl radicals as hydrogen transfer agents.

In view of these inconsistencies, it seemed desirable to re-investigate the reaction of anthracene with thioacetic acid and to extend it to other polycyclic aromatic hydrocarbons and thiols. From such a study it was hoped to gain more information about the mechanism of the reaction, and in general, about the action of thiyl radicals on aromatic hydrocarbons. It is surprising that the thiol-catalysed dehydrogenation of 9,10-dihydroanthracene and its derivatives by aliphatic azo compounds[34,59] does not lead to products containing thio-groups although it involves the intermediate formation of free thiyl radicals.

The inclusion of higher polynuclear hydrocarbons in our investigations arises from the

possible significance of the interactions between these compounds and thiyl radicals in biological syatems, particularly in connection with cancer-production by carcinogenic hydrocarbons. This subject which has been extensively investigated is reviewed briefly in the following section.

POLYCYCLIC AROMATIC HYDROCARBONS AND CARCINOGENESIS

Structure and Activity

Demonstration of the carcinogenic action of coal tar by Yamagiwa and Ichikawa[71] in 1915 marked the beginning of the study of chemical carcinogenesis. It was observed that all the fractions of coal tar that were tumour-inducing showed characteristic bands in their fluorescence spectra similar to those of 1,2-benzanthracene (IV). This stimulated work on the synthesis of polycyclic hydrocarbons related to 1,2-benzanthracene and subsequent testing of such compounds for carcinogenic activity resulted in the first case of tumour production by a pure chemical compound, namely, 1,2-5,6-dibenzanthracene (V). At about the same time, Cook and his co-workers[72] succeeded in isolating 3,4-benzpyrene (I) from coal tar. This hitherto unknown hydrocarbon was found to be a powerful carcinogen. Since then a host of polycyclic aromatic hydrocarbons have been synthesised and tested for carcinogenic activity.

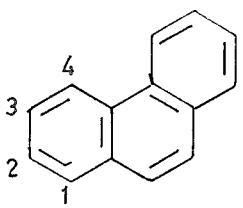
The study of the chemical induction of cancer has not been limited to the polynuclear hydrocarbons. Tumour-inducing activity has been noted in other classes

of chemical compounds such as the sulphur and nitrogen mustards, amines, azo dyes, long-chain polymers and some inorganic compounds. Also, irradiation with ultraviolet light, X-rays, neutrons, α-, β- and γ-rays is known to bring about carcinogenesis.

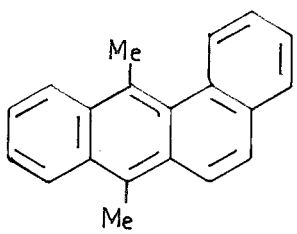
The great increase in the number of known carcinogenic compounds led to attempts to establish a correlation between structure and activity. In 1942, Bergman[73] pointed out that the potent aromatic hydrocarbons possess a planar configuration and that a deviation from such a configuration results in loss of activity. He postulated that the shape and size of a carcinogenic hydrocarbon determined its activity and that it functioned by becoming adsorbed on to a cellular acceptor in a specific way. That carcinogenic hydrocarbons do form addition complexes with cellular constituents is now well established but they have been shown to be covalently bonded[74] and not merely adsorbed as suggested by Bergman. It is interesting that carcinogenic activity has not been detected in hydrocarbons containing more than six or less than three benzenoid rings. This may be taken to mean that there are geometric factors to be considered in tumour production. According to this theory, large substituents in the carcinogen molecule would be expected to hinder

reaction with the cellular receptor and it has been found that the higher alkyl derivatives of 1,2-benzanthracene are less active than the corresponding methyl derivatives.[75] Partial hydrogenation which causes a distortion of the hydrocarbon molecule from a planar configuration was also observed to result in loss of activity in some cases.

In 1946, Robinson[76] suggested that most polycyclic carcinogens contain a phenanthrene type bond which may be activated by suitable substitution or by additional benzene rings. Earlier on it had been pointed out that nearly all the potent hydrocarbons may be considered as phenanthrene derivatives having additional benzene rings and/or methyl substituents at three or four of the 1, 2, 3 and 4 positions.[77] For example, 9,10-dimethyl-1,2-benzanthracene (XLV) which is carcinogenic is a phenanthrene derivative substituted in the four named positions.

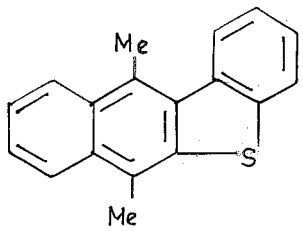


(II)

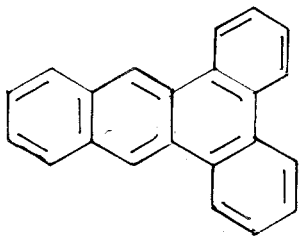


(XLV)

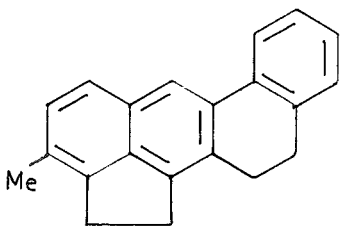
To test Robinson's hypothesis, isomeric dimethylthiophanthrene derivatives were prepared and it was found that those which had the phenanthrene structure were carcinogenic but when the phenanthrene bond was replaced by a sulphur atom as in 4,7-dimethyl-2,3-5,6-dibenzthionaphthene (XLVI), activity was lost. Introduction of sulphur at another site in the molecule, however, had no such effect. Further support is seen in the lack of carcinogenic activity in hydrocarbons such as 1,2-3,4-dibenzanthracene (XLVII) and 6,7-dihydro-20-methyl-cholanthrene (XLVIII) which are devoid of a phenanthrene type bond.



(XLVI)



(XLVII)



(XLVIII)

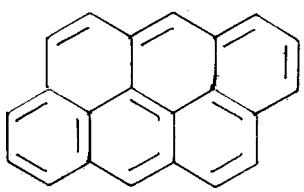
Interestingly, the theoretical calculations of the Pullmans[78] and Daudels[79] indicate that the phenanthrene bond in carcinogenic hydrocarbons, termed the K region, has a particularly high electron density or bond order. These workers postulate that carcinogenic activity is determined by electron density in the K region. The Pullmans used as a measure of the ease of

addition to the K region a complex index which is the sum of the bond localisation energy and the smaller of the two carbon localisation energies. This method gave an excellent agreement with chemical results and was therefore used to interpret carcinogenic activity. It was deduced that a K region with a complex index of not greater than 3.31β is necessary for activity. Thus, pyrene whose K region has a complex index of 3.33β is inactive but fusion of a ring at the 3,4 positions reduces the value to 3.23β and hence 3,4-benzpyrene is a potent carcinogen.

Further, when a hydrocarbon possesses an L region besides the K region, it can exhibit carcinogenic activity only if the L region is not too reactive. The Pullmans suggest that tumour production requires a reaction between the carcinogen and cellular receiver through the K region which therefore has to be sufficiently reactive. If, however, a reactive L region is also present, the molecule becomes involved in different reactions which may not result in malignancy. Hence, the necessity for a rather inactive L region, that is, its complex index should not be less than 5.66β. According to them, 1,2-benznaphthacene which has a favourable K region is not carcinogenic because of its reactive L region. They predict that large cyclic

systems possess, in most cases, a too reactive L region or an insufficiently active K region for carcinogenic activity. This is in agreement with observation.

However, there are a number of cases that are not explained by this theory. 10-Formyl- and 10-cyano-1,2-benzanthracenes would be expected to be inactive on account of the deactivating influence of the substituent groups but they are carcinogenic. Badger[80] suggested that their activity may be due to strong hydrogen bonding between the compounds and tissue components. Methyl substitution in the 1', 2', 3' and 4'-positions of 1,2-benzanthracene fails to produce tumour-inducing properties though it increases electron density in the K region. Anthranthrene (XLIX) is another example of a compound, which according to calculations, should be carcinogenic but is not.



(XLIX)

It was then proposed that carcinogenic activity be studied in relation to "excess charge" in the K region brought about by methyl substitution,[81] and a

satisfactory correlation was obtained for the methylbenzanthracenes and methylbenzacridines. This modification, however, does not account for the anomalies existing in the original theory.

From as early as 1938, attempts were made to correlate tumour-producing activity with chemical reactivity. Various reagents including diazonium compounds[82] and lead tetra-acetate[83] were employed but only limited correlations were obtained. The work of Cook and Schoental[84] on oxidation of polycyclic hydrocarbons with osmium tetroxide showed that the reagent invariably attacked the K region. The reaction is obviously related to the electronic charge in the K region, and so provides a good chemical test of the validity of the quantum mechanical calculations used to correlate carcinogenic activity with electronic structure. Badger and his co-workers[85] measured the rates of reaction of osmium tetroxide with various hydrocarbons and concluded that relative reactivity is related to bond order of the K region, as calculated by the method of molecular orbitals. Methyl and other alkyl substituents in 1,2-benzanthracene increase the rate, the amount of increase depending on the position of substitution. Substitution at the meso-positions produces the most significant activation at the K region, and accordingly

9,10-dimethyl-1,2-benzanthracene was noted to exhibit the greatest reactivity in the substituted 1,2-benzanthracene series. Meso-phenyl groups also accelerate the reaction, although the effect is not so marked. Reaction is slow with 10-cyano-, 9,10-diacetoxy- and 9,10-dibromo-1,2-benzanthracenes, all of which contain deactivating substituents.

There is some correlation between chemical reactivity and carcinogenic activity as seen in Table 1.4.[80] It is obvious that there are exceptions,

Table 1.4.

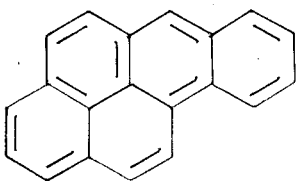
Chemical Reactivity and Carcinogenic Activity

Compound	Relative Reactivity to OsO_4.	Carcinogenic Activity
9,10-dimethyl-1,2-benzanthracene	5.6	++++
9,10-diethyl-1,2-benzanthracene	4.4	+++
9-methyl-1,2-benzanthracene	2.0	+++
10-methyl-1,2-benzanthracene	1.90	++++
9,10-diphenyl-1,2-benzanthracene	1.46	0
10-acetoxymethyl-1,2-benzanthracene	1.27	+
1,2-benzanthracene	1.00	±
10-cyano-9-methyl-1,2-benzanthracene	0.83	++++
10-bromo-1,2-benzanthracene	0.56	0
9,10-diacetoxy-1,2-benzanthracene	0.44	0
10-cyano-1,2-benzanthracene	slow	+

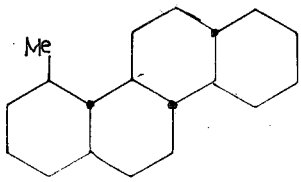
10-cyano-1,2-benzanthracene being one. It may be recalled that this compound also poses a problem to theoretical chemists. The lack of activity in 9,10-diphenyl-1,2-benzanthracene is attributed to a non-planar configuration that hinders complex formation between the hydrocarbon and cellular component.

Heidelberger[74] extended this work to substituted 1,2-5,6-dibenzanthracenes and also obtained a reasonably good agreement between rate of addition of osmium tetroxide and electron density in the K region. Contrary to expectations, however, equal rates of reaction were observed with 9-methoxy-1,2-5,6-dibenzanthracene, a strong carcinogen, and the 9-acetoxy derivative which is inactive.

The most recent development in the search of a relation between activity and chemical structure has resulted from the work of Yang and his collaborators.[86] They postulate that activity of polycyclic aromatic hydrocarbons is determined by a steric resemblance of the hydrocarbon to an active steroid. Thus, 3,4-benzpyrene (I) is compared with 1-methyl-Δ^{1}-norandrostane (L) which represents the basic carbon skeleton of a group of active steroids.

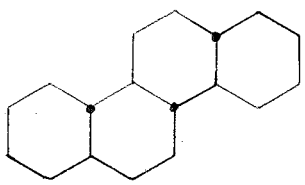


(I)

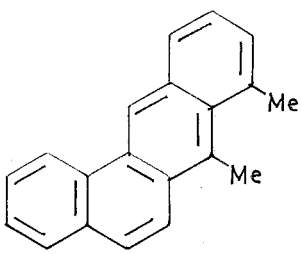


(L)

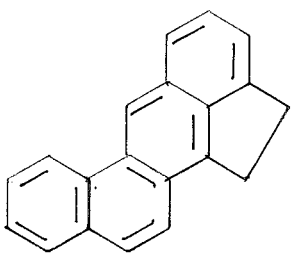
Introduction of methyl substituents at the 5- and 10-positions of 1,2-benzanthracene, which is feebly carcinogenic, yields a molecule similar to di-norandrostane (LI) and 5,10-dimethyl-1,2-benzanthracene (LII) is a strong carcinogen. Similarly, cholanthrene (LIII) which has the same molecular dimensions as the steroid is tumour-producing.



(LI)



(LII)



(LIII)

Introduction of alkyl substituents higher than methyl groups into 1,2-benzanthracene subtracts from the steric similarity between hydrocarbon and steroid and accordingly, these compounds are less carcinogenic than the corresponding methyl derivatives. According to this hypothesis, carcinogenic hydrocarbons participate in complex formation at the same sites as steroids by

virtue of their similarity, and bring about malignancy by interfering with normal steroid functions.

In this connection it is interesting that Kennaway and Cook[87] suggested that carcinogenic hydrocarbons may be formed *in vivo* by an abnormal metabolism of bile acids or other natural compounds of related structure. 20-Methylcholanthrene has been prepared by chemical degradation of deoxycholic acid[88] and of cholic acid. However, attempts to repeat these conversions *in vivo* have not been successful. The biogenesis of carcinogenic hydrocarbons, therefore, must still be considered only as a possibility.

Mode of Action

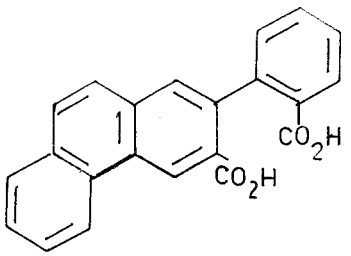
That one of the first steps in chemically-induced carcinogenesis is a reaction between the carcinogen and cellular constituents has been referred to. Fieser[89] suggested that a carcinogenic hydrocarbon combined with protein constituent of the cytoplasm through the disulphide linkage. This was strongly supported by the work of Crabtree[90] which indicates a direct association between sulphur-containing cell constituents and carcinogens during the primary stages of carcinogenesis. He found that the various classes of inhibitors of chemically induced tumours have the

common property of being able to combine with sulphydryl groups and postulated that they operated by competing with carcinogenic hydrocarbons for sulphur-containing enzymes or other cell constituents. Valuable contribution to the theory was made by Miller and Miller[91] who observed the presence of protein-bound aminoazodyes in the livers of rats fed with 4-dimethylaminoazobenzene. Recent work indicates that such dyes are attached to liver proteins through a sulphur atom.[92] Miller has also detected fluorimetrically protein-bound derivatives of 3,4-benzpyrene in the skin of mice treated topically with the carcinogen.[93]

Further evidence of protein-binding resulted from the studies of Heideberger and Moldenhauer[94] using C^{14}-labelled hydrocarbons. They obtained a general correlation between the amount of protein-bound C^{14} in mouse epidermis and the carcinogenecities of the hydrocarbons used. There were three exceptions, namely, 1,2-3,4-dibenzanthracene, 3-methoxy- and 3,4-dimethoxy-1,2-5,6-dibenzanthracenes. These compounds, though non or only slightly carcinogenic, were bound in comparable amounts with the active hydrocarbons. It was concluded that binding to protein is a necessary but not sufficient reaction for skin carcinogenesis. The

essential feature of protein-binding that differentiates between carcinogenecity and inactivity may lie in the type of proteins that are bound. There is some indication that 1,2-5,6-dibenzanthracene and the 1,2-3,4-isomer are bound to different proteins. In comparing the distribution of their protein-bound derivatives, Davenport and Heidelberger[95] found that the active hydrocarbon was bound more strongly than the inactive isomer to a group of proteins similar to the "h" proteins, which had been shown by Sorof and his co-workers[96] to be the main proteins involved in the binding of carcinogenic azo dyes.

The structure of the carcinogen-protein complex is unknown but binding is believed to occur through the K region of the carcinogen. 1,2-5,6-Dibenzanthracene has been shown to be partly bound through amide linkages in the K region by Heidelberger and his co-workers[97,98] who isolated 2-phenylphenanthrene-3,2'-dicarboxylic acid (LIV) from the hydrolysis of peptides from mouse skin treated with the radioactive hydrocarbon. It may be recalled that the Pullmans[78] postulated the participation of the K region in complex formation. Binding through the K region is believed to involve an addition reaction and is subject to steric



(LIV)

hindrance.[99] As the amount of the acid (LIV) isolated represented only 25% of the C^{14} in the mouse skin proteins, it has been suggested that moderately potent hydrocarbons such as 1,2-5,6-dibenzanthracene are bound through both the K and L regions.[99]

Recent studies by Miller and Miller[100] indicate that the two carbon atoms of the K region are not equivalent. This interesting observation resulted from a study of the carcinogenecities of monofluoro derivatives of 10-methyl-1,2-benzanthracene substituted in different positions. The 3-fluoro derivative was found to be inactive and the 4-isomer active. Similar observations were made by Dunning[101] with 3-methyl- and 4-methyl-1,2-benzanthracenes.

Though the actual role of protein-bound derivatives in the induction of cancer is not perfectly understood, a number of theories have been put forward, one of which is the protein deletion hypothesis.[92(b),102]

It is known that nucleic acids are protected by a coating of protein. Binding of the protective protein exposes the nucleic acid to the destructive activity of enzymes which results in the dilution and eventual deletion of the nucleic acid from the cell. If the synthesis of the bound protein were controlled by the affected nucleic acid, loss of the protein also results. Such a mechanism would account for the loss of the "h" proteins from induced liver tumours in rats.[103]

Another theory[94,98] states that growth is controlled by certain enzymes, which become inactivated when bound to a carcinogen. This causes a disruption of growth control which is the beginning of tumour formation. As nucleic acids are involved in the production of enzymes, interactions of these acids with carcinogens leads to the same result, that is, the formation of cells lacking in growth control. Alkylating agents are believed to bring about malignancy through chromosomal interference. This theory may also be applied to tumour production by ionising radiation and by viruses.

Recently attention has been focussed on the investigation of possible interactions between

carcinogenic hydrocarbons and nucleic acids, but the available data is fragmentary and conflicting. Studies of epidermal carcinogenesis with 3,4-benzpyrene[104] and 20-methylcholanthrene[105] revealed the presence of fluorescent material in the cytoplasm but not in the nuclei of tissue cells. On the other hand, there is some evidence of the combination of 1,2-5,6-dibenzanthracene with deoxyribose nucleic acid of mouse epidermis.[106] Attempts to isolate nucleic acid - carcinogen complexes have so far been unsuccessful. It may be that hydrogen bonding and ionic linkages exist in these complexes, making their isolation difficult.

A different approach to the problem of the mechanism of the carcinogenic process is seen in the Warburg hypothesis[107] which relates carcinogenic activity to metabolic oxidation. Warburg postulated that tumours are caused by a partial and irreversible damage to respiration, resulting in an anaerobic glycolytic type of metabolism. Such damage could be brought about through interference with normal cell oxidation processes by carcinogenic hydrocarbons. These compounds have been observed to be eliminated rapidly from their sites of application by metabolic reactions.[108]

Though the mechanism of carcinogenesis is not clearly understood, there is some evidence of the participation of free radicals in the reactions leading to malignancy. Carcinogenesis by radiation almost certainly involves free radicals which could possibly react with nucleic acids, resulting in irreversible cell changes. Free radicals are believed to be involved in the depolymerisation of deoxyribose nucleic acid by X-rays; its products are similar to those formed in the degradation of the acid by chemically produced free radicals.[109] Sulphydryl groups are essential for the activity of many enzymes which are important in cell division and growth. Inactivation of SH-containing enzymes by X-rays is thought to be due to the oxidation of -SH to -S-S- by a free radical mechanism.[110]

Polymeric hydrocarbons are tumour-producing and they decompose with the production of free radicals. Oppenheimer and co-workers[111] have suggested that their carcinogenic action may be due to the inhibition of enzymatic processes by free radicals resulting from their breakdown.

The possible relation between cell oxidative processes and carcinogenesis has been referred to. It is recognised that free radicals play an important part

in biological oxidations.[112,113] Enzymic oxidations are highly sensitive to traces of compounds which are known to inhibit radical reaction chains, and they sometimes show an induction period. There is evidence of the formation of semiquinone type free radicals in reductions by riboflavin nucleotides.

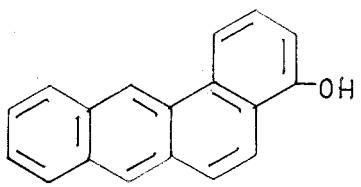
Thiyl radicals, which are efficient hydrogen transfer agents, appear to be particularly significant in biological oxidation-reduction processes. The initiating step in the reduction of coenzyme I is believed to involve a thiyl radical.[114] It has been reported that the hydroxylating enzyme system in rat liver requires oxygen, reduced triphosphopyridine nucleotide and thiol, and that ferrous ions have a catalytic effect, all of which strongly suggest a free radical mechanism.[115]

Finally, the high reactivity of polycyclic aromatic hydrocarbons towards free radicals is not without significance in this connection.

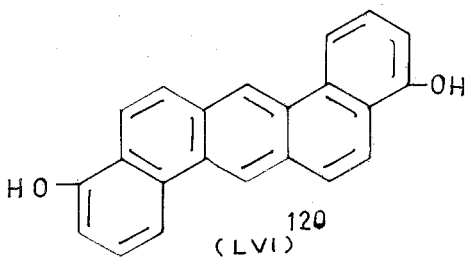
Metabolism

Polycyclic hydrocarbons are metabolised in the animal body to hydroxylated derivatives. Thus, naphthalene is converted to 1- and 2-naphthols[116,117] and the 1,2-dihydrodiol,[118] and anthracene to 1-anthranol

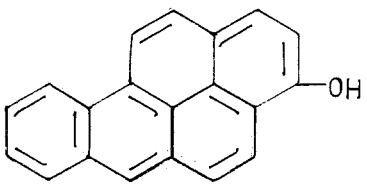
and the 1,2-dihydrodiol. Phenanthrene is metabolised to the 9,10-diol in the rat and to the 1,2-diol in the rabbit.[118] Higher polycyclic hydrocarbons were found to be excreted as phenols (LV)-(LVIII), no dihydrodiols being isolated with these larger cyclic systems. An



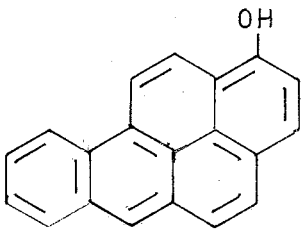
(LV)[119]



(LVI)[120]



(LVIII)[121]



(LVIII)[121]

interesting feature of the metabolism of aromatic hydrocarbons is that hydroxylation occurs at normally unreactive centres of the molecule. The significance of this will be discussed later.

Until 1946, nothing was known about the mode of formation of these hydroxylated derivatives except that the phenols were probably derived from the corresponding diols by the elimination of water. Weigert and Mottram[122] showed, from their extensive investigation

of the metabolism of 3,4-benzpyrene, that the hydrocarbon was converted to the final product F_2 by the steps shown in Fig. 1.5. The chemical nature of R and R' has not been elucidated.

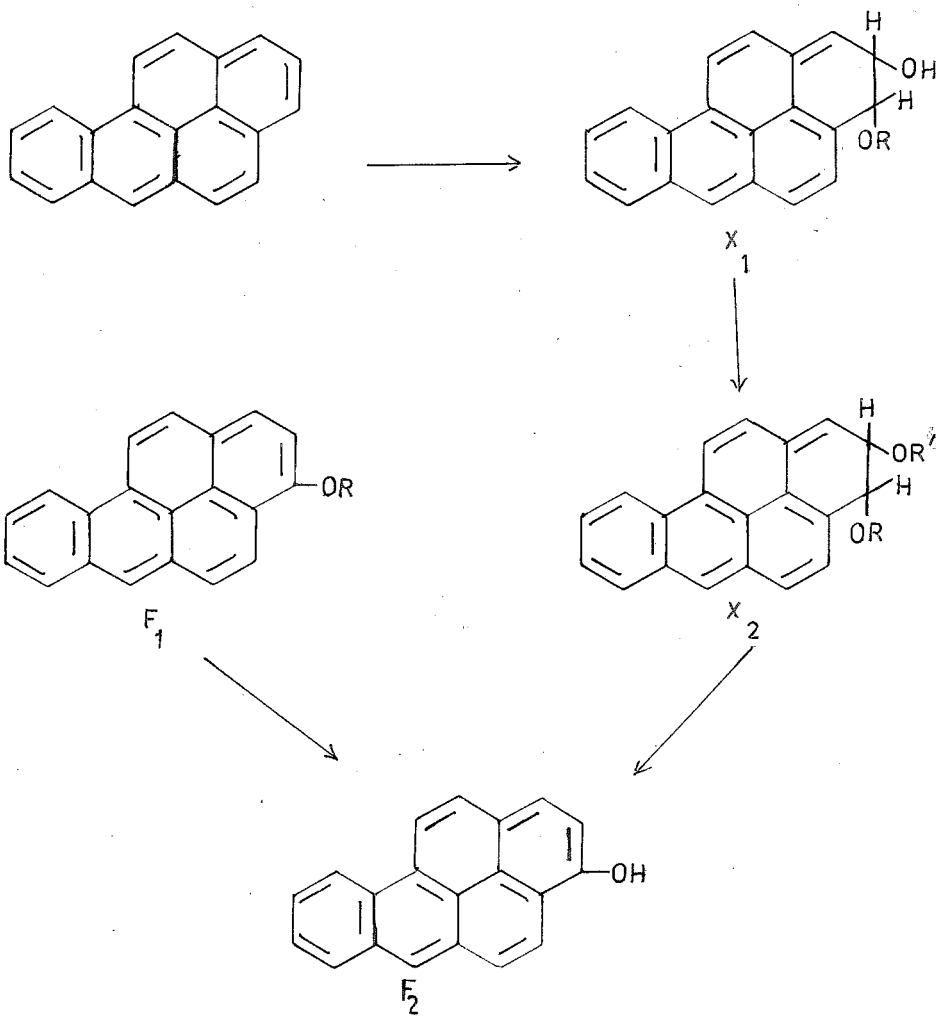


Fig. 1.5. Metabolism of 3,4-Benzpyrene.

The compounds, X_1 and X_2, were reported to be formed when 3,4-benzpyrene was incubated with isolated mouse skin.[123] Further, they appeared to be bound to cell constituents in the skin.

Informative data has resulted from studies of the metabolism of naphthalene and its derivatives by Boyland and his associates. Metabolic products of naphthalene include, besides hydroxylated derivatives, a premercapturic acid which is believed to be N-acetyl-S-(1,2-dihydro-2-hydroxy-1-naphthyl)-L-cysteine (-) (LXII).[124] Similarly benzene, anthracene and halogenobenzenes are converted to analogous derivatives in the animal body.[125] These acid products have been postulated to result from the reaction of an intermediate, believed to be an epoxide, with a SH-containing compound in the body. Tissue protein was at first thought to be the source of the cysteine moiety of the premercapturic acids, but the large amounts of acids isolated in the urine of test animals prompted the suggestion that glutathione might be the SH-containing component involved.[126] This was supported by the observation that the level of glutathione in the liver of test animals fell in proportion with the amount of mercapturic acids formed.[127] On the other hand, there is some evidence that protein-sulphydryl groups are involved in premercapturic acid synthesis.[128]

The metabolic route of naphthalene, as postulated by Boyland and his co-workers,[124,129] is represented schematically in Fig. 1.6. Naphthalene

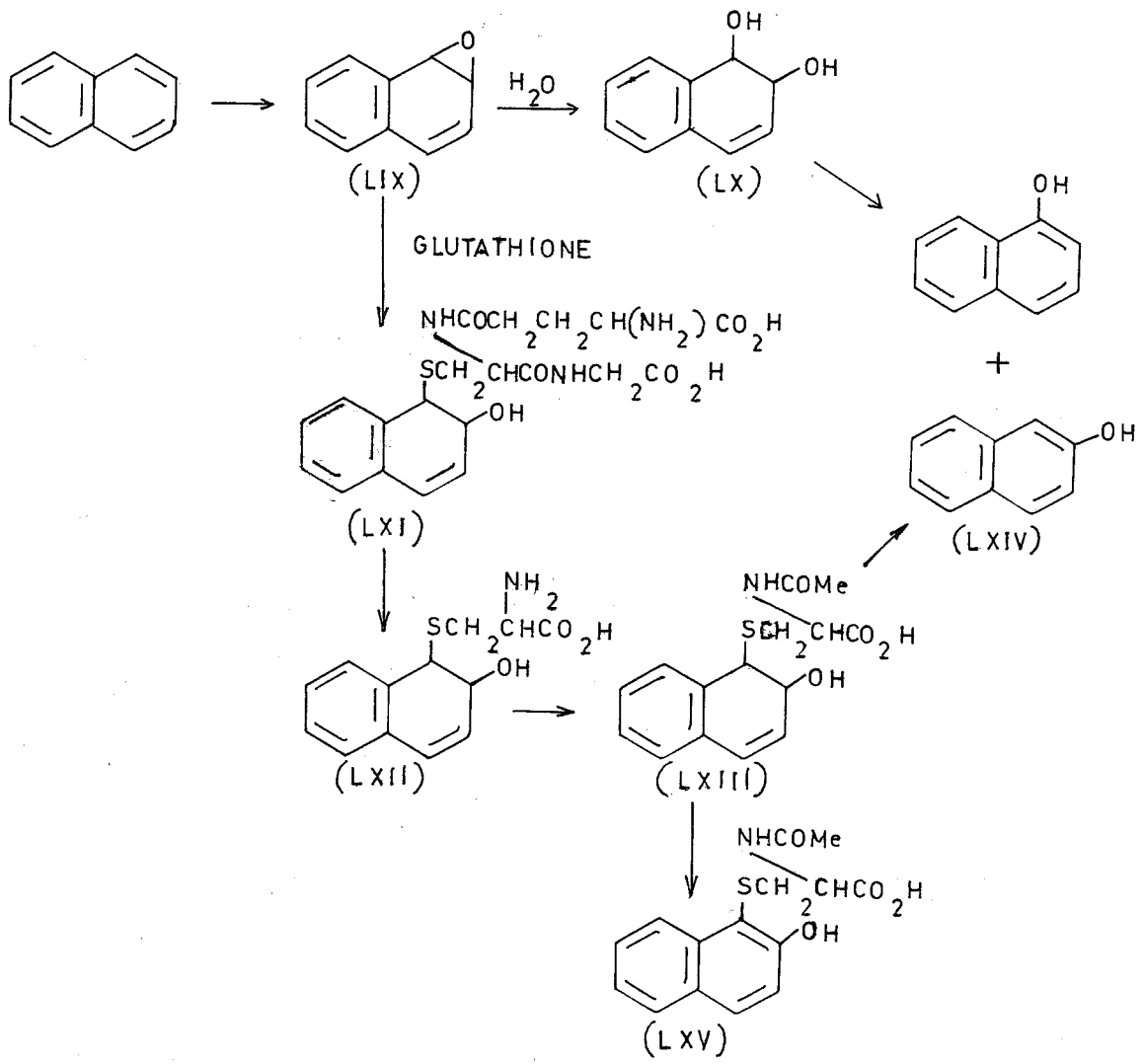


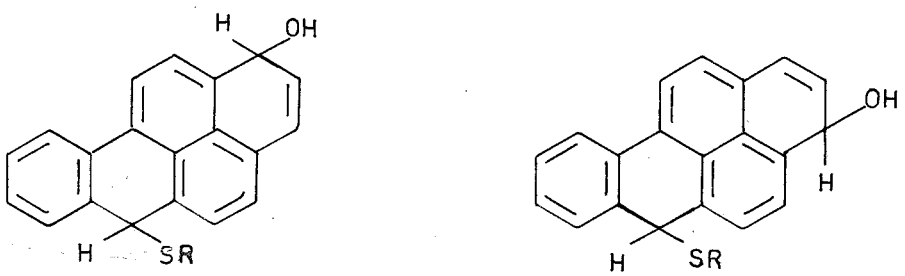
Fig. 1.6. Metabolism of Naphthalene.

is oxidised to a hypothetical epoxide (LIX) which reacts with water to yield the diol (LX), or with glutathione to form (LXI). The latter is probably formed in the liver

and is broken down to the cysteine derivative (LXII) in the kidney. The naphthols (LXIV) may be formed from the diol (LX) or the premercapturic acid (LXIII). The mercapturic acid (LXV) which may be readily formed from (LXIII) by dehydrogenation has been isolated from the urine of test animals but it is not known if it is a true metabolite or an artefact.

Corresponding premercapturic acids, however, have not been detected in the excreta of animals fed with 3,4-benzpyrene[90] and 1,2-5,6-dibenzanthracene.[130] This could mean that the acids are easily broken down to phenolic derivatives, or that they are not formed at all. Weigert and Mottram[122] have suggested that carcinogenic hydrocarbons are metabolised by a different route from the normal detoxication process. If this is so, it is probable then that the active agent in carcinogenesis is not the hydrocarbon but its metabolite. In agreement with such a possibility is the observation that 1,2-5,6-dibenzanthracene, which is metabolised to different phenolic derivatives in rats and rabbits,[120,131] is carcinogenic in rats but practically inactive in rabbits. Attempts, however, to isolate carcinogenic metabolites have not been fruitful. In fact, most of the metabolites examined proved to have little or no potency.

It was pointed out earlier on that a peculiarity of the metabolism of polycyclic hydrocarbons is that the compounds are attacked at normally unreactive centres. For example, the 5-position of 3,4-benzpyrene which is by far the most reactive centre in the molecule, is not hydroxylated; instead the hydrocarbon is metabolised to the 8- and 10-hydroxy derivatives. It would seem as though the reactive centre was protected, possibly through binding with cellular constituents, and the protected complex then reacted with the hydroxylating agent. A similar effect has been observed in the free radical reactions of 9,10-diphenylanthracene, in which the side ring is attacked due to the blocking of the meso-positions by the phenyl substituents.[40] It is conceivable that 3,4-benzpyrene is bound at its 5-position to a sulphydryl-containing compound in the body, and subsequent hydroxylation then occurs at the 8- and 10-positions to give the products (LXVI), which are similar in type to the premercapturic acid of naphthalene.



(LXVI)

These derivatives may readily hydrolyse to the 8- and 10-phenols which are the observed metabolic products of 3,4-benzpyrene.

Conclusion

Over the last twenty years, interesting developments have emerged in the biochemical aspects of carcinogenesis. There is strong evidence for the interaction of carcinogens with tissue proteins; in fact protein bound derivatives of carcinogenic dyes have been isolated. Correlations have been obtained between carcinogenic activity of polycyclic hydrocarbons and protein binding. The K region is predicted to be the main site of binding. Further, sulphur metabolism is believed to be connected with carcinogenesis. Though it is now certain that carcinogenic hydrocarbons are bound to body proteins, not much is known about the protein-carcinogen complex. The next step lies in the determination of its structure and of its role, if existent, in the carcinogenic process. Another hypothesis that has received considerable attention relates carcinogenesis to impaired respiration. As with other theories, there is evidence for and against Warburg's hypothesis, and it continues to be the centre of intensive research. From metabolic studies of

polynuclear hydrocarbons has emerged the theory that the tumour producing agent is not the hydrocarbon itself but its metabolite. However, the available data on carcinogenic metabolites does not allow more than speculation.

There are implications of the participation of free radicals in tumour production. In particular thiyl radicals appear to be significant on account of the wide-spread occurrence of thiol groups in biological systems, and of the dependence of several enzymes on these groups for their activity. In view of these considerations, and of the limited data on the reactions of thiyl radicals with polycyclic aromatic hydrocarbons, the present investigation was undertaken.

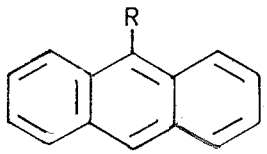
CHAPTER II

Reactions of Some Polycyclic Aromatic Hydrocarbons with Thiols and Oxygen

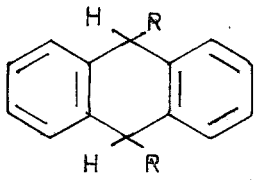
Preliminary to our studies of the reactions of aromatic hydrocarbons with thiols and oxygen, we repeated the reaction of anthracene with thioacetic acid reported by the Russian workers,[68] in order to work out a satisfactory method of carrying out the reaction and of isolating the products. As only limited quantities of thiols were available, it was decided to carry out this and subsequent reactions in the presence of a solvent. Benzene was selected as the solvent in the hope that this non-polar hydrocarbon would have no effect on the reaction, but it was soon evident that additional products, besides those reported, were formed. Therefore, to maintain uniform reaction conditions throughout these studies, all the experiments were performed in benzene except when solubility factors made it necessary to employ a different solvent.

Whereas the Russian workers reported a very rapid reaction between anthracene and thioacetic acid with 700 ml. of oxygen absorbed in 20 min., we found that there was a long induction period followed by an uptake

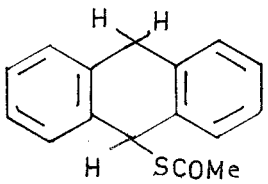
of 550 ml. in 2 hr. The reaction mixture was evaporated under a slightly reduced pressure of nitrogen, and the residue, after treatment with benzene and methanol, was chromatographed on alumina. The major product was a yellow compound, identical with synthetic 9-(acetythio) anthracene (I). The properties of this compound are similar to those of the reputed 9-(acetylthio)-9,10-dihydroanthracene[69] (II), which was obtained by Mikhailow and Blokhina when they carried out the above reaction in ether; the analytical data they reported for their product agree satisfactorily with that required by the fully aromatic compound (I). The close similarity between the two compounds suggests that they are probably identical. Other products from our reaction included the higher melting isomer of the dihydroanthracene derivative (III), di-(9-anthryl)disulphide (IV) and sulphur. The disulphide, which was characterised by comparison with a synthetic sample, appears to be identical with the unidentified yellow compound reported in the Russian work. The formation of elemental sulphur which was also observed in subsequent reactions of other polycyclic hydrocarbons with thioacetic acid and oxygen, is believed to have occurred during the chromatographic separation of the reaction mixture on alumina.



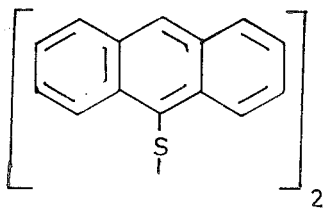
(I), R = SCOMe
(V), R = SCOPh
(VII), R = SCH_2CO_2H
(VIII), R = SCH_2CO_2Me
(XI), R = SPh



(III), R = SCOMe
(VI), R = SCOPh
(IX), R = SCH_2CO_2H
(X), R = $SCH_2CH_2CO_2H$
(XIV), R = SPh



(II)



(IV)

As 9-(acetylthio)anthracene (I) was not reported in the Russian work, it was uncertain if the compound we isolated was a direct reaction product or whether it was formed from the dihydroanthracene derivative (II) during the working-up process. Such dihydroanthracene compounds are readily converted to the fully aromatic substitution derivative in the presence of acid. The experiment was therefore repeated, particular care being taken to keep the temperature as low as possible. To further reduce the possible production of compounds not actually formed in the reaction, chromatography on alumina was avoided; instead the products were separated by fractional crystallisation.

Under these conditions, the major product was again 9-(acetylthio)anthracene, confirming it as a direct reaction product. The lower melting isomer of the dihydroanthracene derivative (III) was the other product formed in appreciable yield. Interestingly, sulphur was present in a much smaller quantity, and no anthryldisulphide was isolated.

In the Russian work, the assignment of the structures to the dihydroanthracene derivatives (III) was based on their oxidation to anthraquinone. There was no evidence of the nature of the bonding between the thioacetoxy substituent and the anthracene nucleus, that is, whether it is a C-S or a C-O linkage. The mesomeric ion of thioacetic acid ($CH_3COS^- \longleftrightarrow CH_3CSO^-$) is known to attack as CH_3COS^- but it has not been shown previously if the radical reacts as $CH_3COS\cdot$ or $CH_3CSO\cdot$ Hence it is significant that the infrared spectra of our products contain strong carbonyl bands, which indicates the formation of a C-S bond between the thioacetoxy radical and anthracene. The two isomeric 9,10-dihydro-9,10-di(acetylthio)anthracenes (III) showed ultraviolet absorption characteristic of 9,10-dihydroanthracenes, while 9-(acetylthio)anthracene (I) had a spectrum similar to that of anthracene, but with the maxima bathochromically shifted (Fig. 2.1.).

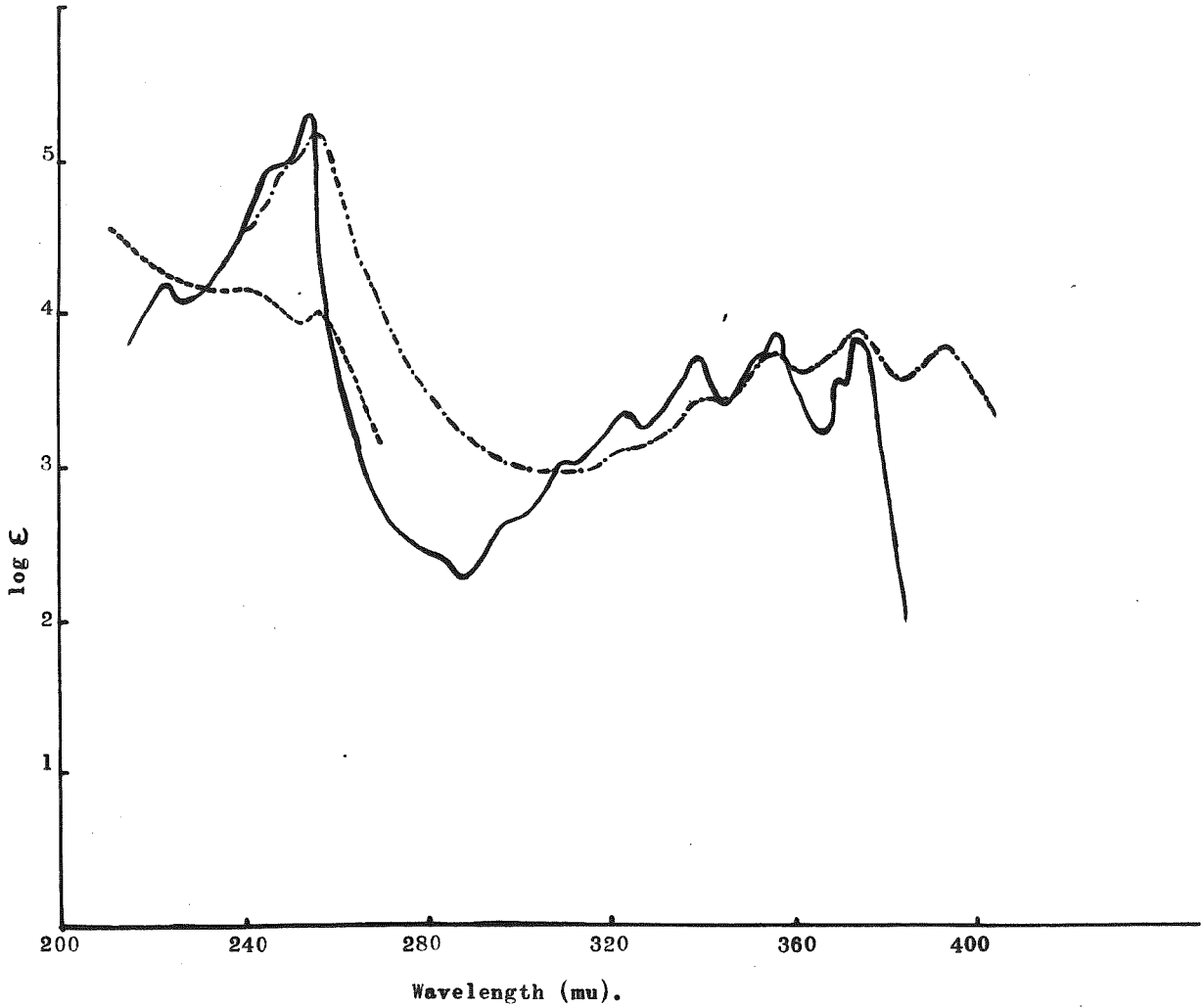


Fig. 2.1. ULTRAVIOLET ABSORPTION SPECTRA

—— anthracene*(in cyclohexane);

—·—·— 9-(acetylthio) anthracene (in ethanol);

– – – – 9.10-di(acetylthio)-9,10-dihydroanthracene, m. p. 124.5-126. (in ethanol)

*Friedel and Orchin, "Ultraviolet Spectra of Aromatic Compounds", John Wiley and Sons, Inc. New York, 1951.

The reaction, when extended to other thiols, was found to vary depending on the type of thiol used. Acidic thiols, such as thioacetic acid, reacted with the hydrocarbon to give dihydroanthracene and/or anthracene derivatives, but with very weakly or non-acidic thiols, such as toluene-ω-thiol, anthraquinone was the only identifiable compound obtained besides unchanged anthracene. Further, the latter type of mercaptans reacted less readily and reaction had to be initiated by the addition of free radical sources such as iodine, pyridine, ferrous sulphate and cumene hydroperoxide.

When anthracene in benzene was treated under oxygen with thiobenzoic acid, there was a rapid reaction in the first half hour during which time the greater volume of the total oxygen utilised was absorbed. When the gas uptake became very slow, small amounts of ferrous sulphate and cumene hydroperoxide were added to catalyse the reaction. In contrast with the reaction of thioacetic acid the major product in this case was the dihydroanthracene derivative (VI), both the cis- and trans- forms of which were isolated. These compounds absorbed in the ultraviolet region in a manner characteristic of 9,10-dihydroanthracenes. Other products from the reaction were 9-(benzoylthio)anthracene, (VII) which had an ultraviolet absorption spectrum

similar to that of anthracene, and a small quantity of di-(9-anthryl)disulphide (IV).

Mercaptoacetic acid reacted vigorously with anthracene and oxygen to yield 9,10-di(carboxymethylthio)-9,10-dihydroanthracene (IX), of which only one isomer was isolated. It was insoluble in most organic solvents but extremely soluble in NN-dimethylformamide. Repeated crystallisation of the acid from the latter, however, failed to yield an analytically pure sample. Its structure was finally confirmed by its conversion into the dimethyl ester (═══) by treatment with diazomethane and to the known (9-anthrylthio)acetic acid (VII)[132] by treatment with hydrochloric acid in acetic acid. From the reaction mixture was also obtained, in smaller yield, a yellow powder, soluble in polar organic solvents. On attempted crystallisation from acetone, it was partly converted to an acetone-insoluble compound which appeared similar to the dihydroanthracene derivative (IX). The yellow powder could possibly be an impure form of the other isomer of (IX) which readily isomerised to the more insoluble form on heating in a polar solvent. The material, however, could not be sufficiently purified for identification.

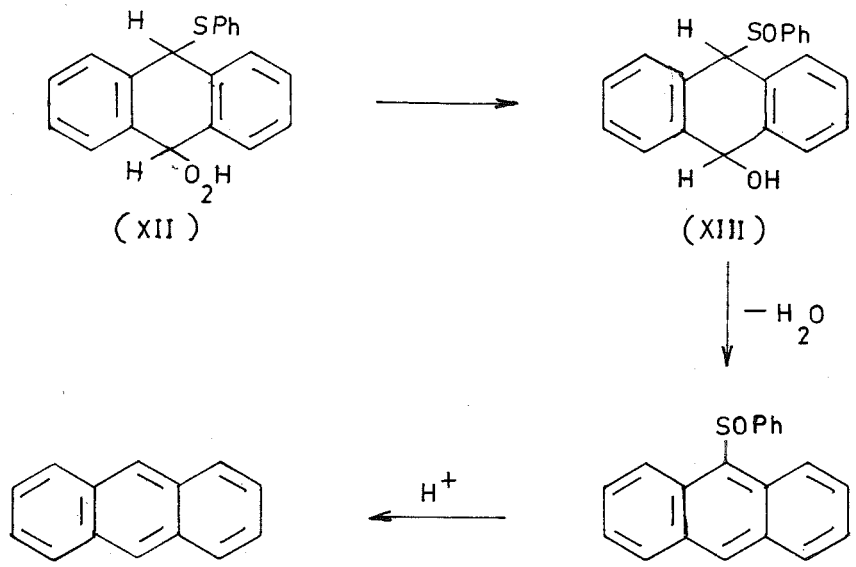
The same reaction when carried out in alcohol yielded an unstable acid which was converted to anthraquinone on attempted purification. The effect of solvent on the reaction was also noted by Mikhailov and Blokhina who obtained different products when they carried out the reaction of anthracene with thioacetic acid and oxygen, first without a solvent[68] and later on in ether.[69]

β-Mercaptopropionic acid, which differs from mercaptoacetic acid in having one more methylene group, was allowed to react with anthracene and oxygen to determine the effect, if any, of the additional methylene group on the reaction. The thiol was found to react quite readily, though with less vigour than its analogue. The sole product was a yellow compound, whose anthracene-like ultraviolet spectrum and analytical data showed it to be 9-(anthrylthio)propionic acid (=).

The reaction with thiophenol proved especially interesting. It yielded a mixture of products from which was isolated 9,10-dihydro-9,10-di(phenylthio)-anthracene (XIV), anthraquinone, a small amount of an unidentified white compound, m.p. 244-245.5°, and an unstable white powder. The powder, which was the major product, turned yellow and partially melted at 62° and decomposed to a black mass at 127°. When kept in a

vacuum desiccator at room temperature it decomposed vigorously. An attempt to dry the compound over phosphorus pentoxide and paraffin wax in the cold resulted in its partial conversion to a fluorescent, pale yellow substance, with the liberation of thiophenol. Due to its instability an elemental analysis was not possible. Interestingly, it liberated iodine from potassium iodide in acetic acid, thus behaving like a hydroperoxide. A rough determination of its equivalent weight based on this property gave a value of 202.

The compound is believed to be a hydroperoxide, having the structure (XII) (see p. 79). An attempt to prepare a derivative with triphenylcarbinol[133] gave only anthracene. This unexpected conversion to the hydrocarbon was also observed on treatment of the hydroperoxide with potassium iodide in acetic acid. This unusual behaviour is probably due to the ready decomposition of the hydroperoxide in the presence of acid, which could conceivably occur by the steps indicated below. The formation of (XIII) from the hydroperoxide (XII) is analogous to the production of sulphoxides in the co-oxidation of indene and thiols.[64,65]



Treatment of the hydroperoxide with mercaptoacetic acid was expected to give rise to substitution of the hydroperoxy group by a carboxymethylthiol group. However, chromatography on acetylated paper[134] of the neutral fraction of the reaction mixture revealed the presence of anthracene and another fluorescent material, while two or possibly three fluorescent spots were detected in the acidic fraction. The identification of the compounds was not attempted due to the small amounts present.

Interestingly, the reaction of thiophenol when repeated in the presence of acetic acid gave no hydroperoxide; instead 9-(phenylthio)anthracene (XI) was obtained, besides unchanged anthracene, anthraquinone and a yellow solid, m.p. 130°, which was shown to be a

mixture of anthracene and 9-(phenylthio)anthracene by suitable admixture of the two compounds. The mixture could not be separated by chromatography on acetylated paper or on alumina, and was finally purified by careful sublimation. The substitution product (XI), which showed an anthracene-type ultraviolet spectrum, was characterised as the 9-phenylthio derivative by comparison with a specimen prepared from (9-anthryl) lithium and diphenyldisulphide.[135] 9-(Phenylthio) anthracene was also obtained by treatment of the corresponding dihydroanthracene derivative (XIV) with acid.

Methylmercaptoacetate, unlike the acid, reacted with anthracene and oxygen only under catalysis to give anthraquinone and an intractable, dark oil. With toluene-ω-thiol, anthracene reacted slowly in the presence of iodine and pyridine. The products were difficult to isolate and the only pure compounds obtained were anthraquinone and unchanged hydrocarbon. The reaction with 2,3-dimercaptopropanol, which was initiated by the addition of ferrous sulphate, also proved difficult. Again anthraquinone and starting material were isolated though three fluorescent bands were observed on chromatography of the acetylated product. It appears that the fluorescent substances were oxidised

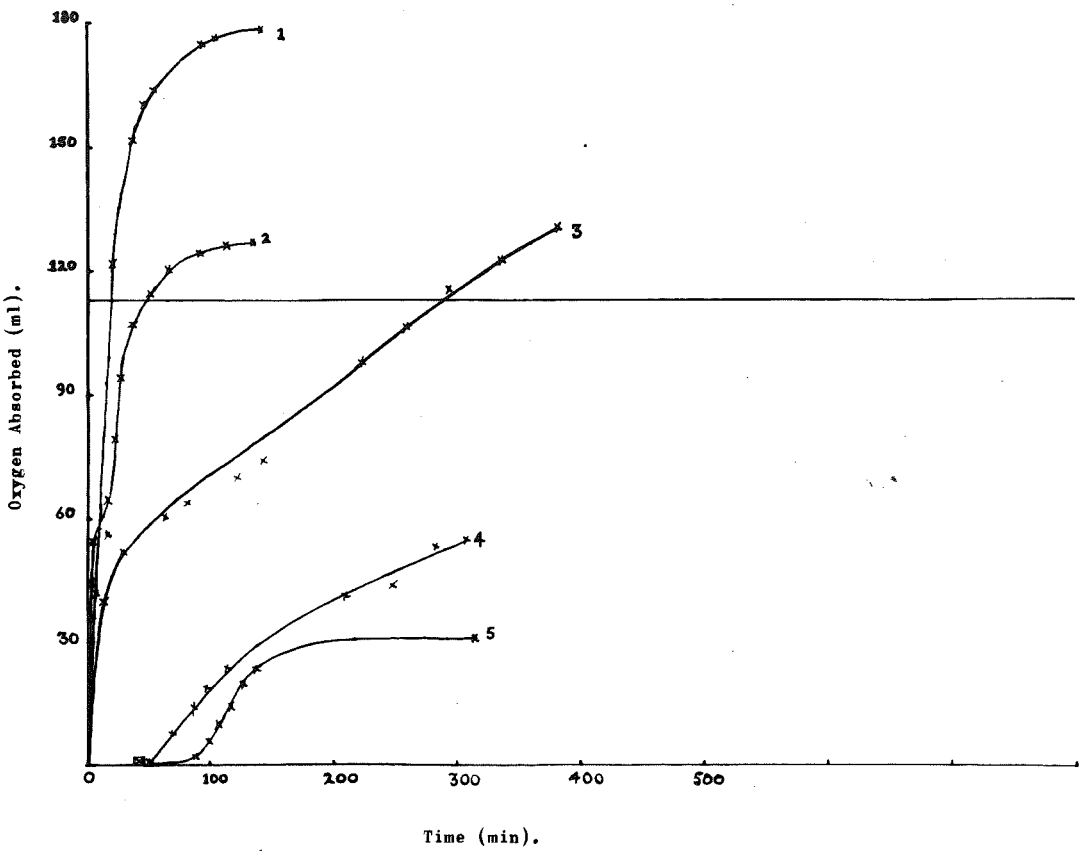


Fig.2.1. REACTIONS OF ANTHRACENE AND DERIVATIVES WITH THIOACETIC ACID AND OXYGEN

(1) and (2) anthracene; (3) 9-methylanthracene;

(4) 9-phenylanthracene (catalysed); (5) 9-phenylanthracene.

▣ added cumene hydroperoxide and ferrous sulphate.

to anthraquinone during their passage through the alumina column. Other anthracene derivatives have been observed to be similarly affected on purification through alumina.[33]

In all our experiments, the rate of oxygen absorption was observed to decrease during the reaction. The oxygen-absorption curves were not accurately reproducible but all had a similar shape (Fig. 2.2.). In some cases there was an induction period of variable duration, characteristic of free radical reactions. Further, the uptake of oxygen could invariably be initiated by the addition of free radical sources. To account for our experimental observations we propose the mechanism shown in Fig. 2.3.

The initiating thiyl radical produced by the interaction of a thiol molecule with oxygen adds on to anthracene to give the radical (XV). This is in accord with the widely accepted view that the first step in free radical substitution and addition reactions of aromatic compounds is the addition of the attacking radical to a reactive centre in the substrate.[34,136] It is probable that this step (2) is reversible, by analogy with the mechanism for the free radical addition of thiols to olefines.[49] The radical (XV) takes up a

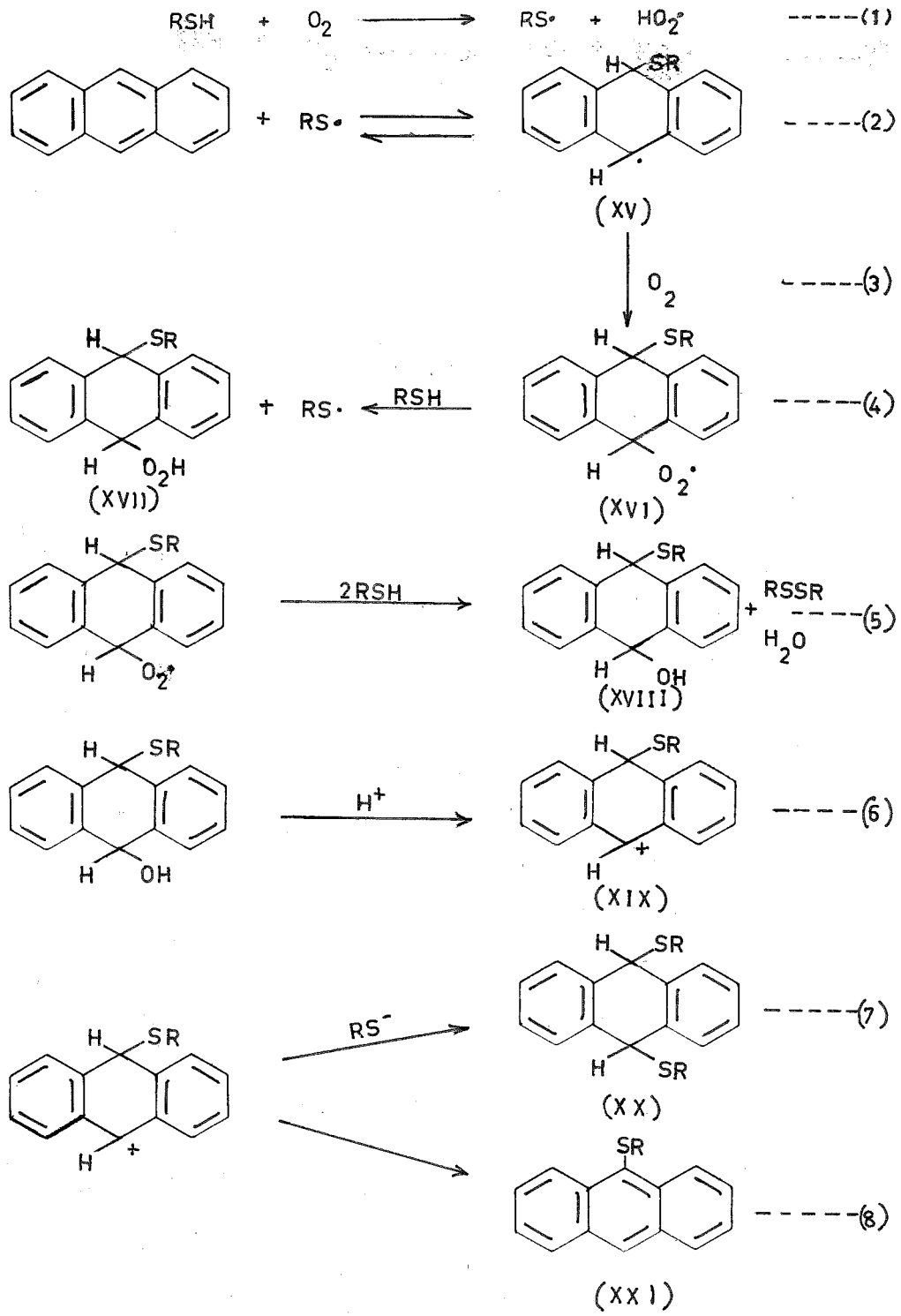


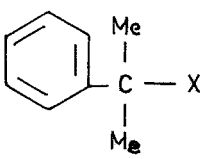
Fig. 2.3. Proposed Mechanism for the Reaction of Anthracene with Thiols and Oxygen.

molecule of oxygen to give (XVI) which abstracts hydrogen from a thiol, forming a hydroperoxide (XVII) and regenerating a thiyl radical. These steps (1-4), which are analogous to the reactions of olefines and of indene with thiols and oxygen,[64,65] account for the observation that the rate of oxygen absorption is proportional to the amount of anthracene present.

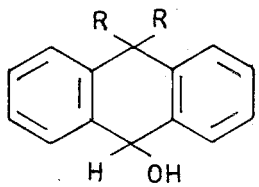
It is suggested that with weakly acidic thiols, the reaction proceeds no further and the products obtained are hydroperoxides or compounds resulting from their decomposition. Earlier on we suggested that the unstable powder produced in the reaction of anthracene with thiophenol is the hydroperoxide (XVII ; R = Ph). The anthraquinone resulting from the reactions with toluene-ω-thiol, with dimercaptopropanol, with methylmercaptoacetate and with mercaptoacetic acid in alcohol was probably formed from similar hydroperoxides. In the presence of acidic thiols, the intermediate hydroperoxide is converted into the final products, (XX) and (XXI), by the reactions (5-8).

Experiments were then designed to test the feasibility of the proposed mechanism. In support of step (2), a mixture of anthracene and dibenzoyldisulphide in benzene was allowed to react in sunlight. The formation of 9-(benzoylthio)anthracene (V) confirmed the

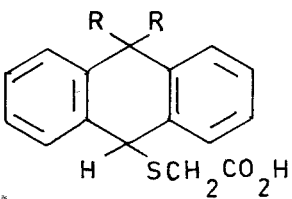
reaction between anthracene and thiyl radicals. The feasibility of the conversion of the hydroperoxide to the final products was demonstrated by the production of (cumylthio)acetic acid (XXII) on treatment of cumene hydroperoxide (XXIII) with mercaptoacetic acid under nitrogen. Of interest in this connection is the isolation of (cumylthio)acetic acid from the reactions of substituted anthracenes with mercaptoacetic acid which were initiated with cumene hydroperoxide. The formation of the same acid (XXII) from 2-phenyl-propan-2-ol (XXIV) and mercaptoacetic acid gives support to steps (6) and (7).



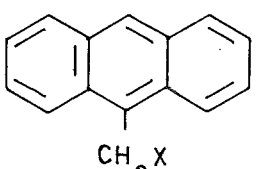
(XXII), X = SCH_2CO_2H
(XXIII), X = O_2H
(XXIV), X = OH



(XXV), R = CH_2Ph
(XXX), R = H



(XXVI), R = CH_2Ph
(XXIX), R = H



(XXVII), X = OH
(XXVIII), X = SCH_2CO_2H

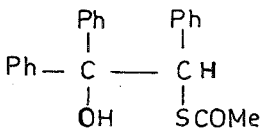
Additional evidence for the substitution of the alcoholic group by a thiol group was provided by the reaction of

10,10-dibenzyl-9,10-dihydro-9-hydroxyanthracene (XXV) with mercaptoacetic acid, whereby the substituted acid (XXVI) was obtained. 9-Hydroxymethylanthracene (XXVII) reacted with the same thiol to give the corresponding acid (XXVIII). Analogies for the formation of both anthracene (XXI) and dihydroanthracene (XX) derivatives by steps (6-8) were seen in the production of anthracene and 9-(carboxymethylthio)-9,10-dihydroanthracene (XXIX) from the hydroxy compound (XXX) and mercaptoacetic acid. That the conversion of the hydroperoxide to the final products (XX) and (XXI) is favoured by acid conditions is indicated by the reaction of anthracene with thiophenol which, when carried out in benzene, gave primarily an unstable hydroperoxide, but in the presence of acetic acid, yielded the substitution product, 9-(phenylthio)anthracene (XIV).

The ratio of dihydroanthracene to anthracene derivatives formed was found to vary from one reaction to another. For example, anthracene reacted with thioacetic acid and oxygen to yield principally the substitution product, but with thiobenzoic acid it gave the dihydroanthracene derivatives predominantly. Whether the intermediate carbonium ion (XIX) adds on a thiyl anion to give (XX) or loses a proton to yield the substitution compound (XXI) is determined by a number

of factors, which include the concentration and acidity of the reacting thiol. The present investigation does not permit any definite conclusions to be drawn regarding the criteria governing steps (7) and (8), which lead to the production of dihydroanthracene or anthracene derivatives respectively.

The proposed mechanism is compatible with the formation of S-(2-hydroxy-1,2,2-triphenylethyl) thioacetate (XXXI) from 1,1,2-triphenylethylene,



(XXXI)

thioacetic acid and oxygen.[69] The product (XXXI) is analogous to the postulated intermediate alcohol (XVIII). Though no alcoholic products were isolated in our experiments, it was observed that during chromatographic separation of the reaction mixtures there was in every case, a strongly adsorbed band, which could have been the alcohol derivative. Elution with ether or extraction with ethanol-acetic acid of the polar substance from the column yielded an impure material that was present in too small a quantity for identification.

One of the unusual features of the reactions is the absence of dianthryl derivatives. This is in sharp contrast to other free radical reactions of anthracene, all of which lead to dimeric products. To account for this unusual behaviour it is suggested that oxygen, which is present in a high concentration acts as a scavenger for radicals of type (XV), thus preventing the formation of dimers.

Di-(9-anthryl)disulphide, which was isolated in small yield in some of the reactions, is probably an artefact. By analogy with the conversion of 10-thiocyano-1,2-benzanthracene to the disulphide by passage through an alumina column,[137] anthryldisulphide was probably formed by the action of alumina on 9-(acetylthio)anthracene or similar derivatives.

The thiol-catalysed dehydrogenation of 9,10-dihydroanthracene and its derivatives by azoisobutyronitrile[34,59] involves the intermediate formation of free thiyl radicals; yet products containing thio-groups are not formed. To account for this, it is suggested that the equilibrium in step (2), under these more vigorous conditions, favours the dissociation of (XV) to such an extent that further reaction cannot occur.

When anthracene was shaken with n-butanethiol under oxygen, there was no absorption of gas. The reaction was then attempted in the presence of (i) ferrous sulphate and cumene hydroperoxide, (ii) ferrous sulphate, cumene hydroperoxide and acetic acid, (iii) iodine, (iv) iodine and acetic acid, (v) iodine, acetic acid and ferrous sulphate, and (vi) iodine, ferrous sulphate and cumene hydroperoxide. Only in the last case was there an uptake of oxygen. From the reaction mixture was obtained, besides much unreacted anthracene, a yellow oil which fluoresced bright blue in benzene solution. As attempts to solidify the oil were not successful, it was decided to identify the product by its R_f value. The fluorescence of the product suggested it to be an anthracene derivative, and by analogy with previous reactions, 9-(n-butylthio)anthracene seemed the most likely product. Accordingly, its preparation was attempted by reduction of (9-anthryl)dithiochloride, followed by treatment of the sodium salt of the resulting thiol with n-butylbromide. However, only oils were obtained besides di-(9-anthryl)disulphide. Paper chromatography of the major oily fraction showed a blue fluorescent spot with a similar R_f value as the product from the reaction of anthracene with n-butanethiol. Hence, it is likely that 9-(n-butylthio)anthracene or

a similar derivative was formed in the above reaction. Such derivatives would probably have low melting points and similar R_f values, which would render their purification by crystallisation or chromatography difficult. Indeed, much difficulty was encountered in the isolation of 9,10-di(n-butylthio)anthracene, m.p. 61-62°, in a later experiment.

The action of the mixture of ferrous sulphate, cumene hydroperoxide and iodine as a radical generator is interesting. It was observed that the addition of iodine, which followed that of the other two reagents, caused the reaction mixture to turn a dark red-brown; the colour was rapidly lost with absorption of oxygen. A combination of iodine and ferrous sulphate or the hydroperoxide was ineffective; the presence of all three compounds was necessary. This unusual radical generator proved more efficient than the mixture of ferrous sulphate and cumene hydroperoxide which had been employed to initiate earlier reactions. It was successfully used to catalyse subsequent reactions. Its mode of action, however, is unknown.

Measurements of the rate of oxygen absorption by aqueous solutions of mercaptoacetic acid indicate that oxidation of the thiol to the disulphide is most

rapid in neutral medium, less in alkaline and least in acidic media (Fig.2.4). Hence, the presence of acetic acid in the reactions of anthracene with thiols and oxygen would serve the double purpose of reducing the extent of thiol oxidation and of promoting the conversion of the intermediate hydroperoxide to the final products. The use of pyridine and other basic compounds as a catalyst in these reactions was avoided to reduce the loss of thiol through disulphide formation.

Reactions of thiols with aromatic compounds in the presence of oxygen may have biological significance. The premercapturic acids produced by metabolic oxidation of aromatic compounds[124,125] are known to have structures similar to, but of different orientation from, the intermediate (XVIII). Further, it is believed that metabolic hydroxylation of aromatic molecules involves reactions utilising a thiol and molecular oxygen and is catalysed by ferrous ion.[115] Other reactions of polycyclic aromatic hydrocarbons with cell constituents containing the thiol group also appear possible. The proposed mechanism could account for the cross-linking of proteins, or for the irreversible binding of aromatic compounds to skin protein.[93,97] Interference with cell hydrogen transfer processes by reactions of such thiols as glutathione or reduced

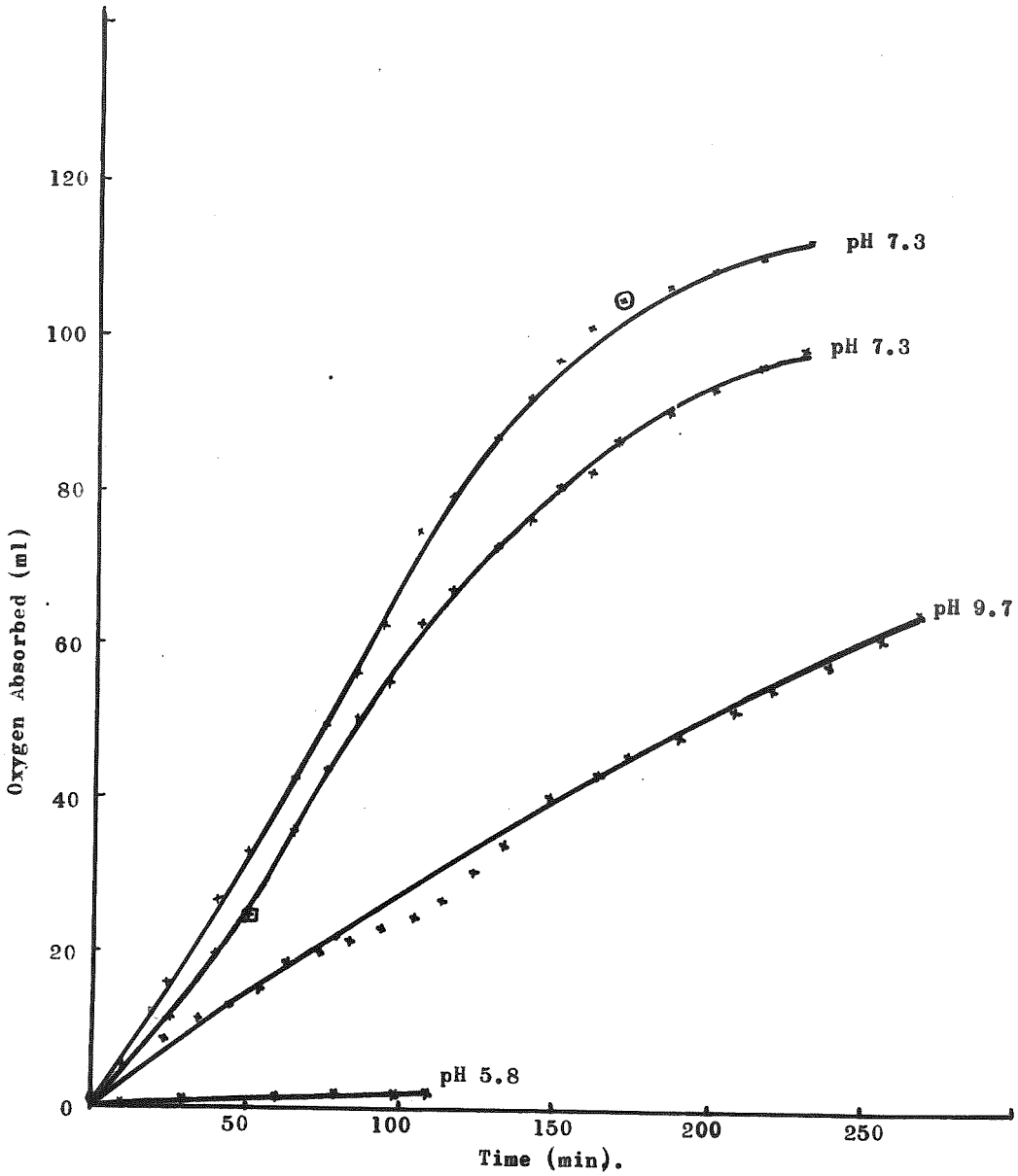


Fig. 2.4. OXIDATION OF MERCAPTOACETIC ACID

● added iodine and potassium iodide

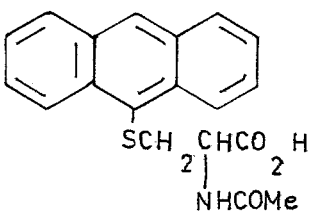
■ added hydrogen peroxide.

The above compounds did not have any significant catalytic effect on the oxidation.

thioctic acid with aromatic hydrocarbons may also occur. In view of the possible biological significance of these reactions, we were particularly interested in the behaviour of cysteine towards polycyclic hydrocarbons. The cysteine moiety occurs in glutathione and in other forms in the body and is present in premercapturic acids in the acetylated form.

An initial attempt to react cysteine hydrochloride with anthracene in a sodium hydroxide-benzene mixture yielded only cystine and unchanged anthracene. Similar results were obtained when the reaction was carried out in alcohol. Failure of the reaction was attributed to the absence of a suitable solvent in which both reactants were moderately soluble. The reaction was then attempted in the presence of deoxycholic acid in a sodium hydroxide-benzene mixture in the hope that the formation of the water-soluble anthracene-deoxycholic acid adduct[138] would initiate the reaction. However, anthracene was recovered quantitatively after the mixture was shaken for three days. Finally, the more soluble N-acetylcysteine was synthesised,[139] and its reaction with anthracene was attempted in tetrahydrofuran, both reactants being reasonably soluble in this solvent. There was a very slow reaction, ca. 60 ml. of oxygen being absorbed in

four days. Alkali extraction of the reaction mixture gave a yellow solid which decomposed to anthraquinone on attempted crystallisation from acetone. Its instability made its purification very difficult. Careful repeated crystallisation from tetrahydrofuran-hexane, with minimum heating, finally yielded a yellow powder, decomposing at 208-212°. Except for carbon, the analytical data of the compound agree satisfactorily with the molecular formula, $C_{19}H_{17}NO_3S$. On the basis of this and its anthracene-type ultraviolet spectrum, we suggest the product is S-(9-anthryl)-N-acetyl cysteine (XXXII). The instability of the compound is

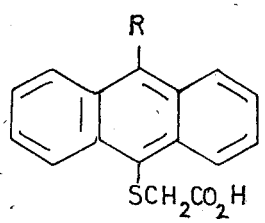


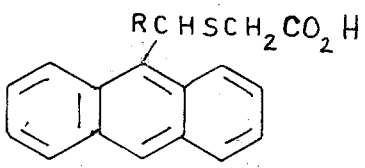
(XXXII)

not unexpected as the cysteine derivative of 3,4-benzpyrene, namely, S-5-(3,4-benzpyrenyl)-DL-cysteine has been reported to decompose readily.[140] It was observed that much anthraquinone precipitated from the mixture during the reaction. Evidently the product (XXXII) underwent decomposition during the four days' shaking.

In extending the reaction to alkyl-substituted anthracenes, mercaptoacetic acid was selected as the thiol reactant as it showed the greatest reactivity among the mercaptans employed in the reactions of anthracene.

9-Methylanthracene reacted readily with mercaptoacetic acid and oxygen, though less readily than anthracene, to yield a yellow compound which analysed for $C_{17}H_{14}O_2S$, and whose ultraviolet spectrum indicated it to be a substitution derivative. Of the two probable structures, (XXXIII) and (XXXIV), the product





(XXXIII), R = Me
(XXXV), R = CH_2Ph
(XXXVI), R = Ph

(XXXIV), R = H

was shown to be 10-(carboxymethylthio)-9-methylanthracene (XXXIII) by admixture with a synthetic specimen of the other isomer (XXXIV), which caused a depression in the melting point. That substitution had occurred in the 10-position of the anthracene nucleus and not in the methyl substituent was confirmed by the infrared spectrum of the product. It did not show an absorption peak

around 840 cm^{-1} due to a meso hydrogen atom.

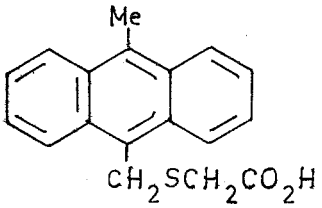
The reaction of methylanthracene also yielded an alkali-soluble oil. The attempt to purify it by chromatography of its methylated product was unsuccessful. The product was strongly adsorbed on the alumina column, and only traces of unidentifiable material were obtained. It is likely that 9-(carboxymethylthio) anthracene (XXXIV) was formed as the side-chain of methylanthracene is readily attacked by free radicals. Thus, Beckwith and Waters,[33] in investigating the thermal decomposition of di-t-butylperoxide in the presence of 9-methylanthracene, observed that both hydrogen abstraction from the substituent and addition of methyl radicals to the 10-position of the hydrocarbon, occurred.

The reaction of 9-benzylanthracene proceeded smoothly with the production of 10-(carboxymethylthio)-9-benzylanthracene (XXXV) as the major product. The identity of the compound was established by comparison with a sample prepared by treatment of 10-mercapto-9-benzylanthracene with chloroacetic acid in alkali. That both the meso hydrogen atoms were substituted was confirmed by its infrared spectrum. The reaction also gave two other yellow substances, in smaller yields, which could not be sufficiently purified for identification.

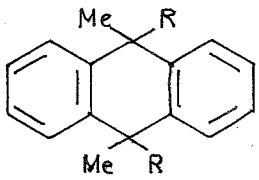
9-Phenylanthracene was found to be less reactive than the methyl and benzyl derivatives. Its reaction which was catalysed by ferrous ion and cumene hydroperoxide yielded 10-(carboxymethylthio)-9-phenylanthracene (XXXVI) and (cumylthio)acetic acid (XXII). The formation of the latter is significant in view of the intermediate hydroperoxide postulated in our mechanism. The phenylanthracene derivative (XXXVI) was characterised by its ultraviolet spectrum which showed it to be a substituted anthracene derivative, its infrared spectrum which indicated the absence of meso hydrogen atoms; and its analytical data which indicated the introduction of only one thio group.

In the Russian work,[69] 9,10-dialkylanthracenes were found to react with thioacetic acid and oxygen, with addition of two thioacetoxy groups across the meso-positions. However, we were not able to reproduce their results. We obtained from the reaction of 9,10-dimethylanthracene and mercaptoacetic acid, a yellow crystalline compound with an anthracene-type ultraviolet spectrum. Oxidation of the product with chromic acid gave anthraquinone, indicating that radical attack on the anthracene nucleus was limited to the meso-positions. The above data coupled with the elemental analysis suggests the compound to be 9-(carboxymethylthiomethyl)-

10-methylanthracene (XXXVII). It is suggested that the product is derived from the initially formed



(XXXVII)

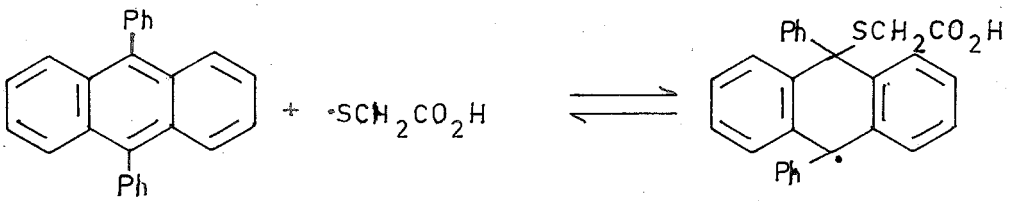


(XXXVIII), R = SCH_2CO_2H
(XXXIX), R = OH

dihydroanthracene derivative (XXXVIII) by an acid-catalysed rearrangement, similar to the acid-catalysed 1,5-anionotropic rearrangements of meso-substituted derivatives of 9,10-dihydro-9,10-dihydroxy-anthracene and -1,2-benzanthracene.[141] To test the feasibility of such a conversion, the dihydroanthracene derivative (XXXVIII) was prepared from the corresponding diol (XXXIX) and mercaptoacetic acid, and treated with acid. The resulting compound was identical with the product from the reaction of 9,10-dimethylanthracene.

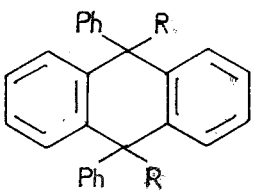
9,10-Diphenylanthracene did not react when shaken with mercaptoacetic acid under oxygen. Addition of ferrous sulphate and cumene hydroperoxide to the mixture initiated a very slow absorption of oxygen but (cumylthio)acetic acid was the only identifiable product obtained. The lack of reactivity of 9,10-diphenyl-

anthracene is not surprising when we consider the formation of the radical (XL). The addition of the attacking thiyl radical to the meso-position of the anthracene nucleus occurs with difficulty due to the presence of the phenyl substituents.[40] Further, the weak C-S bond and steric hindrance in the radical (XL) would shift the equilibrium to the left to such an



(XL)

extent that further reaction does not occur. The instability of 9,10-dihydro-9,10-diphenylanthracene derivatives containing substituents in the meso-positions is reflected in the observation that 9,10-diphenylanthracene is attacked by phenyl radicals in the side ring exclusively,[40] and adds on maleic anhydride across the 1,4-positions and not the 9,10-positions.[142] Further, treatment of the diol (XLI)



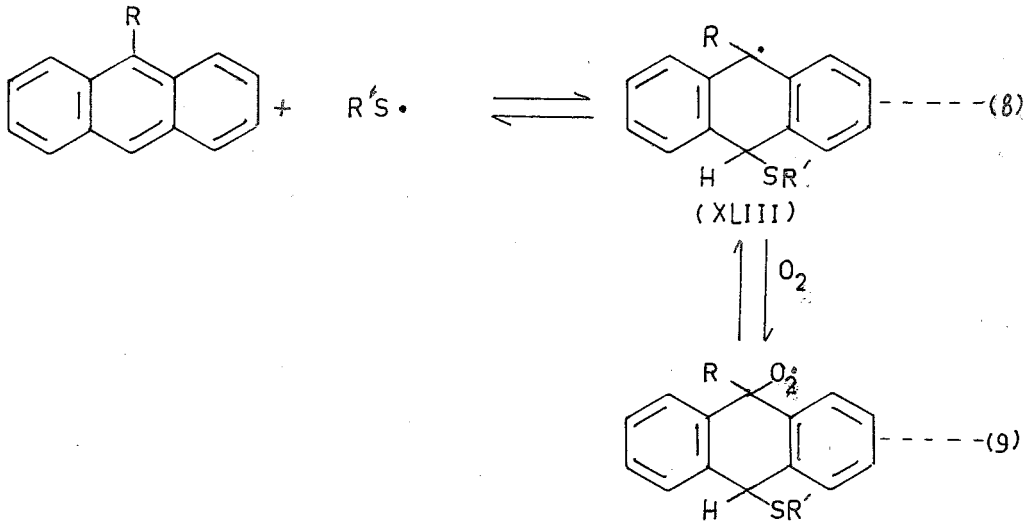
(XLI), R = OH
(XLII), R = SCH_2CO_2H.

with mercaptoacetic acid was found not to yield the expected thio derivative (XLII); instead 9,10-diphenylanthracene was formed, evidently by decomposition of the unstable thio compound (XLII).

Fig. 2.2 shows the rates of oxygen absorption of anthracene, 9-methyl- and 9-phenyl-anthracenes in reactions with mercaptoacetic acid. Though the curves were not accurately reproducible, they indicate that the rate of oxygen absorption decreased as the reaction proceeded, that is, it is dependent on the amount of hydrocarbon present. The significance of this effect in the reaction mechanism has been discussed.

The reaction with anthracene was extremely rapid, being almost complete in the first half hour, that with 9-methylanthracene was less vigorous, and that with 9-phenylanthracene was slow. In the last case a slightly faster rate was observed when the reaction was carried out in the presence of small amounts of ferrous sulphate and cumene hydroperoxide. The reduced reactivity of the substituted anthracenes may seem surprising in view of the activating influence of substituents in free radical reactions. However, it is not contrary to our proposed mechanism. It is reasonable to assume that the addition of a thiyl radical to a 9-substituted anthracene occurs preferentially at the

10-position (8). This reduces the number of positions available for attack, and hence the rate of reaction. Further, the addition of oxygen to the radical (XLIII),



(8)

(9)

which is probably an equilibrium step, is hindered by the substituent. An additional factor that affects the rate of reaction is the stability of the radical (XLIII). The more stable the intermediate radical is, the less readily does it react with oxygen. If R = Ph, as in 9-phenylanthracene, the radical (XLIII) is similar to the triphenylcarbinol radical which is highly stabilised by resonance. Hence, phenylanthracene is much less reactive than anthracene.

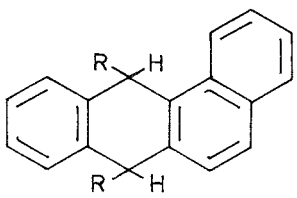
The absorption curves of anthracene and methylanthracene extend beyond the theoretical limit of oxygen absorption, indicated by the horizontal line in the figure. This is due to utilisation of oxygen in the oxidation of the thiol to the disulphide.

The extension of the reaction to other polycyclic aromatic hydrocarbons was initiated by our interest in the behaviour of the strongly carcinogenic 3,4-benzpyrene towards thiyl radicals. It has been mentioned that the interactions of carcinogenic hydrocarbons with sulphur-containing compounds in biological systems are believed to be significant in cancer production.

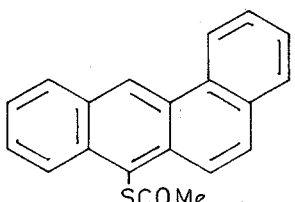
The hydrocarbons were purified before use by chromatography on alumina and crystallisation. However, their melting points did not coincide with literature value in every case. 1,2-5,6-Dibenzanthracene and pyrene were slightly coloured, and perylene, which was a bright yellow colour, melted 3^{0} higher than the literature value. Because of the difficulty encountered in the purification of the products obtained from the reactions using mercaptoacetic acid, it was decided to use thioacetic acid in the reactions with higher polynuclear hydrocarbons. Though the thiol was less reactive than mercaptoacetic acid, its products were usually more easily purified, being readily separated by chromatography on alumina.

Mikhailov and Blokhina[69] reported the formation of 9,10-di(acetylthio)-9,10-dihydro-1,2-benzanthracene (XLIV), m.p. 193-194^{0}, from the reaction of

1,2-benzanthracene with thioacetic acid and oxygen. We repeated the reaction in benzene and obtained principally a white crystalline compound, m.p. 189.5-191°, a small

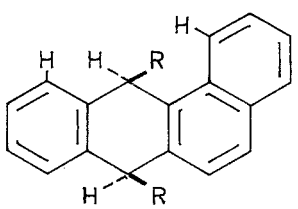


(XLIV), R = SCOMe

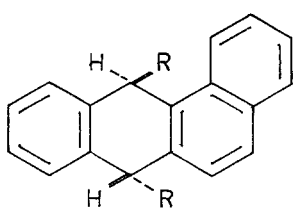


(XLV)

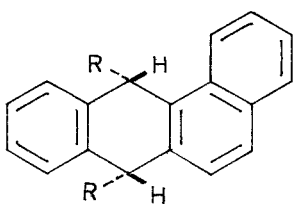
quantity of 10-(acetylthio)-1,2-benzanthracene (XLV), and an unidentified material, m.p. 130-160°. The substitution product (XLV) was identified by a comparison of its melting point and ultraviolet absorption spectrum with those of an authentic sample. The white compound, m.p. 189.5-191°, is believed to be the dihydrobenzanthracene derivative (XLIV). The compound, theoretically, may exist in the four possible conformations, (XLVI) - (XLIX), [redacted]. However, it was not



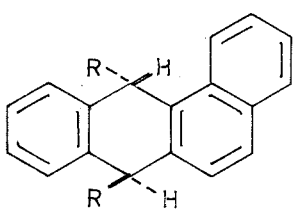
(XLVI), R = SCOMe



(XLVII), R = SCOMe



(XLVIII), R = SCOMe



(XLIX), R = SCOMe

possible to build models of (XLVI) and (XLVII) due to steric interaction between the thio groups and the peripheral hydrogen atoms. Of the other two conformations, there is less steric interaction in (XLVIII), as both the thioacetoxy substituents are mast; hence (XLVIII) should be favoured to (XLIX). The Russian workers described their product, m.p. 193-194°, as a mixture of the cis and trans isomers, but its sharp melting point leads us to suggest that it may, in fact, be the one pure isomer (XLVIII).

1,2-5,6-Dibenzanthracene did not react after shaking with thioacetic acid under oxygen for two days. Small amounts of ferrous sulphate, cumene hydroperoxide and iodine were added in an attempt to initiate the reaction. Though there was an uptake of oxygen, the hydrocarbon was recovered unchanged in a quantitative yield. The reaction was then attempted in the presence of a small amount of anthracene. It was hoped that the radicals produced by the interaction of anthracene with the thiol and oxygen would initiate the reaction of 1,2-5,6-dibenzanthracene. There was an uptake of oxygen, but the volume absorbed was small, being equivalent to the amount of anthracene present. Chromatography of the reaction mixture on acetylated paper showed the presence of the two polycyclic hydrocarbons and 9-(acetylthio)

anthracene. There was no substituted derivative of 1,2-5,6-dibenzanthracene, which, by analogy with the reaction of 1,2-benzanthracene, one would expect to be formed if the hydrocarbon had reacted. A third attempt was made, this time on a larger scale, using 0.65 g. of 1,2-5,6-dibenzanthracene and 0.1 g. of anthracene. The mixture, after having absorbed 12 ml. of oxygen, was boiled under reflux in an oxygen atmosphere for 1.2 hours. However, increased temperature did not have the desired effect of promoting the reaction. Again the sole product formed was 9-(acetylthio)anthracene.

In view of the ready addition of thioacetoxy groups to the 9,10-positions of 1,2-benzanthracene to give (XLIV), it is a little surprising that 1,2-5,6-dibenzanthracene was not attacked at all. On the other hand, the hydrocarbon is inert in reactions such as diazocoupling[82] and lead tetra-acetate oxidation;[83] it is unaffected by sulphur monochloride[140] and by thiocyanogen;[137] it is stable to refluxing with 10% alcoholic potassium hydroxide,[143] and on treatment with N-methylformanilide and phosphorus oxychloride it fails to yield any aldehyde even under forcing conditions.[144] Of interest, too, is the fact that it has no effect on the disulphide groups of cystine and oxidised glutathione.[145] Its lack of reactivity may be explained by the fact that the free valence number of its most reactive positions is

low compared to those of anthracene and 1,2-benzanthracene (Table 2.1). Further, a scale model of the hydrocarbon reveals that the meso-positions are sterically hindered by the angular rings. This steric factor is believed to be partly responsible for the relatively inert nature of 1,2-5,6-dibenzanthracene.

Table 2.1.

Free Valence Numbers of Some Polycyclic Hydrocarbons

Compound	Position	Free Valence Number
Phenanthrene[28]	9,10	0.451
Pyrene[146]	3	0.468
Perylene[147]	3	0.474
1,2-5,6-Dibenzanthracene[147]	9,10	0.498
1-2-Benzanthracene[146]	10	0.514
Anthracene[28]	9,10	0.520
3,4-Benzpyrene[a]	5	0.530

a, calculated from partial bond orders (Hall, Trans.Faraday Soc., 1957, 53, 573)

Phenanthrene and pyrene which have been reported to be little affected by methyl and by benzyl radicals[33] were found to be relatively inert towards thioacetoxy radicals. The reaction of phenanthrene was attempted in the presence of ferrous sulphate, cumene hydroperoxide and iodine.

Though there was an uptake of oxygen, examination of the reaction mixture by paper chromatography indicated much unreacted phenanthrene. There was another very faint fluorescent spot but no product was isolated. The reaction was repeated in the presence of a small quantity of sodium chloride, which has been reported to have catalytic activity in free radical reactions.[148] However, there was no appreciable absorption of oxygen and paper chromatography indicated that the hydrocarbon had undergone little reaction.

The attempted reaction with pyrene was uninteresting except that following the addition of the usual radical generator, a strong odour of hydrogen sulphide was detected, and unlike previous cases, the colour of iodine persisted and there was no absorption of oxygen. Chromatography of the reaction mixture on acetylated paper showed the presence of only starting material.

Perylene was little affected after being shaken with thioacetic acid under oxygen for two days. The addition of the usual mixture of ferrous salt, cumene hydroperoxide and iodine was ineffective in initiating the reaction. Besides unchanged hydrocarbon which was recovered in a 98% yield, a small quantity of an orange

liquid with a green-yellow fluorescence was obtained. However, no identifiable product was isolated from it.

The lack of reactivity of phenanthrene, pyrene and perylene is not surprising in view of their low free valence numbers. The reaction of perylene also suffered from the disadvantage of the limited solubility of the hydrocarbon in benzene.

3,4-Benzpyrene, which is highly reactive to free radical attack, was reported to be unaffected by thiols in the presence of oxygen.[32] When we shook a mixture of the hydrocarbon and thioacetic acid in oxygen, there were no signs of a reaction, but the addition of ferrous sulphate, cumene hydroperoxide and iodine initiated the reaction, as seen in the uptake of oxygen. An attempt to separate the reaction mixture by chromatography on a partially acetylated cellulose column[149] was unsuccessful. However, a satisfactory separation was achieved on deactivated, acid-washed alumina. There was obtained, besides unreacted hydrocarbon and sulphur, a red crystalline compound whose ultraviolet absorption spectrum resembled that of 3,4-benzpyrene, (Fig. 2.5), hence indicating that the product was a substituted derivative of the hydrocarbon. It was later found to be identical with synthetic 5-(acetylthio)-3,4-benzpyrene (L). The alumina used for the separation was prepared by treatment

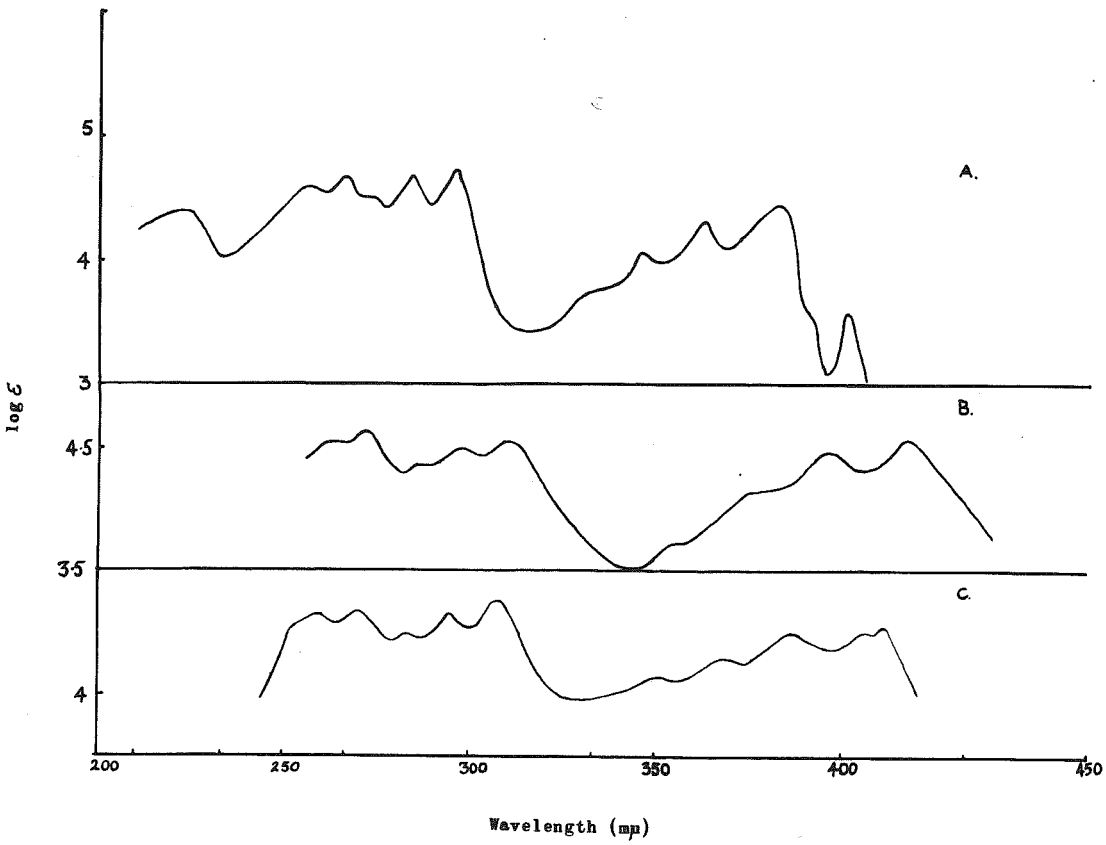


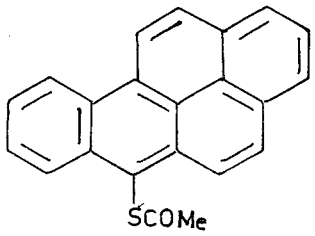
Fig. 2.5 ULTRAVIOLET ABSORBTION SPECTRA

(A) 3,4-benzpyrene* (in ethanol);

(B) dimethyl ester of a di-(carboxymethylthio)-3,4-benzpyrene (in chloroform)

(C) 5-(acetylthio)-3,4-benzpyrene (in chloroform)

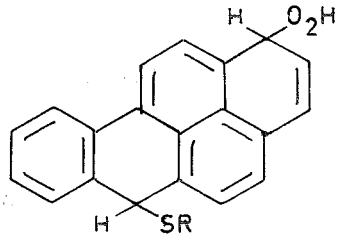
*Friedel and Orchin, "Ultraviolet Spectra of Aromatic Compounds", John Wiley and Sons, Inc. New York, 1951.



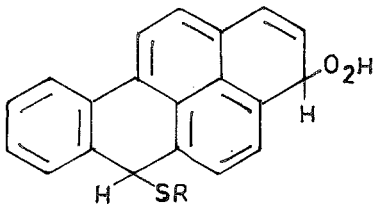
(L)

of Spence alumina with hydrochloric acid, followed by thorough washing with water. The neutral alumina was then dried overnight at 150°, and deactivated by the addition of water (5% by weight). It was observed in a later experiment that the thioacetyl compound (L) was completely converted to di-5-(3,4-benzpyrenyl)disulphide by passage through a column of active alumina.

This reaction is of particular interest in that 3,4-benzpyrene, unlike anthracene and 1,2-benzanthracene, does not possess two meso-positions and as such, the structure of the intermediate hydroperoxide is not as obvious as in the cases of anthracene and 1,2-benzanthracene. As 3,4-benzpyrene is oxidised to the 5,8- and 5,10-quinones,[150] it appears most likely that the introduction of the hydroperoxy group occurred at the 8- and/or 10-positions, resulting in intermediates of the type (LI) and (LII). It is interesting that metabolic hydroxylation of the hydrocarbon occurs at these same two positions.[121]

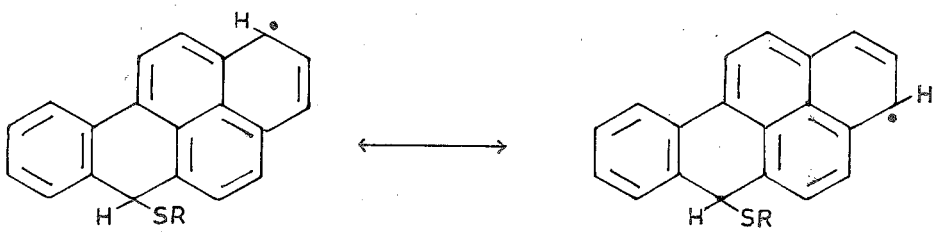


(LI)



(LII)

In view of the exceptional susceptibility of 3,4-benzpyrene to free radical attack,[20] it may seem surprising that the hydrocarbon did not exhibit greater reactivity in its reaction with thioacetic acid and oxygen. The initial step, that is, the attack of a thioacetoxy radical at the 5-position of the hydrocarbon, would be expected to proceed with great ease. However, the resulting radical is a highly resonance-stabilised system; two of its contributing structures are represented by (LIII). It does not add on oxygen as



(LIII)

readily as the corresponding intermediate radical of anthracene or 1,2-benzanthracene, and hence the rate of reaction is reduced. Of course, the argument is valid

only if the initial step is reversible. Our discussion earlier indicated that the addition of a thiyl radical to an aromatic hydrocarbon is very likely a reversible process. It is probable that the lack of reactivity of perylene is due to, besides other factors, the formation of a resonance-stabilised intermediate readical corresponding to (LIII).

Contrary to the report[32] that 3,4-benzpyrene does not react with thiyl radicals, the formation of 5-acetylthio-3,4-benzpyrene, though only in low yield, indicates that the hydrocarbon is susceptible to attack by thiyl radicals. This is of great interest in connection with the mechanism of cancer production by carcinogenic hydrocarbons.

Reactions of Some Polycyclic Aromatic Hydrocarbons with Thiols, t-Butylhydroperoxide and Ferrocene

The reactions of anthracene and other polycyclic aromatic hydrocarbons with thiols and oxygen were often long, taking several hours, sometimes days, and the yields of products were low except in the reactions using anthracene. It was decided to continue our investigations, using a different source of thiyl radicals, in the hope of obtaining a more satisfactory preparative method for thio derivatives of polynuclear hydrocarbons. Further, it was anticipated that such a study would serve as an interesting comparison with the previous reactions, and also yield more information on the reactions of polycyclic aromatic hydrocarbons with thiyl radicals.

As the formation of thio derivatives is not favoured by high temperatures, as indicated by the absence of sulphur-containing products in the thiol-catalysed dehydrogenation of 9,10-dihydroanthracene and its derivatives by azo compounds,[34,59] it was necessary to employ a source of thiyl radicals that was effective at room temperature. A mixture of t-butylhydroperoxide, an excess of thiol and a catalytic amount of ferrocene in benzene proved very suitable for our work. Ferrocene,

being readily soluble in benzene, was found to be much more effective than ferrous sulphate as a source of ferrous-ferric ions. It is believed to react with t-butylhydroperoxide as shown in steps (10) and (11).[151]

$$\text{Ferrocene} + Bu^tO_2H \longrightarrow Bu^tO\cdot + FeC_{10}H_{10}^{+} + OH^- \quad \ldots\ldots (10)$$

$$FeC_{10}H_{10}^{+} + Bu^tO_2H \longrightarrow Bu^tO\cdot + Fe^{2+} + OH^- + 2(C_5H_5) \quad \ldots (11)$$

$$Bu^tO_2H + Fe^{2+} \longrightarrow Bu^tCO\cdot + OH^- + Fe^{3+} \quad \ldots\ldots (12)$$

$$Bu^tO\cdot + RSH \longrightarrow RS\cdot + Bu^tOH \quad \ldots\ldots (13)$$

$$Fe^{3+} + RSH \longrightarrow RS\cdot + Fe^{2+} + H^+ \quad \ldots\ldots (14)$$

The production of ferrous ions is confirmed by the appearance of a deep green colour on mixing ferrocene with the hydroperoxide in benzene solution. The fate of the cyclopentadiene residue is unknown. The t-butoxy radicals and ferric ions, formed by the action of ferrous ions on the hydroperoxide (12),[152] react with the thiol to yield thiyl radicals, by steps (13) and (14). An excess of thiol was used to ensure that the t-butoxy radicals reacted with the thiol and not with the hydrocarbon present in the reaction mixture. The presence of ferrous ions was detected in the final reaction mixture by the blue colour produced on testing the mixture with potassium ferricyanide. Ferric ions were not detected; they were reduced by the excess of thiol present.

Butadiene has been effectively used as a trap for free radicals; the formation of an additive dimer of the type represented by (LIV) is evidence of the presence of free radicals.[60] It was therefore decided to employ this method to prove the production of thiyl radicals by the interaction of t-butylhydroperoxide with a thiol in the presence of ferrocene. Accordingly, thioacetic acid and the hydroperoxide were introduced to a benzene solution containing butadiene and a small quantity of ferrocene. Fractional distillation of the reaction mixture gave four liquid products, one of which, b.p. 148-153°/0.3 mm., is believed to be the additive dimer (LIV). The analytical data, though not within the normal

$(CH_3COSCH_2CH=CHCH_2-)_2$ $CH_3COSCH_2CH=CHCH_3$

(LIV) (LV)

$CH_3COSCH_2CH=CHCH_2SCOCH_3$ $CH_3COSCH_2CH=CHCH_2OH$

(LVI) (LVII)

experimental error, agree sufficiently with the required values for $C_{12}H_{18}O_2S_2$ to indicate that the product is probably the additive dimer. Due to the complex nature of the reaction mixture the separation and purification of all the products were difficult, and as we were

interested in only the additive dimer, no further attempts were made to identify the other products. Their analytical data did not agree with those required for the compounds, (LV) - (LVII), which are the other possible products.

The reactions were carried out at room temperature under nitrogen. The addition of t-butylhydroperoxide and ferrocene to a mixture of the hydrocarbon and thiol in benzene was accompanied, in most cases, by rapid colour changes and liberation of heat. The mixtures were worked up in much the same was as before, that is, by fractional crystallisation and chromatographic separation on alumina. The products obtained were similar to those from the reactions utilising oxygen but were formed in higher yields. Another feature which renders this type of reaction suitable for synthetic work is that it is rapid, often being complete in less than an hour.

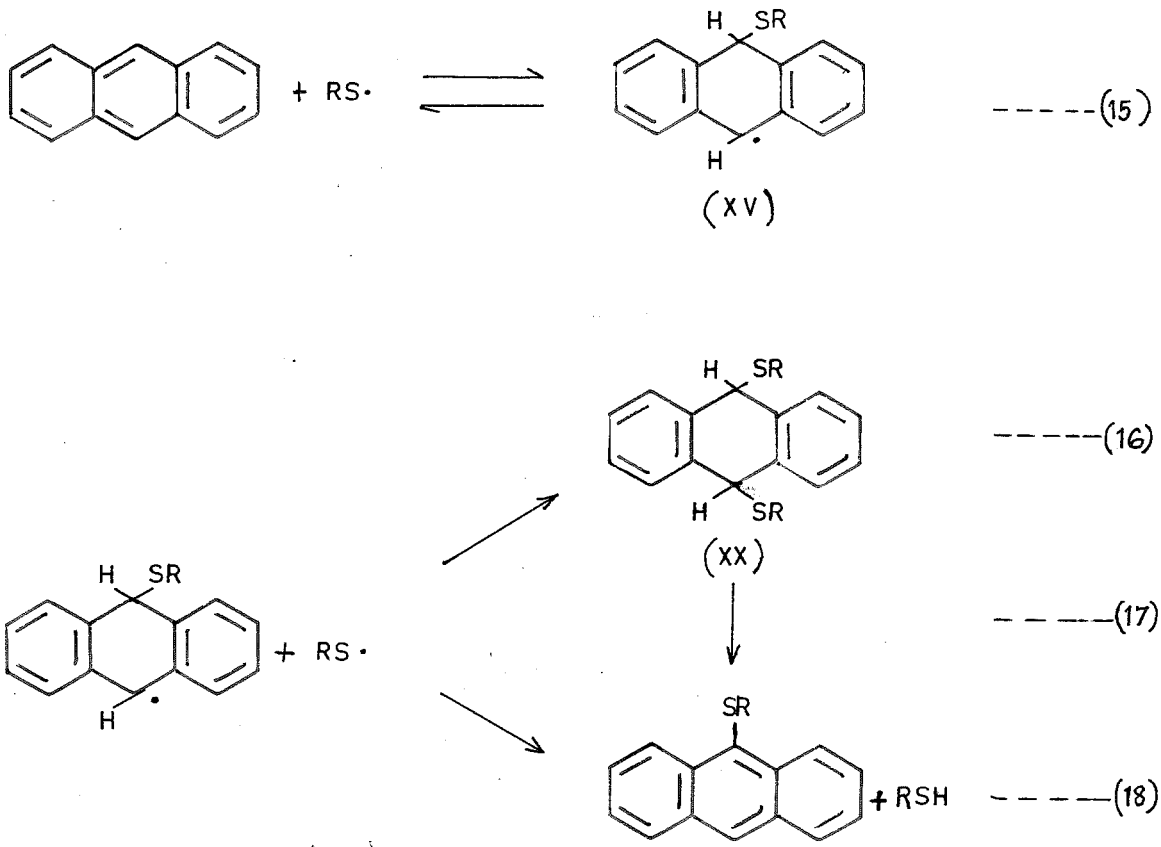
In order to make this a comparative study, the same thiols that had been used in the earlier experiments were now investigated. As before anthracene was used in the initial experiments. In carrying out the reaction of anthracene with mercaptoacetic acid, a catalytic quantity of ferrocene was added to the

hydrocarbon and thiol in benzene, and to the mixture was then carefully added the hydroperoxide. There was a vigorous reaction, the mixture became hot, and an insoluble white powder precipitated from solution almost immediately. The solid after crystallisation from NN-dimethylformamide melted partially at 195° but mainly at 215-218°. Its melting-point was not depressed on admixture with 9,10-di(carboxymethylthio)-9,10-dihydroanthracene (VII), m.p. 217-219°. The product is believed to be a mixture of two stereo isomers of (VII), with a predominance of the higher melting one. Also formed, though in a much lower yield, was a yellow material which melted partially at 163° and completely at 170-192°; it appears to be 9-(carboxymethylthio) anthracene (IX) mixed with a small amount of the dihydroanthracene derivatives (VII). Besides crystallisation from ether, no other attempt was made to purify the material, as previous attempts to purify similar products by chromatography of their methylated derivatives were unsuccessful.

When anthracene was similarly treated with thioacetic acid, ferrocene and t-butylhydroperoxide, there was no sign of a reaction, but the addition of a solution of ferrocene and the hydroperoxide in benzene proved effective in initiating the reaction. The prior mixing

of the last two reagents in a concentrated solution ensured the effective production of t-butoxy radicals and ferrous ions, and hence indirectly the production of thiyl radicals. It is therefore obvious why reaction proceeded more readily when the ferrocene and the hydroperoxide were added as a mixture than when they were introduced separately to the hydrocarbon-thiol mixture.

The suggested reaction mechanism is indicated by equations (15) - (18).



The first step, which is similar to that in the proposed mechanism for the reaction of polycyclic hydrocarbons with thiols and oxygen, involves the addition of a thiyl radical to anthracene. The resulting radical (XVI) may add on another thiyl radical to give the dihydroanthracene derivative (XX), or may undergo hydrogen abstraction to yield the substituted derivative (XXI). It is plausible that the latter compound (XXI) may also be formed from the dihydroanthracene derivative (XX) by loss of a thiol molecule (17). We have demonstrated that such a conversion can occur by a polar mechanism but it is uncertain if the process would be polar or free radical in nature under the conditions of these reactions. As before the ratio of the dihydroanthracene derivative to the substituted product varied from one reaction to another, and obviously depends, to a large extent, on the nature of the attacking thiol.

Unlike the reactions of polycyclic hydrocarbons with thiols and oxygen, these are not chain reactions. The attacking thiyl radicals are generated by the interaction of thiol molecules with t-butoxy radicals and ferric ions, as shown in equations (13) and (14). It was, therefore, necessary for the hydroperoxide to be present in excess with respect to the hydrocarbon. On the other hand, in the reactions involving oxygen,

cumene hydroperoxide was present in a small amount and merely served as a radical initiator. The direct reaction between the hydroperoxide and thiol, which occurred in the earlier experiments, probably does not occur to a significant degree in these reactions. The thiol is likely to react with ferric ions and t-butoxy radicals, (13) and (14), much more readily than with t-butylhydroperoxide.

Beckwith and Waters,[33] in their study of the reaction of anthracene with free radicals derived from di-t-butylperoxide, suggested that intermediates similar to (XV) were dehydrogenated by methyl or t-butoxy radicals. By analogy, the intermediate radical (XV) in our reactions might be expected to be converted to the substitution product (XXI) by donation of a hydrogen atom to a t-butoxy radical. However, this is unlikely. Hydrogen abstraction by thiyl radicals is certainly preferred to abstraction by t-butoxy radicals as the former are present in a much higher concentration and are more efficient hydrogen-acceptors.

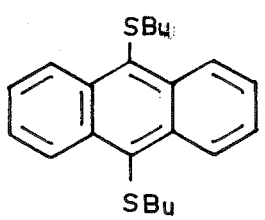
Another reaction which is theoretically possible is that of an aromatic radical with a disulphide. The S-S linkage is slightly weaker than the C-S bond, and should break easily to give thiyl radicals which then could add to aromatic radicals such as the intermediate (XV).

Similar polar reactions are well known. A free radical reaction of this nature would be exothermic, so that it should be favoured energetically. Possibly the addition of diphenyl disulphide to styrene in the presence of iodine[153] occurs by a similar type of free radical mechanism.

$$PhCH=CH_2 + PhSSPh \xrightarrow{I_2} PhCH(SPh)-CH_2Ph$$

The reaction of anthracene with thiobenzoic acid was unexpectedly slow and was preceded by a long induction period. As there was no immediate reaction, the reddish-purple mixture was allowed to stand for three days under nitrogen. Unchanged anthracene and much dibenzoyldisulphide which had precipitated from solution were removed, by filtration, and chromatography on alumina of the concentrated filtrate yielded the two isomers of 9,10-di(benzoylthio)-9,10-dihydroanthracene (V) and a small quantity of 9-(benzoylthio)-anthracene (VI) besides unchanged hydrocarbon. The yields were lower than in the corresponding reaction carried out in the presence of oxygen. As the sample of thiobenzoic acid used in this reaction was not fresh, it is possible that the presence of oxidation products might be responsible for the slow rate of reaction and the low yields of products.

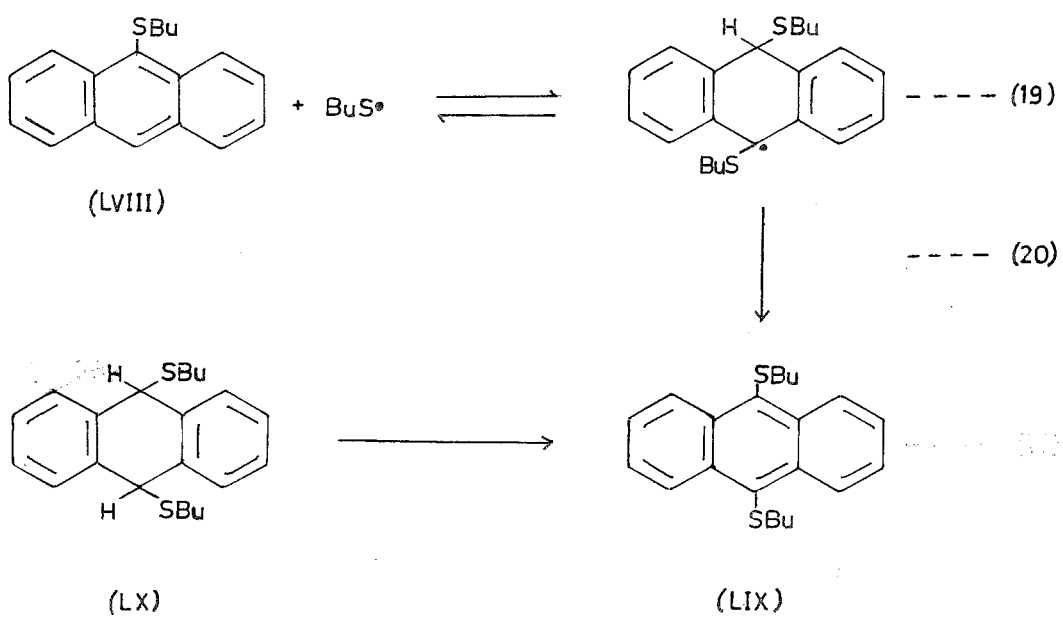
It may be recalled that in the reaction of anthracene with n-butanethiol and oxygen, no crystalline products were isolated though a bright blue fluorescent spot was observed on examination of the reaction mixture by chromatography on acetylated paper. It was hoped that in the presence of t-butylhydroperoxide and ferrocene, anthracene could react sufficiently with the thiol to enable the isolation of pure products. Accordingly, the reaction was attempted using a freshly-distilled sample of n-butanethiol. There were no immediate signs of a reaction but after three days all the hydrocarbon had dissolved, and from the reaction mixture were isolated beautiful fluorescent green-yellow needles, m.p. 61-62°, which gave an anthracene-type absorption spectrum in the ultraviolet region, and analysed satisfactorily for a disubstituted anthracene derivative. The meso-positions of anthracene being the most likely positions of attack, we suggest that the compound is 9,10-di(n-butylthio) anthracene (LIX). It had a higher R_f value than



(LIX)

anthracene on alumina and acetylated paper, and came through rapidly on an alumina column together with a strong-smelling liquid which made its purification very difficult. The liquid fractions obtained after chromatography were cooled in dry ice-ethanol, and the solidified material collected by filtration in the cold and rechromatographed, the process being repeated twice. Petroleum ether (b.p. 32-34°) in which the compound was readily soluble was found to give a satisfactory separation.

This is the first instance of the production of a disubstituted derivative in our investigations. Such a product could arise from further reaction of the monosubstituted compound (LVIII), as indicated by equations (19) and (20). Alternatively, it could be



(LVIII)

(LX)

(LIX)

formed by dehydrogenation of the dihydroanthracene derivative (LX) by thiyl radicals.[34,59]

Though the 9-monosubstituted and 9,10-dihydroanthracene derivatives were not isolated, it does not necessarily mean that they were not formed. As pointed out earlier, they would probably be low melting and would have similar R_f values, thus rendering their separation and purification very difficult.

The next reaction studied was that with N-acetylcysteine. It was carried out in the usual manner except that tetrahydrofuran was used in place of benzene. As only a limited quantity of acetylcysteine was available, it was present in the reaction mixture in a lower concentration than was usual for the thiol component. The characteristic colour changes were not observed and the mixture, even after standing overnight, did not appear to have reacted. Further quantities of ferrocene and t-butylhydroperoxide were introduced, and the mixture was gently warmed on a water-bath. However, only a 6% yield of product was obtained. It was identical with the yellow powder believed to be S-(9-anthryl)-N-acetylcysteine (XXXII), isolated from the reaction using oxygen. Attempts to obtain an analytically pure sample were again unsuccessful. The

poor yield was evidently due to the low concentration of acetylcysteine used. These reactions of anthracene with N-acetylcysteine, though not performed under similar conditions to those in biological systems, add support to current theories concerning the possible role of thiyl radicals in cancer production by carcinogenic hydrocarbons.

In earlier experiments involving oxygen, thiophenol was found to behave differently from the other thiols investigated in that it formed an unstable hydroperoxide. When it was allowed to react with anthracene in the presence of ferrocene and t-butyl-hydroperoxide, it failed to give any identifiable product besides a small amount of anthraquinone. Anthracene was recovered unchanged in 78% yield in spite of efforts to force the reaction by repeated additions of ferrocene and the hydroperoxide, and also by the application of heat.

As only limited success had been achieved in the reactions of higher polycyclic aromatic hydrocarbons with thiols and oxygen, it was decided to attempt the reaction of these higher polycyclics with thiyl radicals generated by the action of ferrocene and t-butyl-hydroperoxide on thiols. Mercaptoacetic acid was found to participate in these reactions very readily but, in

practically every case, the products could not be sufficiently purified for identification. As before thioacetic acid proved more suitable, its derivatives being more easily identified.

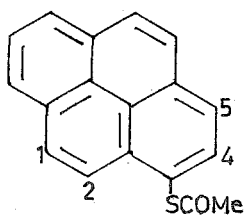
Of the higher cyclic systems studied, 1,2-benzanthracene exhibited the highest reactivity though it was not as reactive as anthracene. Attack of the hydrocarbon by thioacetoxy radicals resulted in good yields of 10-acetylthio-1,2-benzanthracene (XLV) and 9,10-di(acetylthio)-9,10-dihydro-1,2-benzanthracene (XLIV) m.p. 190-192°, the latter being identical with the dihydroanthracene derivative obtained from the reaction with oxygen.

From the reaction of 1,2-benzanthracene with mercaptoacetic acid was isolated a white powder, m.p. 175-9°, which was insoluble in benzene, ether and ethanol, and readily soluble in NN-dimethylformamide in the cold. Repeated crystallisation of the product from aqueous dimethylformamide, and then from acetone-hexane failed to yield an analytically pure sample. In solution the substance gradually decomposed on standing. The solubility properties, and the unstable and non-fluorescent character of the substance suggest it to be a 9,10-dihydroanthracene derivative, probably substituted in both the meso-positions by carboxymethylthio groups. An attempt was made to characterise the product through its

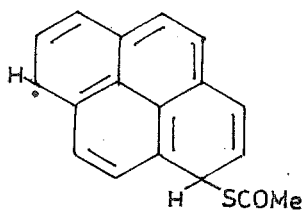
methyl ester. Treatment of the white powder with diazomethane yielded a resinous mass from which was isolated a small quantity (8 m.g.) of a white solid, m.p. 175·5-177°, which contained nitrogen but no sulphur. The same material was obtained when the product from 3,4-benzpyrene and mercaptoacetic acid was similarly treated with diazomethane. The substance, therefore, cannot be a derivative of the reacting hydrocarbon; it is probably an impurity in the sample of nitrosomethylurea used in the preparation of diazomethane. No other product was isolated from the methylation mixture.

Addition of ferrocene and t-butylhydroperoxide to a benzene solution of pyrene and mercaptoacetic acid brought about a vigorous reaction. On cooling of the mixture there was precipitated a green-yellow solid, which melted partially at 200° and decomposed at 225°. Repeated crystallisation from ethylacetate failed to purify the product. Alkali-extraction of the reaction mixture yielded a pale yellow solid, m.p. 130-135°, which could not be identified due to difficulty in its purification. When the experiment was repeated, using thioacetic acid in place of mercaptoacetic acid, the main product was a pale yellow crystalline compound, m.p. 136-137·5°, which had an ultraviolet absorption spectrum similar to that of pyrene. It did not depress the melting-

point of a synthetic specimen of 3-(acetylthio) pyrene (LXI). Substitution of the acetylthio group at the 3-position is in agreement with the results of quantum mechanical calculations of the free valence numbers for the various positions in the pyrene molecule.[146] Also isolated from the reaction mixture was di-(3-pyrenyl)-disulphide which was identified by comparison with a synthetic sample. Its significance is doubtful as it was probably formed during the chromatographic separation of the reaction mixture on alumina.



(LXI)



(LXII)

The absence of a dihydropyrene derivative means that in the intermediate radical (LXII), which is resonance-stabilised, loss of a hydrogen atom to give a fully aromatic system is preferred to the addition of another thiyl radical.

The attempted reactions of phenanthrene and of 1,2-5,6-dibenzanthracene with mercaptoacetic acid, t-butylhydroperoxide and ferrocene gave negative results, which is not surprising in view of the lack of reactivity

of these hydrocarbons towards thiols and oxygen.

Perylene, which was little affected when shaken with thioacetic acid under oxygen, was found to react with the thiol in the presence of t-butylhydroperoxide and ferrocene. The major portion of the crude product, which melted partially at 130° and completely at 160-167°, yielded, after several crystallisations from benzene, a fine crystalline yellow material, m.p. 232·5-237°. It fluoresced a bright green in benzene solution and had an ultraviolet spectrum similar to that of perylene. It is believed to be a mixture of di(acetylthio)perylene isomers, though the difference between the analytical data and the required values is not within the normal limits of error. It appears from the marked difference in the melting-points of the crude and final products that the material underwent some change during the many attempts to purify it from benzene. Another portion of the reaction product, m.p. 200-233°, when chromatographed on acid-washed, deactivated alumina yielded perylene and a red liquid that fluoresced yellow-green in benzene. The latter appeared to be formed on the alumina column.

Surprisingly, there was no appreciable reaction between perylene and mercaptoacetic acid, the only product being a small quantity of an unidentified orange powder that sintered at 185°, darkened at 215° and finally melted

at 227°. Unchanged hydrocarbon was recovered in an 87% yield.

In the reaction of 3,4-benzpyrene with mercaptoacetic acid, much difficulty was again encountered in purifying the benzene-insoluble product. As crystallisation of the material from various solvents proved unsatisfactory, it was decided to attempt identification of the product through its methyl ester. Treatment with diazomethane of the crude product from a second experiment followed by chromatography on neutral "Woelm" alumina of the resulting orange oil yielded fine yellow needles, m.p. 113-115°, the analytical data of which indicated the compound to be a dimethyl ester of a di(carboxymethyl thio)-derivative of either 3,4-benzpyrene or dihydro-3,4-benzpyrene. However, its ultraviolet spectrum which was of the benzpyrene type, provided evidence of its fully aromatic nature (Fig. 2.5). The positions of substitution have not been established. The unidentified white solid that was obtained after methylation of the product from 1,2-benzanthracene and mercaptoacetic acid was also isolated.

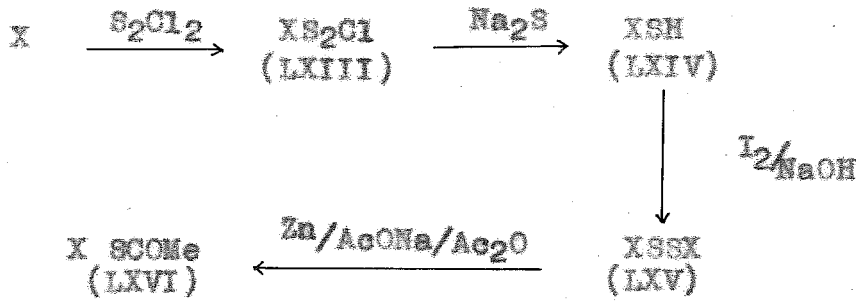
3,4-Benzpyrene was converted in good yield to 5-(acetylthio)-3,4-benzpyrene (L) on treatment with ferrocene, t-butylhydroperoxide and thioacetic acid.

The compound when chromatographed on acid-washed "Spence" alumina (dried overnight at 150°) was converted quantitatively to di-5-(3,4-benzpyrenyl)disulphide.

It was observed that with the increase in size of the ring system, the thio derivatives were less stable. Thus, while 9-(acetylthio) anthracene (I) was unappreciably affected by passage through an alumina column, the corresponding derivative of 3,4-benzpyrene was completely oxidised to the disulphide. Due to their relative instability the derivatives of the higher cyclic systems, that is, pyrene, perylene and 3,4-benzpyrene, were difficult to purify. Though much care was exercised in the handling of these compounds, some decomposition appeared to occur.

Reference Compounds

Compounds required for reference were prepared by standard methods. A convenient synthetic route to the disulphides and acetylthio derivatives of polycyclic hydrocarbons is indicated below:



X = polycyclic aromatic hydrocarbon.

Treatment of the hydrocarbon with sulphur monochloride gave the dithiochloride (LXIII), which was reduced to the thiol (LXIV) with sodium sulphide; the latter on treatment with iodine in alkaline solution was readily oxidised to the disulphide (LXV) which was converted to the required acetylthio derivative (LXVI) by heating with zinc dust and sodium acetate in acetic anhydride. This method gave satisfactory yields of di-(9-anthryl)disulphide (IV), 9-(acetylthio)anthracene (I) and 10-(acetylthio)-1,2-benzanthracene (XLV). The assumption that 1,2-benzanthracene was attacked in the 10-position in the above reactions is based on the formation of the 10-dithiochloride from the hydrocarbon.[140]

5-(Acetylthio)-3,4-benzpyrene (L) was similarly prepared except that the hydrocarbon was converted to the 5-thiocyanate[137] by treatment with thiocyanagen. The attempt to prepare the dithiochloride of 3,4-benzpyrene was not successful. The thiocyanate was converted to the thiol by heating with sodium sulphide. Di-(3-pyrenyl) disulphide and 3-(acetylthio)pyrene (LXI) were also synthesised by the above method via the thiocyanate. As the 3-position in the pyrene molecule is the most reactive centre it is reasonable to assume that reaction occurred at this position. The compounds were difficult to purify and could not be obtained in analytically pure forms in spite of careful chromatographic separation and crystallisation from benzene. However, by analogy with previous similar preparations there is no doubt as to the structures of the compounds.

9-Benzylanthracene was converted to the 10-mercapto compound via the dithiochloride; treatment of the thiol with chloroacetic acid in alkaline solution yielded 10-carboxymethylthio-9-benzylanthracene (XXXV).

(α,α-Dimethylbenzylthio)acetic acid (XXII) was prepared in good yield (80%) by the acid-catalysed addition of mercaptoacetic acid to α-methylstyrene.

CHAPTER III

Experimental

Ultraviolet Spectra. - These were determined on an Optica CF_4 Spectrophotometer recording instrument in 95% ethanol unless otherwise stated.

Infrared Spectra. - The infrared spectra of the compounds obtained from the reaction of anthracene with thioacetic acid and oxygen were determined on a Grubb Parsons Model S4 double beam spectrophotometer. All other infrared spectra were determined on a Perkin-Elmer Infracord Spectrophotometer Model 137. The compounds were examined in nujol or in chloroform solution.

Chromatography. - (i) On alumina. Spence alumina which had been neutralised with hydrochloric acid and activated at 150° was generally used in the separation of anthracene derivatives. For the higher cyclic systems it was found necessary to use deactivated alumina (5% water). Hexane and benzene were generally used as solvents and elutants. In some cases ether and alcohol were also used.

(ii) Paper chromatography. All paper chromatography was carried out on partially acetylated paper made by the method of Spotswood.[134] For anthracene and 1,2-benzanthracene derivatives, methanol : ether : water - 4 : 4 : 1 was used as the solvent system; for the other

compounds, ethanol : benzene : water - 17 : 4 : 1 was found to give a better separation.

Reagents. - All the hydrocarbons, except anthracene, were purified by chromatography on alumina and crystallisation. Liquid thiols, except thiobenzoic acid, were redistilled under nitrogen. The benzene used was thiophen-free and sodium-dried.

Reaction of Anthracene with Thioacetic Acid. - (a) Anthracene (5 g.) was dissolved in warm benzene (50 ml.) and the solution was rapidly cooled. Redistilled thioacetic acid (20 ml.; b.p. 91-94°) was added to the fine suspension and the mixture shaken at room temperature under oxygen. There was an induction period of *ca.* 7 hr. followed by rapid absorption of oxygen (550 ml.) during 2 hr. When the gas uptake stopped, the solvent and excess of thioacetic acid were removed by distillation under a slightly reduced pressure of nitrogen. The residue was treated with benzene (50 ml.) and filtered, and the solid was separated by hand-picking into anthracene (20 mg.) and 9-(acetylthio)anthracene (0·74 g.), m.p. and mixed m.p. 146-147°. The benzene filtrate was evaporated and the oily residue treated with methanol. Fractional recrystallisation of the resulting solid from methanol and from hexane gave 9-(acetylthio)anthracene (1·5 g.), and one isomer of 9,10-di(acetylthio)-9,10-

dihydroanthracene (0·1 g.). The latter crystallised in prisms from hexane, m.p. 145-7° (lit.[68] m.p. 148-9°) (Found: C, 65·6; H, 5·0; S, 19·9. Calc. for $C_{18}H_{16}O_2S_2$: C, 65·8; H, 4·9; S, 19·5%). Its ultraviolet spectrum showed an inflexion at 2360 Å (ε 17,080). The mother-liquors were evaporated, the residue was taken up in benzene-hexane and chromatographed, and the following compounds were collected: (i) sulphur (0·16 g.), (ii) 9-(acetylthio)anthracene (ca. 1 g.), and (iii) di-(9-anthryl)disulphide (0·5 g.), m.p. and mixed m.p. 218-221°.

(b) In a second experiment conducted under identical conditions, reaction started immediately with a slow but steady uptake of oxygen. After 7 hr. (340 ml. oxygen absorbed), anthracene (2·4 g.) was removed by filtration and the solvent and excess of thiol were evaporated at a reduced pressure of nitrogen. The residue, consisting of a mixture of a yellow solid and a viscous orange oil, was treated with methanol (50 ml.) and filtered. The yellow solid (1·87 g.), m.p. 130-205°, on further treatment with methanol (60 ml.) left anthracene (1 g.). Concentration of the methanol solution gave the yellow 9-(acetylthio)-anthracene. The first portion of the methanol filtrate, on standing overnight, deposited a mixture of crystals, which were purified by fractional recrystallisation from hexane to yield sulphur (20 mg.), 9-(acetylthio)anthracene

(total yield, 1·6 g.), and the other isomer of 9,10-di(acetylthio)-9,10-dihydroanthracene (0·4 g.), m.p. 124·5-126° (lit.[68] m.p. 124·5-125°) (Found: C, 66·1; H, 5·1; S 19·9%). Its ultraviolet spectrum showed an inflexion at 2340 Å (ε 15,000) and a maximum at 2547 Å (ε 10,810).

All anthracene derivatives containing the acetylthio group showed strong infrared carbonyl absorption at 1685-1695 cm^{-1}.

Reaction of Anthracene with Thiobenzoic Acid. - When anthracene (1·8 g.), thiobenzoic acid (7 g.) and benzene (25 ml.) were shaken together under oxygen, there was an initial rapid absorption of gas (ca. 90 ml. in 10 mins.) but the reaction slowed down to a negligible rate after 0·5 hr. Small amounts of cumene hydroperoxide and ferrous sulphate were added to initiate the reaction (276 ml. oxygen absorbed altogether). The mixture was washed with water and sodium carbonate solution, and evaporated at a reduced pressure of nitrogen. The residue was chromatographed following unsuccessful attempts to isolate pure products by crystallisation from methanol and from hexane. Elution with hexane-benzene, benzene-ether, and ether brought through the following fractions, in the order of elution from the column: (1) anthracene (0·5 g.),

(ii) a yellow solid (A) (0·78 g.), m.p. 160-170°, (iii) 9-(benzoylthio)anthracene (0·2 g.) which crystallised from benzene-hexane in yellow prisms, m.p. 225-7° (Found: C, 80·1; H, 4·6; S, 10·1. $C_{21}H_{14}OS$ requires C, 80·2; H, 4·5; S, 10·2%), max. 2490 (ε 129,000)(infl.), 3254 (ε 3,322)(infl.), 3410 (ε 5,902)(infl.), 3570 (ε 10,800), 3747 (ε 15,440) and 3950 Å (ε 13,380), and (iv) di-(9-anthryl)disulphide (10 mg.). Fractional recrystallisation of solid (A) from benzene-hexane gave the two isomers of 9,10-di(benzoylthio)-9,10-dihydroanthracene - (i) colourless plates (0·5 g.), m.p. 202-204° (Found: C, 74·5; H. 4·3; S, 13·9. $C_{28}H_{20}O_2S_2$ requires C, 74·3; H, 4·45; S, 14·2%), max. (in cyclohexane) 2390 (ε 37,000) and 2773 Å (ε 19,400), and (ii) colourless prisms (0·2 g.), m.p. 193·5-5° (Found: C, 74·6; H, 4·6; S, 13·7%), max. (in cyclohexane) 2390 (ε 31,410) and 2731 Å (ε 17,700). A mixture of the two isomers melted at ca. 170°.

Reaction of Anthracene with Mercaptoacetic Acid. - (a) In Benzene. Anthracene (5 g.), mercaptoacetic acid (21 g.) and benzene (50 ml.) were shaken together under oxygen. There was an immediate and rapid absorption of oxygen, the anthracene dissolved, the reaction mixture turned a pale yellow and a white powder precipitated from solution. Reaction was complete in 1·2 hr. (660 ml. oxygen absorbed). The mixture was well shaken with a

solution of sodium carbonate; the aqueous layer was washed with ether, and acidified with hydrochloric acid. The yellow precipitate collected by filtration partly dissolved on treatment with hot acetone. Repeated crystallisation of the insoluble material (2·8 g.), m.p. 201-204°, from NN-dimethylformamide yielded fine crystals of 9,10-di(carboxymethylthio)-9,10-dihydroanthracene, m.p. 218-220° (Found: C, 59·0; H, 4·7; S, 17·8. $C_{18}H_{16}O_4S_2$ requires C, 60·0; H, 4·5; S, 17·8%). Its ultra-violet spectrum showed an inflexion at 2507 Å (3,660). On concentrating the acetone solution a yellow solid (2·05 g.) was obtained, m.p. 183-196°, which after several recrystallisations from acetone gave the above diacid. An unidentified pale yellow material which was insoluble in acetone was formed at every crystallisation. Attempts to crystallise the residue after evaporation of the combined mother liquors from acetic acid and ethylacetate gave only impure powders, m.p. 197-205° and 198-210°, respectively.

Esterification of the dicarboxylic acid with diazomethane yielded the dimethylester which crystallised from ether in colourless plates, m.p. 99-101·5° (Found: C, 61·7; H, 5·2; S, 16·6. $C_{20}H_{20}O_4S_2$ requires C, 61·8; H, 5·2; S, 16·5%).

When a suspension of the dicarboxylic acid (0·33 g.) in acetic acid (5 ml.) and concentrated hydrochloric acid (0·5 ml.) was heated, it rapidly afforded a clear yellow solution. Dilution with water precipitated yellow needles of (9-anthrythio)acetic acid (0·2 g.) which, after crystallisation from ether-hexane, melted at 166-7° (lit.[132] m.p. 164°) (Found: C, 72·0; H, 4·7. Calc. for $C_{16}H_{12}O_2S$: C, 71·6; H, 4·5%). Its ultraviolet absorption spectrum was characteristic of a substituted anthracene derivative, λmax. 2517 (ε 82,390) (infl.), 3220 (ε 1,348)(infl.), 3410 (ε 3,040)(infl.), 3557 (ε 4,673), 3733 (ε 8,519) and 3937 Å (ε 7,560).

(b) In Alcohol. A mixture of anthracene (0·9 g.), mercaptoacetic acid (5 ml.) and ethanol (20 ml.), when shaken under oxygen, absorbed gas very rapidly (322 ml. in 1·6 hr.). The hydrocarbon dissolved and a fine yellow solid (0·15 g.) was formed which was identified as anthraquinone. Evaporation of the solvent and treatment of the residue with hexane gave more anthraquinone (0·15 g.) and a resinous material. The latter was taken up in ether, extracted with aqueous sodium carbonate, and the alkaline layer acidified. Attempts to purify the resulting oil by crystallisation were not successful. The oily mass was treated with diazomethane but only anthraquinone was seperated from the product. Chromato-

graphy on alumina did not yield any other identifiable product.

Reaction of Anthracene with β-Mercaptopropionic Acid. - A mixture of anthracene (0·89 g.), β-mercaptopropionic acid (5 ml.) and benzene (30 ml.) was shaken together under oxygen for 1 hr. without any uptake of gas. Reaction was initiated by the addition of catalytic amounts of ferrous sulphate, cumene hydroperoxide and iodine, and the mixture turned from an orange to a pale yellow colour. After 2 hr. (180 ml. oxygen absorbed) ββ'-dicarboxydiethyldisulphide (4·2 g.), which had precipitated, was filtered off and the benzene solution was evaporated under a reduced pressure of nitrogen. The residue which solidified on cooling in the refrigerator was thoroughly washed with warm water and dried. Attempts to purify it by crystallisation from benzene were not satisfactory. The impure material was then taken up in ether, extracted with aqueous sodium carbonate, and the alkaline layer and an insoluble sodium salt were carefully washed with ether and acidified. (9-Anthrylthio)propionic acid (0·63 g.) which precipitated crystallised from benzene in pale yellow, fine crystals, m.p. 176-177° (Found: C, 72·6; H, 5·0; S, 11·0. $C_{17}H_{14}O_2S$ requires C, 72·3; H, 5·0; S, 11·4%). λmax. 2192 (ε 11,600), 2302 (ε 8,275) (infl.), 2613 (ε 37,260), 3227 (ε 1,065)(infl.), 3400

(ε 2,330), 3558 (ε 4,810), 3734 (ε 7,450) and 3923 Å (ε 6,990). Anthracene (0·24 g.) was recovered on evaporation of the ether solution.

Reaction of Anthracene with Thiophenol. - A mixture of anthracene (1·8 g.), thiophenol (10 ml.) and benzene (25 ml.) was shaken under oxygen for 4·5 hr. during which time 219 ml. of oxygen were absorbed. A fine crystalline white solid (A) which precipitated from the reaction mixture was filtered off and washed with benzene. The benzene solution was concentrated to ca. 10 ml. under a reduced pressure of nitrogen, and anthraquinone (30 mg.) was removed by filtration. The solution was chromatographed, using hexane-benzene as elutant and the following fractions were obtained: (i) diphenyldisulphide, (ii) a strong-smelling liquid that was not identified, (iii) a pale yellow, flaky solid (B) (0·45 g.), m.p. 105-120°, and (iv) an impure yellow solid (C), m.p. 185-230°. Fractional recrystallisation of part of (B) from hexane gave anthracene (10 mg.), flat crystals (12 mg.), m.p. 94-145°, and white needles of 9,10-di(phenylthio)-9,10-dihydroanthracene, m.p. 117-127° (Found: C, 79·3; H, 5·3; S, 16·0. $C_{26}H_{20}S_2$ required C, 78·8; H, 5·1; S, 16·1%). Chromatographic separation of the rest of (B) gave anthracene (3 mg.) and white plates which melted partially at 110° and completely over the range of 160-185°

(hexane). The solid (C) was rechromatographed and crystallisation from benzene of the product yielded white plates (30 mg.), m.p. 244-245·5° (Found: C, 85·5; H, 5·4%).

Compound (A), believed to be a hydroperoxide, oxidised potassium iodide in acetic acid to iodine. It turned yellow and melted partially at 62°, decomposing to a black mass at 127°. When kept in a desiccator over phosphorus pentoxide and paraffin wax in the refrigerator, it was partly converted to a fluorescent, yellow compound, and the smell of thiophenol was detected. In a vacuum desiccator, it decomposed, liberating heat and forming a dark green coating on the walls of the dessicator. On exposure to air at room temperature it was relatively stable for a period that varied from a few minutes to 4-5 hr.

Addition of compound (A) to potassium iodide in acetic acid caused an immediate liberation of iodine and anthracene was precipitated. Chromatography on acetylated paper of the acetic acid solution showed only an anthracene spot.

Compound (A) (*ca.* 70 mg.) when added to mercaptoacetic acid (2 ml.) in benzene (10 ml.) dissolved slowly on shaking. The mixture was set aside overnight, then extracted with alkali and the aqueous layer was acidified.

The acid fraction, which was a yellow viscous material, was shown by paper chromatography to contain 2 (or 3?) fluorescent compounds. The benzene solution showed a purple (anthracene) and a bright yellow fluorescent spots on paper.

Compound (A) (0·78 g.) dissolved readily when added to a mixture of triphenylcarbinol (0·64 g.) and acetic acid containing a drop of concentrated sulphuric acid. The mixture was set aside overnight and filtration afforded anthracene (0·37 g.). The acid solution was poured on to ice and the resulting yellow oil solidified on treatment with hexane. Crystallisation of the impure material (0·17 g.) from benzene-hexane gave anthracene (10 mg.) and a brown-yellow solid that melted partially at 125° and completely at 145°. Paper chromatography indicated the presence of two fluorescent compounds.

To determine its equivalent weight compound (A) (15 mg.) was refluxed with potassium iodide and acetic acid (5 ml.) for 2-3 min. The condenser was washed out with acetic acid (3 ml.) and the mixture, after dilution with water, was titrated with sodium thiosulphate solution (0·01N), using starch as indicator. A blank titration was carried out. A value of 202 was obtained for the equivalent weight of compound (A).

(b) When anthracene (2.6 g.) was shaken with thiophenol (10 ml.) in benzene (30 ml.) and acetic acid (10 ml.) under oxygen, there was a rapid uptake of gas in the first 10 mins. (80 ml.) after which the absorption slowed down considerably. Addition of acetic acid and later of ferrous sulphate failed to catalyse the reaction. After 6 hr. unchanged anthracene (0.36 g.) was filtered off, and the benzene solution was washed with water and aqueous sodium hydroxide, dried and evaporated under a reduced pressure of nitrogen. Treatment of the residue with hot hexane (70 ml.) left a mixture of anthracene and anthraquinone (0.2 g.). Chromatographic separation of the hexane-soluble fraction yielded diphenyldisulphide and a yellow mixture (0.73 g.). Part of the latter (0.2 g.) on careful sublimation yielded more disulphide, anthracene, a yellow solid, m.p. 130°, and 9-(phenylthio)anthracene[135] (ca. 70 mg.), m.p. 100.5-102° (Found: C, 83.9; H, 4.9; S, 11.25. $C_{20}H_{14}S$ requires C, 83.9; H, 4.9; S, 11.2%). The yellow solid, m.p. 130°, was found to be a mixture of anthracene and its 9-phenylthio derivative which was very difficult to separate.

Reaction of Anthracene with 2,3-Dimercaptopropanol. - A mixture of anthracene (1 g.), 2,3-dimercaptopropanol (5 ml.) and benzene (30 ml.), when shaken in oxygen, did not react till the addition of a catalytic amount of ferrous

sulphate. After an uptake of 180 ml. of oxygen, the benzene solution was decanted from a yellow viscous oil (A) that had formed. The benzene solution was evaporated under a reduced pressure of nitrogen, the semi-solid residue was treated with methanol (10 ml.) and the resulting solid was crystallised from benzene. Anthracene (10 mg.) and anthraquinone (0·1 g.) were obtained. Attempts to solidify the oil (A) were unsuccessful. It was then acetylated by heating with acetic anhydride (7 ml.) on the water bath for 0·5 hr. The mixture was diluted with water, extracted with ether, and the combined ether extracts were washed with aqueous sodium carbonate and water, dried and evaporated. The residual yellow oil was taken up in benzene-hexane and chromatographed on alumina. Three fluorescent bands were observed on the column, but the only identifiable compounds were anthracene (20 mg.) and anthraquinone (50 mg.).

Reaction of Anthracene with Toluene-ω-thiol. - Anthracene (8 g.) when shaken with toluene-ω-thiol (25 g.) and benzene (80 ml.) in oxygen for 4 hr. did not react. Addition of an iodine crystal caused a rapid but momentary uptake of oxygen. Subsequent addition of pyridine (2 drops) initiated a slow steady absorption and further addition of iodine did not affect the rate of reaction. When the oxygen uptake became negligible (438 ml.

absorbed) anthracene (5·1 g.) was filtered off, and a further quantity (0·4 g.) of the hydrocarbon was obtained on evaporation of the solvent under a reduced pressure of nitrogen. Treatment of the liquid residue with methanol (60 ml.) gave dibenzyldisulphide (6 g.) and on cooling the methanol solution in the refrigerator, anthracene (50 mg.) and the disulphide (1·5 g.) were deposited. Further quantities of these compounds and anthraquinone (16 mg.) were isolated by chromatography of the residue after evaporation of the methanol solution under a reduced pressure of nitrogen. No other products were isolated.

(b) A mixture of anthracene (2·7 g.), toluene-ω-thiol (10 ml.) and benzene (30 ml.) was shaken together in oxygen. Reaction was very slow and addition of ferrous sulphate did not increase the rate. After 11 hr. (ca. 100 ml. oxygen absorbed) anthracene (1·3 g.) was removed by filtration, and the benzene solution was washed twice with water, dried and concentrated to ca. 10 ml. under a reduced pressure of nitrogen. The precipitated anthracene (0·25 g.) was filtered off and the filtrate, after dilution with an equal volume of hexane, was chromatographed. Anthracene (0·2 g.) and anthraquinone (90 mg.) were the only compounds identified.

Reaction of Anthracene with Methylmercapto-acetate. - Anthracene (0·89 g.) when shaken with methylmercaptoacetate (3 ml.) and benzene (25 ml.) under oxygen for 3 hr. did not react. Addition of pyridine (2 drops) had no effect. The reaction started 3 hr. after the addition of catalytic amounts of ferrous sulphate and cumene hydroperoxide. Shaking was continued for another 4 hr. after which the solution was concentrated to ca. 10 ml. under a reduced pressure of nitrogen, diluted with hexane and chromatographed. Elution with benzene-hexane yielded anthracene (0.3 g.) and anthraquinone (75 mg.). A dark oil and anthraquinone were obtained from a slow-moving, yellow fluorescent band that was eluted with ether.

Reaction of Anthracene with n-Butanethiol. - A mixture of anthracene (0·89 g.), n-butanethiol (5 ml.) and benzene (30 ml.) containing catalytic amounts of ferrous sulphate, cumene hydroperoxide and iodine was shaken in oxygen for 7·2 hr. (190 ml. oxygen absorbed). The reaction mixture, which had turned from a dark orange to a yellow colour, was filtered and anthracene (0.18 g.) was recovered. When the benzene solution was washed with water, dried, and evaporated under a reduced pressure of nitrogen, a further quantity of anthracene (0·5 g.) was obtained. Chromatography of the strong-smelling liquid yielded a trace of anthracene, a colourless liquid with an

unpleasant odour (probably di-n-butyldisulphide), and a yellow oil which was readily soluble in petroleum ether (b.p. 30-40°). The last substance did not solidify after being cooled in the refrigerator for a week. Paper chromatography of the oil showed a blue fluorescent spot.

The reaction of anthracene with n-butanethiol and oxygen in benzene was attempted in the presence of the following: (i) ferrous sulphate and cumene hydroperoxide, (ii) ferrous sulphate, cumene hydroperoxide and acetic acid, (iii) iodine, (iv) iodine and acetic acid, and (v) iodine, acetic acid and ferrous sulphate. There was no uptake of oxygen in every case.

Reaction of Anthracene with N-Acetylcysteine. - A mixture of anthracene (0·45 g.), N-acetylcysteine (3 g.) and tetrahydrofuran (20 ml.) was shaken in oxygen for 4 days (ca. 60 ml. oxygen absorbed). Filtration of the yellow reaction mixture afforded anthraquinone (70 mg.), a further quantity (0·32 g.) of which was obtained on concentration of the tetrahydrofuran solution under a reduced pressure of nitrogen. Benzene was added to the concentrate and the mixture was then extracted with aqueous sodium carbonate. Acidification of the alkaline extracts with hydrochloric acid gave a yellow solid (0·31 g.) which melted partially at 135° and completely over the range 160-190°. Repeated crystallisation of the product from tetra-

hydrofuran-hexane gave a yellow powder of S-(9-anthryl)-N-acetylcysteine, m.p. 208 -212° (decomp.) (Found: C, 65·4; H, 5·2; N, 4·0; S, 9·6. $C_{19}H_{17}O_3NS$ requires C, 67·2; H, 5·1; N, 4·1; S, 9·4%). λmax. 2215 (ε 13,650), 2492 (ε 42,600)(infl.), 2585 (ε 78,150), 3390 (ε 1,815), 3573 (ε 3,660), 3746 (ε 5,460) and 3934 Å (ε 5,190).

Attempted Reaction of Anthracene with Cysteine Hydrochloride. - (a) To a solution of cysteine hydrochloride (3 g.) in 10% sodium hydroxide solution (7 ml.) and water (13 ml.) were added anthracene (1 g.) and benzene (20 ml.). The mixture was shaken in oxygen for 3·5 hr. (84 ml. oxygen absorbed). 10% Sodium hydroxide solution was added to bring the mixture to pH10. Sufficient benzene was added to dissolve unchanged anthracene and the mixture was filtered. Cystine (2·5 g.) was collected. The aqueous layer was acidified to pH5 when more cystine (0·16 g.) precipitated from solution. Evaporation of the benzene solution yielded anthracene (0·94 g.).

(b) Anthracene (0·5 g.) failed to react when shaken with cysteine hydrochloride (1·5 g.) in alcohol under oxygen.

(c) Solutions of cysteine hydrochloride (7 g.) and of deoxycholic acid (5 g.) in sodium hydroxide were added to powdered anthracene (2 g.) in benzene (25 ml.), and the

mixture was shaken in oxygen. Uptake of gas was very slow, and on the third day a small amount of ferrous sulphate was added to catalyse the reaction. After 3 days (87 ml. oxygen absorbed) the aqueous phase was washed with ether and acidified. Deoxycholic acid (5 g.) was precipitated. Anthracene (2 g.) was recovered quantitatively by evaporation of the benzene solution.

Reaction of 9-Methylanthracene with Mercaptoacetic Acid. - A mixture of 9-methylanthracene (1 g.), mercaptoacetic acid (5 ml.) and benzene (25 ml.) was shaken in oxygen for 5 hr. (155 ml. oxygen absorbed) after which gas absorption became negligible. On shaking the reaction mixture with aqueous sodium carbonate, the sodium salt of 10-(carboxymethylthio)-9-methylanthracene was precipitated. The yellow solid was collected by filtration, taken up in warm water and acidified. The acid (0·3 g.) crystallised from benzene-hexane in yellow needles, m.p. 165-8° (Found: C, 72·3; H, 5·1; S, 11·2. $C_{17}H_{14}O_2S$ requires C, 72·3; H, 5·0; S, 11·4 %). λ max. 2180 (ε 16,170), 2555 (ε 55,500)(infl.), 2620 (ε 111,000), 3452 (ε 2,625), 3639 (ε 4,550), 3815 (ε 7,099) and 4035 Å (ε 5,499). Admixture with α-(carboxymethylthio)-9-methylanthracene, m.p. 166-167·5°, depressed the melting point (120-135°). Its infrared spectrum did not show an absorption band around 840 cm.$^{-1}$, confirming the absence of a meso hydrogen atom.

Acidification of the ether-washed alkaline extract gave a viscous oil, which after treatment with diazomethane, was chromatographed. It appeared to be strongly adsorbed on the alumina column and only traces of unidentifiable material were obtained. Crystallisation from benzene-hexane of the orange residue, on evaporation of the benzene solution, yielded yellow crystals (ca. 5 mg.), m.p. 253°.

Reaction of 9-Phenylanthracene with Mercaptoacetic Acid. - A mixture of 9-phenylanthracene (1·27 g.), mercaptoacetic acid (5 ml.) and benzene (20 ml.) was shaken in oxygen. Absorption of gas was initiated by the addition of catalytic amounts of ferrous sulphate and cumene hydroperoxide, and was virtually complete after 5 hr. (55 ml. oxygen absorbed). The reaction mixture was washed with water, extracted with aqueous sodium carbonate, and the alkaline extract after washing with ether was made acid. The precipitated solid was treated with hot hexane and (α-dimethylbenzylthio)acetic acid (0·5 g.) crystallised from the solution. Crystallisation of the hexane-insoluble fraction from benzene-hexane gave yellow crystals (0·7 g.) of 10-(carboxymethylthio)-9-phenylanthracene, m.p. 218-220°. (Found: C, 76·4; H, 4·8; S, 9·3. $C_{22}H_{16}O_2S$ requires C, 76·7; H, 4·7; S, 9·3%). λ max. 2617 (ε 117,100), 3614 (ε 7,350), 3817 (ε 11,610) and

4030 Å (ε 11,090).

Reaction of 9-Benzylanthracene with Mercaptoacetic Acid. - When 9-benzylanthracene (1·12 g., $\frac{1}{200}$ mole) was shaken with mercaptoacetic acid (4 ml.) in benzene (20 ml.) under oxygen, gas absorption occurred mainly in the first hour (115 ml.) and was complete in 5 hr. (total 133 ml.). After evaporation of the benzene solution, the residue (1·38 g.) was washed with water, dried and treated with warm ether. Crystallisation from benzene of the ether-insoluble fraction (0·72 g.) gave fine yellow needles of 10-(carboxymethylthio)-9-benzylanthracene, m.p. and mixed m.p. 214-5°. From the concentrated ether solution was obtained a yellow solid (0·17 g.) which crystallised from benzene to give pale yellow crystals, m.p. 197-205°, and fine yellow needles which melted partially at 145° and completely by 165°. The mixture could not be separated in spite of repeated crystallisations from benzane-hexane.

Reaction of 9,10-Dimethylanthracene with Mercaptoacetic Acid. - A mixture of 9,10-dimethylantracene (0·7 g.), mercaptoacetic acid (5 ml.) and benzene (30 ml.) was shaken in oxygen for 2 hr. (124 ml. oxygen absorbed). The yellow fluorescent solution was evaporated under a reduced pressure of nitrogen and the residue, which partly solidified on cooling in ice, was filtered. The solid,

when washed well with warm water and crystallised from benzene, yielded 9-(carboxymethylthiomethyl)-10-methylanthracene (0·6 g.), m.p. and mixed m.p. 197-199°, and a small amount of an unidentified substance (3 mg.), m.p. 120-125°. The liquid portion of the residue was diluted with water and the precipitated solid, after crystallisation from acetic acid, melted over the range 147-175°.

Attempted Reaction of 9,10-Diphenylanthracene with Mercaptoacetic Acid. - 9, 10-Diphenylanthracene (1 g.) did not react when shaken in oxygen with mercaptoacetic acid (5 ml.) in benzene (25 ml.). Following the addition of small amounts of ferrous sulphate and cumene hydroperoxide, there was a very slow absorption of oxygen (ca. 40 ml. in 2 days). The reaction mixture was washed with water and shaken with aqueous sodium carbonate. Acidification of the alkaline extract gave a yellow oil from which was isolated (αα-dimethylbenzylthio)acetic acid (0·7 g.), and a yellow material (1·3 g.) which formed oily drops on attempted crystallisation from benzene-hexane.

Reaction of 1,2-Benzanthracene with Thioacetic Acid. - When a solution of 1,2-benzanthracene (1 g.) and thioacetic acid (5 ml.) in benzene (15 ml.) was shaken in oxygen, there was a rapid reaction, 87 ml. of oxygen being absorbed in the first 11 mins. When the gas uptake became

slow, addition of a small amount of ferrous sulphate had no effect on the rate of oxygen absorption. After 2 hr. (total 104 ml.) the benzene solution was decanted from the inorganic material, and was evaporated under a reduced pressure of nitrogen. The solid (A) obtained on treatment of the dark oily residue with methanol (1 ml.) was washed with methanol (10 ml.) and collected by filtration. From the filtrate was isolated 10-acetylthio-1,2-benzanthracene (70 mg.) which crystallised from petroleum ether in pale yellow needles, m.p. and mixed m.p. 153-5°. The solid (A) (1·2 g.), m.p. 110-155°, on crystallisation from hexane gave a dark solid (B) (0·2 g.), m.p. 80-140°, and 9,10-di(acetylthio)-9,10-dihydro-1,2-benzanthracene (0·65 g.). The latter, after several crystallisations from methanol, melted at 189·5-191° (lit.[69] m.p. 193-4°). When dried over phosphorus pentoxide at 110° under reduced pressure, it turned pale yellow and melted at 187-189·5° (Found: C, 69·6; H, 4·9; S, 16·8. Calc. for $C_{22}H_{18}O_2S_2$: C, 69·8; H, 4·8; S, 16·9%). Repeated crystallisation of the solid (B) from hexane gave a salmon-coloured material, m.p. 130-160°, which was not identified.

Attempted Reaction of 1,2-5,6-Dibenzanthracene with Thioacetic Acid. - (a) When a mixture of 1,2-5,6-dibenzanthracene (0·5 g.), thioacetic acid (3 ml.) and benzene (20 ml.) was shaken in oxygen, there was no reaction. Addition of catalytic amounts of ferrous sulphate, cumene hydroperoxide and iodine initiated a slow absorption of oxygen which became very rapid on further addition of cumene hydroperoxide (0·5 ml.). After 2 days (200 ml. oxygen absorbed) 1,2-5,6-dibenzanthracene (0·39 g.) was removed by filtration. Evaporation of the filtrate under a reduced pressure of nitrogen gave more unchanged hydrocarbon (0·1 g.) and a dark red liquid. Chromatography of the liquid residue yielded sulphur (30 mg.) and a red liquid (probably dithiodiacetyl and iodine).

(b) 1,2-5,6-Dibenzanthracene (50 mg.) was dissolved in warm benzene (15 ml.), and thioacetic acid (2 ml.) was added to the cooled solution. When the mixture was shaken in oxygen there was no absorption of gas till the addition of anthracene (20 mg.) (3 ml. absorbed in 1·5 hr.). Chromatography of the reaction mixture on acetylated paper, using ethanol : benzene : water - 17 : 4 : 1 as the solvent system, showed the presence of anthracene, 9-(acetylthio)-anthracene and 1,2-5,6-dibenzanthracene. There was no fluorescent derivative of 1,2-5,6-dibenzanthracene.

(c) When a mixture of 1,2-5,6-dibenzanthracene

(0·1 g.), thioacetic acid (5 ml.) and benzene (50 ml.) was shaken in oxygen, 12 ml. of gas were absorbed in the first 20 min. after which absorption was negligible. The mixture was then refluxed under oxygen for 1·2 hr. Paper chromatography of the mixture showed that no fluorescent derivative of 1,2-5,6-dibenzanthracene was formed.

Attempted Reaction of Phenanthrene with Thio-Acid. - A solution of phenanthrene (0·45 g.), m.p. 97-99°,[154] and thioacetic acid (2 ml.) in benzene (4 ml.) did not react when shaken in oxygen. Pyridine had no effect. Addition of ferrous sulphate and cumene hydroperoxide initiated a very slow absorption of oxygen which became rapid on addition of iodine. Paper chromatography of the mixture before and after the introduction of iodine showed a strong phenanthrene spot and another very faint fluorescent spot. The benzene solution was evaporated under reduced pressure and the liquid residue, on cooling in ice, gave a white precipitate which dissolved again at room temperature.

(b) A similar mixture of reactants was shaken in oxygen in the presence of a catalytic amount of finely powdered sodium chloride. There was no absorption of oxygen. Paper chromatography of the solution showed the same spots as the previous reaction mixture.

Attempted Reaction of Pyrene with Thioacetic Acid. - A mixture of pyrene (0·5 g.), thioacetic acid (2 ml.) and benzene (10 ml.) did not react when shaken in oxygen. Addition of small amounts of ferrous sulphate, cumene hydroperoxide and iodine had no effect. The iodine colour persisted in the mixture and a strong odour of hydrogen sulphide was detected. Paper chromatography showed only one fluorescent spot (pyrene).

Attempted Reaction of Perylene with Thioacetic Acid. - A mixture of perylene (0·5 g.), m.p. 276-280°, (lit.[155] m.p. 273-274°), thioacetic acid (2 ml.) and benzene (25 ml.) was shaken in oxygen for 2 days without any absorption of gas. Following the addition of ferrous sulphate, cumene hydroperoxide and iodine there was an uptake of oxygen (25 ml.). Examination of the reaction mixture on acetylated paper revealed a green-yellow fluorescent spot besides that of perylene. The unchanged hydrocarbon (0·45 g.) was removed by filtration. Chromatographic separation on alumina of the concentrated filtrate yielded a little more of the hydrocarbon (40 mg.), sulphur (0·16 g.), and an orange liquid (ca. 50 mg.) which fluoresced green-yellow in benzene solution.

Reaction of 3,4-Benzpyrene with Thioacetic Acid. - The reaction of 3,4-benzpyrene (0·53 g.) with thioacetic acid (4 ml.) and oxygen in benzene (15 ml.) was initiated by the addition of small quantities of ferrous sulphate, cumene hydroperoxide and iodine. Oxygen (31 ml.) was absorbed in the first 0·5 hr. after which the gas upteke slowed down. After 24 hr. the benzene solution was evaporated under a reduced pressure of nitrogen. About a quarter of the dark residue was unsuccessfully chromatographed on a partially acetylated cellulose column[149], using ethanol : benzene : water - 17 : 4 : 1. Chromatography of the rest of the residue on acid-washed, deactivated alumina (5% water) yielded sulphur (80 mg.), 3,4-benzpyrene (0·33 g.) and 5-acetylthio-3,4-benzpyrene (30 mg.), m.p. and mixed m.p. 206-207.5°.

Reactions of Anthracene with Thiols, t-Butylhydroperoxide and Ferrocene

All experiments were performed under nitrogen.

(a) Mercaptoacetic Acid. - Ferrocene (50 mg.) and t-butylhydroperoxide (3 g.) were carefully added to a mixture of anthracene (2 g.), mercaptoacetic acid (8 ml.) and benzene (35 ml.). The mixture, which was swirled during the dropwise addition of the hydroperoxide, became warm and turned a green-blue colour that rapidly changed to yellow. After 15 min. filtration of the reaction mixture afforded a white powder (3·1 g.), m.p. 194-202°, which after crystallisation from NN-dimethylformamide melted partially at 195° and completely at 215-8°. Its melting-point was not depressed by admixture with 9,10-di(carboxymethylthio)-9,10-dihydroanthracene, m.p. 217-219°. The benzene solution was extracted with aqueous sodium hydroxide, and the alkaline solution was washed with ether and acidified. The oily residue (0·32 g.) which solidified on washing with warm water was treated with warm ether. From the ether solution was obtained yellow crystals (0·12 g.) which melted partially at 163° and completely at 170-192°. It is probably an impure form of 9-(carboxymethylthio)-anthracene. The ether-insoluble fraction (90 mg.) was a pale yellow solid, m.p. 178-198°.

(b) Thioacetic Acid. - When t-butylhydroperoxide (3 g.) was added in small portions to a mixture of anthracene (2 g.), thioacetic acid (10 g.), ferrocene (50 mg.) and benzene (30 ml.) there was no visible reaction. A solution of the hydroperoxide (0·3 g.) and ferrocene (5 mg.) in benzene was then added. The mixture turned a purple-red colour, and after 0·5 hr. it became warm and changed to a turbid yellow. The addition of ferrocene and the hydroperoxide was repeated, and after 2 hr. the yellow solution was evaporated under a reduced pressure of nitrogen. The green oily residue was chromatographically separated into sulphur (80 mg.), anthracene (0·16 g.), the two isomers of 9,10-di(acetylthio)-9,10-dihydroanthracene, m.p. 145-7° (0·18 g.) and m.p. 124-6° (0·1 g.), 9-(acetylthio)-anthracene (0·74 g.) and di-(9-anthryl)disulphide (0·3 g.).

(c) Thiobenzoic Acid. - A solution of ferrocene (50 mg.) and t-butylhydroperoxide (3 g.) in benzene (0·5 ml.) was added in small portions to a mixture of anthracene (2 g.), thiobenzoic acid (14 g.) and benzene (30 ml.). The mixture which became red-purple in colour was set aside for 3 days. Filtration of the yellow mixture afforded dibenzoyldisulphide (7·2 g.) and anthracene (0·1 g.). Evaporation of the filtrate under a reduced pressure of nitrogen yielded more of the disulphide (2·4 g.) and a green oily residue. Chromatography of the

oil yielded liquid fractions mixed with crystalline dibenzoyldisulphide. The liquids solidified on treatment with methanol, and after repeated crystallisations of the solid fractions from benzene-hexane, the following compounds were identified: (i) anthracene (50 mg.), (ii) the two isomers of 9,10-di(benzoylthio)-9,10-dihydroanthracene, m.p. 193-194° (0·25 g.) and m.p. 201-203° (0·22 g.), and (iii) 9-(benzoylthio)anthracene (50 mg.).

(d) n-Butanethiol. - A mixture of anthracene (2 g.), freshly-distilled n-butanethiol (10 g.) and benzene (30 ml.) to which a solution of ferrocene (50 mg.) and t-butylhydroperoxide (3 g.) in benzene was added, showed no signs of an immediate reaction. It was set aside for 3 days during which time the anthracene dissolved, the reaction mixture turned dark red in colour and a red powder (iron salt) was precipitated. The benzene solution was decanted from the inorganic material and was shaken with aqueous sodium hydroxide and water, dried, and evaporated under a reduced pressure of nitrogen. Anthracene (0·41 g.) was precipitated on treatment of the red oily residue with benzene-hexane. The solution on chromatography gave more unchanged anthracene (0·13 g.), anthraquinone (80 mg.), a brown oil that did not solidify on cooling in dry ice - ethanol, and a yellow liquid (A) that came through the column before anthracene. The

liquid (A) was rechromatographed twice, using hexane as elutant in the first separation and petroleum ether (b.p. 32-34°) in the second. 9,10-Di(n-butylthio)-anthracene (0·14 g.) which crystallised from the purest fraction was collected by filtration in the cold and washed with cold petroleum ether. After several crystallisations from the same solvent it was obtained as fluorescent green-yellow needles, m.p. 61-62° (Found: C, 74·6; H, 7·4; S, 77·7. $C_{22}H_{26}S_2$ requires C, 74·5; H, 7·4; S, 18·1%), λ max. 2223 (ε 10,845), 2441 (ε 21,000) (infl.), 2530 (ε 37,800)(infl.), 2635 (ε 77,400), 3516 (ε 2,317)(infl.), 3700 (ε 4,980), 3873 (ε 7,537) and 4091 Å (ε 8,070).

(e) Thiophenol. - t-Butylhydroperoxide (2 g.) was added to a mixture of anthracene (2 g.), thiophenol (10 g.), ferrocene (50 mg.) and benzene (30 ml.). After 0·5 hr. when there was no sign of a reaction, the mixture was warmed, and on addition of a further quantity of the hydroperoxide (1 g.), it became hot but there was still much undissolved anthracene. Further application of heat and addition of the hydroperoxide (0·5 g.) had no effect. The mixture was set aside overnight. Anthracene (1·24 g.) was recovered and the filtrate was washed with sodium hydroxide solution and water and dried. On concentrating the solution under a reduced pressure of nitrogen more

anthracene (0·26 g.) was obtained. Chromatography of the residue yielded diphenyldisulphide, anthracene (50 mg.), anthraquinone (25 mg.) and a green resinous material (ca. 50 mg.).

(f) N-Acetylcysteine. - Anthracene (0·5 g.) and N-acetylcysteine (2 g.), m.p. 105-110°, were taken up in warm tetrahydrofuran (15 ml.), and to the cooled solution was added a solution of ferrocene (10 mg.) and t-butylhydroperoxide (0·5 g.) in tetrahydrofuran (2 ml.) in four portions, the mixture being well swirled after each addition. The characteristic colour change was not observed and the reaction mixture remained cool. It was set aside overnight. When a drop of the solution was tested for Fe^{2+} with potassium ferricyanide, anthracene was precipitated. Consequently more ferrocene (5 mg.) and t-butylhydroperoxide were added to the reaction mixture which was then gently warmed on a water-bath for 0·5 hr. Filtration of the concentrated solution afforded anthracene (0·23 g.). The filtrate was diluted with benzene and shaken with water and aqueous sodium carbonate. Acidification of the alkaline extract yielded S-(9-anthryl)-N-acetylcysteine (55 mg.) which was obtained as a yellow powder, m.p. 209-211° (dec.), on crystallisation from tetrahydrofuran-hexane. Evaporation of the organic layer gave anthracene (024 g.).

Reactions of Some Polycyclic Aromatic Hydrocarbons with Mercaptoacetic Acid, t-Butylhydroperoxide and Ferrocene

All experiments were performed under nitrogen.

(a) 1,2-Benzanthracene. - When a solution of ferrocene (15 mg.) and t-butylhydroperoxide (1·4 g.) in benzene (1 ml.) was added to a mixture of 1,2-benzanthracene (0·7 g.), mercaptoacetic acid (2 ml.) and benzene (5 ml.), there was a vigorous reaction, and the mixture became warm, and changed from a deep green to a yellow colour. After 15 min. the solvent was removed under pressure, yielding 1,2-benzanthracene (0·15 g.) and a yellow viscous oil. The oil was taken up in benzene, and on shaking the solution with aqueous sodium hydroxide, an insoluble sodium salt was precipitated, and an oil separated. The oil solidified (0·33 g.), m.p. 174-8°, when washed with warm water. The solid was combined with the yellow product (0·24 g.), m.p. 170-4°, obtained on acidification of the alkaline extract and the sodium salt. The product was found to be insoluble in benzene, ethanol and ether, moderately soluble in acetone and readily in NN-dimethylformamide. Attempted crystallisation from aqueous dimethylformamide resulted in an impure powder; most of the product remained in solution. It was observed that the solution became a dark yellow colour

after 2 days. Crystallisation from acetone-hexane gave a white powder, m.p. 175-9°, which could not be further purified by crystallisation. When treated with diazomethane, it gave a resinous mass which was taken up in benzene. On cooling of the solution in the refrigerator for 3 days, a white solid (8 mg.) separated. It crystallised from benzene in white rods, m.p. 175·5-177° (Found: C, 42·25; H, 5.3%; M [Rast] 172). It contained nitrogen but no sulphur. It is believed to be an impurity in the ethereal solution of diazomethane used. Evaporation of the benzene solution after alkali extraction yielded 1,2-benzanthracene (0·1 g.).

(b) 1,2-5,6-Dibenzanthracene. - A benzene solution of ferrocene (15 mg.) and t-butylhydroperoxide (1·4 g.) was added to a slightly warm solution of 1,2-5,6-dibenzanthracene (0·7 g.), m.p. 260° (lit.[156], m.p. 269-270°) and mercaptoacetic acid (2 ml.) in benzene (150 ml.). The mixture turned green momentarily and then became turbid yellow. After 0·5 hr. filtration of the reaction mixture afforded unchanged hydrocarbon (0·4 g.) and dimercaptodiacetic acid. The latter was removed by washing with water. The benzene solution was then extracted with aqueous sodium hydroxide and on acidification, the aqueous solution became turbid but there was no precipitation of acidic products. A further quantity of 1,2-5,6-dibenzanthracene

(0·25 g.) was recovered by evaporation of the benzene solution.

(c) Phenanthrene. - When ferrocene (8 mg.) and t-butylhydroperoxide (0·7 g.) were added to a solution of phenanthrene (0·4 g.) and mercaptoacetic acid (1·8 ml.) in benzene (3 ml.), the mixture became hot and turned cloudy yellow. After 1 hr. the benzene solution was decanted from a heavy liquid (ca. 0·2 ml.). The latter was readily soluble in water and the aqueous solution gave a positive test for Fe^{2+} with potassium ferricyanide, and a negative test for Fe^{3+} with ammonium thiocyanate. Extraction of the organic solution with aqueous sodium hydroxide followed by acidification gave no acidic products. Phenanthrene (0·39 g.) was recovered quantitatively, by evaporation of the benzene solution.

(d) Pyrene. - On addition of ferrocene (8 mg.) and t-butylhydroperoxide (0·7 g.) to a solution of pyrene (0·4 g.), m.p. 149-151° [156,157] and mercaptoacetic acid (2 ml.) in benzene (5 ml.), the mixture underwent the normal colour change from dark green to turbid yellow, and became hot. On cooling of the mixture, a green-yellow solid (0·14 g.) was collected by filtration and, after washing with water, it melted partially at 200° and decomposed at 225°. Crystallisation from ethylacetate failed to yield a purer product. On shaking the benzene solution with

aqueous sodium hydroxide a pale yellow precipitate (0·17 g.), m.p. 130-135°, was formed which was collected, washed with water and dried. Crystallisation from ethanol was not satisfactory. Repeated crystallisation from benzene-hexane gave pale yellow fine crystals, m.p. 120-143°. Acidification of the alkaline extract yielded a yellow powder (50 mg.) which melted partially at 160° and completely at 185-195°. On evaporation of the benzene solution, pyrene (0·23 g.) was recovered.

(e) Perylene. - When a benzene solution of ferrocene (10 mg.) and t-butylhydroperoxide (1 g.) was added to perylene (0·46 g.), m.p. 273-277° (lit.[155], m.p. 273-274°) and mercaptoacetic acid (2 ml.) in benzene (50 ml.), the mixture became slightly warm and darkened to a red colour. It was set aside overnight. Unchanged perylene (0·32 g.) was removed, and the benzene solution was shaken with water, yielding an orange-red precipitate (50 mg.) which sintered at 185°, darkened at 215° and melted at 227°. Attempted crystallisation from benzene and from ethanol gave impure orange powders. No solid products were obtained by extracting the benzene solution with alkali and acidifying the extract. Evaporation of the dried benzene solution yielded a further quantity of perylene (70 mg.)

(f) (i) 3,4-Benzpyrene. - A benzene solution of ferrocene (8 mg.) and t-butylhydroperoxide (0·7 g.) was added to 3,4-benzpyrene (0·39 g.) and mercaptoacetic acid (1 ml.) in benzene (10 ml.), and the mixture was set aside for 1 hr. Filtration afforded a mixture of yellow and orange solids (0·31 g.), m.p. 165-195°, which was washed with warm water, dried and treated with hot benzene. 3,4-Benzpyrene (10 mg.) was recovered from the benzene solution. Crystallisation from acetone of the insoluble fraction gave a yellow powder (0·13 g.), m.p. 240-253° (dec.), which could not be further purified by crystallisation. Most of the material was lost in attempts of purification. The benzene filtrate was shaken with water and then with aqueous sodium hydroxide. Acidification of the alkaline extract yielded a dark precipitate (20 mg.). Attempts to purify the solid by crystallisation were not successful. Evaporation of the benzene solution gave 3,4-benzpyrene (70 mg.).

(ii) The experiment was repeated, using the same quantities of reactants. The mixture was set aside overnight. The solid (0·43 g.), m.p. 160-200°, was collected by filtration and treated with hot benzene (5 ml.) to remove unchanged 3,4-benzpyrene. The insoluble portion (0·34 g.) was treated with diazomethane in ether.

The resulting orange resinous mass, after removal of the solvent, did not solidify on treatment with petroleum ether (b.p. 32°). It was cooled in the refrigerator for 4 days during which time a white solid (A) (35 mg.) separated. The compound was identical with the unidentified material isolated from the reaction of 1,2-benzanthracene. Chromatography of the residual red-brown tar on alumina ("Woelm", neutral, activity 2) yielded a further quantity of compound (A) (50 mg.) and a dimethyl ester of a di(carboxymethylthio)-3,4-benzpyrene (62 mg.). The latter crystallised from ether in fine yellow needles, m.p. 113-115° (Found: C, 67·8; H, 4·4; S, 13·7. $C_{26}H_{20}O_4S_2$ requires C, 67·8; H, 4·4; S, 13·9%). Its ultraviolet absorption spectrum is of the 3,4-benzpyrene type, λmax. (in chloroform) 2612 (ε 35,520), 2725 (ε 42,080), 2870 (ε 23,280), 2996 (ε 33,120), 3111 (ε 37,200), 3530 (ε 5,000)(infl.), 3758 (ε 12,840), 3976 (ε 27,200) and 4190 Å (ε 34,520). On shaking the benzene solution with aqueous sodium hydroxide, a yellow precipitate was formed. Acidification of the alkaline extract and the precipitate gave a green solid (20 mg.), m.p. 97-120°.

Reactions of Some Polycyclic Aromatic Hydrocarbons with Thioacetic Acid, t-Butylhydroperoxide and Ferrocene

All experiments were performed under nitrogen.

(a) 1,2-Benzanthracene. - A benzene solution of ferrocene (20 mg.) and t-butylhydroperoxide (1·8 g.) was added to a solution of 1,2-benzanthracene (1 g.) and thioacetic acid (5·5 ml.) in benzene (15 ml.). The mixture was set aside for 3 hr. during which time it changed from red-brown to turbid yellow, and dark green droplets were formed. The benzene solution was decanted from the green droplets which were found to contain Fe^{2+} but no Fe^{3+}. The benzene solution was evaporated under a reduced pressure of nitrogen. Chromatography of the residue yielded sulphur (10 mg.), 1,2-benzanthracene (70 mg.), 10-acetylthio-1,2-benzanthracene (0·48 g.), m.p. 152-4°, and 9,10-di(acetylthio)-9,10-dihydro-1,2-benzanthracene (0·48 g.), m.p. 190-192°, mixed m.p. with an authentic sample (m.p. 187-187·5°) was 188·5-191°.

(b) Perylene. - When a benzene solution of ferrocene (15 mg.) and t-butylhydroperoxide (1·2 g.) was added to perylene (0 59 g.), m.p. 273-278.5°, and thioacetic acid (3 ml.) in benzene (80 ml.), the mixture immediately became red and then changed to yellow after ca. 5 min. The mixture was set aside overnight. Filtration afforded

a solid, which on treatment with hot benzene, left undissolved perylene (0·1 g.). From the benzene solution was obtained a yellow solid (0·15 g.), m.p. 200-233°, which was chromatographed on acid-washed, deactivated alumina (5% water). Perylene (80 mg.) was recovered, and elution with ether yielded a dark red liquid which fluoresced yellow-green in solution and appeared to be formed on the column. Evaporation of the benzene solution under a reduced pressure of nitrogen gave a residue (0·5 g.) which melted partially at 130° and completely at 160-167°. It was difficult to purify and after several crystallisations from benzene it was obtained as fine yellow crystals which sintered at 225° and melted at 232·5-237° to a red liquid. It analysed for a di(acetylthio)-perylene derivative (Found: C, 72·6; H, 4·2; S, 15·4. $C_{24}H_{16}O_2S_2$ requires C, 72·0; H, 4·0; S, 16·0%). The compound fluoresced bright green in solution and had a perylene-type absorption spectrum in the ultraviolet region. λmax. (in chloroform) 2555 (ε 25,120)(infl.), 2598 (ε 31,320), 3456 (ε 3,200)(infl.), 3800(ε 5,240)(infl.), 4094 (ε 15,200), 4330 (ε 30,080), and 4605 Å (ε 36,720).

(c) Pyrene. - When a benzene solution of ferrocene (10 mg.) and t-butylhydroperoxide (1 g.) was added to pyrene (0·5 g.) and thioacetic acid (3 ml.) in benzene (6 ml.), the mixture became slightly warm and changed from red to cloudy yellow. After 4 hr., the reaction mixture was evaporated under reduced pressure. The water-soluble fraction of the residue gave a positive test for Fe^{2+} and a negative test for Fe^{3+}. The semi-solid was washed with water and solidified on treatment with methanol (6 ml.). The yellow product (0·51 g.), which melted partially at 80° and completely by 160°, was chromatographed following unsuccessful attempts at crystallisation from methanol and benzene-hexane. The following compounds, in order of elution from the column, were collected: (i) sulphur (35 mg.), (ii) pyrene (0·13 g.), (iii) dipyrenyldisulphide (90 mg.), m.p. and mixed m.p. 220-222° (benzene), (iv) 3-(acetylthio)pyrene (0·14 g.), m.p. and mixed m.p. 136-137·5° (benzene-hexane), and (v) a yellow solid (8 mg.), m.p. 283-288° (dec.).

(d) 3,4-Benzpyrene. - When a solution of 3,4-benzpyrene (0·42 g.), m.p. 175-8°, and thioacetic acid (2·5 ml.) in benzene (10 ml.) was treated with ferrocene (10 mg.) and t-butylhydroperoxide (0·8 g.), it changed from red to yellow after 5 min. but no heat was liberated. After 4 hr. the mixture was evaporated under reduced

pressure and the residue was shaken with a little water. The aqueous extract was found to contain Fe^{2+} but no Fe^{3+}. The solid residue (0·57 g.), which was further washed with warm water and dried, crystallised from benzene in dark yellow prisms, which melted partially at 187° and completely at 205-207°. Admixture with 5-acetylthio-3,4-benzpyrene did not depress the melting-point. As it could not be satisfactorily purified by crystallisation the mixture was chromatographed on acid-washed alumina. It was observed that a red material was formed on the column as a fluorescent yellow band became fainter. Besides a trace of 3,4-benzpyrene (2 mg.), only di-5-(3,4-benzpyrenyl)disulphide (0·15 g.) was obtained. The disulphide crystallised from chlorobenzene in shiny red plates, m.p. 278·5-280° (dec.).[140] No 5-acetylthio-3,4-benzpyrene was recovered from the column. Chromatography of the combined benzene mother-liquors on acid-washed, deactivated alumina (5% water) yielded 5-acetylthio-3,4-benzpyrene (0·2 g.), di-5-(3,4-benzpyrenyl)disulphide (20 mg.), and a trace of an impure yellow material that fluoresced green-yellow on the column and purple in benzene solution.

Reaction of Butadiene with Thioacetic Acid, t-Butylhydroperoxide and Ferrocene. - Ferrocene (0·1 g.) was dissolved in benzene (200 ml.) through which butadiene had been bubbled for 0·5 hr. While a rapid flow of the gas through the well-stirred solution was maintained, thioacetic acid (20 ml.) in benzene (30 ml.) and t-butylhydroperoxide (13 g.) made up to 50 ml. with benzene, were introduced simultaneously at the same rate. The reaction mixture became warm. After the addition of the thiol and the hydroperoxide (1 hr.), the introduction of butadiene was continued for another 0·75 hr. A sample of the mixture when tested with potassium iodide in acetic acid was found not to contain any hydroperoxide. The benzene was removed by distillation under a reduced pressure of nitrogen, and the product was fractionally distilled to give: (i) a colourless liquid (9·5 g.), b.p. 30-33°/0·6 mm. (probably dithiodiacetyl), (ii) a colourless liquid (4 g.), b.p. 76-78°/0·7 mm. (M [Rast] 128; found: C, 40·2; H, 5·3; S, 35·8; butenyl thioacetate, $C_6H_{10}OS$ requires C, 55·4; H, 7·7; S, 24·6; 1-hydroxybutenyl thioacetate, $C_6H_{10}O_2S$ requires C, 49·3; H, 6·9; S, 21·9; butenylene bis-thioacetate, $C_8H_{12}O_2S_2$ requires C, 47·0; H, 5·9; S, 31·4%), C_3H_5OS requires C, 40.45; H, 5.6; S, 36.0%).

(iii) a yellow liquid (2·1 g.), b.p. 129-140°/0·7 mm. (Found: C, 53·5; H, 7·0; S, 25·8%), and (iv) the additive dimer (2·5 g.), b.p. 148-153°/0·3 mm. (M [Rast] 224; found: C, 56·5; H, 7·1; S, 24·0. $C_{12}H_{18}O_2S_2$ requires C, 55·8; H, 7·0; S, 24·8%). There was a non-volatile, tarry residue.

Reaction of Cumene Hydroperoxide with Mercaptoacetic Acid. - A solution of cumene hydroperoxide (1 g.) and mercaptoacetic acid (3 ml.) in benzene (10 ml.) was stored under nitrogen at room temperature for 2 weeks. The mixture was shaken with sodium carbonate solution, and the alkaline extract was washed with ether, acidified with hydrochloric acid and cooled. There was deposited (αα-dimethylbenzylthio)acetic acid (0·72 g.) which crystallised from hexane in needles, m.p. and mixed m.p. 69·5-70·5°.

When a similar mixture of reactants was shaken under oxygen for 5 days, no absorption of gas was observed. Treatment of the reaction mixture as above yielded the same acid derivative (0·34 g.).

Reaction of αα-Dimethylbenzyl Alcohol with Mercaptoacetic Acid. - An ethereal solution of freshly distilled acetophenone (18·5 g., 3/20 mole) was added dropwise to a well-stirred, warm solution of methylmagnesium iodide prepared from methyl iodide (43 g., 3/10 mole) and magnesium (7·5 g., 3/10 mole) in ether (150 ml.). cf. 158 The mixture was refluxed for 1 hr. and set aside overnight. The Grignard complex was hydrolysed with ammonium chloride solution containing ice, and the ethereal solution was washed with water, dried and the solvent was removed. The required alcohol (5·1 g., 24%) was collected as a colourless liquid, b.p. 82°/ 8·5 mm.

A mixture of the above alcohol (5 g.) and mercaptoacetic acid (10 ml.) in benzene (20 ml.) was stored under nitrogen for 6 days and then extracted twice with sodium carbonate solution. On acidification of the combined alkaline extracts, (αα-dimethylbenzylthio)acetic acid (0·11 g.) precipitated as an oil which solidified on cooling in the refrigerator for 1 week.

Reaction of 9-Hydroxymethylanthracene with Mercaptoacetic Acid. - Sodium borohydride (0·16 g.) was added to a suspension of 9-anthraldehyde (3 g.) in methanol (100 ml.) and the mixture was set aside overnight. The precipitate of 9-hydroxymethylanthracene (1·22 g.) was

collected by filtration, and the methanol solution was treated with acetic acid (2 ml.) to destroy the excess of hydride and evaporated at a reduced pressure of nitrogen. The residue of the hydroxy compound (1·73 g.), after washing with water, was combined with that obtained earlier and crystallised from benzene. It formed pale yellow needles, m.p. 158-160° (lit., m.p. 163°[159], 153°[160]).

When mercaptoacetic acid (2·5 ml.) was added to a suspension of 9-hydroxymethylanthracene (0·5 g.) in benzene (15 ml.), a clear solution was rapidly obtained. The mixture was set aside for 2 days, and evaporated under a reduced pressure of nitrogen. Addition of water to the liquid residue gave a yellow precipitate, m.p. 142-165°, which could not be purified by repeated crystallisation from benzene-hexane. It was taken up in ether, extracted with aqueous sodium carbonate, and 9-(carboxymethylthiomethyl)anthracene (0·12 g.) was precipitated on acidification of the alkaline extract. After several recrystallisations from benzene-hexane, it formed yellow shiny plates, m.p. 166-167·5° (Found: C, 72·1; H, 5·2; S, 11·2. $C_{17}H_{14}O_2S$ requires C, 72·3; H, 5·0; S, 11·4%). Its infrared absorption spectrum showed a band at 849 cm^{-1} indicative of a meso hydrogen atom. Evaporation of the ethereal solution yielded a yellow solid (0·31 g.), m.p.

135-200°.

Reaction of 9,10-Dihydro-9-hydroxyanthracene with Mercaptoacetic Acid. - (a) A suspension of lithium, aluminium hydride (0·2 g.) in ether was added dropwise to a well-stirred solution of anthrone (2 g.) in ether (150 ml.). Stirring was continued for 1·5 hr., and the mixture was then poured directly on to mercaptoacetic acid (10 ml.), kept overnight and treated with dilute sulphuric acid. The aqueous portion was discarded, the ethereal solution was shaken with sodium carbonate solution and the alkaline extract was washed with ether and acidified. The precipitate of 9-(carboxymethylthio)-9,10-dihydroanthracene (0·5 g.) crystallised from benzene-hexane in plates, m.p. 147-9° (Found: C, 71·0; H, 5·3; S, 12·4. $C_{16}H_{14}O_2S$ requires C, 71·1; H, 5·2; S, 11·9%). λmax. 2129 (ε 22,300), 2521 (ε 1,525), 2660 (ε 1,300) and 2751 Å (ε 1,065). Evaporation of the ether solution yielded anthracene (0·32 g.).

(b) Anthrone (4 g.) was reduced with lithium aluminium hydride (0·4 g.) in ether (200 ml.) as above. The mixture was treated with aqueous sodium hydroxide, and the ether layer was separated, washed with water, dried and evaporated under a reduced pressure of nitrogen. The residue of 9,10-dihydro-9-hydroxyanthracene (2 g.) crystallised from light petroleum in fine white needles,

m.p. 74° (lit.[161] m.p. 76°).

A solution of the foregoing hydroxy compound (1 g.) and mercaptoacetic acid (10 ml.) in ether (25 ml.) was stored under nitrogen for 28 hr. Anthracene (80 mg.) precipitated from the mixture and a further quantity (60 mg.) of the hydrocarbon was deposited on shaking the ether solution with aqueous sodium carbonate. The alkaline extracts, after washing with ether, were acidified and a precipitate (0·22 g.) of 9-(carboxymethylthio)-9,10-dihydroanthracene was obtained. Evaporation of the ether solution yielded anthracene (0·21 g.).

Reaction of 9,9-Dibenzyl-9,10-dihydro-10-hydroxyanthracene with Mercaptoacetic Acid. - 10,10-Dibenzylanthrone (4 g.), prepared by the benzylation of anthrone,[162] and lithium aluminium hydride (0·15 g.) in ether (30 ml.) were refluxed for 1·8 hr., and the excess of hydride was then destroyed by the addition of ethylacetate and water. When the mixture was shaken with dilute sulphuric acid, a precipitate of 9,9-dibenzyl-9,10-dihydro-10-hydroxyanthracene was formed and a further quantity was obtained by evaporation of the ethereal solution. The hydroxy compound crystallised from benzene in prisms (2·8 g.; 70%), m.p. 174-177°.

When a solution of the foregoing hydroxyanthracene (1·3 g.) and mercaptoacetic acid (5 ml.) in benzene (17 ml.)

was kept under nitrogen for 3 days, a crystalline precipitate (0·25 g.) of (9,9-dibenzyl-9,10-dihydro-10-anthrylthio) acetic acid was slowly formed. After filtration, the benzene solution was washed three times with aqueous sodium carbonate and the extracts were acidified. The precipitated acid (0·63 g.) was collected, combined with that previously obtained, and crystallised from benzene in white needles, m.p. 208-210°. (Found: C, 80·3; H, 5·9; S, 6·9. $C_{30}H_{26}O_2S$ requires C, 80·0; H, 5·8; S, 7·1%). It showed no distinct maxima in its ultraviolet absorption spectrum.

Reaction of 9,10-Dihydro-9,10-dihydroxy-9,10-dimethylanthracene with Mercaptoacetic Acid. - An ethereal solution of methylmagnesium iodide prepared from methyl iodide (72 g.), magnesium (12 g.) and ether (250 ml.) was added dropwise to a well-stirred suspension of anthraquinone (52 g.) in ether. After the addition stirring was continued for 3 hr., and the mixture was carefully added to 20% ammonium chloride solution containing ice. A pale yellow solid (63 g.) was obtained. Treatment of part of the solid (20 g.) with warm ethylacetate (200 ml.) left behind anthraquinone; evaporation of the solution gave the required diol, which crystallised from benzene in shiny plates (3·5 g.), m.p. 178°.[141,161] A second preparation of the diol carried out under identical

conditions yielded a sample which melted partially at 180° and completely at 202° (probably a mixture of the *cis* and *trans* isomers).

A mixture of the above diol (0·86 g.), m.p. 180-202°, mercaptoacetic acid (6 ml.) and benzene (25 ml.) was kept under nitrogen for 2 days. A precipitate of white prisms (0·23 g.), m.p. 178-180°, that had slowly formed was collected and carefully washed with benzene. Analytical data indicated the compound to be *9,10-di(carboxymethylthio)-9,10-dihydro-9,10-dimethylanthracene* (Found: C, 61·3; H, 5·4; S, 16·7. $C_{20}H_{20}O_4S_2$ requires C, 61·8; H, 5·2; S, 16·5%). The benzene solution was shaken with aqueous sodium carbonate, and the yellow precipitate was collected. However, it could not be purified by crystallisation. The solid (0·33 g.) obtained on acidification of the alkaline extract was crystallised from acetic acid. It melted partially at 160° and completely at 185°. Chromatography of the residue (0·15 g.), after evaporation of the benzene solution, gave a yellow solid that decomposed at *ca.* 155°.

The above dicarboxylic acid (20 mg.), when warmed in acetic acid containing hydrochloric acid (2 drops), readily dissolved and the solution turned yellow. When the mixture was diluted with water and cooled, *9-(carboxymethylthiomethyl)-10-methylanthracene* (12 mg.) was

obtained. It crystallised from benzene in yellow needles, m.p. 197-9° (Found: C, 72·9; H, 5·6; S, 10·9. $C_{18}H_{16}O_2S$ requires C, 72·9; H, 5·4; S, 10·8%). λ max. 2190 (ε 14,800), 2630 (ε 57,500), 3246 (ε 775)(infl.), 3433 (ε 2,240), 3620 (ε 5,240) 3793 (ε 8,626) and 4017 Å (ε 8,050).

Reaction of 9,10-Dihydro-9,10-dihydroxy-9,10-dimethylantracene with Thiophenol. - A mixture of the above diol (0·5 g.), m.p. 183-193°, and thiophenol (2 ml.) in benzene was stored under nitrogen for 6 days. Filtration of the reaction mixture afforded a crystalline solid (0·39 g.) which, after being washed with dilute sodium hydroxide solution and water was crystallised from benzene-hexane. The fine crystals of 9,10-dihydro-9,10-dimethyl-9,10-di(phenylthio)anthracene turned yellow at 175° and melted at 184-190° (Found: C, 79·3; H, 6·0; S, 14·9. $C_{28}H_{24}S_2$ requires C, 79·2; H, 5·7; S, 15·1%). It was observed that a solution of the compound turned yellow on heating. Chromatography of the concentrated benzene solution gave a further quantity of the compound (50 mg.), α-phenylthio-9,10-dimethylanthracene (ca. 20 mg.) which crystallised from hexane in flat yellow needles, m.p. 141-142·5° (Found: C, 83·2; H, 5·9; S, 10·1. $C_{22}H_{18}S$ requires C, 84·0; H, 5·8; S, 10·2%), and an unidentified yellow solid (10 mg.), m.p. 210-215° (benzene-hexane).

Addition of concentrated hydrochloric acid (4 drops) to a warm suspension of the foregoing di(phenylthio) compound (0·1 g.) in acetic acid (2·5 ml.) caused the mixture to turn yellow immediately. Heating was continued for 10 min. during which time the addition compound dissolved and a strong smell of thiophenol was detected. The mixture was diluted with water, cooled in ice, filtered and the precipitated solid (75 mg.) was washed with sodium hydroxide solution and water. Crystallisation from hexane yielded yellow needles of α-phenylthio-9,10-dimethylanthracene.

α-Phenylthio-9,10-dimethylanthracene (50 mg.) was oxidised with chromic acid in hot acetic acid (15 ml.) containing sulphuric acid (2 drops) and water (1 ml.) On cooling, anthraquinone (15 mg.) was precipitated.

Attempted Reaction of 9,10-Dihydro-9,10-dihydroxy-9,10-diphenyl-anthracene with Mercaptoacetic Acid. - A mixture of the above diphenylanthracene diol (0·5 g.) and mercaptoacetic acid (4 ml.) in benzene (25 ml.) was stored under nitrogen for 24 hr. On shaking the reaction mixture with aqueous sodium carbonate a thick emulsion formed and was broken by centrifugation. The ether-washed aqueous layer, when acidified, became turbid but no solid product was precipitated. Extraction of the acid solution with ether, followed by evaporation of the solvent

yielded a strong-smelling liquid which was probably a mixture of mercaptoacetic acid and its disulphide. The dried benzene solution was evaporated, and crystallisation of the residue from benzene–hexane afforded 9,10-diphenylanthracene (0·35 g.) and a small quantity of anthraquinone (4 mg.).

The Action of Acid on 9,10-di(phenylthio)-9,10-dihydroanthracene. - A suspension of the above compound (0·11 g.), m.p. 115–123°, in acetic acid (5 ml.) containing a drop of concentrated hydrochloric acid was boiled for 1 min., diluted with water and cooled in ice. The precipitated solid (60 mg.), after being washed with warm water, crystallised from hexane in yellow plates of 9-(phenylthio)anthracene, m.p. 100·5–102°.

Reaction of Anthracene with Dibenzoyldisulphide in Sunlight. - Dibenzoyldisulphide (2·74 g., $\frac{1}{100}$ mole) was added to a solution of anthracene (0·89 g., $\frac{1}{200}$ mole) in oxygen-free benzene, and the mixture was kept in sunlight under nitrogen for 10 hr. As the disulphide gradually dissolved the solution turned brown, and dianthracene precipitated from solution. The mixture, after filtration, was evaporated under a reduced pressure of nitrogen. Dibenzoyldisulphide (1·65 g.) and anthracene (25 mg.) were recovered by crystallisation of the residue from benzene. Chromatography of the mother-liquor yielded

sulphur (5 mg.), anthracene (0·11 g.), anthraquinone (20 mg.) and 9-(benzoylthio)anthracene (0·1 g.).

Oxidation of Mercaptoacetic Acid in Aqueous Solution.

The pH of the solutions was measured with B.D.H. indicator paper.

(a) pH 5·8. - A solution of mercaptoacetic acid (5 ml.) in 10% sodium hydroxide solution (22·6 ml.) and water (20 ml.) was shaken in oxygen. The rate of oxygen absorption was measured at 10-20 min. intervals with a gas burette. The results obtained are shown in Table 3.1.

Table 3.1

Oxidation of Mercaptoacetic Acid in Aqueous Solution (pH 5·8)

Time (min.)	Oxygen Absorbed (ml.)
10	0·2
30	0·4
48	0·7
62	1·0
78	1·2
97	1·7
108	1·9

(b) pH 7·3. - Two mixtures, each containing mercaptoacetic acid (5 ml.), 10% sodium hydroxide solution (23·8 ml.) and water (20 ml.), were shaken in oxygen simultaneously. In run (I) the addition of hydrogen peroxide after 50 min. caused a slight increase in the rate of oxygen uptake. In run (II) the addition of iodine (0·5 g.) and potassium iodide (0·8 g.) in water (2 ml.) after 170 min. did not have any catalytic effect; instead a slight fall in the rate of oxidation was observed. The results are indicated in Table 3.2.

Table 3.2

Oxidation of Mercaptoacetic Acid in Aqueous Solution (pH 7·3)

Time (min.)	Oxygen Absorbed (ml.) (I)	(II)	Time (min.)	Oxygen Absorbed (ml.) (I)	(II)
10	4·8		130	72·7	87·1
25	11·6	16	140	76·5	92·3
40	19·6	26·7	150	80·4	97·5
50	24·5	33·1	160	82·7	101·9
	Added H_2O_2		170	86·5	105·5
65	35·5	42·4			Added I_2+KI
75	43·0	48·7	185	90·4	106·4
85	50·1	56·3	200	93·9	109·0
94	55·3	62·3	215	96·4	110·0
105	63·3	74·9	230	98·7	113·2
115	67·0	79·5			

(c) pH 9.7. - The oxidation of mercaptoacetic acid (5 ml.) by molecular oxygen was studied in 10% sodium hydroxide (30 ml.) and water (20 ml.). The measurements of gas absorption made at 10-15 min. intervals are shown in Table 3.3.

Table 3.3

Oxidation of Mercaptoacetic Acid in Aqueous Solution (pH 9.7)

Time (min.)	Oxygen Absorbed (ml.)	Time (min.)	Oxygen Absorbed (ml.)
9	3.6	134	34.0
14	5.8	149	41
24	8.8	164	43.8
34	11.3	174	45.8
45	13.0	191	48.4
55	15.8	208	51.8
64	18.2	222	54.6
74	20.0	239	58.0
84	21.4	256	61.8
94	23.0	268	64.5
104	24.5		
114	26.8		
124	30.4		

The rates of oxygen absorption in (a), (b) and (c) are presented graphically in Fig. 2.4.

Kinetics of the Reactions of Anthracene and Derivatives with Mercaptoacetic Acid and Oxygen. - The rates of reaction of anthracene, 9-methyl- and 9-phenylanthracenes with mercaptoacetic acid and oxygen were compared by measuring the rate of oxygen uptake in each case. The reaction mixture of the hydrocarbon ($\frac{1}{200}$ mole), mercaptoacetic acid (5 ml.) and benzene (20 ml.) was shaken in oxygen, and the volume of gas absorbed was measured at short intervals. Duplicate experiments using anthracene were carried out concurrently, and though the rates of oxygen absorption differed slightly, they were much faster than the rates observed with the substituted anthracenes. The reaction of 9-phenylanthracene was repeated, the second run being carried out in the presence of catalytic quantities of ferrous sulphate (0·5 g.) and cumene hydroperoxide (0·5 ml.). The results are shown in Tables 3.4 and 3.5 and also graphically in Fig. 2.2.

Table 3.4

Reaction of Anthracene with Mercaptoacetic Acid and Oxygen

I		II	
Time (min.)	Oxygen Absorbed (ml.)	Time (min.)	Oxygen Absorbed (ml.)
3	35·4	3	44·0
8	42·4	8	53·5
14	44·6	14	54·6
19	56·7	19	63·4
21	78·9	24	80·7
25	122·9	29	94·6
29	131·9	31	99·0
34	143·9	34	102·4
39	152·4	39	108·6
44	158·0	44	112·4
49	161·7	49	115·0
54	163·9	54	116·8
59	165·9	59	118·0
64	167·9	64	119·2
76	170·7	69	121·5
86	173·0	81	123·4
96	174·2	91	124·0
108	175·9	101	125·4
118	177·0	113	126·0
129	177·7	123	126·6
139	178·3	134	127·0

Table 3.5

Reactions of 9-Methyl- and 9-Phenyl-anthracenes with Mercaptoacetic Acid and Oxygen

9-Methylanthracene		9-Phenylanthracene			
		I		II	
Time (min.)	Oxygen Absorbed (ml.)	Time (min.)	Oxygen Absorbed (ml.)	Time (min.)	Oxygen Absorbed (ml.)
15	40·6	50	0	50	0·6
30	52·2	89	2·5	Added $FeSO_4$ + $PhCMe_2O_2H$	
45	56·0	101	5·3	70	7·3
65	60·8	111	10·4	90	14·9
85	64·0	121	14·8	100	18·5
105	67·6	131	19·4	115	24·1
125	70·2	137	21·4	210	41·6
145	74·2	317	33·6	250	43·3
225	98·0			265	44·9
260	106·6			285	53·7
295	114·6			295	54·3
340	122·8			310	55·1
385	130·6				

Preparation of Reference Compounds

(αα-Dimethylbenzylthio)acetic Acid. - Concentrated sulphuric acid (5 ml.) was added dropwise with stirring to α-methylstyrene (5 g.) and mercaptoacetic acid (10 ml.) in acetic acid (25 ml.). The warm solution was set aside for 2 hr., then diluted with water and extracted with ether. The ethereal solution was washed with water and extracted with aqueous potassium hydroxide. The oily precipitate of the required acid, which was formed on acidification of the alkaline extract, solidified on cooling. It crystallised from hexane in rods (7·2 g., 80%), m.p. 70-71° (Found: C, 63·1; H, 6·8; S, 15·5. Calc. for $C_{11}H_{14}O_2S$: C, 62·9; H, 6·7; S, 15·2%).

Di-(9-anthryl)disulphide. - Anthracene was converted into 9-mercaptoanthracene via the dithio-chloride.[132] The crude thiol was dissolved in aqueous sodium hydroxide and oxidised to the disulphide with iodine. Di-(9-anthryl)disulphide crystallised from benzene in orange prisms, m.p. 218-221° (Found: C, 80·2; H, 4·4; S, 15·6. Calc. for $C_{28}H_{18}S_2$: C, 80·4; H, 4·3; S, 15·3%).

9-(Acetylthio)anthracene. - Zinc dust (3·5 g.) was added in small portions to a warm mixture of di-(9-anthryl)disulphide (1·7 g.), sodium acetate (1 g.) and acetic anhydride (15 ml.). The mixture was boiled for

5 min., filtered whilst hot and diluted with water. The precipitate of 9-(acetylthio)anthracene was collected, washed with water and crystallised from hexane, forming yellow prisms (1·1 g., 54%), m.p. 146-147° (Found: C, 76·4; H, 4·9; S, 12·7. $C_{16}H_{12}OS$ requires C, 76·2; H, 4·8; S, 12·7%), λmax. 2487 (ε 82,680(infl.), 2564 (ε 144,250), 3222 (ε 1,250)(infl.), 3400 (ε 2,800), 3557 (ε 5,395), 3739 (ε 7,597) and 3939 Å (ε 6,200).

10-(Carboxymethylthio)-9-benzylanthracene. - 9-Benzylanthracene (0·5 g.) was treated with sulphur monochloride (1 ml.), and the resulting dithiochloride was washed with petroleum ether and refluxed with hydrated sodium sulphide (4 g.) for 6 hr. The sodium salt of the 10-mercapto compound, which was precipitated by treatment of the reduction mixture with saturated sodium chloride solution, was rapidly collected by filtration. Chloroacetic acid was added to a suspension of the salt in sodium hydroxide solution, and the mixture was warmed on a water-bath for 0·5 hr., cooled and acidified. Crystallisation from benzene of the precipitated solid yielded yellow fine needles of 10-(carboxymethylthio)-9-benzylanthracene (0·13 g.), m.p. 214-215° (Found: C, 76·5; H, 5·3; S, 8·8. $C_{23}H_{18}O_2S$ requires C, 77·0; H, 5·1; S, 8·9%), λmax. 2205 (ε 20,200), 2635 (ε 104,700), 3466 (ε 2,800), 3645 (ε 6,250), 3820 (ε 10,950) and

4045 Å (ε 10,700), and a yellow crystalline compound (50 mg.), m.p. 228-230·5°.

10-Acetylthio-1,2-Benzanthracene. - 1,2-Benzanthracene (1 g.) was converted to 10-mercapto-1,2-benzanthracene via the dithiochloride.[140] The mercaptan was collected as its sodium salt, which was then taken up in aqueous sodium hydroxide and oxidised to the disulphide with iodine. The yellow precipitate (1 g.) was collected, washed with water and dried. To a hot solution of the disulphide and sodium acetate (0·7 g.) in acetic anhydride (20 ml.) was added zinc dust. The mixture after boiling for 10 min. was filtered, diluted with water and cooled in the refrigerator. 10-Acetylthio-1,2-benzanthracene (0·33 g.) crystallised from petroleum ether in pale yellow needles, m.p. 153-154° (Found: C, 79·9; H, 4·7; S, 10·4. $C_{20}H_{14}OS$ requires C, 79·4; H, 4·7; S, 10·6%), λmax. 2229 (ε 31,650), 2313 (ε 27,000), 2481 (ε 15,300)(infl.), 2563 (ε 16,575)(infl.), 2639 (ε 17,400)(infl.), 2741 (ε 23,550), 2836 (ε 42,000), 2950 (ε 50,400), 3290 (ε 3,000) (infl.), 3430 (ε 4,950), 3600 (ε 6,060), 3729 (ε 4,560), and 3909 Å (ε 2,370).

Di-(3-pyrenyl)disulphide. - A well-stirred mixture of 3-thiocyanopyrene (2 g.), m.p. 115-8° (lit.[163] m.p. 117-8°), hydrated sodium sulphide (5 g.) and ethanol (25 ml.) was boiled under reflux (nitrogen) for 1·5 hr. The residue, after evaporation of the solution, was taken up in aqueous sodium hydroxide solution, and 3-mercapto-pyrene was precipitated on acidification. The mercaptan was collected and heated with iodine in aqueous sodium hydroxide on a boiling water-bath for 1 hr. On cooling the oxidation product (1·77 g.) was collected by filtration, washed with water, dried and chromatographed on acid-washed, deactivated alumina. The major fraction was crystallised from benzene, yielding yellow crystalline di-(3-pyrenyl)disulphide, m.p. 220-222° (Found: C, 81·3; H, 4·25; S, 13·4. $C_{32}H_{18}S_2$ requires C, 82·3; H, 3·9; S, 13·7%).

3-(Acetylthio)pyrene. - Zinc dust was added in small portions to a warm mixture of di(3-pyrenyl)disulphide (1 g.), sodium acetate (2 g.) and acetic anhydride (25 ml.). The mixture was boiled under reflux for 2·5 hr., concentrated to ca. 2 ml. and then was diluted with water. On cooling crude 3-(acetylthio)pyrene (1·1 g.) precipitated from solution. It crystallised from benzene in pale yellow needles, m.p. 136-137·5° (Found: C, 77·6; H, 4·4;

S, 11·7. $C_{18}H_{12}OS$ requires C, 78·25; H, 4·4; S, 11·6%), λmax. 2365 (ε 35,200), 2445 (ε 52,300), 2592 (ε 12,550), 2697 (ε 22,000), 2797 (ε 35,900), 3059 (ε 6,250)(infl.), 3190 (ε 13,100), 3345 (ε 26,400), 3490 (ε 37,200), 3686 (ε 1,660) and 3765 Å (ε 2,260).

5-Acetylthio-3,4-benzpyrene. - 5-Thiocyano-3,4-benzpyrene (0·32 g.), m.p. 225-228°, prepared by the action of thiocyanogen on 3,4-benzpyrene (0·5 g.)[137] was reduced with hydrated sodium sulphide (1 g.) in ethanol (15 ml.). The mixture was refluxed for 1 hr., cooled, filtered and the mercaptan was precipitated on acidification of the filtrate. It was collected by filtration and oxidised to the disulphide (0·22 g.), m.p. 235°, with iodine in sodium hydroxide solution; the yellow precipitate was collected, washed with water and dried. The disulphide, after an unsatisfactory crystallisation from toluene-chloro-benzene, was suspended in warm acetic anhydride (30 ml.). Sodium acetate and zinc dust were added and the mixture was boiled for 0·5 hr. The red-brown solution (ca. 5 ml.) was decanted from the inorganic residue and was diluted with water. After vigorous shaking of the mixture a precipitate (0·18 g.) was formed, which was washed well with water and dried. 5-Acetylthio-3,4-benzpyrene, after chromatography on deactivated alumina, crystallised from benzene in orange prisms, m.p. 206-207·5°.

(Found: C, 81·0; H, 4·6; S, 9·5. $C_{22}H_{14}OS$ requires C, 81·0; H, 4·3; S, 9·8%), λmax. (in chloroform) 2614 (ε 41,500), 2709 (ε 48,750), 2841 (ε 32,070), 2951 (ε 48,100), 3077 (ε 59,400), 3490 (ε 13,400)(infl.), 3690 (ε 20,600), 3858 (ε 31,800), 4056 (ε 32,000) and 4109 (ε 33,600).

Attempted Preparation of 9-(n-Butylthio)anthracene. - A well-stirred suspension of (9-anthryl)dithiochloride (4 g.) in benzene (50 ml.) was treated slowly with lithium aluminium hydride (1·5 g.) in ether (40 ml.). The excess of hydride was decomposed with ethyl acetate, and after the addition of 10% sulphuric acid, the organic layer was separated off and extracted with 3% potassium hydroxide solution. Acidification of the alkaline extract with acetic acid yielded 9-mercaptoanthracene which was heated with n-butyl-bromide (2 ml.) in aqueous sodium hydroxide (50 ml.) on a steam-bath for 1 hr. On cooling, di-(9-anthryl)disulphide (0·1 g.) and an oil precipitated. The oil when chromatographed on alumina showed several fluorescent bands. The major fraction was an oil which was readily soluble in petroleum ether (b.p. 30-40°), and had a strong blue fluorescence. Attempts to crystallise the oil were not successful.

Preparation of Starting Materials

9-Benzylanthracene. cf.[164] – Anthrone (20 g., $\frac{1}{10}$ mole) was added in portions to a well-stirred, slightly warm solution of benzylmagnesium chloride prepared from benzyl chloride (38 g., $\frac{3}{10}$ mole), magnesium (7·5 g., $\frac{3}{10}$ mole) and ether. The mixture was set aside overnight, and hydrolysed with dilute hydrochloric acid. Evaporation of the ether solution yielded 9-benzyl-9,10-dihydro-10-hydroxyanthracene which, when kept overnight in a vacuum desiccator, was converted to 9-benzylanthracene (17·8 g.). It was purified by chromatography on alumina; it crystallised from hexane in colourless needles, m.p. 133° (lit.,[165] m.p. 133°).

9,10-Dimethylanthracene. cf.[161] – Anthrone (20 g., $\frac{1}{10}$ mole) was added to sodium (2·4 g., $\frac{1}{10}$ mole) partly dissolved in ethanol (120 ml.), and the mixture was refluxed with methyl iodide (28 g., $\frac{1}{5}$ mole) for 4 hr. On cooling, a purple powder (2·3 g.) and crude 10-methoxy-9-methylanthracene (4 g.) precipitated from solution. The methyl ether was converted to the anthrone by refluxing with acetic acid (30 ml.) and concentrated hydrochloric acid (2·5 ml.) for 2 hr.[162] The mixture was set aside overnight. The precipitated solid (1·9 g.), m.p. 170-190° was collected by filtration, and the filtrate was

poured into ice-water (200 ml.). The brown oil which separated from solution was extracted with ether. The alcohol solution was treated with acetic acid and extracted with benzene. The oily methyl anthrone obtained on evaporation of the benzene extract was taken up in ether and combined with the portion prepared from the methyl ether. The combined solutions were washed with aqueous sodium carbonate and water, dried and added to a well-stirred ethereal solution of methylmagnesium iodide prepared from methyl iodide (18·5 ml.) and magnesium (8·5 g.). The mixture was refluxed for 2 hr., set aside overnight and hydrolysed with ice-cold ammonium chloride solution. Evaporation of the dried ether solution yielded a black residue which partly dissolved on treatment with hot benzene. Chromatography of the soluble fraction gave 9,10-dimethylanthracene (0·7 g.), m.p. 177-179° (lit.[161] m.p. 180·5 -181°), and a green fluorescent solid, m.p. 156-160° which was the major product.

9,10-Diphenylanthracene. - Crude 9,10-dihydro-9,10-dihydroxy-9,10-diphenylanthracene (68 g.), m.p. 175-210°, was obtained on hydrolysis of the lithium compound prepared from anthraquinone (50 g.) and phenyllithium made from bromobenzene (104 g.) and lithium (8·4 g.).[40] The diol (20 g.) was converted to 9,10-diphenylanthracene

(15 g., 83%), m.p. 254-255.5°, by refluxing with potassium iodide in acetic acid (600 ml.) for 0.5 hr.[166]

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SUMMARY

The reactions of thiols and oxygen with a number of polycyclic aromatic hydrocarbons, including the potent carcinogen 3,4-benzpyrene, have been investigated. Anthracene reacted readily with thioacetic acid and oxygen, yielding 9-(acetylthio)anthracene and 9,10-di(acetylthio)-9,10-dihydroanthracene. Similar products were obtained with 1,2-benzanthracene. 3,4-Benzpyrene was found to react, though less readily, to give the substituted derivative. Phenanthrene, pyrene, perylene and 1,2-5,6-dibenzanthracene were not appreciably affected. The rate of reaction varied with the thiol used; acidic thiols gave the highest yields of products. It is proposed that the reaction proceeds by free radical chain addition, yielding a hydroperoxide which, in the presence of acids, is reduced to an alcohol, and so converted into the final products by the usual ionic mechanism.

The reactions of the same hydrocarbons with thiyl radicals generated by the action of t-butylhydroperoxide and ferrocene on thiols gave similar products as the reactions with thiols and oxygen. They were more rapid and gave higher yields of products than the

earlier reactions. Under these conditions pyrene and perylene were converted to substitution products but phenanthrene and 1,2-5,6-dibenzanthracene were again not attacked. 3,4-Benzpyrene gave better yields of substituted derivatives. A free radical mechanism is also suggested for these reactions.

The results support the current theory that the interactions of thiyl radicals with carcinogenic hydrocarbons are significant in the production of cancer by these compounds.

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