Meso-Heterocyclic Analogues of 9,10-Dihydroanthracene. XIV. Some Indoles and Carbazoles Derived from Phenoxathiin (1).

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2-Aminophenoxathiin undergoes easy condensation with different ω-bromoketones to give 2-aroylmethylaminophenoxathiins. These compounds give pyrrolo[2,3-*b*]phenoxathiins by the Möhlau-Bischler cyclisation. Some carbazolo[2,1-*b*]phenoxathiins were also synthesised from 7-oxo-7,8,9,10-tetrahydrobenzo[*b*]phenoxathiin.

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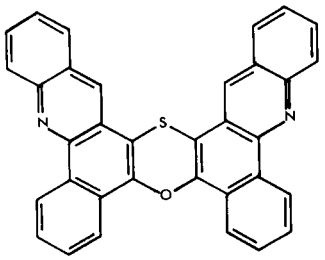
We have recently reported the synthesis of benzo[*b*]- and dibenzo[*b,i*]phenoxathiins (2). It seems worthwhile to extend the investigation to some other polynuclear molecules, particularly to heterocyclic nitrogen analogues of the ring system of phenoxathiin. So far, only the diquinolo[3,2-*a*:3′,2′-*j*]dibenzo[*c,h*]phenoxathiin **1** have been described (3). Recently, Martin, *et al.*, (4,5) have studies 1-aza phenoxathiin analogues **2**.



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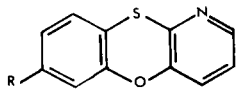
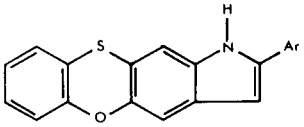


2

We have synthesised a number of indoles and carbazoles of general formula **3** and **4** derived from phenoxathiin.



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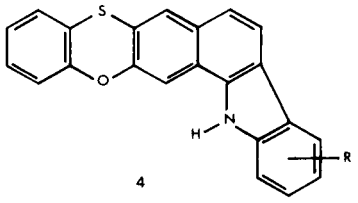

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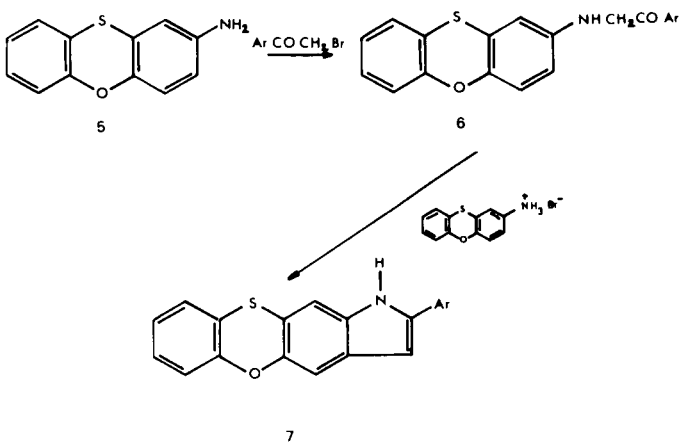
These compounds are of potential biological interest since we have recently demonstrated (6) that similar compounds derived from dibenzo-*p*-dioxine show considerable effect on the P450 hydroxylase system in animals and which may eventually provide interesting information on their activity in cancer chemotherapy.

Pyrrolo[2,3-*b*]phenoxathiins.

These systems, which essentially consists of an indole moiety in their molecules are most conveniently obtained by the Mohlau-Bischler reaction (7-10). This reaction as we have previously reported (6,11,12) involves the cyclisation of an ω-arylaminoketone by heating it in the presence of an appropriate salt of the arylamine. The aminoketone



5 6 7

SCHEME 1

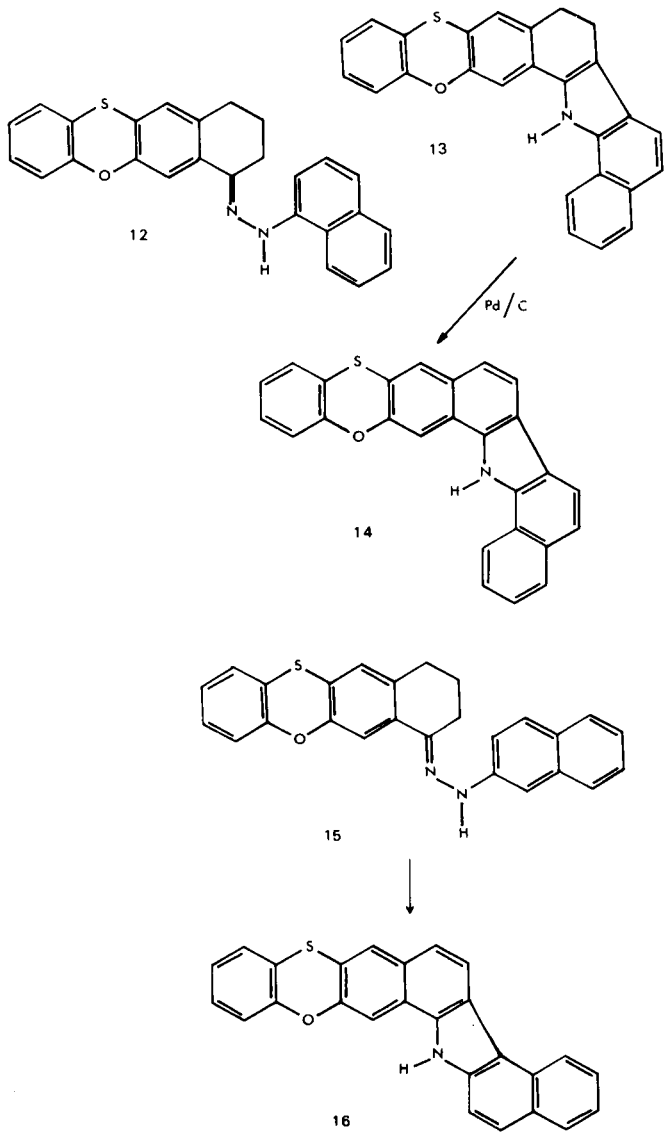
in its turn is obtained by reacting the ω-bromoketone with the arylamine, as shown in Scheme 1.

Carbazolo[2,1-*b*]phenoxathiins.

7-Oxo-7,8,9,10-tetrahydrobenzo[*b*]phenoxathiin **8** (2) undergoes condensation quite easily with phenylhydrazines as well as its methyl homologues. The resulting hydrazones **9** give indoles by the Fischer-Borsche method (14-16), by the action of acetic acid saturated with hydrogen chloride gas. The 5,6-dihydrocarbazolo[2,1-*b*]-phenoxathiins **10** could be easily aromatized to the corresponding carbazolophenoxathiins by heating with 10% palladium on charcoal (Scheme 2).

In a similar way the reaction of α- and β-naphtyl hydrazines with the cyclic ketone **8**, followed by cyclisation and dehydrogenation led to the bis-angular carbazoles **14** and **16**.

2-Aminophenoxathiin was obtained in excellent yield by hydrolysis of the acetamido derivative obtained by the Beckmann Rearrangement from 2-acetylphenoxathiin. The aroylmethylaminophenoxathiins **6** were obtained from the known ω-bromoketones. The physical properties of the aminoketones are represented in Table 1 and those of the indoles are recorded in Table 2. The use of



silicone oil (technical grade) as a medium for the reactions allows a better control of heating and also minimises the decomposition of the cyclised product, which is usually associated with this reaction.

Infra red spectra (potassium bromide pellets) of these compounds show all the vibrations characteristic of phenoxathiin and indole. The strong absorption around 1370-1360 cm^{-1} characteristic of the C-O-C moiety noted in our compounds can also be found in phenoxathiin, dibenzo-*p*-dioxine and diphenyloxide. The rather intense band around 840-830 cm^{-1} can be attributed to the C-H vibration of the positions 4 and 11, which is typically observed (13) when the *ortho*-position is occupied. This provides evidence for the linear structure and proves conclusively that the cyclisation took place on the 3-position. The NH band appears characteristically at exactly 3470 cm^{-1}.

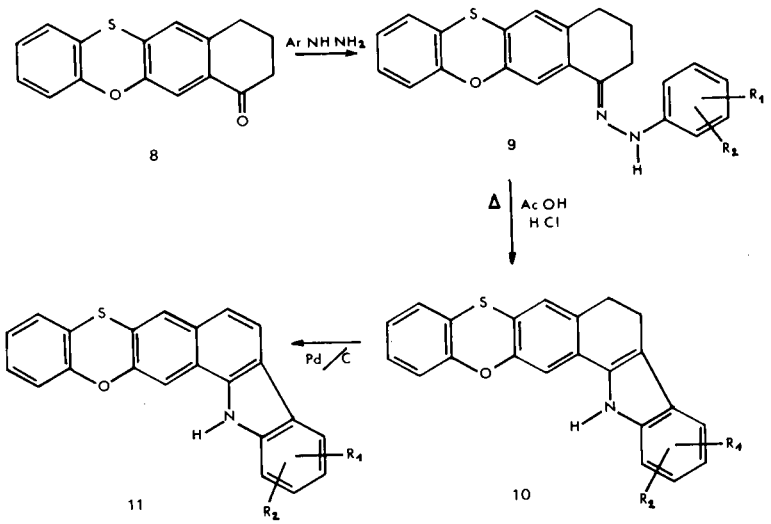
These compounds are interesting from the point of view of chemical carcinogenesis, since these are analogues of dibenzocarbazoles which are well known for their carcinogenic properties (17-19).

EXPERIMENTAL

2-Aminophenoxathiin (5).

Phosphorus pentachloride (9.7 g., 0.046 mole) was added in small portions to 9.7 g. (0.038 mole) of the oxime of 2-acetylphenoxathiin in 150 ml. of benzene. After stirring for 10 minutes, the reaction mixture was poured into ice, neutralized with sodium carbonate and extracted with benzene. The organic layer after drying was evaporated under vacuum to give the acetamide in the form of an oil.

The amide was hydrolyzed by boiling under reflux with concentrated hydrochloric acid (100 ml.). The precipitated hydrochloride was filtered, washed and the free amine was liberated by treating it with ammonia, m.p. 95-96° (cyclohexane) (lit. (20) m.p. 93-95°; yield 48%).



SCHEME 2

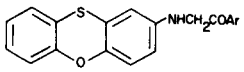
2-Aroylmethylaminophenoxathiins (**6**).

The preceeding amine was refluxed with an equimolar amount of the corresponding ω-bromoketone in ethanol with a catalytic amount of sodium bicarbonate. The precipitate formed on cooling was filtered, washed thoroughly with warm water and crystallized from benzene. The details of these compounds are recorded in Table 1.

Pyrrolo[2,3-*b*]phenoxathiins (**7**).

A mixture of 0.01 mole of the aroylmethylaminophenoxathiin, 0.02 mole of 2-aminophenoxathiin and 0.005 mole of the hydrobromide of the latter was heated at a temperature of 230-240° for 10 minutes in silicone oil. After cooling, petroleum ether was added to the reaction mixture, the precipitated solid was separated by filtration and recrystallized from chlorobenzene. The details of these compounds are recorded in Table 2.

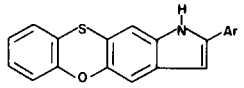
Table 1



2-Aroylmethylaminophenoxathiins

Ar	Yield %	M.p. °C	Formula	Analysis Calculated % C	H	N	Found % C	H	N
phenyl	95	191	$C_{20}H_{15}NO_2S$	72.00	4.54	4.20	71.85	4.50	4.05
p-tolyl	50	190	$C_{21}H_{17}NO_2S$	72.61	4.93	4.03	72.46	4.89	3.98
p-methoxyphenyl	65	188	$C_{21}H_{17}NO_3S$	69.41	4.72	3.86	69.23	4.64	3.78
p-xenyl	45	198	$C_{26}H_{19}NO_2S$	76.26	4.68	3.42	76.31	4.72	3.35
p-chlorophenyl	70	216	$C_{20}H_{14}ClNO_2S$	65.30	3.84	3.81	65.26	3.79	3.72

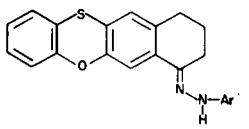
Table 2



Pyrrolo[2,3-*b*]phenoxathiins

Ar	Yield %	M.p. °C	Formula	Analysis Calculated % C	H	N	Found % C	H	N
phenyl	70	298	$C_{20}H_{13}NOS$	76.17	4.16	4.44	76.16	4.13	4.52
p-tolyl	65	297	$C_{21}H_{15}NOS$	76.57	4.59	4.25	76.67	4.57	4.18
p-methoxyphenyl	65	295	$C_{21}H_{15}NO_2S$	73.03	4.38	4.06	72.81	4.35	3.90
p-xenyl	50	357	$C_{26}H_{17}NOS$	79.78	4.38	3.58	79.43	4.42	3.45
p-chlorophenyl	70	320	$C_{20}H_{12}ClNOS$	68.68	3.47	4.00	68.76	3.56	3.87

Table 3

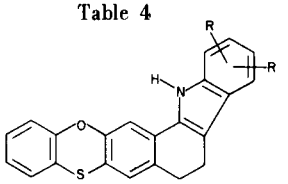


Hydrazones of 7-Oxo-7,8,9,10-tetrahydrobenzo[*b*]phenoxathiins

Ar	Formula	M.p. °C	Analysis Calculated % C	H	N	Found % C	H	N
phenyl	$C_{22}H_{18}N_2OS$	200	73.7	5.7	7.8	73.5	5.5	7.6
xylyl-2,3	$C_{24}H_{22}N_2OS$	212	74.6	5.7	7.2	74.4	5.7	7.0
xylyl-2,4	$C_{24}H_{22}N_2OS$	206	74.6	5.7	7.2	74.6	5.8	7.0
xylyl-2,5	$C_{24}H_{22}N_2OS$	172	74.6	5.7	7.2	74.5	5.8	7.0
xylyl-3,4 (a)								
α-naphtyl	$C_{26}H_{18}N_2OS$	203	76.8	4.47	6.9	76.4	4.8	4.0
β-naphtyl	$C_{26}H_{18}N_2OS$	190	76.8	4.47	6.9	76.6	4.8	6.0

(a) Has not been isolated, but has been used in the crude state.

Table 4

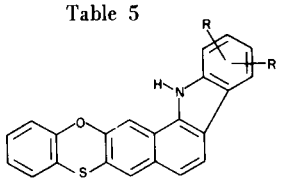


5,6-Dihydrocarbazolo[2,1-*b*]phenoxathiins (a)

R	Formula	M.p. °C	Analyses Calculated % C	H	N	Found % C	H	N
H	$C_{22}H_{15}NOS$	224	77.4	4.4	4.1	77.4	4.4	3.9
Me (1,2)	$C_{24}H_{19}NOS$	212	78.1	5.2	3.8	77.9	5.2	3.6
Me (2,4) (b)	$C_{24}H_{19}NOS$							
Me (2,5) (b)	$C_{24}H_{19}NOS$							
M3 (3,4)	$C_{24}H_{19}NOS$	264	78.1	5.2	3.8	78.0	5.3	3.5

(a) Numbers in parentheses indicate positions occupied by R. (b) Not isolated.

Table 5



Carbazolo[2,1-*b*]phenoxathhins (a)

R	Formula	M.p. °C	Analysis Calculated % C	H	N	Found % C	H	N
H	$C_{22}H_{13}NOS$	268	77.7	3.9	4.1	77.6	3.9	3.1
Me (1,2)	$C_{24}H_{17}NOS$	252	78.4	4.7	3.8	78.5	4.8	3.5
Me (1,3)	$C_{24}H_{17}NOS$	212	78.4	4.7	3.8	78.4	4.8	3.5
Me (1,4)	$C_{24}H_{17}NOS$	216	78.4	4.7	3.8	78.6	4.6	3.6
Me (3,4)	$C_{24}H_{17}NOS$	258	78.4	4.7	3.8	78.4	4.8	3.6

(a) Numbers in parentheses indicate positions occupied by R.

Carbazolo[2,1-*b*]phenoxathiins (**11**).

The hydrazones **9** were prepared by refluxing an alcoholic solution of the cyclic ketone (0.01 mole) and the hydrochloride of the hydrazine (0.02 mole) with sodium acetate (0.02 mole) and water (1 ml.). The solid separated on cooling was crystallized from acetic acid (Table 3).

The dihydrocarbazoles **10** were obtained by boiling these hydrazones in acetic acid saturated with hydrogen chloride for two minutes and were crystallized from ethanol (Table 4).

The title compounds **11** were obtained by sublimating a mixture of these dihydrocompounds and 10% palladium on charcoal under reduced pressure and were crystallized from benzene (Table 5).

Benzo[*i*]phenoxathiino[3,2-*a*]carbazole (**14**).

The dehydrogenation of the crude cyclized product **13** with palladium on charcoal in the usual way gave the title compound which was crystallized from benzene as off-white microcrystals, m.p. 258°.

Anal. Calcd. for $C_{26}H_{15}NOS$: C, 80.2; H, 3.9; N, 3.6. Found: C, 80.3; H, 4.0; N, 3.5.

Benzo[*g*]phenoxathiino[3,2-*a*]carbazole (**16**).

These compounds were obtained in a similar manner from the hydrazone **15** and crystallized from benzene as colourless microcrystals, m.p. 280°.

Anal. Calcd. for $C_{26}H_{15}NOS$: C, 80.2; H, 3.9; N, 3.6. Found: C, 80.1; H, 4.0; N, 3.4.

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