465. *Oxygen Heterocycles. Part V.* Phenoxathiin Derivatives.*

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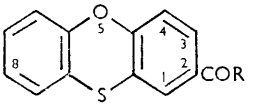
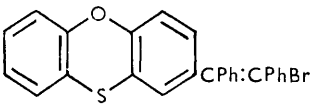
The chemistry of phenoxathiin has been investigated, particularly in respect of Friedel–Crafts reactions and the use of the resulting ketones for the synthesis of, *e.g.*, a large number of phenoxathiin compounds bearing a nitrogen-heterocyclic substituent.

Although phenoxathiin has long been known, its reactivity and derivatives have rarely been investigated. A separate study of the biological properties of polycyclic sulphur compounds required the preparation of various derivatives of phenoxathiin,† especially compounds with nitrogen-heterocyclic substituents. The most accessible intermediates for such syntheses appeared to be acylphenoxathiins, whose preparation was therefore investigated. Suter, McKenzie, and Maxwell [1] obtained 2-acetylphenoxathiin from acetyl chloride and aluminium chloride in carbon disulphide; this procedure has now been extended to higher aliphatic acid chlorides and to phenylacetyl chlorides, giving in all cases 2-acylphenoxathiins (I) in good yield. Wolff–Kishner–Huang-Minlon reduction [2] was then a convenient route to 2-alkyl- and 2-arylalkyl-phenoxathiins, which could be reacylated to give monoketones whose constitution was not established but which were probably 2 : 8-derivatives, in view of Tomita's results on the bischloroacetylation of

(I) 



(II)

phenoxathiin.[3] Acid anhydrides could also be used for acylation, *e.g.*, succinic and phthalic anhydride. From 2-benzoylphenoxathiin and benzylmagnesium chloride, a trisubstituted ethylene was obtained, which underwent bromination to the œstrogenic α-bromo-β-2-phenoxathiinylstilbene (II). 2-Acetamidophenoxathiin, which may be compared with the carcinogenic 2-acetamidofluorene and 2-anthramide, was readily prepared by Beckmann

* Part IV, Bisagni, Buu-Hoï, and Royer, *J.*, 1955, 3693.

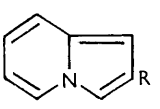
† The numbering adopted for this compound is that given in Patterson and Capell's "The Ring Index," Reinhold Publ. Corp., New York, 1940.

[1] Suter, McKenzie, and Maxwell, *J. Amer. Chem. Soc.*, 1936, **58**, 717.

[2] Huang-Minlon, *ibid.*, 1946, **68**, 2487.

[3] Tomita, *J. Pharm. Soc. Japan*, 1938, **58**, 510.

rearrangement of the oxime of 2-acetylphenoxathiin; hydrolysis yielded the tuberculostatic 2-aminophenoxathiin, which Irie [4] prepared previously by another method.



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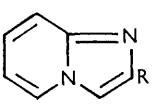

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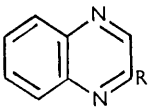

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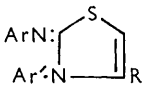

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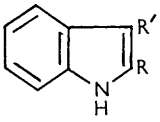
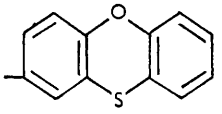


(VII)



For the synthesis of derivatives of nitrogen heterocycles, the ω-bromo-ketone obtained by bromination of 2-acetylphenoxathiin proved convenient; condensation with 2-picoline, 2 : 4-lutidine, and 5-ethyl-2-methylpyridine, and Tschitschibabin cyclisation of the corresponding quaternary derivatives,[5] gave 2-2′-pyrrocolinylphenoxathiin (III) and its 7-methyl and 6-ethyl homologues. A similar condensation with 2-aminopyridine [6] led to 2-2′-phenoxathiinyl-1 : 3*a*-diazaindene (IV); prolonged heating of 2-ω-bromoacetylphenoxathiin with *o*-phenylenediamine [7] caused condensation and dehydrogenation to give 2 : 2′-quinoxalinylphenoxathiin (V). In the thiazole group, the von Walther reaction [8] of 2-ω-bromoacetylphenoxathiin with *NN*′-diarylthioureas gave a series of 3-aryl-2-arylimino-4-2′-phenoxathiinyl-Δ^4-thiazolines (VI). Other nitrogen-heterocyclic derivatives were prepared directly from 2-acylphenoxathiins: the indole (VII; R′ = H and Me) by indolisation of the phenylhydrazones of 2-acetyl- and 2-propionyl-phenoxathiin; and from these two ketones with isatin, 2-2′-phenoxathiinylcinchoninic acid and its 6-methyl homologue; thermal decarboxylation of these acids yielded the quinolines.

Experimental

Friedel–Crafts Acylation of Phenoxathiin.—To a solution of phenoxathiin (0·1 mole) and acetyl chloride (0·12 mole) in dry carbon disulphide (100 c.c.), finely powdered aluminium chloride (0·1 mole) was added in small portions, and the mixture refluxed for 3—4 hr.; after decomposition with water, the product was taken up in chloroform, and the chloroform layer washed with dilute aqueous sodium hydroxide, then with water, and dried (Na_2SO_4). The residue from evaporation of the solvent gave 2-acetylphenoxathiin (82%), b. p. 258—260°/20 mm., m. p. 113° (from ethanol) (Suter *et al.*[1] recorded a 58% yield and m. p. 111°). This procedure was used in all the other acylations,

2-*Acetamidophenoxathiin.*—2-*Acetylphenoxathiin oxime* formed needles, m. p. 153°, from ethanol (Found: C, 65·5; H, 4·2. $C_{14}H_{11}O_2NS$ requires C, 65·4; H, 4·3%). To an ice-cooled suspension of this oxime (25 g.) in dry ether (500 c.c.), finely powdered phosphorus pentachloride (20 g.) was added in small portions with shaking, and the mixture stirred for a further 10 min. After addition of crushed ice, the ethereal layer was washed repeatedly with water, then dried (Na_2SO_4), and the solvent distilled off; the residue, on recrystallisation from benzene, gave needles of 2-*acetamidophenoxathiin* (20 g.), m. p. 159° (Found: C, 65·2; H, 4·1. $C_{14}H_{11}O_2NS$ requires C, 65·4; H, 4·3%). Hydrolysis with hydrochloric acid, and treatment of 2-aminophenoxathi-in hydrochloride with aqueous sodium hydroxide, afforded the base, b. p. 250—260°/20 mm.

2-p-*Chlorocinnamoylphenoxathiin.*—A warm solution of 2-acetylphenoxathiin (1 g.) and *p*-chlorobenzaldehyde (0·5 g.) in ethanol was treated with a few drops of 20% aqueous sodium

[4] Irie, *J. Fac. Sci. Hokkaïdo Univ.*, 1951, **3/4**, 70.
[5] Tschitschibabin, *Ber.*, 1927, **60**, 1607.
[6] *Idem*, *Ber.*, 1925, **58**, 1704; 1926, **59**, 2048; Buu-Hoï, Jacquignon, Xuong, and Lavit, *J. Org. Chem.*, 1954, **19**, 1370.
[7] Hinsberg, *Annalen*, 1896, **292**, 246; Buu-Hoï and Khôi, *Bull. Soc. chim. France*, 1950, **17**, 753.
[8] Von Walther, *J. prakt. Chem.*, 1907, **75**, 188.

hydroxide and kept for 1 hr. at room temperature; the precipitated *ketone* obtained on dilution with water crystallised as bright yellow needles, m. p. 195°, from benzene (Found: C, 69·4; H, 3·8. $C_{21}H_{13}O_2SCl$ requires C, 69·1; H, 3·6%).

2-p-*Methoxycinnamoylphenoxathiin*, prepared from *p*-anisaldehyde, formed pale yellow needles, m. p. 122° (Found: C, 73·6; H, 4·5. $C_{22}H_{16}O_3S$ requires C, 73·3; H, 4·4%).

2-2′-*Indolylphenoxathiin* (VII; R′ = H).—A mixture of 2-acetylphenoxathiin (3 g.) and phenylhydrazine (3 g.) was heated at 150° until evolution of water ceased; fused zinc chloride (7 g.) was added to the crude phenylhydrazone, and the mixture heated at 180—195° for 5 min. After cooling, the product was treated with aqueous acetic acid and benzene, the benzene solution washed with water and dried (Na_2SO_4), and the solvent distilled off. The residual *product* crystallised as needles (3·5 g.), m. p. 202°, from benzene (Found: C, 75·9; H, 4·1. $C_{20}H_{13}ONS$ requires C, 76·2; H, 4·1%).

2-2′-*Phenoxathiinylcinchoninic Acid.*—A solution of 2-acetylphenoxathiin (2·5 g.), isatin (1·5 g.), and potassium hydroxide (1·7 g.) in ethanol (15 c.c.) was refluxed for 24 hr.; after dilution with water and ether-extraction, the aqueous layer was acidified with acetic acid, and the precipitated *acid* recrystallised from ethanol, giving yellowish prisms (80% yield), m. p. 255° (Found: C, 71·0; H, 3·3. $C_{22}H_{13}O_3NS$ requires C, 71·2; H, 3·5%). The potassium salt was sparingly soluble in water.

Heating the acid above its m. p. and distillation of the residue *in vacuo*, gave 2-2′-*quinolylphenoxathiin*, needles, m. p. 132° (from ethanol) (Found: C, 77·0; H, 3·7. $C_{21}H_{13}ONS$ requires C, 77·1; H, 4·0%), giving a picrate, leaflets, m. p. 223°, from ethanol.

2-*Propionylphenoxathiin* (I; R = Et).—Obtained in 78% yield, this *ketone*, b. p. 275—277°/25 mm., formed yellowish prisms, m. p. 71—72°, from ethanol (Found: C, 70·5; H, 4·4. $C_{15}H_{12}O_2S$ requires C, 70·3; H, 4·7%).

2-(3-*Methyl*-2-*indolyl*)*phenoxathiin* (VII; R = Me).—Prepared as for the lower homologue, this *indole* formed needles, m. p. 151°, from benzene (Found: C, 76·3; H, 4·5. $C_{21}H_{15}ONS$ requires C, 76·6; H, 4·6%).

3-*Methyl*-2-2′-*phenoxathiinyl*)*cinchoninic Acid.*—This *acid* formed yellow needles, m. p. 316°, from ethanol (Found: C, 71·5; H, 4·1. $C_{23}H_{15}O_3NS$ requires C, 71·7; H, 3·9%).

2-n-*Butyrylphenoxathiin* (I; R = Pr).—Prepared in 89% yield, this *ketone*, b. p. 276—278°/21 mm., formed needles, m. p. 64°, from ethanol (Found: C, 71·1; H, 5·1. $C_{16}H_{14}O_2S$ requires C, 71·1; H, 5·2%). 2-n-*Valerylphenoxathiin* (77% yield), b. p. 279—280°/20 mm., crystallised as needles, m. p. 63—64°, from ethanol (Found: C, 71·8; H, 5·5. $C_{17}H_{16}O_2S$ requires C, 71·8; H, 5·6%) and gave a *semicarbazone*, prisms, m. p. 177° (from ethanol) (Found: N, 12·0. $C_{18}H_{19}O_2N_3S$ requires N, 12·3%). 2-*Decanoylphenoxathiin* (80% yield) formed prisms, m. p. 68—69° (Found: C, 74·6; H, 7·0. $C_{22}H_{26}O_2S$ requires C, 74·5; H, 7·3%). 2-*Phenylacetylphenoxathiin* (79% yield), b. p. 310—311°/18 mm., formed prisms, m. p. 127° (Found: C, 75·2; H, 4·1. $C_{20}H_{14}O_2S$ requires C, 75·5; H, 4·4%).

2-*Alkylphenoxathiins.*—2-*Ethylphenoxathiin* was obtained in 88% yield from 2-acetylphenoxathi in (20 g.), 95% hydrazine hydrate (10 g.), and potassium hydroxide (10 g.) in diethylene glycol (150 c.c.), as a pale yellow oil, b. p. 217—219°/25 mm., n_D^{23} 1·6548 (Found: C, 73·8; H, 5·2. $C_{14}H_{12}OS$ requires C, 73·6; H, 5·2%). Similarly were prepared 2-n-*pentyl*-, b. p. 249—250°/18 mm., n_D^{22} 1·6152 (Found: C, 75·4; H, 6·5. $C_{17}H_{18}OS$ requires C, 75·5; H, 6·6%), 2-n-*decyl*-, b. p. 305—307°/22 mm., n_D^{22} 1·5758 (Found: C, 77·3; H, 8·1. $C_{22}H_{28}OS$ requires C, 77·6; H, 8·2%), and 2-*benzyl-phenoxathiin*, b. p. 277—278°/16 mm., needles, m. p. 53° (from light petroleum) (Found: C, 78·4; H, 5·0. $C_{19}H_{14}OS$ requires C, 78·6; H, 4·8%).

8(?)-*Acetyl*-2-*ethylphenoxathiin.*—Prepared in 80% yield from 2-ethylphenoxathiin (15 g.), acetyl chloride (5 g.), and aluminium chloride (9 g.) in carbon disulphide (100 c.c.), this *ketone* had b. p. 249—250°/13 mm., n_D^{25} 1·6561 (Found: C, 71·4; H, 5·3. $C_{16}H_{14}O_2S$ requires C, 71·1; H, 5·2%); its semicarbazone formed prisms, m. p. 212°, from ethanol.

2-ω-*Bromoacetylphenoxathiin.*—To a solution of 2-acetylphenoxathiin (20 g.) in acetic acid (100 c.c.), bromine (13 g.) in acetic acid (20 c.c.) was added dropwise with stirring, and the mixture kept overnight at room temperature, then poured in ice–water. The solid *product*, on recrystallisation from ethanol, formed yellowish needles (83% yield), m. p. 134° (Found: C, 52·6; H, 2·8. $C_{14}H_9O_2SBr$ requires C, 52·3; H, 2·8%).

2-2′-*Pyrrocolinylphenoxathiin* (III).—A mixture of the foregoing bromo-ketone (2 g.), 2-picoline (1·5 g.), and ethanol (10 c.c.) was heated for 1 hr. on the water-bath; the solid picolinium salt which crystallised on cooling was collected, washed with ether, and dissolved in a 10% aqueous solution of hydrogen sodium carbonate (120 c.c.), and this solution brought to the boil. The precipitate was collected after cooling and, recrystallised from benzene, gave the *pyrrocoline*

(2 g.), sublimable prisms, m. p. 199—200° (Found: C, 76·4; H, 4·4. $C_{20}H_{13}ONS$ requires C, 76·2; H, 4·1%).

2-(6-*Ethyl*-2-*pyrrocolinyl*)*phenoxathiin* formed needles, m. p. 155°, from benzene (Found: N, 4·2. $C_{22}H_{17}ONS$ requires N, 4·1%); 2-(7-*methyl*-2-*pyrrocolinyl*)*phenoxathiin* formed needles, m. p. 209°, from benzene (Found: N, 4·3. $C_{21}H_{15}ONS$ requires N, 4·3%); it gave with sodium nitrite and hydrochloric acid [9] a nitroso-derivative, crystallising as green prisms, m. p. 245° (decomp.) from ethanol.

2-2′-*Phenoxathiinyl*-1 : 3a-*diazaindene* (IV).—2-ω-Bromoacetylphenoxathiin (3 g.) and 2-aminopyridine (1·5 g.) in ethanol (12 c.c.) were heated at 60° for 2 hr.; the precipitate obtained on dilution with ether was basified with aqueous sodium carbonate; the *base* recrystallised from ethanol as yellowish prisms (2·5 g.), m. p. 185° (Found: N, 8·6. $C_{19}H_{12}ON_2S$ requires N, 8·9%).

2-2′-*Quinoxalinylphenoxathiin* (V).—A solution of 2-ω-bromoacetylphenoxathiin (1·7 g.) and *o*-phenylenediamine (0·5 g.) in ethanol (10 c.c.) was refluxed with sodium acetate (0·5 g.) for 2 hr.; the *product* precipitated on dilution with water crystallised as needles, m. p. 174°, from ethanol (Found: N, 8·2. $C_{20}H_{12}ON_2S$ requires N, 8·5%).

2-β-*Carboxypropionylphenoxathiin*.—To a solution of phenoxathiin (30 g.) and succinic anhydride (18 g.) in nitrobenzene (175 c.c.), aluminium chloride (20 g.) was added in small portions, and the mixture kept overnight at room temperature. After treatment with dilute hydrochloric acid, the nitrobenzene was removed by steam-distillation, and the crude *acid* purified *via* its sodium salt; it formed prisms (3 g.), m. p. 167°, from aqueous ethanol (Found: C, 64·0; H, 3·7. $C_{16}H_{12}O_4S$ requires C, 64·0; H, 4·0%).

2-o-*Carboxybenzoylphenoxathiin*.—Prepared in the same way from phthalic anhydride (30 g.), this *acid* formed yellowish prisms, m. p. 186°, from ethanol (Found: C, 68·8; H, 3·1. $C_{20}H_{12}O_4S$ requires C, 69·0; H, 3·4%).

α-*Bromo*-β-2-*phenoxathiinylstilbene* (II).—To a cooled solution of a Grignard reagent prepared from benzyl chloride (10·6 g.) and magnesium (2 g.) in anhydrous ether (200 c.c.), 2-benzoylphenoxathiin [1] (17 g.) in ether (50 c.c.) was added in small portions with shaking, and the mixture refluxed for 30 min.; after addition of a cold dilute aqueous solution of sulphuric acid, the organic layer was separated, the solvent distilled off, and the residue heated with 99% formic acid (35 g.). After dilution with water, the crude stilbene was taken up in benzene, and distilled *in vacuo*; it formed a viscous resin (19 g.), which was treated in chloroform with bromine (8 g.). Evaporation of the solvent gave the *bromostilbene* (II), which formed needles, m. p. 129—130°, from ethanol (Found: C, 67·9; H, 3·5. $C_{26}H_{17}OSBr$ requires C, 68·3; H, 3·7%).

3-*Aryl*-2-*arylimino*-4-2′-*phenoxathiinyl*-Δ⁴-*thiazolines* (VI).

			Found (%)		Reqd. (%)	
Ar = Ar′	M. p.	Formula	C	H	C	H
Phenyl	151°	$C_{27}H_{18}ON_2S_2$	71·8	4·3	72·0	4·0
4-Tolyl	159	$C_{29}H_{22}ON_2S_2$	73·1	4·7	72·8	4·6
4-*n*-Propylphenyl	143	$C_{33}H_{30}ON_2S_2$	73·9	5·8	74·2	5·6
4-*n*-Heptylphenyl	113	$C_{41}H_{46}ON_2S_2$	75·9	7·0	76·2	7·1
2 : 4-Xylyl	143	$C_{31}H_{26}ON_2S_2$	73·8	5·0	73·5	5·1
2-Diphenylyl	129	$C_{39}H_{26}ON_2S_2$	77·9	4·4	77·7	4·3
4-Diphenylyl	199	$C_{39}H_{26}ON_2S_2$	77·4	4·0	77·7	4·3
α-Naphthyl	156	$C_{35}H_{22}ON_2S_2$	76·0	4·0	76·3	4·0
p-Fluorophenyl	188	$C_{27}H_{16}ON_2S_2F_2$	66·8	3·5	66·6	3·3
p-Chlorophenyl	176	$C_{27}H_{16}ON_2S_2Cl_2$	62·1	3·2	62·4	3·1
p-Bromophenyl	176	$C_{27}H_{16}ON_2S_2Br_2$	52·9	2·7	53·3	2·6
p-Phenethyl	176	$C_{31}H_{26}O_3N_2S_2$	68·8	4·9	69·1	4·8

Thiazolines (VI).—These were prepared by refluxing for 1 hr. equimolar amounts of 2-ω-bromoacetylphenoxathi-in and the appropriate *NN′*-diarylthiourea in ethanol; after cooling, the mixture was basified with aqueous sodium hydroxide, and the precipitate collected, washed with water, and recrystallised from ethanol. *E.g.*, 2-p-*chlorophenyl*-3-p-*fluorophenylimino*-4-2′-*phenoxathiinyl*-Δ⁴-*thiazoline*, prepared from 4-chloro-4′-fluorothiocarbanilide,[10] formed needles, m. p. 164° (Found: C, 64·2; H, 3·0. $C_{27}H_{16}ON_2S_2ClF$ requires C, 64·5; H, 3·2%). Other *products* are listed in the Table.

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[9] Borrows, Holland, and Kenyon, *J.*, 1946, 1075.
[10] Cf. Buu-Hoï, Xuong, and Nam, *J.*, 1955, 1573.