478. *Carcinogenic Nitrogen Compounds. Part XLV.*[1] *Thiophen Analogues of Carcinogenic Benzacridines and Dibenzacridines*

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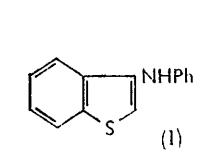
A number of heterocyclic compounds containing both nitrogen and sulphur, and isosteric with carcinogenic angular benzacridines and dibenzacridines, have been prepared from 3-hydroxythianaphthen by known methods. These compounds show physical and chemical properties similar to those of their non-sulphur analogues.

In the group of polycyclic aromatic hydrocarbons, it is often possible to replace one or even two of the benzene rings by thiophen ones without suppressing thereby the carcinogenic activity; such, for instance, is the case with the potent 7,12-dimethylbenz[*a*]anthracene, the sulphur analogue of which, obtained by replacing ring A by a thiophen

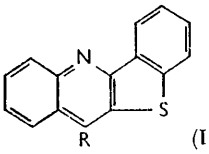
[1] Part XLIV, N. P. Buu-Hoï and G. Saint-Ruf, preceding Paper.

one, is likewise a powerful carcinogen,[2] and with several analogues of dibenz[*a*,*h*]- and dibenz[*a*,*j*]-anthracene bearing one or two thiophen rings, which are also active.[3] Hence it was of interest to synthesise heterocyclic compounds containing a thiophen ring and which could be considered as isosteric with carcinogenic benz[*c*]acridines and dibenz[*a*,*h*]- and dibenz[*c*,*h*]-acridines. Compounds of this type had not so far been prepared, save for a few non-*meso*-substituted thieno[2,3-*c*]acridines [4] biologically inactive (*meso*-methylation being essential for activity in the benzacridine group).

The starting material throughout the present work was 3-hydroxythianaphthen. 3-Anilinothianaphthen (I), readily obtained therefrom by condensation with aniline, underwent a modified Bernthsen reaction [5] with acetic anhydride, to give 6-methylthiaquindoline (II; R = Me), an isostere of the strongly carcinogenic 7-methylbenz[*c*]acridine,



(I)



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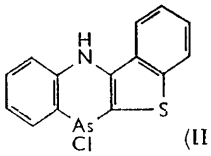

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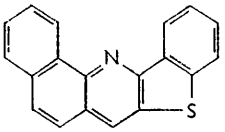

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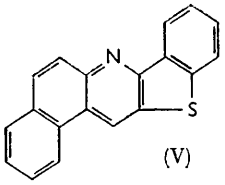

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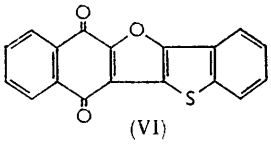

(VI)

which it closely resembles in physical and chemical properties. 6-Ethylthiaquindoline was similarly prepared, from propionic anhydride. The consistently low yields in these Bernthsen reactions, in contrast with what is observed in the equivalent benzacridine syntheses from *N*-phenyl-α-naphthyl-amine, were due to the sensitivity of 3-anilinothianaphthen to heat and to Lewis acids (here, zinc chloride). On the other hand, this last compound reacted readily with arsenic trichloride to give 6-chloro-6,11-dihydro[1,4]benzarsazine[3,2-*b*]thianaphthen (III), an analogue of the angular chlorodihydrobenzophenarsazines, some of which are carcinogenic;[6] unlike most chlorodihydrophenarsazines, compound (III) is surprisingly devoid of sternutatory properties.

Although an attempt to prepare unsubstituted thianaphtheno[3,2-*b*]quinoline by condensation of 3-hydroxythianaphthen with aniline and paraformaldehyde (Ullmann–Fetvadjian reaction) failed, a similar reaction was successful with both α- and β-naphthylamine, giving, in good yields, benzo[*h*]thianaphtheno[3,2-*b*]quinoline (IV) and benzo[*f*]thiaquindoline (V), respectively. With regard to physical (m. p., ultraviolet absorption spectrum) and chemical properties, compound (IV) closely resembles dibenz[*c*,*h*]acridine, and its isomer (V) is similarly strikingly akin to dibenz[*a*,*h*]acridine.

By the condensation of 3-hydroxythianaphthen with 2,3-dichloro-1,4-naphthoquinone in pyridine we have obtained a dark reddish-brown product, which was inadequately described in a German patent [7] and assigned the structure naphtho[2',3':4,5]furo[3,2-*b*]-thianaphthen-6,11-quinone (VI) by Eistert [8] without analytical proof.

Results of carcinogenesis tests will be reported elsewhere.

[2] See J. L. Hartwell, " Survey of Compounds Which Have Been Tested for Carcinogenic Activity," Fed. Security Agency (Bethesda, 1941).
[3] S. S. Waravdekar and K. J. Ranadive, *J. Nat. Cancer Inst.*, 1957, **18**, 555.
[4] N. P. Buu-Hoï and R. Royer, *Compt. rend.*, 1946, **232**, 806; N. P. Buu-Hoï, N. Hoán, and N. H. Khôi, *Rec. Trav. chim.*, 1950, **69**, 1053; N. P. Buu-Hoï, N. Hoán, and N. D. Xuong, *ibid.*, p. 1083.
[5] N. P. Buu-Hoï and J. Lecocq, *Rec. Trav. chim.*, 1945, **64**, 250; *Compt. rend.*, 1944, **218**, 792; N. P. Buu-Hoï, *J.*, 1946, 792.
[6] A. Lacassagne, G. Rudali, N. P. Buu-Hoï, and R. Royer, *Compt. rend. Soc. Biol.*, 1951, **145**, 1451.
[7] D.R.P. 197,037 (to Kalle & Co.), cited by B. Eistert (ref. 8).
[8] B. Eistert, *Chem. Ber.*, 1947, **80**, 47.

Experimental

6-*Methylthiaquindoline* (II; R = Me).—3-Anilinothianaphthen was prepared according to Fries and Bartholomäus;[9] a mixture of this compound (5 g.), acetic anhydride (4 g.), and anhydrous zinc chloride (3·6 g.) was refluxed for 18 hr., and after being cooled, was treated with 15% aqueous sodium hydroxide, and the product taken up in toluene. The toluene layer was filtered, washed with water, and dried ($CaCl_2$), the solvent was removed, and the residue fractionated *in vacuo*; the orange-yellow oil, b. p. 255°/20 mm., was converted into a *picrate*, which crystallised as bright yellow needles, m. p. 237° (decomp. >230°), from chlorobenzene (Found: N, 11·7. $C_{22}H_{14}N_4O_7S$ requires N, 11·7%). The free *base* (II; R = Me), regenerated from the picrate by treatment with ammonia, formed colourless prisms (0·6 g., low yield due to considerable charring during the Bernthsen reaction), m. p. 138°, from ethanol; the halochromy in sulphuric acid was greenish-yellow, as is the case with benz[*c*]acridines (Found: C, 77·3; H, 4·5; N, 5·6. $C_{16}H_{11}NS$ requires C, 77·1; H, 4·4; N, 5·6%). 6-*Ethylthiaquindoline* (II; R = Et), similarly prepared, from propionic acid and in only 15% yield, formed colourless prisms, m. p. 114°, from methanol (Found: N, 5·3; S, 12·0. $C_{17}H_{13}NS$ requires N, 5·4; S, 12·2%). The *picrate* formed deep yellow needles, m. p. 226° (decomp. >200°), from xylene (Found: N, 11·2. $C_{23}H_{16}N_4O_7S$ requires N, 11·4%).

6-*Chloro*-6,11-*dihydro*-[1,4]*benzarsazino*[3,2-b]*thianaphthen* (III).—A solution of 3-anilinothianaphthen (1·2 g.) and arsenic trichloride (1 g.) in anhydrous *o*-dichlorobenzene (5 c.c.) was gently refluxed for 2 hr., and the *precipitate* which formed on cooling was filtered off, washed with methanol, dried, and recrystallised from chlorobenzene, to give shiny yellow prisms (1 g.), m. p. 248° (decomp. >225°); the halochromy in sulphuric acid was orange-red (Found: N, 4·2; S, 9·6. $C_{14}H_9AsClNS$ requires N, 4·2; S, 9·6%).

Benzo[h]*thiaquindoline* (IV).—To a mixture of 3-hydroxythianaphthen (4·5 g.) and α-naphthylamine (5·5 g.) heated at *ca.* 250°, paraformaldehyde (3 g.) was added in small portions; distillation of the reaction *product* furnished an orange, sticky resin (4·5 g.), b. p. 320—325°/21 mm., which crystallised as pale yellow needles, m. p. 189°, from ethanol-benzene, giving a greenish-yellow halochromy in sulphuric acid (Found: C, 79·9; H, 3·9; N, 4·8. $C_{19}H_{11}NS$ requires C, 80·0; H, 3·9; N, 4·9%). The compound showed an ultraviolet absorption spectrum in ethanol similar to that of the isosteric dibenz[*c*,*h*]acridine; absorption bands were at 223, 245, 256w, 297, 352, 358w, and 380 mμ for compound (IV), as compared with 225, 235w, 257, 293, 357, 383, and 396 mμ for the acridine (the m. p., 185°, for the latter is also very close to that of compound (IV)). The addition compound with picric acid formed orange-yellow prisms, m. p. 161°, from ethanol.

Benzo[f]*thiaquindoline* (V).—Similarly prepared from 3-hydroxythianaphthen (4·5 g.), β-naphthylamine (5·5 g.), and paraformaldehyde (3 g.), this *compound*, b. p. *ca.* 335°/22 mm., formed pale yellow needles (3 g.), m. p. 214°, from benzene (Found: C, 79·9; H, 4·1; N, 5·0%). The u.v. absorption spectrum (in ethanol; bands at 228, 239w, 292, 341, 367, and 388 mμ) was similar to that of the isosteric dibenz[*a*,*h*]acridine (bands at 229, 247, 253w, 289w, 296, 351, 358w, and 380 mμ). The *picrate* formed bright yellow needles, m. p. 256° (decomp. >230°), from ethanol (Found: N, 10·7. $C_{25}H_{14}N_4O_7S$ requires N, 10·9%). The good yields recorded here contrast sharply with the repeated failures encountered in attempts to replace the naphthylamines by aniline in the Bernthsen reaction with 3-hydroxythianaphthen, no distillable reaction product being thus obtained.

Naphtho[2′,3′:4,5]*furo*[3,2-b]*thianaphthen*-6,11-*quinone* (VI).—A solution of 3-hydroxythianaphthen (1·5 g.) and 2,3-dichloro-1,4-naphthoquinone (2·3 g.) in anhydrous pyridine (10 c.c.) was refluxed for 4 hr.; the precipitate formed on cooling was washed with water and recrystallised from nitrobenzene, giving dark reddish-brown microprisms (1 g.), m. p. 335° (Found: C, 70·7; H, 3·1; S, 10·4. $C_{18}H_8O_3S$ requires C, 71·0; H, 2·6; S, 10·5%). The halochromy in sulphuric acid was brown, turning green in the air.

This work was supported in part by a research grant from the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service, and we thank the authorities concerned.

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[9] K. Fries and E. Bartholomäus, *Annalen*, 1914, **405**, 373.