Thiophen Derivatives. Part XV.[1] 3- and 4-Hydroxythianaphthen in the Synthesis of some Thia-derivatives of Polycyclic Carcinogens

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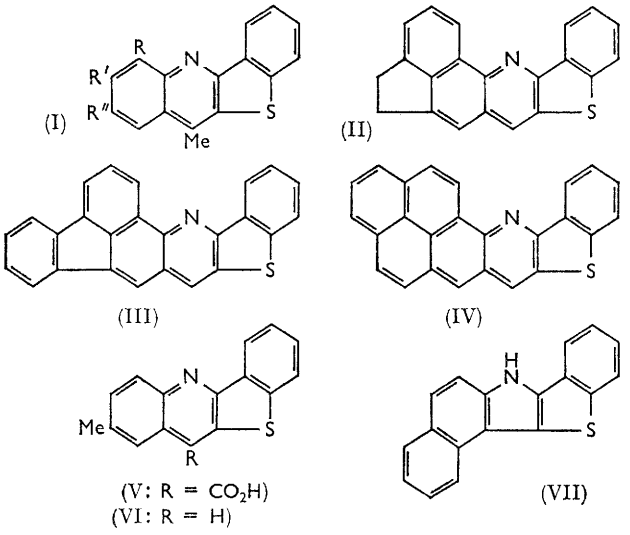
The behaviour of 3- and 4-hydroxythianaphthen, as compared with that of the naphthols, in various reactions leading to heterocyclic compounds analogous to known polycyclic carcinogens has been investigated.

In the synthesis of several types of polycyclic carcinogens, especially nitrogen-bearing, α- and β-naphthol are used as the starting material. Thus, a current method for preparing angular benzacridines unsubstituted on the carbon atom *para* to the nitrogen is based on the Ullmann–Fetvadjian reaction (thermal condensation of the naphthol with a primary arylamine in presence of paraformaldehyde);[2] N-arylnaphthylamines used in the Bernthsen reaction for the synthesis of *meso*-substituted benzacridines are prepared from naphthols, with[3] or without[4] catalyst; and lastly, the angular dibenzocarbazoles can be prepared either directly from the naphthols (Japp and Maitland's method[5]) or indirectly from a hydroxynaphthoic acid (Bucherer's method[6]). In view of the close electronic similarity between the naphthols and the hydroxythianaphthens, it was of interest to examine the behaviour of the latter in the same reactions.

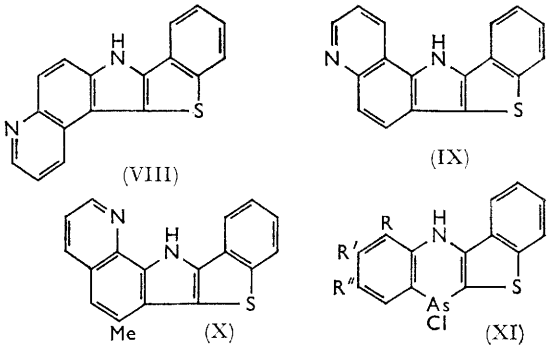
The most readily accessible hydroxythianaphthens are the 3- and, to a lesser degree, the 4-isomer. 4-Hydroxythianaphthen resisted Ullmann–Fetvadjian condensation with α-naphthylamine (where α-naphthol readily gives dibenzo[*c*,*h*]acridine); an attempt to condense it with aniline in presence of iodine to the corresponding amine also failed, and here again, 4-hydroxythianaphthen was less reactive than α-naphthol, which is known to give *N*-phenyl-α-naphthyl-amine in similar conditions.[3] 3-Hydroxythianaphthen, on the other hand, was even more reactive than β-naphthol, and condensed readily with a variety of primary arylamines, even in the absence of a

[1] Part XIV, E. Lescot, N. P. Buu-Hoï, and N. D. Xuong, *J. Chem. Soc.*, 1959, 3234.
[2] Cf. N. P. Buu-Hoï, *J. Chem. Soc.*, 1946, 795; N. P. Buu-Hoï, V. Bellavita, A. Ricci, J. P. Hoeffinger, and D. Balucani, *J. Chem. Soc.*, 1965, 2646.
[3] E. Knoevenagel, *J. prakt. Chem.*, 1914, **89**, 17.
[4] P. Friedländer, *Ber.*, 1883, **16**, 2085.
[5] F. R. Japp and W. Maitland, *J. Chem. Soc.*, 1903, **83**, 267.
[6] H. Th. Bucherer, *J. prakt. Chem.*, 1909, **79**, 387, 415; 1920, **81**, 6, 27.

catalyst, to give 3-arylaminothianaphthens. These rather heat-unstable compounds nevertheless underwent Bernthsen reactions in many instances, and thus were prepared 6,8-, 6,9-, and 6,10-dimethylthiaquindoline (general formula I), which are isosteric with the strongly carcinogenic 7,9-, 7,10-, and 7,11-dimethylbenz[*c*]acridine, respectively. In the Ullmann–Fetvadjian reaction, 3-hydroxythianaphthen gave satisfactory results only with reactive arylamines which are able to form the



quinoline ring before decomposition of 3-hydroxythianaphthen occurs; in this respect, amines derived from polycyclic hydrocarbons were particularly successful, as shown in the synthesis of the hexa- and hepta-cyclic thiaquindolines (II), (III), and (IV), from 5-aminoacenaphthene, 3-aminofluoranthene, and 1-aminopyrene. This narrows the usefulness of the Ullmann–Fetvadjian reaction for the synthesis of simpler thiaquindolines: whereas 3,4-dimethylaniline afforded 8,9-dimethylthiaquindoline, aniline failed to give thiaquindoline itself. This latter, together with its simple higher homologues such as 8-methylthiaquindoline (VI), had therefore to be prepared by a Pfitzinger condensation of 3-hydroxythianaphthen with the appropriate isatin,[7] and thermal decarboxylation of the cinchoninic acid formed. The strongly ketonic character of 3-hydroxythianaphthen is further demonstrated by the ready formation of hydrazones with arylhydrazines and heterocyclic analogues. Indolisation of these hydrazones furnished derivatives of the basic nucleus, thianaphtheno[3,2-*b*]indole, which had previously been prepared by a Japp–Maitland-type reaction.[8] It is, therefore, easier to pass from 3-hydroxythianaphthen to the corresponding thianaphthenoindoles than from β-naphthol to benzocarbazoles, which necessitates the more drastic Japp–Maitland and Bucherer procedures. Compound (VII) is isosteric with the carcinogenic 7H-dibenzo[*a*,*g*]carbazole, and compounds (VIII), (IX), and (X) with benzopyridocarbazoles, in which group many carcinogens are encountered.[9] The 6-chloro-6,11-dihydro[1,4]benzarsazino[3,2-*b*]thianaphthens (XI), also bearing an imino group, were obtained by condensation of the 3-tolylaminothianaphthens with arsenic trichloride.



Biological tests for carcinogenicity are under way and results will be reported elsewhere.

EXPERIMENTAL

Preparation of 3-Tolylaminothianaphthens.—The following procedure, derived from that of Fries and Bartholomäus for the preparation of 3-anilinothianaphthen,[10] was used: a mixture of 3-hydroxythianaphthen (1 g.) and the appropriate toluidine (5 g.) was heated for 3 hr. at 190—200°; the product was treated with ether, the ethereal solution washed with dilute aqueous hydrochloric acid, then with water, and dried (Na_2SO_4); the solvent was distilled and the residue fractionated in high vacuum. 3-o-*Tolylaminothianaphthen*, b. p. 122—124°/0·001 mm., crystallised as colourless prisms (1 g.), m. p. 54°, from hexane (Found: C, 75·0; H, 5·5; N, 5·8. $C_{15}H_{13}NS$ requires C, 75·3; H, 5·5; N, 5·9%); 3-m-*tolylaminothianaphthen* was a viscous yellow oil, b. p. 115—120°/0·001 mm. (Found: C, 75·0; H, 5·4; N, 5·8%); 3-p-*tolylaminothianaphthen*, b. p. 120—122°/0·001 mm., formed colourless prisms, m. p. 52°, from hexane (Found: C, 75·4; H, 5·5; N, 5·8%). All these secondary amines darken rapidly on exposure to light and air, with formation of a red resin. A similar reaction with 2,4-dimethylaniline failed to give the desired amine.

Bernthsen Reactions.—A mixture of 3-*m*-tolylaminothianaphthen (6 g.), acetic anhydride (4 g.), and freshly-fused powdered zinc chloride (4 g.) was heated under reflux for 18 hr.; after cooling, the mixture was triturated with aqueous sodium hydroxide in presence of benzene, the benzene solution dried ($CaCl_2$), the solvent removed, and the residue fractionated *in vacuo*. The viscous orange oil (3·5 g.), b. p. 280—285°/20 mm., was converted into 6,9-*dimethylthiaquindoline picrate*, which crystallised as shiny yellow leaflets, m. p. 248° (decomp. >230°), from *o*-dichlorobenzene (Found: N, 11·0. $C_{23}H_{16}N_4O_7S$ requires N, 11·4%). Treatment with ammonia afforded the free *base* (I; R = R″ = H, R′ = Me), which formed colourless needles, m. p. 127°, from ethanol, whose solutions in sulphuric acid were greenish-yellow (Found: C, 77·4; H, 5·1; N, 5·2; S, 12·1. $C_{17}H_{13}NS$ requires C, 77·5; H, 5·0; N, 5·3; S, 12·2%). The following isomers were similarly prepared: 6,8-*dimethylthiaquindoline* (I; R = R′ = H,

[7] Cf. E. Noelting and A. Herzbaum, *Ber.*, 1911, **44**, 2585.
[8] E. W. McClelland and J. L. D'Silva, *J. Chem. Soc.*, 1932, 227; C. E. Dalgliesh and F. Mann, *J. Chem. Soc.*, 1947, 653.
[9] A. Lacassagne, N. P. Buu-Hoï, F. Zajdela, F. Périn, and P. Jacquignon, *Nature*, 1916, **191**, 1005; *Compt. rend.*, 1963, **257**, 818.
[10] K. Fries and E. Bartholomäus, *Annalen*, 1914, **405**, 373.

R″ = Me), b. p. 275°/16 mm., almost colourless leaflets, m. p. 153°, from cyclohexane (Found: C, 77·2; H, 5·2; N, 5·1; S, 12·1%); *picrate*, yellow microprisms, m. p. 234°, from nitrobenzene (Found: N, 11·2%); 6,10-*dimethylthiaquindoline* (I; R = Me, R′ = R″ = H), b. p. 217—220°/0·07 mm., silky colourless needles, m. p. 108°, from ethanol (Found: C, 77·5; H, 5·2; N, 5·2; S, 12·2%); *picrate*, yellow needles, m. p. 192° (decomp. >180°), from chlorobenzene (Found: N, 11·1%).

Reaction of 3-Tolylaminothianaphthens with Arsenic Trichloride.—A solution of the amine (1·3 g.) and arsenic trichloride (1 g.) in *o*-dichlorobenzene (10 c.c.) was heated under reflux for 2 hr., and the precipitate obtained in 80% yield on cooling was recrystallised from chlorobenzene. Thus were obtained: 6-*chloro*-6,11-*dihydro*-8-*methyl*[1,4]-*benzarsazino*[3,2-b]*thianaphthen* (XI; R = R′ = H, R″ = Me), from 3-*p*-tolylaminothianaphthen, as deep yellow needles, m. p. 269° (decomp. >250°), from *o*-dichlorobenzene (Found: N, 4·2; As, 21·4. $C_{15}H_{11}AsClNS$ requires N, 4·0; As, 21·6%); 6-*chloro*-6,11-*dihydro*-9-*methyl*[1,4]-*benzarsazino*[3,2-b]*thianaphthen* (XI; R = R″ = H, R′ = Me), m. p. 286° (decomp. >260°) (Found: N, 4·0; S, 9·3. $C_{15}H_{11}AsClNS$ requires N, 4·0; S, 9·2%); 6-*chloro*-6,11-*dihydro*-10-*methyl*[1,4]*benzarsazino*[3,2-b]*thianaphthen* (XI; R = Me, R′ = R″ = H), m. p. 232° (decomp. >210°) (Found: N, 3·8; S, 9·3%).

8-*Methylthiaquindoline* (VI).—A solution of 5-methylisatin (1·6 g.), 3-hydroxythianaphthen (1·5 g.), and potassium hydroxide (1·7 g.) in ethanol (10 c.c.) was heated under reflux for 20 hr.; after addition of water, a deep violet precipitate (probably thioindigo) was filtered off and the filtrate acidified with acetic acid, to give 8-*methylthiaquindoline*-6-*carboxylic acid* (V), crystallising as yellow microprisms (0·7 g.), m. p. 320° (decomp.), from acetic acid (Found: C, 69·3; H, 4·0. $C_{17}H_{11}NO_2S$ requires C, 69·6; H, 3·8%). Heating above its m. p. yielded 8-*methylthiaquindoline* as colourless needles, m. p. 160°, from ethanol (Found: C, 77·0; H, 4·5. $C_{16}H_{11}NS$ requires C, 77·1; H, 4·5%); *picrate*, yellow needles, m. p. 225°, from ethanol (Found: N, 11·7. $C_{22}H_{14}N_4O_7S$ requires N, 11·7%).

8,9-*Dimethylthiaquindoline*.—To a boiling mixture of 3,4-dimethylaniline (4 g.) and 3-hydroxythianaphthen (5 g.), paraformaldehyde (3·5 g.) was added in small portions, and, after the vigorous reaction had subsided, the mixture was fractionated *in vacuo*; the portion (3·5 g.) boiling at 170—180°/0·25 mm. was converted into the *picrate*, yellow microprisms, m. p. 277° (decomp. >260°), from chlorobenzene (Found: N, 11·0. $C_{23}H_{16}N_4O_7S$ requires N, 11·4%). The free *base* formed colourless prisms (0·7 g.), m. p. 173°, from ethanol (Found: N, 5·5; S, 12·3. $C_{17}H_{13}NS$ requires N, 5·3; S, 12·2%).

Acenaphtheno[4,5-e]*thianaphtheno*[3,2-b]*pyridine* (II).—Similarly prepared from 5-aminoacenaphthene (3 g.), 3-hydroxythianaphthen (3 g.), and paraformaldehyde (1·8 g.), at 250°, this *compound* formed cream-coloured leaflets (0·5 g.), m. p. 230°, from benzene (Found: N, 4·5; S, 10·1. $C_{21}H_{13}NS$ requires N, 4·5; S, 10·3%).

Fluorantheno[5,4-e]*thianaphtheno*[3,2-b]*pyridine* (III).—Prepared from 3-aminofluoranthene (3 g.) 3-hydroxythianaphthen (2·5 g.), and paraformaldehyde (1·4 g.), this *compound* (b. p. *ca.* 350°/0·5 mm.) formed cream-coloured prisms (0·5 g.), m. p. 268°, from toluene (Found: C, 83·5; H, 3·9; N, 4·0; S, 8·8. $C_{25}H_{13}NS$ requires C, 83·6; H, 3·7; N, 3·9; S, 8·9%).

Pyreno[2,1-e]*thianaphtheno*[3,2-b]*pyridine* (IV).—Prepared from 1-aminopyrene (3 g.), 3-hydroxythianaphthen (2·3 g.), and paraformaldehyde (1·5 g.), this *compound* (b. p. *ca.* 370°/0·4 mm.) formed orange-yellow microprisms (0·5 g.), m. p. 308°, from toluene, giving a violet halochromism in sulphuric acid (Found: N, 3·6; S, 8·6. $C_{25}H_{13}NS$ requires N, 3·9; S, 8·9%). This substance is isosteric with the sarcomagenic benzo[*a*]phenaleno[1,9-*ij*]-acridine.[11]

Pyrido[3,2-e]*thianaphtheno*[3,2-b]*indole* (VIII).—A solution of 6-quinolylhydrazine dihydrochloride (2·5 g.) and 3-hydroxythianaphthen (1·3 g.) in ethanol (35 c.c.) was heated under reflux for 2 hr. with sodium acetate; after cooling and basification with aqueous ammonia, the precipitate of 2,3-dihydro-3-oxothianaphthen 6-quinolylhydrazone was recrystallised from ethanol, giving prisms (2 g.), m. p. 232°. Indolisation, effected with a solution of sulphuric acid (2 c.c.) in acetic acid (10 c.c.),[12] afforded the *indole*, which, after sublimation *in vacuo*, formed yellowish needles (1 g.), m. p. 317° (Found: C, 74·2; H, 3·9; N, 10·0. $C_{17}H_{10}N_2S$ requires C, 74·4; H, 3·7; N, 10·2%). *Picrate*, orange-yellow prisms, m. p. 297°, from nitrobenzene–ethanol (Found: N, 12·8. $C_{23}H_{13}N_5O_7S + C_2H_5OH$ requires N, 12·8%).

Pyrido[2,3-g]*thianaphtheno*[3,2-b]*indole* (IX).—2,3-Dihydro-3-oxothianaphthen 5-quinolylhydrazone, prepared from 5-quinolylhydrazine dihydrochloride, crystallised as prisms, m. p. 237°, from ethanol; the *indole* (IX), purified by sublimation *in vacuo*, formed pale yellow needles, m. p. 344° (Found: C, 74·3; H, 4·1; N, 10·1%). *Picrate*, yellow prisms, m. p. 318°, from nitrobenzene (Found: N, 14·2. $C_{23}H_{13}N_5O_7$ requires N, 13·9%).

6-*Methylpyrido*[3,2-g]*thianaphtheno*[3,2-b]*indole* (X).—Prepared from 6-methyl-8-quinolylhydrazine,[13] this *indole*, purified by sublimation *in vacuo*, formed yellowish needles, m. p. 265° (Found: C, 74·7; H, 4·5; N, 9·5. $C_{18}H_{12}N_2S$ requires C, 75·0; H, 4·2; N, 9·7%); *picrate*, orange-yellow needles, m. p. 296°, from nitrobenzene (Found: N, 13·4. $C_{24}H_{15}N_5O_7S$ requires N, 13·5%).

Benzo[e]*thianaphtheno*[3,2-b]*indole* (VII).—Prepared from β-naphthylhydrazine, this *indole* formed colourless prisms, m. p. 192°, from acetic acid (Found: C, 79·0; H, 4·1; N, 5·3. $C_{18}H_{11}NS$ requires C, 79·1; H, 4·1; N, 5·1%). Its 1 : 1 *π-complex* with tetrachlorophthalic anhydride crystallised as red needles, m. p. 221°, from acetic acid (Found: C, 55·5; H, 2·3. $C_{26}H_{11}Cl_4NO_3S$ requires C, 55·8; H, 2·0%).

Attempted Condensations of 4-Hydroxythianaphthen.—(*a*) *With aniline.* Refluxing of a solution of 4-hydroxythianaphthen [14] (5 g.) in aniline (10 c.c.) with iodine (0·2 g.) for 24 hr. failed to give the expected 4-anilinothianaphthen. (*b*) *With α-naphthylamine and paraformaldehyde.* This, performed as for α-naphthol, failed to give an acridine.

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[11] N. P. Buu-Hoï, O. Roussel, and L. Petit, *J. Chem. Soc.*, 1963, 956.

[12] Cf. N. P. Buu-Hoï and G. Saint-Ruf, *Israel J. Chem.*, 1963, **1**, 369.

[13] N. P. Buu-Hoï, P. Jacquignon, and J. P. Hoeffinger, *J. Chem. Soc.*, 1963, 4754.

[14] Prepared according to L. F. Fieser and R. G. Kennelly, *J. Amer. Chem. Soc.*, 1935, **57**, 1611; cf. N. P. Buu-Hoï, N. Hoán, N. H. Khôi, and N. D. Xuong, *J. Org. Chem.*, 1949, **14**, 802.