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Synthesis of Thiophene Isosters of Benzacridines and Dibenzacridines From Hydroxy- and Amino-thianaphthenes

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In the Ullmann-Fetvadjian synthesis of dibenzacridines (thermal condensation of a naphthol with a naphthylamine in the presence of paraformaldehyde), 5-hydroxy-3-methylthianaphthene and 3-phenyl-5-aminothianaphthene behave like β-naphthol and β-naphthylamine respectively; several analogs of the carcinogenic dibenzacridines, bearing both nitrogen- and sulfur-heteroatoms, have thus been prepared. 3-Hydroxythianaphthene, which fails to undergo an Ullmann-Fetvadjian reaction with aniline, readily does so with 4-aminobiphenyl.

Early research has shown that in the molecule of several carcinogenic polycyclic hydrocarbons, replacement at the appropriate site of a benzene ring by a thiophene one does not cause the biological activity to disappear. For instance, 7,11-dimethylbenzo[*g*]thiophanthrene (I), prepared by Sandin and Fieser (1), and which is isosteric with 7,12-dimethylbenz[*a*]anthracene, is itself highly carcinogenic (2); similarly, in the series of thiophene isosters of the angular dibenzanthracenes, compounds II and III also display carcinogenic activity (3). As the angular dibenzacridines IV and V and some of their homologs are known to be to a greater or lesser extent carcinogenic (4), it was of interest to prepare a number of thienobenzacridines structurally related both to dibenzacridines and to dibenzanthracenes.

A particularly useful route of access to compounds of the dibenzacridine type is the thermal condensation of a naphthol with a naphthylamine in the presence of paraformaldehyde (Ullmann-Fetvadjian reaction (5)), a method we recently extended with success to 3-hydroxythianaphthene (6); however, the sulfur heteroatom in the dibenzacridine analogs thus obtained with this compound occupies a *meso*phenanthrenic site, a fact which might be detrimental to their carcinogenicity. In order to keep the thiophene ring in an "external" position, we therefore now had recourse to thianaphthenes having hydroxy or amino groups in the benzene ring. 5-Hydroxy-3-methylthianaphthene (VI) was readily prepared from the previously described (7) 5-amino-3-methylthianaphthene by diazotation, and decomposition in boiling water of the diazo compound. Compound VI behaved very much like a β-naphthol, giving a positive brazanquinone reaction with 2,3-dichloro-1,4-naphthoquinone (8), and condensing readily with α-naphthylamine in presence of paraformaldehyde to give 1-methylthieno[3,2-*a*]benz[*h*]acridine (VII); with β-naphthylamine, however, it gave a mixture of the expected 1-methylthieno[3,2-*a*]benz[*j*]acridine and considerable amounts of dibenz[*a*,*j*]acridine from which the former could not be isolated.

Another convenient intermediate was 5-amino-3-phenylthianaphthene (VIII) (9), which readily gave an Ullmann-Fetvadjian reaction with both β- and α-naphthol to afford 1-phenylthieno[3,2-*a*]benz[*j*]-acridine (IX) and 1-phenylthieno[3,2-*a*]benz[*h*]acridine (X) respectively. Compound IX has an interesting "crowded" structure.

3-Hydroxythianaphthene, which resists Ullmann-Fetvadjian reaction with simple arylamines such as aniline (6), condensed however with both 4-aminobiphenyl and the amine VIII, to give 8-phenylthiaquindoline (XI) and 7-phenylthieno[3,2-*f*]thiaquindoline (XII).

All the nitrogen- and sulfur-containing heterocycles thus prepared possess physical and chemical properties closely resembling those of dibenzacridines, in particular as regards their considerable stability, which allows them to distil without decomposition, even in a moderate vacuum. Tests for carcinogenicity are being performed, and results will be reported at a later date.

EXPERIMENTAL

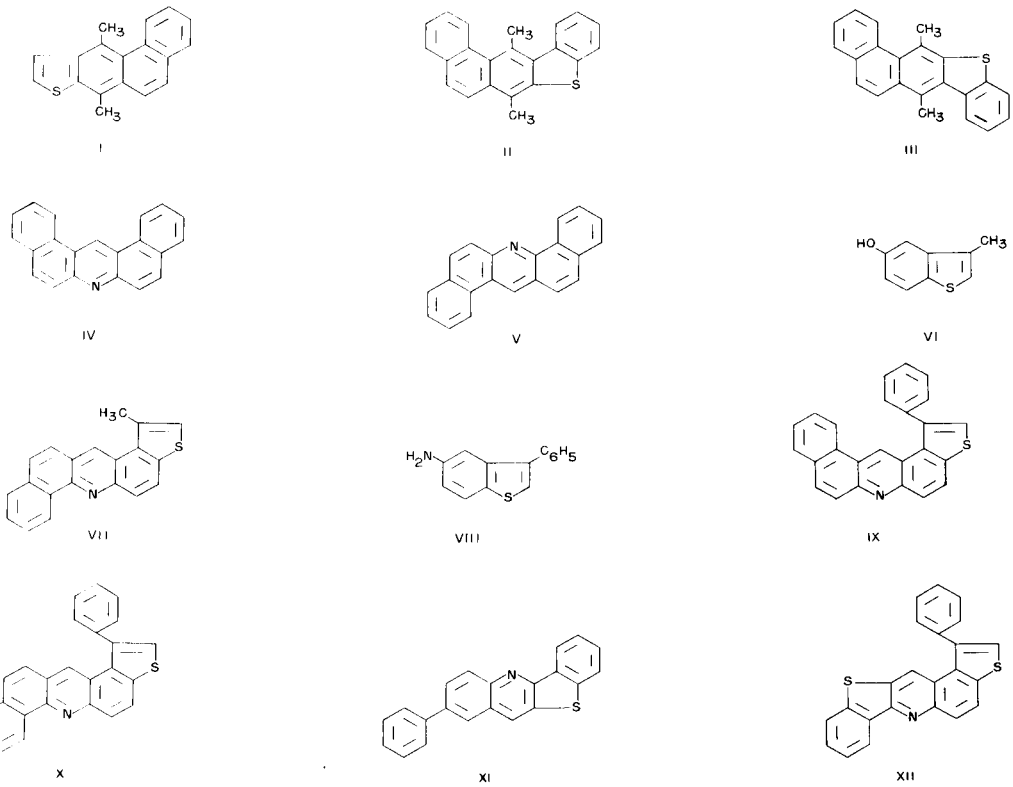
5-Hydroxy-3-methylthianaphthene (VI).

Ten grams of 5-amino-3-methylthianaphthene, prepared according to Ricci and Cagnoli (7), was dissolved in a warm 10% aqueous solution of sulfuric acid (250 ml.); the fine suspension of the sulfate of amine VI thus obtained on cooling was treated dropwise at 0° with an aqueous solution of 4.5 g. of sodium nitrite. The solution of the diazonium sulfate was poured in boiling water and vigorous agitation was continued until evolution of nitrogen had ceased. The reaction-product which precipitated was extracted several times with boiling water, and crystallized on cooling in colorless, sublimable needles, m.p. 97°. Yield: 50%.

Anal. Calcd. for C_9H_8OS: C, 65.9; H, 4.9. Found: C, 65.8; H, 4.8. This compound, heated in pyridine with 2,3-dichloro-1,4-naphthoquinone, gave a brazanquinone which dissolved in sulfuric acid with a brown-violet halochromism.

1-Methylthieno[3,2-*a*]benz[*h*]acridine (VII).

To a boiling mixture of 2.5 g. of the foregoing hydroxy compound and 2.5 g. of α-naphthylamine, 1.7 g. of paraformaldehyde was added in small portions; fractionation of the reaction-product in a high



vacuum afforded a portion b.p. 265°/0.1 mm., which was converted into a picrate in ethanol medium. Recrystallization of this picrate from xylene afforded deep yellow microprisms, m.p. 260° (decomp. > 220°).

Anal. Calcd. for $C_{28}H_{16}N_4O_7S$: N, 10.6. Found: N, 10.3.

Basification with aqueous ammonia gave the free acridine (1 g.), which crystallized from ethanol in yellowish needles, m.p. 230°.

Anal. Calcd. for $C_{20}H_{13}NS$: C, 80.3; H, 4.4; N, 4.7. Found: C, 80.0; H, 4.7; N, 4.6.

Ullmann-Fetvadjian Reaction of VI with β-Naphthylamine.

A similar reaction, performed with 2 g. of β-naphthylamine, 2 g. of the hydroxy compound (VI), and 1.2 g. of paraformaldehyde, gave a portion boiling at 315°/15 mm., which crystallized from a mixture of ethanol and benzene in yellowish needles, m.p. 194°, whose analyses (Found: C, 86.9; H, 4.4) showed it to be largely made up of dibenz-[*a*,*j*]acridine (Calcd. for $C_{21}H_{13}N$: C, 90.3; H, 4.7), with small amounts of 1-methylthieno[3,2-*a*]benz[*j*]acridine. Attempts to separate the two compounds *via* their picrates were also unsuccessful.

1-Phenylthieno[3,2-*a*]benz[*j*]acridine (IX).

The Ullmann-Fetvadjian reaction of 4 g. of 5-amino-3-phenylthianaphthene, 4 g. of β-naphthol, and 2.2 g. of paraformaldehyde afforded the acridine (IX) in 35% yield; purification was effected *via* the picrate, which formed yellow microprisms, m.p. 271° (decomp.), from *o*-dichlorobenzene.

Anal. Calcd. for $C_{31}H_{18}N_4O_7S$: N, 9.5. Found: N, 9.9.

The free base crystallized from ethanol in yellowish needles, m.p. 198°.

Anal. Calcd. for $C_{25}H_{15}NS$: C, 83.1; H, 4.2; N, 3.9. Found: C, 83.1; H, 4.2; N, 3.9.

1-Phenylthieno[3,2-*a*]benz[*h*]acridine (X).

Prepared as for the above, from α-naphthol, this acridine (30% yield) crystallized from a mixture of ethanol and benzene in faintly yellow prisms, m.p. 179°.

Anal. Calcd. for $C_{25}H_{15}NS$: C, 83.1; H, 4.2; N, 3.9. Found: C, 82.9; H, 4.3; N, 4.0.

The corresponding picrate crystallized from toluene in red needles, and from *o*-dichlorobenzene in orange-yellow needles, both forms melting with decomposition at 230°, and having the same analyses.

Anal. Calcd. for $C_{31}H_{18}N_4O_7S$: N, 9.5. Found: N, 9.4.

8-Phenylthiaquindoline (XI).

Prepared in *circa* 30% yield from 4 g. of 3-hydroxythianaphthene, 4 g. of 4-aminobiphenyl, and 2.5 g. of paraformaldehyde, this compound was purified *via* its picrate, which crystallized from *o*-dichlorobenzene in yellow leaflets, m.p. 240° (decomp.).

Anal. Calcd. for $C_{27}H_{16}N_4O_7S$: N, 10.4. Found: N, 10.5.

7-Phenylthieno[3,2-*f*]thiaquindoline (XII).

This compound, prepared from 5-amino-3-phenylthianaphthene (2 g.), 3-hydroxythianaphthene (2 g.), and paraformaldehyde (1.5 g.) in the usual way, was purified *via* its picrate, which crystallized from *o*-dichlorobenzene in yellow prisms, m.p. 240° (decomp.).

Anal. Calcd. for $C_{29}H_{16}N_4O_7S_2$: N, 9.8. Found: N, 9.4.

The free base crystallized from 1-butanol in shiny colorless prisms, m.p. 191°, giving a greenish-yellow halochromism with sulfuric acid. Yield: *circa* 25-30%.

Anal. Calcd. for $C_{23}H_{13}NS_2$: C, 75.2; H, 3.6; N, 3.8. Found: C, 75.3; H, 3.7; N, 3.6.

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