# The Synthesis of Thia-olivacine and Related Compounds

By E. CAMPAIGNE,* L. HEWITT, and JOHN ASHBY
(*Chemistry Laboratories, Indiana University, Bloomington, Indiana* 47401)

*Summary* 1,5-Dimethylbenzothieno[2,3-*g*]isoquinoline (thia-olivacine), its parent unsubstituted ring system, and one example of the isomeric ring system, 11-methylbenzothieno[3,2-*g*]isoquinoline, have been synthesized and characterized.

RECENTLY a synthesis of thia-ellipticine, the sulphur isostere of the indole alkaloid ellipticine, was reported.[1] We have now synthesized the sulphur isostere (I) of the isomeric alkaloid olivacine and some related compounds. The reported anti-tumour properties of these alkaloids[2] have stimulated interest in these isosteric heterocycles.

Electrophilic substitution of 4-methyldibenzothiophen[3] (II; X = H) normally occurs in the 2-position;† however, bromination unexpectedly yielded 3-bromo-4-methyldibenzothiophen (II; X = Br) which was converted into the corresponding aldehyde (II; X = CHO) by lithium exchange followed by treatment with *NN*-dimethylformamide.

The original position of substitution was determined by an analysis of the 100 MHz. n.m.r. spectra of (II; X = CHO) and of (II; X = Me) produced by Wolff–Kishner reduction of (II; X = CHO). Striking confirmation of 3-substitution was afforded by the resonance of the 4-methyl group. In the parent heterocycle (II; X = H)

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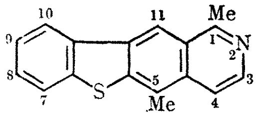
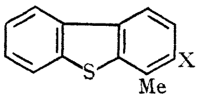
† A survey of the substitution reactions of 4-methyldibenzothiophene, including an analysis of the 100 MHz. n.m.r. spectra of the products will be published shortly. Satisfactory elemental analyses have been obtained for all new compounds described herein.

this appeared at $\delta$ 2·42 whilst in (II; X = CHO) a shift of 42 Hz. downfield was observed for this resonance, consistent with the presence of a formyl group *ortho* to the 4-methyl group. Upon reduction of the formyl group to form (II; X = Me) the resonance of the 4-methyl group reverted back to $\delta$ 2·33. Doublets (8 Hz.) at $\delta$ 7·1 (2-H) and 7·72 (1-H) in the spectrum of (II; X = Me) also confirm a 3,4-disubstituted dibenzothiophen system.



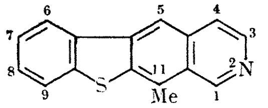
(I)



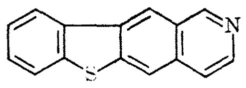
(II)

Condensation of (II; X = CHO) with nitromethane yielded the nitrovinyl compound (II; X = $CH{=}CHNO_2$) which was reduced with $LiAlH_4$ to (II; X = $CH_2{\cdot}CH_2NH_2$). Thia-olivacine (I) was obtained essentially by the method Schmutz and Wittwer[4] used for the synthesis of olivacine. The 3,4-dihydrothia-olivacine had m.p. 178—180° and the thia-olivacine m.p. 139—141° (from benzene), and $\lambda_{max}$ 230, 239, 257, 270 (sh) 280, and 286 nm. ($\epsilon$ 30,700, 29,800, 27,200, 42,100, 68,000, and 69,760). The 100 MHz. spectrum was essentially the same as that described for thia-ellipticine.[1] A sharp singlet at $\delta$ 8·24 was assigned to 11-H. In this and related compounds deshielding of the carbon atom $\gamma$ to the nitrogen (C-11) of the isoquinoline ring was observed.

Condensation of (II; X = CHO) with aminoacetaldehyde diethylacetal gave the Schiff base [II; X = $CH{:}NCH_2CH(OEt)_2$] which was cyclized in 105% phosphoric acid yielding 11-methylbenzothieno[3,2-*g*]isoquinoline (III) m.p. 158—159° from aqueous ethanol, $\lambda_{max}$ 230, 244, 269, and 267 nm. ($\epsilon$ 24,900, 30,200, 45,400, and 68,900). In the 100 MHz. spectrum of (III) 5-H gave a singlet at $\delta$ 8·2 along with a multiplet assigned to 6-H whilst the C-11 methyl resonance appeared downfield at $\delta$ 2·87, again due to the $\gamma$-positioned isoquinoline nitrogen.



(III)



(IV)

The parent ring system of (I), benzothieno[2,3-*g*]isoquinoline (IV), was prepared from 2-bromodibenzothiophen[5] by a similar sequence of reactions. Lithium exchange followed by treatment with *NN*-dimethylformamide gave dibenzothiophencarbaldehyde which, after condensation with aminoacetaldehyde diethylacetal, was cyclized in 105% phosphoric acid to yield (IV), m.p. 174—175° from benzene; $\lambda_{max}$. 231, 238, 268 (sh), 276, and 284 nm. ($\epsilon$ 41,200, 32,300, 41,200, 65,600, and 80,300). The rings of (IV) were shown to be linearly fused by the presence of singlets at $\delta$ 8·06 and 8·48 in its 100 MHz. n.m.r. spectrum, associated with 5-H and 11-H. Had cyclization occurred at C-1 instead of C-3 doublets for 3-H and 4-H (numbering for dibenzothiophen) would have been observed.

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