Journal of Medicinal and Pharmaceutical Chemistry

VOL. 3, No. 2 (1960)

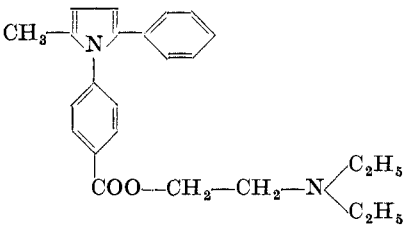
Note

Basic Esters and Hydrazides Derived from Substituted Pyrrylbenzoic Acids

N. D. Xuong and N. P. Buu-Hoï, *Radium Institute, University of Paris*

Within the last few years, several substances of pharmacological interest have been encountered in the group of 1-substituted pyrroles,[1] especially in respect of local anaesthetic and spasmolytic activities. The Knorr–Paal condensation of γ-diketones with esters of 4-aminobenzoic acid was reported in 1946 by Avakian,[2] who prepared the ethyl and *N*,*N*-diethylaminoethyl esters of 4-(2,5-dimethyl-1-pyrryl)benzoic acid with a view to obtaining substances endowed with local anaesthetic activity. However, no description of such properties features in the author's patent. This paper reports some investigations in the same field, initiated around the same period and with a similar object in view. In the course of this study, we performed similar condensations, the resulting products being either investigated for local anaesthetic activity, or converted into their corresponding, potentially antimycobacterial hydrazides.

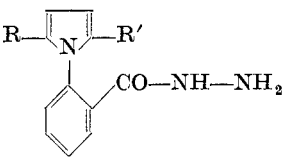
The condensation of 1-phenyl-1,4-pentanedione with procaine (*N*,*N*-diethylaminoethyl 4-aminobenzoate) yielded *N*,*N*-diethylaminoethyl 4-(2-methyl-5-phenyl-1-pyrryl)benzoate (I). Determination of local anaesthetic properties, performed on the cornea of the eye in the rabbit, showed the hydrochloride of (I) to possess



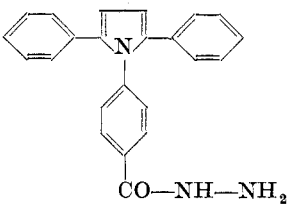
(I)

considerable activity, greater and more lasting than that of procaine, although in high concentrations it had an irritant effect on the cornea and conjunctiva.

Condensation of hexane-2,5-dione, of 1-phenyl-1,4-pentanedione, and of 1,4-diphenyl-1,4-butanedione with methyl 2-aminobenzoate led to esters which did not show any local anaesthetic potency; they were readily converted by means of hydra-



(II)



(III)

zine hydrate into 2-(2,5-dimethyl-1-pyrryl)benzhydrazide (II; $R = R' = CH_3$), 2-(2-methyl-5-phenyl-1-pyrryl)benzhydrazide (II; $R = CH_3$, $R' = C_6H_5$), and 2-(2,5-diphenyl-1-pyrryl)benzhydrazide (II; $R = R' = C_6H_5$), respectively. 4-(2,5-Diphenyl-1-pyrryl)benzhydrazide (III) was similarly obtained from 1,4-diphenyl-1,4-butanedione and ethyl 4-aminobenzoate. These various hydrazides showed only weak bacteriostatic activity *in vitro* against *Mycobacterium tuberculosis* var. *hominis* (strain H37 Rv).

Experimental

Condensation of hexane-2,5-dione with procaine (base). The following procedure was found more convenient than the one reported by Avakian:[2] an equimolar mixture of the two reagents was refluxed until steam had ceased to evolve, and the residue was fractionated *in vacuo*. An 80 per cent yield of a pale yellow, viscous oil was obtained, b.p. 236–238°/16 mm, $n_D^{24.5}$ 1·5585.

N,N-*Diethylaminoethyl 4-(2-methyl-5-phenyl-1-pyrryl)benzoate* (I). An equimolar mixture of procaine (*base*) and 1-phenyl-1,4-pentanedione was heated at *ca.* 180° until steam had ceased to evolve, and the reaction product was then fractionated *in vacuo*, giving a 70 per cent yield of a highly viscous oil, b.p. 268°/12 mm.

Anal. Calcd. for $C_{24}H_{28}N_2O_2$: C, 76·6; H, 7·5. Found: C, 76·3; H, 7·8.

The corresponding *hydrochloride*, prepared in ether, crystallized from a mixture of ethanol–ether as fine colourless prisms, m.p. 169°.

Anal. Calcd. for $C_{24}H_{29}ClN_2O_2$: N, 6·8. Found: N, 6·7.

2-(2,5-Dimethyl-1-pyrryl)benzhydrazide (II; R = R′ = CH_3). An equimolar mixture of methyl anthranilate and hexane-2,5-dione was refluxed in the usual way, giving an almost theoretical yield of methyl 2-(2,5-dimethyl-1-pyrryl)benzoate as a colourless liquid, b.p. 158°/12 mm. A solution of this ester in ethanol was refluxed for 4 h with 95 per cent hydrazine hydrate in slight excess. The *hydrazide* that precipitated on cooling crystallized from ethanol as shiny, colourless prisms, m.p. 129°.

Anal. Calcd. for $C_{13}H_{15}N_3O$: N, 18·3. Found: N, 18·1.

2-(2-Methyl-5-phenyl-1-pyrryl)benzhydrazide (II; R = CH_3, R′ = C_6H_5). Knorr–Paal condensation of 1-phenyl-1,4-pentanedione with methyl anthranilate gave a viscous yellow oil, b.p. 208°/13 mm, which was converted into the corresponding *hydrazide* as above; this formed shiny, microscopic needles, m.p. 163°, from ethanol.

Anal. Calcd. for $C_{18}H_{17}N_3O$: N, 14·4. Found: N, 14·1.

2-(2,5-Diphenyl-1-pyrryl)benzhydrazide (II; R = R′ = C_6H_5). Prepared in the usual way *via* methyl anthranilate and 1,4-diphenyl-1,4-butanedione, this *hydrazide* formed fine colourless prisms, m.p. 221°, from ethanol.

Anal. Calcd. for $C_{23}H_{19}N_3O$: N, 11·9. Found: N, 11·7.

4-(2,5-Diphenyl-1-pyrryl)benzhydrazide (III). Knorr–Paal condensation of ethyl 4-aminobenzoate with 1,4-diphenyl-1,4-butanedione gave an ester, b.p. 250°/14 mm, which gave a *hydrazide*, crystallizing as silky, colourless needles, m.p. 265°, from ethanol.

Anal. Calcd. for $C_{23}H_{19}N_3O$: N, 11·9. Found: N, 11·8.

Determination of local anaesthetic activity. The method used was based on the inhibition of the oculo-palpebral reflex of the eye in rabbit following instillation of the compound dissolved in physiological saline. The degree of anaesthesia was measured by the number of touch-contacts necessary for reproducing the reflex. In these conditions, a 4 per cent solution of the hydro-

chloride of (I) showed an activity equalling that of a 15 per cent solution of procaine; a 12 per cent solution of the hydrochloride of (I) had an extremely prolonged effect, but produced an irritation of the cornea and conjunctiva which lasted for several days.

Determination of tuberculostatic activity. This was effected on *Mycobacterium tuberculosis* var. *hominis* (strain H37 Rv D) on Dubos medium, the inoculation being made with 10 μg of bacteria per 5 ml of culture medium; the hydrazides to be tested were dissolved in diethylene glycol and the cultures kept at 37° for 12 days. Inhibition of growth was measured by opacimetry by means of an electrophotometer. The hydrazides showed an inhibitory effect at concentrations of 10^{-4}.

(*Received 8 June, 1960*)

References

[1] Buu-Hoï, N. P., Xuong, N. D. and Gazave, J. M. *J. org. Chem.*, **20**, 639 (1955); Buu-Hoï, N. P., Rips, R. and Cavier, R. This Journal, **1**, 23 (1959); **1**, 319 (1959); Morelli, G. and Stein, M. L. This Journal, **2**, 79 (1960)

[2] Avakian, S. U.S. Patent 2,448,408 (1946)

Erratum

'Comparative Activity of Bufadienolides', by Chen and Henderson, **3**, 111 (1961)

Page 117. The formulas (XVII), (XVIII) and (XIX) are in error. Hofer and Meyer (*Helv. chim. acta*, **43**, 1496 (1960)) presented a partial formula for cinobufotalin and ruled out the possibility of its being an analogue of digoxigenin. The comparison between desacetyl cinobufotalin and digoxigenin (p. 121, par. 3) therefore does not apply.