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Note

Spasmolytic Activity of 1-Pyridylpyrroles

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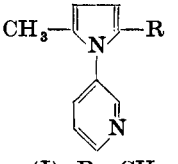
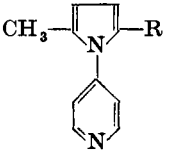
In two previous papers, we reported the considerable musculotropic antispasmodic activity of various basically-substituted pyrroles bearing an open-chain amino group in a radical attached to position 1.[1,2] It was of interest to determine whether this spasmolytic effect would persist, and to what degree, in derivatives of pyrroles in which the basic nitrogen atom is part of a heterocycle, for instance pyridine. For this reason, several 1-pyridylpyrroles carrying various substituents in positions 2 and 5 were prepared, and their spasmolytic activity was investigated.

The synthesis of these compounds was achieved by Knorr–Paal condensations of 3- and 4-aminopyridine, each with acetonylacetone and phenacylacetone. With 3-aminopyridine, 1-(3′-pyridyl)-2,5-dimethylpyrrole (I) and 1-(3′-pyridyl)-2-methyl-5-phenylpyrrole (II) were prepared in this way, and from 4-aminopyridine, 1-(4′-pyridyl)-2, 5-dimethylpyrrole (III) and 1-(4′-pyridyl)-2-methyl-5-phenylpyrrole (IV) were obtained.



(I); R = CH_3
(II); R = C_6H_5



(III); R = CH_3
(IV); R = C_6H_5

These various pyridylpyrroles are compounds with distinct basic properties, and give well-crystallized hygroscopic hydrochlorides. All the hydrochlorides, tested for musculotropic antispasmodic activity against barium chloride induced spasm in the perfused rat duodenum, proved active at doses similar to those

customary for papaverine hydrochloride, the hydrochloride of compound (III) being the most active. The neurotropic spasmolytic activity, determined on the same organ and using acetylcholine chloride as the spasmogen, showed these compounds to be several hundred times less effective than atropine sulphate.

It is to be noted that in this series, there is no appreciable difference in activity between the *meta* and the *para* compounds, whereas in the 1-(β-diethylaminoethoxyphenyl)pyrrole group already investigated,[1] the *meta* compound was noticeably more active than the *para* isomer. Likewise, in this new series, the replacement of a methyl group by a phenyl group in position 5 of the pyrrole moiety causes no marked increase in the spasmolytic activity such as was observed[1] when passing from 1-(2-β-diethylaminoethoxyphenyl)-2,5-dimethylpyrrole to 1-(2-β-diethylaminoethoxyphenyl)-2-methyl-5-phenylpyrrole.

Experimental

1-(3'-Pyridyl)-2,5-dimethylpyrrole (*I*). A mixture of acetonylacetone (10 g) and redistilled 3-aminopyridine (8 g) was gently refluxed for 6 h, and the reaction-product fractionated *in vacuo*; the yield of pyrrole was 13·5 g (90 per cent), in the form of a colourless oil, b.p. 137°/13 mm, which smelt of cooked apple. This oil solidified on cooling, and after recrystallization from aqueous methanol, fine colourless needles, m.p. 40°, were obtained.

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76·7; H, 7·0; N, 16·3. Found: C, 76·1; H, 7·2; N, 16·5.

The corresponding *hydrochloride* crystallized from ethanol ether in shiny prisms, m.p. 171–172°.

Anal. Calcd. for $C_{11}H_{13}ClN_2$: Cl, 17·0. Found: Cl, 17·0.

1-(3'-Pyridyl)-2-methyl-5-phenylpyrrole (*II*). Prepared in a similar manner from phenacylacetone (10 g) and 3-aminopyridine (5 g), this *pyrrole* (11 g; 83 per cent yield) had b.p. 197–199°/17 mm, and crystallized from cyclohexane in silky colourless needles, m.p. 107°.

Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82·0; H, 6·0; N, 12·0. Found: C, 82·3; H, 6·2; N, 11·8.

The *hydrochloride* crystallized from ethanol ether in colourless needles, m.p. 170°.

Anal. Calcd. for $C_{16}H_{15}ClN_2$: Cl, 13·1. Found : Cl, 13·1.

1-(4'-Pyridyl)-2,5-dimethylpyrrole (III). Prepared from acetonylacetone (10 g) and 4-aminopyridine (8 g), this *pyrrole* (9·6 g; 64 per cent yield) had b.p. 150°/17 mm, and crystallized from aqueous ethanol in long colourless rods, m.p. 101°.

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76·7; H, 7·0; N, 16·3. Found: C, 77·2; H, 7·2; N, 15·8.

The *hydrochloride* crystallized from ethanol ether in colourless prisms, m.p. 194°.

Anal. Calcd. for $C_{11}H_{13}ClN_2$: Cl, 17·0. Found : Cl, 17·1.

1-(4'-Pyridyl)-2-methyl-5-phenylpyrrole (IV). This *pyrrole* was prepared from phenacylacetone (10 g) and 4-aminopyridine (5 g). Yield: 9·5 g (71 per cent) of a product, b.p. 265–267°/18 mm, crystallizing from ethanol in fine colourless needles, m.p. 246°.

Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82·0; H, 6·0; N, 12·0. Found: C, 82·1; H, 6·2; N, 11·7.

The *hydrochloride* crystallized from ethanol ether in colourless prisms, m.p. 227°.

Anal. Calcd. for $C_{16}H_{15}ClN_2$: Cl, 13·1. Found : Cl, 13·2.

Table I. Curative spasmolytic activity of some 1-pyridylpyrroles (hydrochlorides)

Substance	Musculotropic spasmolytic activity equivalent to one μg of papaverine hydrochloride, μg	Neurotropic spasmolytic activity equivalent to one μg of atropine sulphate, μg
I	1–2	*ca.* 400
II	1	300–400
III	2	500
IV	1	*ca.* 400

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References

[1] Buu-Hoï, N. P., Rips, R. and Cavier, R. This Journal, **1**, 23 (1959)
[2] Buu-Hoï, N. P., Rips, R. and Cavier, R. This Journal, **1**, 319 (1959)