Journal of Medicinal and Pharmaceutical Chemistry

VOL. 1, No. 4 (1959)

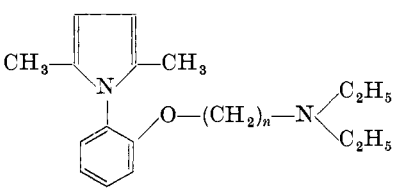
Relationship between Constitution and Activity in a Series of 2,5-Disubstituted 1-(2-Dialkylaminoalkoxyphenyl) Pyrroles

N. P. BUU-HOÏ, RICHARD RIPS and R. CAVIER

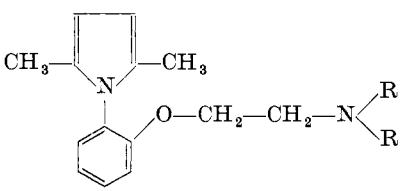
Radium Institute and Faculty of Pharmacy, University of Paris

In a recent paper[1] we reported the considerable antispasmodic activity of 1-(2-β-diethylaminoethoxyphenyl)-2,5-dimethylpyrrole (I); it was then thought of interest to investigate the effect of various chemical changes in this molecule on pharmacodynamic properties.

In order to determine the influence of the dialkylaminoalkoxy moiety of the molecule, we first synthesized 1-(2-γ-diethylaminopropoxyphenyl)-2,5-dimethylpyrrole (II), whose papaverine index (representing the musculotropic spasmolytic activity) and atropine index (representing the neurotropic spasmolytic activity) both proved lower than those of the parent compound. The detrimental effect brought about by the replacement of the ethyl groups on the nitrogen atoms by methyl groups is shown by the fact that 1-(2-β-dimethylaminoethoxyphenyl)-2,5-dimethylpyrrole (III) has a much lower activity than compound (I), whereas in the case of replacement by *iso*propyl groups, i.e. 1-(2-β-di*iso*propylaminoethoxyphenyl)-2,5-dimethylpyrrole (IV),

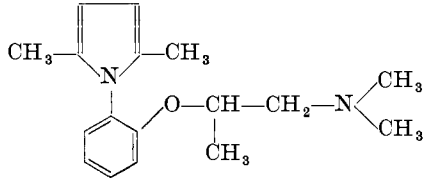


(I); $n = 2$
(II); $n = 3$

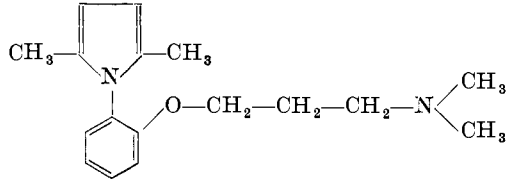


(III); R = CH_3
(IV); R = i-C_3H_7

the papaverine-like activity is only slightly below that of compound (I), although the atropine-like activity is 5 to 10 times less. The low degree of activity of 1-(2-β-dimethylaminopropoxyphenyl)-2,5-dimethylpyrrole (V) and 1-(2-γ-dimethylaminopropoxyphenyl)-2,5-dimethylpyrrole (VI) demonstrates the detrimental effect of changes brought about both on the alkoxy chain and on the *N*-dialkyl groups.



(V)

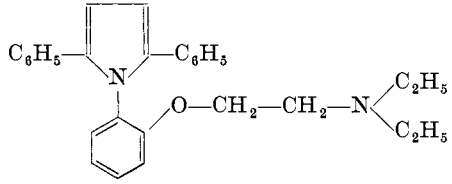


(VI)

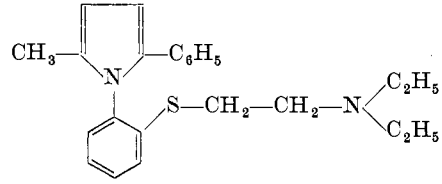
Although it was shown in the previous paper[1] that replacement of one of the methyl groups in positions 2 and 5 by a phenyl group enhanced the antispasmodic activity, replacement of both methyl groups by phenyl groups, leading to 1-(2-β-diethylaminoethoxyphenyl)-2,5-diphenylpyrrole (VII), leaves the papaverine-like activity intact whilst reducing the atropine-like activity. Finally, replacement of the oxygen atom by a sulphur atom, leading to the aminothioether (VIII), produces an increase in the activity.

The preparation of the various aminoethers described above was effected by condensation of the appropriate pyrrolic phenol or thiophenol[2] with the requisite dialkylaminoalkyl chloride in the presence of sodium hydroxide, in the usual way. The pyrrolic phenols were prepared either by direct Knorr–Paal condensations[3] of aminophenols with 1,4-diketones, or by demethylation with pyridine hydrochloride of the products of Knorr–Paal condensations of anisidines with the same 1,4-diketones.

From this series of investigations it emerges that 1-(2-β-diethylaminoethoxyphenyl)-2-methyl-5-phenylpyrrole represents the most favourable molecular structure thus far encountered as regards antispasmodic activity in the pyrrole series. It should be noted,



(VII)



(VIII)

however, that all the compounds reported herein possess a musculotropic spasmolytic activity higher than that of papaverine, although the neurotropic spasmolytic activities are in most cases considerably lower than that of atropine.

Experimental

Preparation of 2,5-Disubstituted 1-(Methoxyphenyl)Pyrroles

These pyrroles were prepared in yields ranging from 70 to 94 per cent, by heating hexane-2,5-dione, phenacylacetone, or 1,2-dibenzoylethane with equimolar amounts of *o*-, *m*-, or *p*-anisidine until evolution of water had ceased; the reaction product was fractionated *in vacuo*, and purified by re-crystallization from an appropriate solvent. The following compounds have not been reported hitherto:

1-(2-Methoxyphenyl-2-methyl-5-phenylpyrrole, b.p. 208°/14 mm (94 per cent yield), colourless plates, m.p. 71°, from petroleum ether. *Anal.* Calcd. for $C_{18}H_{17}NO$: C, 82·1; H, 6·5. Found: C, 82·2; H, 6·3.

1-(2-Methoxyphenyl)-2,5-diphenylpyrrole, b.p. 258°/15 mm (70

per cent yield), shiny colourless needles, m.p. 144°, from *cyclo*hexane. *Anal.* Calcd. for $C_{23}H_{19}NO$: C, 84·9; H, 5·9. Found: C, 84·9; H, 5·9.

1-(3-Methoxyphenyl)-2-methyl-5-phenylpyrrole, b.p. 206–208°/11 mm (83 per cent yield), colourless prisms, m.p. 82°, from petroleum ether. *Anal.* Calcd. for $C_{18}H_{17}NO$: C, 82·1; H, 6·5. Found: C, 82·3; H, 6·5.

1-(3-Methoxyphenyl)-2,5-diphenylpyrrole, b.p. 245°/13 mm (75 per cent yield), shiny colourless needles, m.p. 146°, from *cyclo*hexane. *Anal.* Calcd. for $C_{23}H_{19}NO$: C, 84·9; H, 5·9. Found: C, 84·9; H, 5·9.

1-(4-Methoxyphenyl)-2-methyl-5-phenylpyrrole, b.p. 220°/17 mm (80 per cent yield), shiny colourless needles, m.p. 108°, from *cyclo*hexane. *Anal.* Calcd. for $C_{18}H_{17}NO$: C, 82·1; H, 6·5. Found: C, 81·9; H, 6·5.

1-(4-Methoxyphenyl)-2,5-diphenylpyrrole, b.p. 266–268°/14 mm (75 per cent yield), colourless prisms, m.p. 229°, from benzene. *Anal.* Calcd. for $C_{23}H_{19}NO$: C, 84·9; H, 5·9. Found: C, 85·0; H, 5·9.

Preparation of 2,5-Disubstituted 1-(Hydroxyphenyl)Pyrroles

These compounds were prepared either by Knorr–Paal reactions starting from aminophenols (with yields ranging from 76 to 99 per cent), or by gently refluxing for 4 h, a mixture of equal weights of the methoxy compounds described above and freshly re-distilled pyridine hydrochloride; after cooling, water was added, the precipitate washed with water, and the residue re-crystallized from the appropriate solvent (yields: 70 to 75 per cent.) The following hydroxypyrroles have not been described previously:

1-(3-Hydroxyphenyl)-2-methyl-5-phenylpyrrole, b.p. 232°/16 mm, shiny colourless needles, m.p. 110°, from *cyclo*hexane. *Anal.* Calcd. for $C_{17}H_{15}NO$: C, 81·9; H, 6·1. Found: C, 81·8; H, 6·1.

1-(4-Hydroxyphenyl)-2-methyl-5-phenylpyrrole, b.p. 227°/10 mm, colourless prisms, m.p. 125°, from *cyclo*hexane. *Anal.* Calcd. for $C_{17}H_{15}NO$: C, 81·9; H, 6·1. Found: C, 81·8; H, 6·1.

1-(2-Hydroxyphenyl)-2,5-diphenylpyrrole, b.p. 240°/11 mm, colourless plates, m.p. 183°, from *cyclo*hexane. *Anal.* Calcd. for $C_{22}H_{17}NO$: C, 84·8; H, 5·5. Found: C, 85·0; H, 5·4.

1-(3-Hydroxyphenyl)-2,5-diphenylpyrrole, colourless, sublimable needles, m.p. 227°, from *cyclo*hexane. *Anal.* Calcd. for $C_{22}H_{17}NO$: C, 84·8; H, 5·5. Found: C, 84·9; H, 5·5.

1-(4-Hydroxyphenyl)-2,5-diphenylpyrrole, colourless, sublimable leaflets, m.p. 275°, from methanol. *Anal.* Calcd. for $C_{22}H_{17}NO$: C, 84·8; H, 5·5. Found: C, 84·8; H, 5·5.

Preparation of Aminoethers

1-(2-γ-Diethylaminopropoxyphenyl)-2,5-dimethylpyrrole (II). Ten g of 1-(2-hydroxyphenyl)-2,5-dimethylpyrrole was added to a solution of 2·2 g of sodium hydroxide in 15 ml of ethanol, and the mixture, when well homogenized, treated with 9 g of γ-diethylaminopropyl chloride in small portions and with stirring; stirring was continued for a further hour, and the reaction completed by a brief heating on a water-bath. The ethanol was then evaporated off, water was added, the aminoether extracted into chloroform, the chloroform solution dried (Na_2SO_4 anhyd.), the solvent removed, and the residue fractionated *in vacuo*. Yield: 11·4 g of a pale yellow oil, b.p. 196–197°/16 mm, $n_D^{27\cdot5}$ 1·5380. The corresponding *hydrochloride*, prepared by treating the free base with hydrogen chloride in anhydrous ether, crystallized from ethanol benzene in colourless needles, m.p. 143°. *Anal.* Calcd. for $C_{19}H_{29}ClN_2O$: C, 67·7; H, 8·7; N, 8·3. Found: C, 67·8; H, 8·7; N, 8·3.

1-(2-β-Dimethylaminoethoxyphenyl)-2,5-dimethylpyrrole (III). Prepared as above, from 10 g of the phenol and 6·5 g of β-dimethylaminoethyl chloride, this *aminoether* (11·8 g) was a pale yellow oil, b.p. 176–178°/16 mm, n_D^{28} 1·5585. *Anal.* Calcd. for $C_{16}H_{22}N_2O$: C, 74·4; H, 8·6; N, 10·8. Found: C, 74·4; H, 8·6; N, 11·0.

The corresponding *hydrochloride* crystallized from ethanol/benzene in colourless needles, m.p. 173°.

1-(2-β-Diisopropylaminoethoxyphenyl)-2,5-dimethylpyrrole (IV). This compound (11 g) was obtained from 10 g of the phenol and 9·1 g of β-di*iso*propylaminoethyl chloride, as a pale yellow oil, b.p. 185°/15 mm, n_D^{27} 1·6079. The *hydrochloride* formed colourless needles, m.p. 166°, from carbon tetrachloride. *Anal.* Calcd. for $C_{20}H_{31}ClN_2O$: C, 68·4; H, 8·9; N, 8·0. Found: C, 68·2; H 8·7; N, 8·0.

1-(2-β-Dimethylaminopropoxyphenyl)-2,5-dimethylpyrrole (V). Prepared from 10 g of the phenol and 8·8 g of β-dimethylaminopropyl chloride, this *compound* (10 g) was a pale yellow oil, b.p. 177°/17 mm, $n_D^{27\cdot5}$ 1·5536. *Hydrochloride*, m.p. 151–152°, from carbon tetrachloride. *Anal.* Calcd. for $C_{17}H_{25}ClN_2O$: C, 66·1; H, 8·2; N, 9·1. Found: C, 66·1; H, 8·2; N, 9·1.

1-(2-γ-Dimethylaminopropoxyphenyl)-2,5-dimethylpyrrole (VI). This *aminoether* (9·3 g) was obtained as a pale yellow oil, b.p. 175–176°/17 mm, n_D^{25} 1·5551. *Hydrochloride*, m.p. 180°, from carbon tetrachloride. *Anal.* Calcd. for $C_{17}H_{25}ClN_2O$: C, 66·1; H, 8·2; N, 9·1. Found: C, 66·1; H, 8·3; N, 9·0.

1-(2-β-Diethylaminoethoxyphenyl)-2,5-diphenylpyrrole (VII). This *compound* (12 g) was prepared from 13 g of the phenol, 2 g of sodium hydroxide, and 9 g of β-diethylaminoethyl chloride and formed a pale yellow viscous oil, b.p. 279°/22 mm; *hydrochloride*, m.p. 195–196°, from carbon tetrachloride. *Anal.* Calcd. for $C_{28}H_{31}ClN_2O$: C, 75·2; H, 7·0; N, 6·3. Found: C, 75·3; H, 7·0; N, 6·3.

1-(4-β-Diethylaminoethoxyphenyl)-2-methyl-5-phenylpyrrole. Prepared from 12 g of the corresponding phenol, 3 g of sodium hydroxide, and 9·5 g of β-diethylaminoethyl chloride, this *compound*, b.p. 255°/16 mm, crystallized from ethanol in fine colourless needles, m.p. 116° (*hydrochloride*, m.p. 156°). *Anal.* Calcd. for $C_{23}H_{28}N_2O$: C, 79·3; H, 8·1. Found: C, 79·3; H, 7·9.

1-(2-β-Diethylaminoethylthiophenyl)-2,5-dimethylpyrrole (VIII). Prepared from 12 g of the corresponding thiophenol, 5 g of sodium hydroxide, and 10·5 g of the hydrochloride of β-diethylaminoethyl chloride, this *thioether* (11·8 g) was an almost colourless oil, b.p. 187–189°/18 mm, n_D^{27} 1·6079; *hydrochloride*, m.p. 150°, from ethanol benzene. *Anal.* Calcd. for $C_{18}H_{26}N_2S$: N, 9·3; S, 10·6. Found: N, 9·3; S, 10·3.

Determination of Spasmolytic Activity

The measurements of musculotropic and neurotropic spasmolytic activity were performed according to the technique described in the previous paper,[1] using as standards papaverine hydrochloride for the musculotropic, and atropine sulphate for the neurotropic activity. Results are summarized in Table I.

Table I. Curative spasmolytic activity of new β-Diethylaminoethyl ethers of 2,5-disubstituted 1-(hydroxyphenyl)pyrroles (hydrochlorides)

Substance	Musculotropic spasmolytic activity equivalent to 1 γ of papaverine hydrochloride	Neurotropic spasmolytic activity equivalent to 1 γ of atropine sulphate
II	0·20γ	500–1,000γ
III	0·20γ	5,000γ
IV	0·06–0·10γ	1,000–2,000γ
V	0·20γ	2,000γ
VI	0·20γ	1,000–1,500γ
VII	0·04γ	not determined
VIII	0·05γ	500γ

(*Received 22 May, 1959*)

Summary. A number of 2,5-disubstituted 1-(2-dialkylaminoalkoxyphenyl)pyrroles and related compounds have been synthesized for the study of the relationship between chemical constitution and antispasmodic activity in this series. Most of them proved to possess a musculotropic spasmolytic activity higher than that of papaverine hydrochloride, although the neurotropic spasmolytic activities were considerably lower than that of atropine sulphate.

References

[1] Buu-Hoï, N. P., Rips, R. and Cavier, R. *J. med. pharm. Chem.* **1,** 23 (1959)

[2] *cf.* Buu-Hoï, N. P., Xuong, N. D. and Gazave, J. M. *J. org. Chem.* **20,** 639 (1955); Buu-Hoï, N. P. and Xuong, N. D. *J. org. Chem.* **20,** 850 (1955)

[3] Paal, C. *Ber. dtsch. chem. Ges.* **18,** 2254 (1885); Knorr, L. *Liebigs Ann.* **236,** 313 (1886)