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New Derivatives of 1-Phenylpyrrole of Pharmacological Interest

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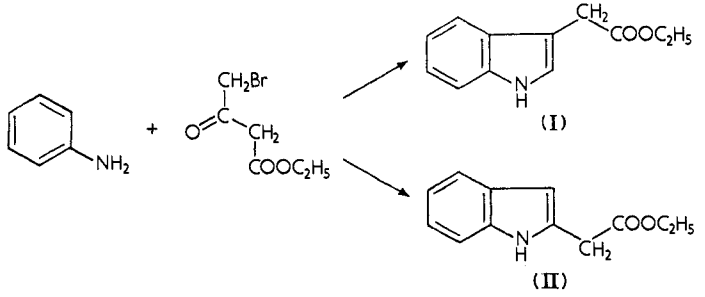
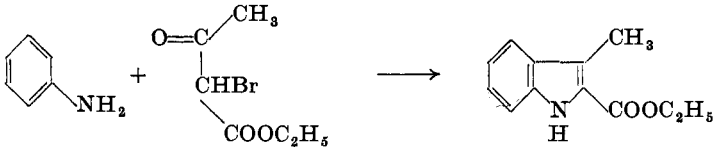
Quite recently a paper appeared by Buu-Hoï *et al.*[1] about a new class of antispasmodics with considerable activity. They are basic ethers derived from 1-phenylpyrrole; this substance thus became interesting, for the first time, in the pharmacological field. However, some indications existed previously concerning the significance of the pyrrole nucleus for the formation of physiologically active substances; the above paper lists a survey of the bibliography on this subject.

Since many of the synthetic antispasmodics are dialkylaminoalkyl esters of suitable acids, and the aromatic ethers described by Buu-Hoï are to be considered an exception to the rule, a search was justified for spasmolytic agents among the basic esters and amides of an acid derived from 1-phenylpyrrole. Moreover, we had available a new acid of this kind, i.e., 1-phenyl-2-methyl-3-carboxypyrrole-5-acetic acid, obtained in the course of a synthesis of indole-2-acetic acid. For this and similar syntheses, the reaction between aniline and ethyl γ-bromoacetoacetate was studied, since such reactions had already been employed in the preparation of ethyl indole-2-isobutyrate.[2]

Owing to the possibility of formation of the two isomeric products (I) and (II), difficulties in this reaction were to be expected.

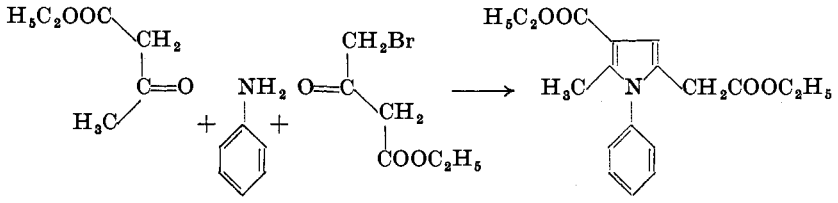


However, under the conditions of Mohlau[3] and Bischler[4] and in agreement with the theories elaborated to explain and forecast the positions of the substituents in the indole nucleus to be formed,[5] the desired isomer (II) could be expected to be at least the major product. We ascertained also that the reaction between ethyl α-bromoacetoacetate and aniline proceeds according to expectation: ethyl 3-methylindole-2-carboxylate[6] is formed regardless of whether the reaction is effected with the bromoester alone or in the presence of some acetoacetic ester.



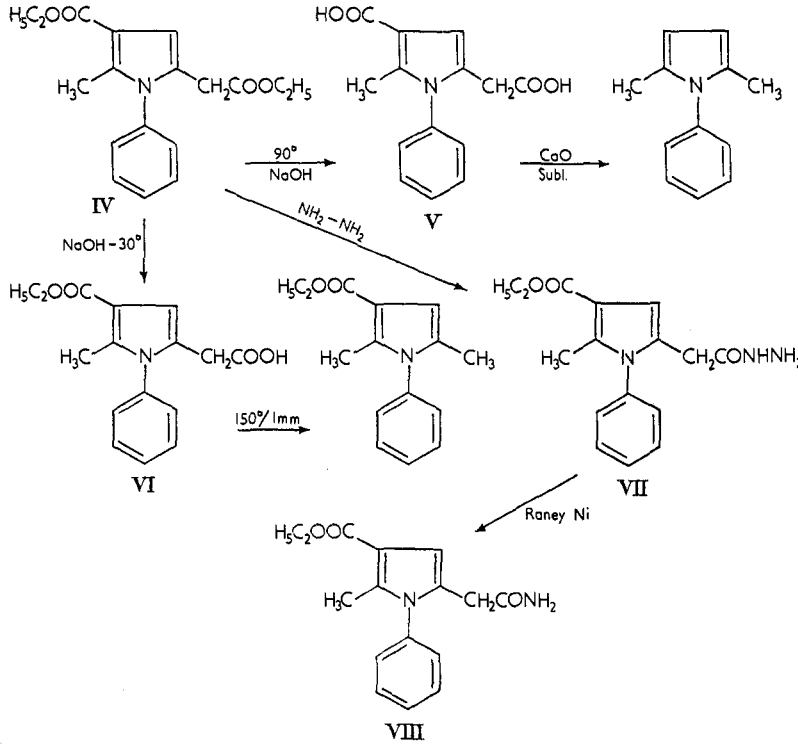
(III)

The reaction with γ-bromoacetoacetic ester and aniline (III) was different: no product of indolic nature was obtained, which may be explained on the basis of the known instability of ethyl indole-2-acetate.[7] By contrast, small amounts of a crystalline diester of pyrrolic nature were obtained, which could be identified as (IV). This resulted from the fact that in order to avoid a partial isomerization of the γ-bromo- to the α-bromoacetoacetic ester during the distillation, a crude product had been used, containing some non-brominated acetoacetic ester. It was therefore a synthesis similar to that of Hantzsch[8] and Feist,[9] and, in fact, good yields of (IV) could be obtained by using aniline, acetoacetic ester and γ-bromoacetoacetic ester in the molecular ratios of 2 : 1 : 1.



(IV)

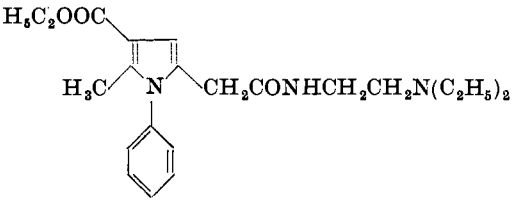
Below are summarized the transformations to which product (IV) was subjected to demonstrate its structure: by decarboxylation of the corresponding acid (V) with calcium oxide, 1-phenyl-2, 3-dimethylpyrrole was obtained, identical with a sample prepared according to Paal.[10]



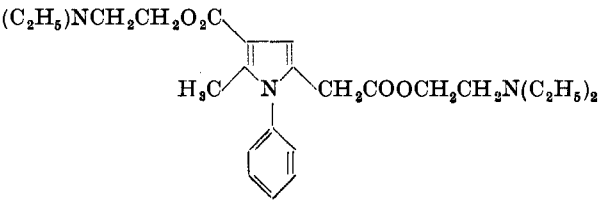
The infrared spectrum of the diester showed two bands in the carbonyl region, i.e. one with a maximum at $5 \cdot 75\,\mu$ corresponding to the aliphatic ester group, the other with a maximum at $5 \cdot 8\,\mu$ corresponding to the aromatic one; of the two ester groups the aliphatic was more easily saponifiable, as could be anticipated and as was proved by the transformation of the acid ester (VI) into ethyl 1-phenyl-2,5-dimethylpyrrole-3-carboxylate.[8]

The same held for aminolysis reactions: by heating the diester (IV) with hydrazine, or with diethylaminoethylamine, there were

obtained the monohydrazide (VII) and the corresponding monoamide (IX) respectively; the latter was an oil giving difficultly crystallizable salts. The bis-diethylaminoethyl ester (XI) was formed by refluxing the acid (V) in acetic ester solution with diethylaminoethyl chloride in the presence of triethylamine. Both (IX) and (XI) gave crystalline ethiodides, (X) and (XII) respectively, which were readily soluble in water. Attempts to obtain the bis-diethylaminoethylamide (XIII) through the reaction of the acid chloride with the diamine, gave poor yields of the desired product, which was difficult to purify.



(IX)



(XI)

Biological Activities

Orientative assays were carried out regarding the anaesthetic and spasmolytic activity of some of the compounds. From the point of view of the anaesthetic activity the most interesting was compound (IX), perhaps because it contains, besides the diethylaminoethyl group, like the basic diester (XI) and diamide (XIII), a lipophilic ethyl ester group which may favourably influence its absorption. The quaternary salts have, as expected, no value as anaesthetics, but are active as spasmolytics. However, also the unquaternized compounds present antispasmodic activity not

only of the myotropic type, as often observed for local anaesthetics,[11] but also of the neurotropic type. In general the spasmolytic activity does not reach that of 1-(2-β-diethylaminoethoxyphenyl)-2-methyl-5-phenylpyrrole, but is of the order of magnitude of the dimethyl substituted 1-(β-diethylaminoethoxyphenyl)-pyrroles;[1] a more active compound should therefore result in the diethylaminoethylamide of 1,2-diphenyl-3-carbethoxypyrrole-5-acetic acid, which will be reported later.

Experimental

Ethyl 3-methylindole-2-carboxylate (*III*). Aniline (11·5 g, 2 moles) was added with cooling to α-bromoacetoacetic ester (12·9 g, 1 mole).[12] During the exothermic reaction crystals of aniline hydrochloride separated. After cooling, chloroform and dilute hydrochloric acid were added and the chloroform layer was washed with water, dried and evaporated. The dark residue was distilled under vacuum: a product boiling at 190–195°/0·5 mm, distilled and soon crystallized. After recrystallization from alcohol, it melted at 135°C, and its elementary analysis closely corresponded to theoretical values. By saponification with aqueous-alcoholic potassium hydroxide in a sealed tube at 150°C, an acid was obtained, which melted at 165–167°, as described in the literature[6] for 3-methylindole-2-carboxylic acid. By heating with calcium oxide, it furnished 3-methylindole, m.p. 95°C.

Ethyl 1-phenyl-2-methyl-3-carbethoxypyrrole-5-acetic acid (*IV*). To a mixture of ethyl γ-bromoacetoacetate (20 g, 1 mole)[12] and ethyl acetoacetate (12·5 g, 1 mole), aniline (17·8 g, 2 moles) was added with cooling. After standing at room temperature, the mixture was heated for 4 h at 130–140°. Then ether and dilute hydrochloric acid were added and the ethereal layer was separated. The residue of the ether solution was distilled, and about 24 g of a thick, slightly yellow liquid, boiling at 175°/0·2 mm, was collected. It crystallized by adding a small amount of methanol and cooling. After purification the melting point was 65–66°.

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68·55; H, 6·71; N, 4·44. Found: C, 68·75; H, 6·74; N, 4·39.

The infrared absorption spectrum, which is discussed in the introduction, was measured in carbon tetrachloride solution, at

1 per cent concentration w/v, using a Perkin–Elmer C 21 double-beam automatic recording spectrophotometer.

1-Phenyl-2-methyl-3-carbethoxypyrrole-5-acethydrazide (*VII*). Ester (IV) (2 g), dissolved in anhydrous ethyl alcohol was refluxed for 1 h with an excess of hydrazine. By concentration and cooling, a precipitate was obtained from which some unchanged starting product was washed out with ether. Crystals (from benzene) melted at 80°, then solidified and melted again at 102°. They lost the solvent of crystallization by heating under vacuum and then melted at 103–104°.

Anal. Calcd. for $C_{16}H_{19}N_3O_3$: C, 63·77; H, 6·36; N, 13·95. Found: C, 63·57; H, 6·36; N, 14·05.

1-Phenyl-2-methyl-3-carbethoxypyrrole-5-acetamide (*VIII*). The hydrazide (VII) was refluxed in alcoholic solution with Raney nickel for 4 h; after filtration and partial evaporation, an equal volume of water was added. The product separated by cooling and was recrystallized from benzene-petroleum ether; m.p. 133–134°.

Anal. Calcd. for $C_{16}H_{18}N_2O_3$: C, 67·11; H, 6·34; N, 9·78. Found: C, 67·10; H, 6·36; N, 10·01.

1-Phenyl-2-methyl-3-carboxypyrrole-5-acetic acid (*V*). The ester (IV) was refluxed with 2 N alcoholic potassium hydroxide for 1 h. After cooling, dilute sulphuric acid was added; a product precipitated which crystallized from ethyl alcohol–water; m.p. 193–194°. The same product was obtained by heating (VII) or (VIII) with alkali.

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64·86; H, 5·05; N, 5·40. Found: C, 64·72; H, 5·23; N, 5·38.

When a mixture of this acid and calcium oxide was slowly heated and the vapours formed were condensed on a cold surface, a crystalline product melting at 51–52° was formed: the melting point of a mixture of this product and a sample of 1-phenyl-2, 5-dimethylpyrrole[10] did not show any depression.

1-Phenyl-2-methyl-3-carbethoxypyrrole-5-acetic acid (*VI*). Ethyl 1-phenyl-2-methyl-3-carbethoxypyrrole-5-acetate was kept in 2 N alcoholic potassium hydroxide at room temperature overnight. After dilution with water, unchanged starting product was extracted with ether. By acidification of the alkaline solution, an oil separated which was dissolved in a little benzene. Some acid

melting at 194° remained undissolved and was separated; the filtrate was precipitated with petroleum ether and recrystallized from alcohol–water, m.p. 125°.

Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66·88; H, 5·96; N, 4·88. Found: C, 66·74; H, 5·87; N, 5·04.

If the substance is distilled at reduced pressure, a product boiling at 150–155°/1 mm, is obtained which crystallizes from petroleum ether and melts at 42–43°. It is ethyl 1-phenyl-2,5-dimethylpyrrole-3-carboxylate;[8] in fact, when it is refluxed with alcoholic potassium hydroxide, the corresponding acid melting at 205° is obtained.

1-Phenyl-2-methyl-3-carbethoxypyrrole-5-diethylaminoethylacetamide (*IX*). A mixture of the diester (IV) (4 g) and more than two moles of diethylaminoethylamine was refluxed for 30 h. The mixture was dissolved in dilute hydrochloric acid and extracted with ether. From the acid solution, treated with NaOH, an oily layer separated which was distilled as a thick oil boiling at 205–210°/0·4 mm.

Anal. Calcd. for $C_{22}H_{31}N_3O_3$: C, 68·54; H, 8·11; N, 10·90. Found: C, 68·35; H, 8·16; N, 10·86.

The ethiodide (X) is obtained by heating a benzene solution of (X) and ethyl iodide at 80°C for 3 h. The precipitated oil crystallized from anhydrous alcohol and ether and melted indefinitely at about 180°.

Anal. Calcd. for $C_{24}H_{36}IN_3O_3$: I, 23·44. Found: I, 23·22.

1-Phenyl-2-methyl-3-carboxypyrrole-5-acetic bis-(diethylaminoethyl ester) (*XI*). A solution of diethylaminoethyl chloride hydrochloride (3 g, 2 moles) and triethylamine (3·8 g, 4 moles) in a small amount of absolute alcohol, was added to the diacid (V) (2·5 g, 1 mole) dissolved in ethyl acetate. After refluxing for 3 h and cooling, the triethylamine hydrochloride was filtered and washed with ether. The filtrate was extracted with dilute hydrochloric acid, the acid extract made alkaline with NaOH and again extracted with ether. The residue from the ether was subjected to vacuum distillation: a slightly yellow oil, boiling at 195°/0·2 mm, was obtained.

Anal. Calcd. for $C_{26}H_{39}N_3O_4$: C, 68·24; H, 8·59; N, 9·18. Found: C, 68·52; H, 8·50; N, 8·91.

The bis-ethiodide (XII) was obtained as described for (X), but

with a larger excess of ethyl iodide. It crystallized readily from absolute alcohol, but was strongly delinquescent, m.p. 132–5° (d.).

Anal. Calcd. for $C_{30}H_{49}I_2N_3O_4$: I, 32·99. Found: I, 32·5.

1-Phenyl-2-methyl-3-carboxypyrrole-5-acetic bis-(diethylaminoethylamide) (XIII). The diacid (V) was treated with cooling with about 5 parts by weight of thionyl chloride and, when the first hydrogen chloride had ceased to develop, the mixture was heated between 40–50° for 15 min. Then it was evaporated under vacuum, dissolved in some anhydrous benzene and evaporated again. The benzene solution of the residue was poured slowly into a cooled solution of excess diethylamine in benzene. The reaction mixture was extracted with dilute hydrochloric acid, made alkaline, and the product transferred into ether. The residue from the ether solution was dissolved in alcohol, and picric acid added. The dark yellow, thick oil which precipitated, was purified several times by dissolving in warm alcohol and letting it precipitate in the cold. A further purification was accomplished by chromatography of the free base on alumina. This base is a very thick pale-brown oil, which does not give crystallizable salts.

Anal. Calcd. for $C_{26}H_{41}N_5O_2$: N, 15·37. Found: N, 15·45.

Determination of Local Anaesthetic Activity

In a 1 per cent boric acid aqueous solution the substances (IX), (XI) and (XIII) were dissolved in concentrations of 1 per cent. A few drops of the solutions were instilled in the conjunctival sac of a rabbit and the reactions to stimulation were observed. After instillation of the substances (IX) and (XI), palpebral and corneal anaesthesia took place immediately and lasted for 240 min in the case of (IX) and about 60 min for (XI). Compound (XIII) promoted anaesthesia of minor intensity, but only after about 10 min, and lasted less than one hour. The compounds produced no irritation and no variations in the size of the pupil.

Determination of the Spasmolytic Activity

For this test the same method was adopted as described by Buu-Hoï.[1] The musculotropic spasmolytic activity was determined on rat duodenum fragments at 38° in oxygenated Tyrode

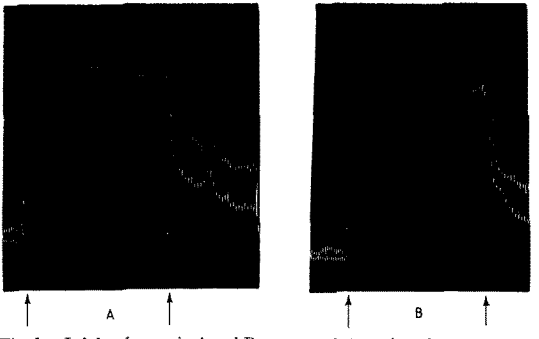


Fig. 1. *Left-hand arrow* in A and B corresponds to action of 5μg of acetylcholine chloride per 20 ml of Tyrode medium; *right-hand arrow* in A corresponds to addition of 40μg of compound (IX), and in B corresponds to addition of 20μg of compound (X).

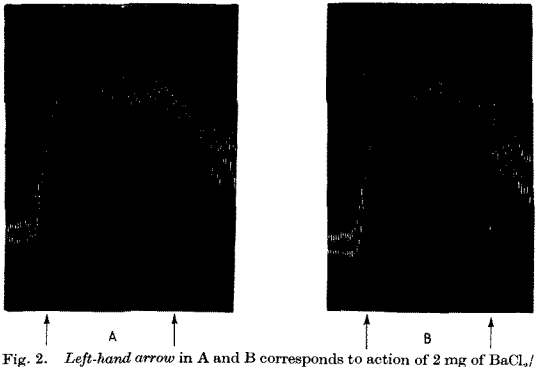


Fig. 2. *Left-hand arrow* in A and B corresponds to action of 2 mg of $BaCl_2$/20 ml of Tyrode medium; *right-hand arrow* in A and B corresponds to the action of 80μg of compound (IX), and in B corresponds to the action of 40μg of compound (X).

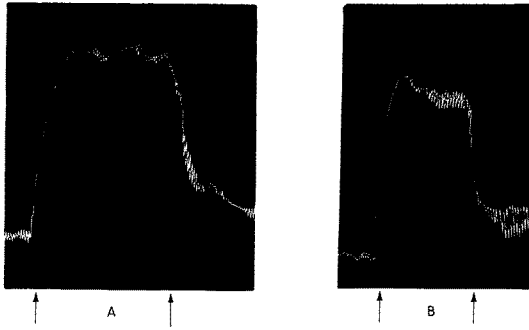


Fig. 3. Experiments with 5μg of acetylcholine chloride as in Fig. 1: *right-hand arrow* in A and B corresponds to the addition of 24μg of compound (XI) and 20μg of compound (XII), respectively.

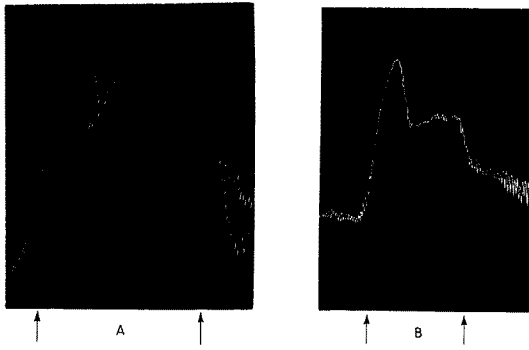


Fig. 4. Experiments with 2 mg of $BaCl_2$ as in Fig. 2: *right-hand arrow* in A and B corresponds to the addition of 60μg of compound (XI) and 50μg of compound (XII), respectively.

medium and compared with that of papaverine hydrochloride (=1) against spasm induced by barium chloride; the neurotropic spasmolytic activity was compared with atropine sulphate (=1) against spasm induced by means of acetylcholine chloride. The ethiodides were found the most active. The results are summarized in Table I.

Table. I. Antispasmodic activities

Substance	Curative musculotropic spasmolytic activity compared with papaverine hydrochloride (=1)	Curative neurotropic spasmolytic activity compared with atropine sulphate (=1)
IX	0·3	1/400
X	0·6	1/200
XI	0·4	1/240
XII	0·5	1/200

Summary. Diethyl 1-phenyl-2-methyl-3-carboxypyrrole-5-acetate has been obtained by the reaction between aniline, acetoacetic ester and γ-bromoacetoacetic ester; the isomeric α-bromoester under the same conditions furnished ethyl 3-methylindole-2-carboxylate. The bis-(diethylaminoethyl)ester, the bis-(diethylaminoethyl)amide, and the ethyl ester-diethylaminoethylamide of 1-phenyl-2-methyl-3-carboxypyrrole-5-acetic acid were prepared and their anaesthetic activity was studied. The last compound was the most effective, giving an immediate and long lasting anaesthesia. All the compounds are active as spasmolytics, especially the quaternary ammonium salts.

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References

[1] Buu-Hoï, N. P. and Cavier, R. *J. med. pharm. Chem.* **1,** 23 (1959)
[2] Jönson, A. *Svensk kem. Tidskr.* **67,** 188 (1955)
[3] Mohlau, R. *Ber. dtsch. chem. Ges.* **14,** 171 (1881)
[4] Bischler, A. *Ber. dtsch. chem. Ges.* **25,** 2860 (1892); **26,** 1336 (1893)

[5] Julian, P. L. *et al.* *J. Amer. chem. Soc.* **67,** 1203 (1945)
Brown, F. and Mann, F. *J. chem. Soc.* 847, 858 (1948)
[6] Wislicenus, W. and Arnold, E. *Ber. dtsch. chem. Ges.* **20,** 3395 (1887)
Wislicenus, W. *Ann.* **246,** 334 (1888)
[7] Giuliano, R. and Stein, M. L. *Ann. Chim. appl., Roma* **48,** 1284 (1958);
Schindler, W. *Helv. chim. acta* **41,** 1441 (1958)
[8] Hantzsch, A. *Ber. dtsch. chem. Ges.* **23,** 1474 (1890)
[9] Feist, F. *Ber. dtsch. chem. Ges.* **35,** 1546 (1902)
[10] Paal, C. *Ber. dtsch. chem. Ges.* **18,** 2254 (1885); Knorr, L. *Ann.* **236,**
290 (1886)
[11] Lehmann, G. and Knoefel, P. K. *J. Pharmacol.* **74,** 274 (1942)
[12] Conrad, M. and Schmidt, L. *Ber. dtsch. chem. Ges.* **29,** 1043 (1896)