ethylamine hydrochloride was filtered the ether distilled through a Vigreux column, and the ester fractionated at reduced pressure; yield, 10.7 g. (81%), b.p. 68°/21 mm. Liberation of the amino acid ester by passing dry ammonia through the suspension of the hydrochloride in ether also gave satisfactory yields.

t-Butyl hippurate (benzoyl glycine t-butyl ester). A 3.35-g. sample of glycine *t*-butyl ester hydrochloride was dissolved in 10 ml. of water; a solution of 2.0 g. sodium hydroxide in 10 ml. of water was added, the mixture was cooled with ice, and 2.8 g. benzoyl chloride was added while the mixture was shaken. The crystalline material which separated was dissolved in 50 ml. of benzene. The benzene layer was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Addition of Skelly B immediately caused crystallization of a colorless substance. After standing at low temperature for some hours, the crystalline material was filtered and dried; yield, 3.5 g. (74%), m.p. 109–110°. The substance crystallizes well from hot Skelly B.

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.49; H, 7.37; N, 6.11.

The same compound was obtained by reaction of hippuryl chloride and *t*-butyl alcohol in the presence of pyridine, by the silver salt method (*t*-butyl bromide and silver hippurate) and by ester interchange of methyl hippurate with *t*-butyl alcohol and sodium *t*-butoxide. However, the yields never exceeded 30% by any of these methods.

t-Amyl hippurate. Preparation was analogous to the *t*-butyl ester. Yield, 76%; m.p. 76–77°, recrystallized from Skelly B.

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68. Found: C, 67.28; H, 7.75.

Benzoyl-DL-alanine-t-butyl ester. Preparation was analogous to the glycine derivative. Yield, 68%, m.p. 99°, recrystallized from Skelly B.

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68. Found: C, 67.70; H, 7.59.

DL-Phenylalanine t-butyl ester hydrochloride. A 50-g. sample of α-bromo-β-phenylpropionic acid, obtained from bromobenzylmalonic acid[20b] by decarboxylation, was dissolved in 50 ml. of ether. The solution was placed in a 250 ml. pressure bottle, chilled in an ice bath, and 2.5 ml. of concentrated sulfuric acid and 50 ml. of liquid isobutylene were added. The mixture was shaken at room temperature for 7 hr., cooled before opening the bottle, and transferred to a separatory funnel containing a solution of 34 g. sodium hydroxide in 125 g. water, 130 g. ice, and 50 ml. of ether. The mixture was shaken vigorously, the ether layer was separated, and the aqueous phase was extracted twice with 70-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate. The isobutylene and the ether were distilled through a Vigreux column, and the solvents were removed at 20 mm. and a bath temperature not exceeding 50°. The 48 g. of slightly yellow-colored oil obtained was used without further purification.

A 38.7-g. sample of the ester was dissolved in 100 ml. of acetone. This solution was added to a mixture of 19 g. sodium azide in 50 ml. of water and the mixture was refluxed for 20 hr. The acetone was removed by distillation and the remaining oil was worked up in the usual way. The fractionation gave 30.4 g. (90%) of the azido ester as a colorless oil, boiling near 112° at 1 mm.; $n_D^{25} = 1.4976$.

Anal. Calcd. for $C_{13}H_{17}N_3O_2$: C, 63.13; H, 6.92; N, 16.99. Found: C, 62.96; H, 7.03; N, 17.04.

A 12.3-g. sample (0.05 mol.) of the azide was dissolved in 300 ml. of methanol and hydrogenated as described before. The solution was adjusted to *p*H 4.9 with methanolic hydrogen chloride and evaporated under reduced pressure. Addition of ether gave 10.9 g. (85%) of the hydrochloride as colorless needles; m.p. near 228–230° (dec.).

Anal. Calcd. for $C_{13}H_{19}NO_2 \cdot HCl$: C, 60.57; H, 7.82; N, 5.43. Found: C, 60.52; H, 7.72; N, 5.56.

The benzoyl derivative of the ester was obtained in a yield of 79%; m.p. near 84°. It can be recrystallized from Skelly B.

Anal. Calcd. for $C_{20}H_{23}NO_3$: C, 73.81; H, 7.12. Found: C, 73.86; H, 7.05.

Infrared-Spectra. Infrared data were obtained by measuring the absorption of 10% solutions of the esters in chloroform with a Perkin-Elmer Model 21 Spectrophotometer.

NOTE ADDED IN PROOF: Since this work was completed two communications on t-butyl esters of amino acids[22] and its acyl derivatives[23] have appeared.

LOS ANGELES 24, CALIF.

(21) B. Abramovitch, J. C. Sivers, B. E. Hudson, and C. R. Hauser, *J. Am. Chem. Soc.*, **65**, 986 (1943).

(22) R. W. Roeske, *Chem. & Ind.*, 1121 (1959).

(23) E. Taschner, B. Liberek, Cz. Wasielewski, and J. Biernat, *Z. angew. Chem.*, **71**, 743 (1959).

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

1,2,5-Trisubstituted Pyrroles of Pharmacologic Interest

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Received September 9, 1959

A large number of 2,5-disubstituted pyrroles bearing an aromatic or a heterocyclic substituent in position 1 have been prepared, most of them for evaluation of their antispasmodic activity.

In previous papers, we have recorded the pronounced antispasmodic activity of several 2,5-dimethyl- and 2-methyl-5-phenyl- pyrroles bearing in position 1 an alkoxyphenyl group.[1] These compounds, especially 1-(2-β-diethylaminoethoxyphenyl)-2-methyl-5-phenylpyrrole (I), showed a musculotropic spasmolytic activity several times greater than that of papaverine, although their neurotropic spasmolytic potency was generally considerably less than that of atropine. Spasmolytic activity has also been encountered in a number of 2,5-disubstituted 1-pyridylpyrroles,[2] although to a lesser degree. These various observations prompted the synthesis of further members of

(1) N. P. Buu-Hoï, R. Rips, and R. Cavier, *J. Med. Pharm. Chem.*, **1**, 23 (1959).

(2) N. P. Buu-Hoï, R. Rips, and R. Cavier, *J. Med. Pharm. Chem.*, in press.

TABLE I

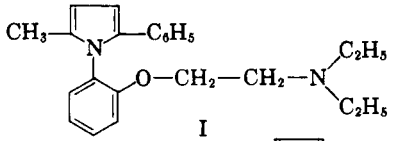
1,2,5-TRISUBSTITUTED PYRROLES WITH A NITROGEN HETEROCYCLIC SUBSTITUENT

Pyrrole	Formula	M.P., °C.	B.P., °C.	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1-(2-Pyridyl)-2,5-dimethyl-[a]	$C_{11}H_{12}N_2$	—	151–152/15 mm.	—	—	—	—	—	—
1-(2-Pyridyl)-2-methyl-5-phenyl-	$C_{16}H_{14}N_2$	97	215/18	82.0	6.0	11.9	82.1	6.0	11.9
1-(2-Pyridylmethyl)-2,5-dimethyl-[b]	$C_{12}H_{14}N_2$	53	152–153/14			15.0			15.1
1-(2-Pyridylmethyl)-2-methyl-5-phenyl-[c]	$C_{17}H_{16}N_2$	78	213/14			11.3			11.3
1-(2-Pyridylmethyl)-2,5-diphenyl-	$C_{22}H_{18}N_2$	143	261/14			9.0			9.3
1-(3-Pyridylmethyl)-2,5-dimethyl-	$C_{12}H_{14}N_2$	61	174/17			15.0			15.0
1-(3-Pyridylmethyl)-2-methyl-5-phenyl-[d]	$C_{17}H_{16}N_2$	77	221–222/17			11.3			11.2
1-(3-Pyridylmethyl)-2,5-diphenyl-[e]	$C_{22}H_{18}N_2$	145	266/18			9.0			9.1
1-(4-Pyridylmethyl)-2,5-dimethyl-[f]	$C_{12}H_{14}N_2$	75	182/18			15.0			15.2
1-(4-Pyridylmethyl)-2-methyl-5-phenyl-[g]	$C_{17}H_{16}N_2$	82	224–225/18			11.3			11.4
1-(4-Pyridylmethyl)-2,5-diphenyl-[h]	$C_{22}H_{18}N_2$	171	267–268/14			9.0			9.1
1-(6-Methyl-2-pyridylmethyl)-2,5-dimethyl-	$C_{13}H_{16}N_2$	61	148–150/12			14.0			14.0
1-(6-Methyl-2-pyridylmethyl)-2-methyl-5-phenyl-	$C_{18}H_{18}N_2$	100	210–212/13			10.6			10.5
1-(6-Methyl-2-pyridylmethyl)-2,5-diphenyl-	$C_{23}H_{20}N_2$	106	258–260/13			8.6			8.5
1-Picolinoylamino-2,5-dimethyl-	$C_{12}H_{13}N_3O$	151	218/17	67.0	6.1	19.5	66.8	6.4	19.7
1-Nicotinoylamino-2-methyl-5-phenyl-	$C_{17}H_{15}N_3O$	163	282–284/14	73.6	5.5	15.2	73.8	5.7	15.2
1-Nicotinoylamino-2,5-diphenyl-	$C_{22}H_{17}N_3O$	248	316–318/14	77.9	5.1	12.4	77.8	5.5	12.4
1-Isonicotinoylamino-2-methyl-5-phenyl-	$C_{17}H_{15}N_3O$	185	279/13	73.6	5.5	15.2	73.6	5.7	15.2
1-Isonicotinoylamino-2,5-diphenyl-	$C_{22}H_{17}N_3O$	260	—	77.9	5.1	12.4	77.9	5.1	12.6
1-[5-(1,3,4-Triazolyl)]-2,5-dimethyl-	$C_8H_{10}N_4$	203	263/18			34.6			34.4
1-[5-(1,3,4-Triazolyl)]-2-methyl-5-phenyl-	$C_{13}H_{12}N_4$	198	215/15			25.0			24.7

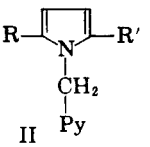
[a] *Cf.* N. P. Buu-Hoï, *J. Chem. Soc.*, 2882 (1949); the hydrochloride had m.p. 127°. [b] Hydrochloride, m.p. 175–176°. [c] Hydrochloride, m.p. 165°. [d] Hydrochloride, m.p. 149–150°. [e] Hydrochloride, m.p. 174–175°. [f] Hydrochloride, m.p. 175°. [g] Hydrochloride, m.p. 150°. [h] Hydrochloride, m.p. 140°.

both categories of pyrroles for pharmacological evaluation.

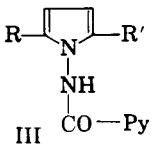
The Knorr-Paal condensation[3] of hexane-2,5-dione, phenacylacetone, and 1,2-dibenzoylethane with the three isomeric picolylamines and 2-aminomethyl-6-methylpyridine was affected with excellent yields in all instances. The characteristics of the reaction products obtained (Formula II) are listed in Table I, along with the Knorr-Paal condensation-products (Formula III) of the same γ-diketones with the hydrazides derived from the three isomeric pyridinecarboxylic acids. It is to be noted that both hexane-2,5-dione and phenacyl-



I

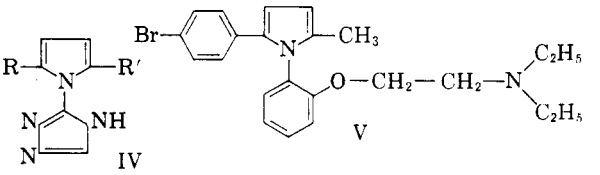


II



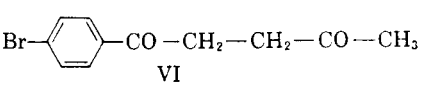
III

acetone readily yielded pyrroles with 2-aminopyridine, although Bishop,[4] using a different technique, was unable to condense hexane-2,5-dione with 2-aminopyridine. Our technique was also applied with success to the condensation of the above γ-diketones with more complex heterocyclic amines, such as 5-amino-1,3,4-triazole which gave compounds of Formula IV.



IV V

In order to investigate the influence of the introduction of a bromine atom on spasmolytic activity in compound I, 1-(2-β-diethylaminoethoxyphenyl)-2-methyl-5-*p*-bromophenylpyrrole (V) was prepared. Its synthesis involved a Friedel-Crafts condensation of levulinic acid chloride with bromobenzene to give *p*-bromophenacylacetone (VI) whose Knorr-Paal condensation with *o*-aminophenol yielded 1-*o*-hydroxyphenyl-2-methyl-5-*p*-



VI

bromophenylpyrrole; alkylation of this last with β-diethylaminoethyl chloride afforded the required basic ether V. For assessing the effect of the replacement of the ether linkage in compound I by a thioether bond, 1-(2-β-diethylaminoethylthiophenyl)-2-methyl-5-phenylpyrrole (VII) was synthesized in the usual way, from 1-*o*-mercaptophenyl-2-methyl-5-phenylpyrrole. Lastly, a basic ester of a pyrrole acid, namely the β-diethylamino-

(3) L. Knorr, *Ann.*, **236**, 313 (1886); C. Paal, *Ber.*, **18**, 2254 (1885).

(4) W. S. Bishop, *J. Am. Chem. Soc.*, **67**, 2261 (1945).

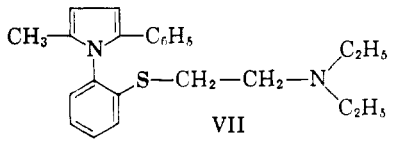
TABLE II

2,5-DISUBSTITUTED 1-ARYLPYRROLES

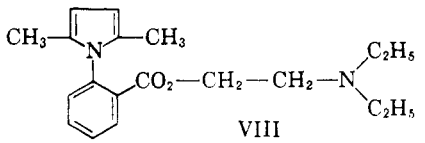
Pyrrole	Formula	M.P., °C.	B.P., °C.	Analyses Calcd. C	Calcd. H	Found C	Found H
1-(2-Mercaptophenyl)-2-methyl-5-phenyl-[a]	$C_{17}H_{15}NS$	91	212/14 mm.	76.9	5.7	77.0	5.7
1-(2-Mercaptophenyl)-2,5-diphenyl-[a]	$C_{22}H_{17}NS$	139	258/14	80.7	5.2	80.7	5.2
1-(5-Hydroxy-1-naphthyl)-2-methyl-5-phenyl-[b]	$C_{21}H_{17}NO$	157	—	84.2	5.7	83.9	5.8
1-(3-Hydroxy-2-naphthyl)-2-methyl-5-phenyl-[b]	$C_{21}H_{17}NO$	118	—	84.2	5.7	84.2	5.7
1-(7-Hydroxy-2-naphthyl)-2-methyl-5-phenyl-[b]	$C_{21}H_{17}NO$	162	285–287/11	84.2	5.7	83.7	5.7
1-(2-Hydroxyphenyl)-2-methyl-5-(4-bromophenyl)-[b]	$C_{17}H_{14}BrNO$	144	245/11	62.2	4.3	62.6	4.5
1-(2-Carboxyphenyl)-2-methyl-5-phenyl-[c]	$C_{18}H_{15}NO_2$	187	255/17	78.0	5.5	77.8	5.6
1-(2-Carboxyphenyl)-2,5-diphenyl-[c]	$C_{23}H_{17}NO_2$	252	296/15	81.4	5.1	81.3	5.0

[a] Crystallization from cyclohexane. [b] Crystallization from a mixture of benzene and cyclohexane. [c] Crystallization from acetic acid.

ethyl ester of 1-*o*-carboxyphenyl-2,5-dimethylpyrrole (VIII) was prepared; this acid, obtained by



VII



VIII

Knorr-Paal condensation of hexane-2,5-dione with anthranilic acid, is included in Table II along with other new 2,5-disubstituted 1-arylpyrroles prepared in the course of this work.

Preliminary experiments show compounds V and VII to possess a musculotropic spasmolytic activity greater than papaverine hydrochloride when tested in the perfused rat duodenum against spasms induced by barium chloride; compound VIII proved to be only slightly active in the same test.

EXPERIMENTAL

Knorr-Paal reactions. The condensation of the various γ-diketones with aromatic and heterocyclic primary arylamines was performed in every instance without a catalyst, by heating the mixture for 15 min. to 1 hr. to above 100°, until steam had ceased to evolve. An excess of the diketone was used, and the reaction product was in most cases separated by vacuum fractionation; in the other cases, direct crystallization was effected. Yields ranged from 35% (condensations with aminonaphthols) to 90% (condensations with low-boiling amines). Recrystallizations were from benzene or cyclohexane in the case of pyridyl-substituted pyrroles, and from cyclohexane or acetic acid in the case of aryl-substituted pyrroles.

p-Bromophenacylacetone (VI). To 58 g. of levulinic acid was added 62.5 g. of thionyl chloride (both freshly redistilled), in small portions with stirring, and the mixture was heated at 50° for 1 hr.; the excess thionyl chloride was distilled off, and the residue vacuum-fractionated, giving 46.5 g. of a colorless liquid, b.p. 80°/15 mm. To a well stirred suspension of 55 g. of aluminum chloride in 300 ml. of bromobenzene, the foregoing chloride was added dropwise; the mixture was kept at room temperature for 15 min., then heated at 65° for 1 hr., and left overnight at room temperature. After decomposition with ice and hydrochloric acid, the organic layer was collected, washed with water, then with 5% aqueous sodium hydroxide, and dried over sodium sulfate. The bromobenzene was distilled off *in vacuo*, and the residue fractionated, giving a 60% yield of *p*-bromophenacylacetone, b.p. 180°/13 mm., crystallizing from cyclohexane in shiny colorless needles, m.p. 85°.

Anal. Calcd. for $C_{11}H_{11}BrO_2$: C, 51.8; H, 4.4. Found: C, 51.8; H, 4.4.

1-(2-β-Diethylaminoethoxyphenyl)-2-methyl-5-p-bromophenylpyrrole (V). To a solution of 11.5 g. of 1-(2-hydroxyphenyl)-2-methyl-5-(4-bromophenyl)pyrrole and 2.5 g. of sodium hydroxide in 50 ml. of ethanol, 8 g. of freshly distilled β-diethylaminoethyl chloride was added portionwise with stirring; once the reaction had subsided, the mixture was refluxed for 1 hr. The ethanol was then distilled off, water added, and the reaction product taken up in chloroform; the organic layer was washed with water and dried over sodium sulfate. The residue from evaporation of the solvent afforded on vacuum fractionation, 10 g. of a viscous yellow oil, b.p. 253–255°/11 mm.

Anal. Calcd. for $C_{23}H_{27}BrN_2O$: C, 64.7; H, 6.4; N, 6.6. Found: C, 64.5; H, 6.4; N, 6.7.

The corresponding *hydrochloride*, prepared by treating the free base in ethereal solution with the equimolar amount of hydrogen chloride, crystallized from ethanol benzene in colorless prisms, m.p. 156°.

1-(2-β-Diethylaminoethylthiophenyl)-2-methyl-5-phenylpyrrole (VII). Prepared similarly from 1-*o*-mercaptophenyl-2-methyl-5-phenylpyrrole, this ether was a viscous yellow oil which could not be distilled without decomposition, and which yielded a *hydrochloride*, crystallizing from ethanol-ether in colorless prisms, m.p. 135°.

Anal. Calcd. for $C_{23}H_{29}ClN_2S$: C, 68.9; H, 7.2. Found: C, 68.6; H, 7.5.

β-Diethylaminoethyl ester of 1-o-carboxyphenyl-2,5-dimethylpyrrole (VIII). This ester, obtained from the sodium salt of the corresponding acid (prepared from 6 g. of the acid and 1.1 g. of sodium hydroxide) and 4 g. of β-diethylaminoethyl chloride, was a pale yellow oil, b.p. 217°/17 mm., n_D^{17} 1.5432; yield: 5.2 g.

Anal. Calcd. for $C_{19}H_{26}N_2O_2$. C, 72.6; H, 8.3; N, 8.9. Found: C, 72.3; H, 8.3; N, 9.2.

The corresponding *hydrochloride* crystallized from ethanol-ether in fine colorless prisms, m.p. 121°.

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