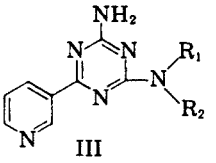
The 2-pyridyl guanamines gave colored solutions or precipitates with ferrous ion, whereas the 3- and 4-pyridyl compounds did not.

Since pyridylguanamines can be envisioned as derivatives of nicotinamide and isonicotinamide with the triazine ring supplying the carboxamide type function,[5] as shown for III,



III

a variety of pharmacological effects associated with these pyridine derivatives was evaluated.

No systematic pharmacological response was noted which would permit an analysis of structure *vs.* activity,[6] although in general, the most active structures were found with the alkylamino derivatives of I, Py = 3- and 4-pyridyl. Upon evaluation[7] the following compounds showed antiinflammatory activity: 7(15 units/g.), 26 (4 units/g.); analgesic activity: 27 (33% at 75 mg./kg.), 28 (83% at 330 mg./kg.). Compounds 2 and 24 showed diuretic action in rats, and also lowered blood pressure significantly. Compound 17 had 4+ anticonvulsant activity associated with a negative Evipal sleeping time response.

(5) F. C. Schaefer, J. R. Dudley and J. T. Thurston, *J. Am. Chem. Soc.*, **73**, 3004 (1951).

(6) For pharmacological study of 5-(4-pyridyl)-3-amino-1,2,4-triazols, see K. Biemann and H. Bretschneider, *Monatsch. Chem.*, **89**, 603 (1958).

(7) The following screening techniques applied have been described. (a) Antiinflammatory activity: S. L. Shapiro, H. Soloway, and L. Freedman: *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 333 (1957); (b) analgesic: C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954); (c) anticonvulsant activity and Evipal sleeping time: S. L. Shapiro, I. M. Rose, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 1648 (1958); also ref. 1b; (d) diuretic: see ref. 1a; (e) blood pressure: S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 2743 (1958).

## EXPERIMENTAL

*Reactants.* The biguanides utilized in this study have been described.[8] Ethyl picolinate was prepared in 58% yield, b.p. 118–122° (14 mm.), following the procedure described for ethyl nicotinate.[9]

*Pyridylguanamines of Table I.* The compounds of Table I were prepared by the same general procedure. A solution of 0.025 mole of the biguanide hydrochloride (or nitrate) in 25 ml. of methanol was treated with 24 ml. (0.05 mole) of 23% sodium methoxide in methanol followed by 0.025 mole of the pyridine carboxylic acid ester. The reaction mixture was maintained at 20° for 24–48 hr. and then decanted into 60 ml. of water. After 72 hr., the precipitate was separated, dried, and recrystallized.

*Color reactions.* Ferrous ion (200 mg./l.)[10] gave brown solutions with compounds 46 and 47, and purple precipitates with compounds 48 and 52. Compound 53 did not react under these test conditions and may have been too insoluble. The 2-pyridylguanamines having an alkylamino substituent give a different color response from those with the arylamino substituent.

The related compounds (1, 2, 7, 18, 23, 29, 24, 40) in the 3- and 4-pyridyl series gave no color with ferrous ion under these conditions.

With cupric ion (500 mg./l.) a brown color was noted with compound 46, and when the hydroxylamine hydrochloride solution was not added, a green color was obtained. Compound 52 under similar conditions gave a brown and green precipitate, respectively.

*Acknowledgment.* The authors are indebted to Dr. G. Ungar and his staff for the pharmacological screening of the compounds.

YONKERS 1, N. Y.

(8) (a) S. L. Shapiro, V. A. Parrino, E. Rogow, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3725 (1959); (b) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3728 (1959).

(9) H. Gilman and H. S. Broadbent, *J. Am. Chem. Soc.*, **70**, 2755 (1948).

(10) The procedure used was adapted from *Official Methods of Analysis of the Association of Official Agricultural Chemists*, Association of Official Agricultural Chemists, Washington, D. C., 8th Ed., 1955, p. 208; using 1 ml. of test solution, 0.1 ml. of hydroxylamine hydrochloride solution, 0.5 ml. of acetate buffer solution and about 2 mg. of the pyridylguanamine, and heating to boiling.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

# A Convenient Synthesis of *t*-Alkyl Esters of Amino Acids[1a]

ARNULF VOLLMAR AND MAX S. DUNN

*Received October 22, 1959*

The preparation of *t*-alkyl esters of glycine, alanine and phenylalanine *via* the corresponding azido derivatives is described and some of the characteristics of the compounds are pointed out.

A convenient synthesis of *t*-alkyl esters of amino acids, desired for certain kinetic and microbiological investigations, is reported in this paper. Standard procedures for the preparation of amino acid esters of primary and secondary alcohols are well known and have been reviewed recently,[1b] but amino acid esters of *t*-alcohols are less readily accessible because of the lability of *t*-alcohols in acid media. Amino acid esters of *t*-alcohols should be of interest in peptide synthesis in view of their ready hydrolysis under mild acid conditions.

The *t*-butyl and trichloro-*t*-butyl esters of *N*,*N*-

dimethylglycine have been obtained through amination of the corresponding chloroacetates with dimethylamine[2,3]; Sheehan[4,5] prepared *t*-butyl 4-carboxy-5,5-dimethyl-$\alpha$-amino-2-thiazolidine, an intermediate in the synthesis of penicillin by hydrazinolysis of the protective phthalyl group.

In the present work it was practicable to introduce the amino group by the hydrogenolytic reduction of azides, a method first described by Bertho and Maier,[6] who obtained glycine ethyl ester in 80% yield by the hydrogenolysis of ethyl azidoacetate with platinum oxide. More recently, Bretschneider *et al.*[7] prepared *O*-ethyl serine ethyl ester by this method. The bromo carbonic ester derivatives, required for the synthesis of azido carbonic esters, were prepared as colorless liquids by acylating *t*-alcohols with bromoacetyl bromide and $\alpha$-bromopropionyl bromide. Minor acid-catalysed decomposition sometimes occurred during distillation of the esters, especially the high boiling *t*-amyl esters. Under such circumstances the *t*-esters were washed with potassium carbonate solution to remove traces of acids. Decomposition was minimal when the distillation was carried out at low pressure. The *t*-butyl ester of $\alpha$-bromo-$\beta$-phenylpropionic acid was prepared by the addition of isobutylene to the acid.[8]

The azido derivatives, prepared by refluxing the bromo esters with sodium azide in aqueous acetone, distilled smoothly to give colorless liquids. These products may be stored without apparent change in the refrigerator but become yellow within a few days at room temperature. As alkyl azides[9] act to lower the blood pressure, azido esters may possess similar toxic properties.

The *t*-alkyl esters of amino acids, obtained by catalytic reduction of the azido group, were isolated in high yields, usually as the hydrochlorides. These salts melt at relatively high temperatures and are virtually non-hygroscopic. This is in contrast to the *n*-butyl, isobutyl, *n*-amyl, and isoamyl ester hydrochlorides of glycine[10] and alanine,[11] which are strongly deliquiescent, apparently because of coordination with water molecules.[12] It was advantageous to isolate glycine *sec*-butyl ester as the non-hygroscopic oxalate rather than the hygroscopic hydrochloride.

The azido esters showed characteristic infrared absorption at 2120 cm.$^{-1}$ and 1345–1353 cm.$^{-1}$ because of the asymmetrical and symmetrical vibrations of the $N_3$ group.[13]

Branched alkyl groups of alkanes show splitting of the band correlated with the methyl symmetrical deformation modes.[14] *t*-Butyl has two bands at 1397 and 1370 cm.$^{-1}$, 3,3-dimethylpropyl at 1384 and 1367 cm$^{-1}$.[15] In close accord with these results obtained from the alkanes the *t*-alkyl esters absorbed in the same range. The *t*-butyl esters absorb at 1393 and 1367 cm.$^{-1}$, the intensity of the second band being about twice as much as the first; the *t*-amyl esters absorb at 1383 and 1368 cm.$^{-1}$ with less intensity differences and can be distinguished thereby from the *t*-butyl esters.

Aqueous solutions of *t*-alkyl esters of amino acid hydrochlorides turn acid on standing a few hours at room temperature and this hydrolysis is accelerated by heating the solutions. The main products are alkenes and *t*-alcohols. *t*-Butyl alcohol was identified by its boiling point, refractive index, and 3,5-dinitrobenzoate as a product of the hydrolysis of glycine *t*-butyl ester hydrochloride.

Gordon *et al.*[16,17] studied the aminolysis of several series of esters varying the alkyl ester group. They found a decreasing reaction rate in the order of *n*-butyl, isobutyl, *sec*-butyl, and *t*-butyl and attributed that result to the increasing electron release effects as well as to steric hindrance. As the self-condensation of free amino acid esters[18,19] leading to peptide esters is also an ester aminolysis a similar order could be expected for the stability toward condensation. Glycine *t*-butyl ester is fairly stable when stored at 26°. After one week the refractive index had not changed and only traces of

(1) (a) Paper No. 131. This work was supported by grants from the American Cancer Society, the National Tuberculosis Association, the United States Public Health Service and the University of California. (b) Theodor Wieland *et al.*, "Methoden der organischen Chemie" (Houben-Weyl), ed. Eugen Mueller, Vol. XI/2, 4. Aufl., Thieme Verlag Stuttgart, 1958, p. 355.

(2) R. Wolffenstein, A. Loewy, and M. Bachstez, *Chem. Ber.*, **48**, 2035 (1915).

(3) F. H. Westheimer and M. F. Shookhoff, *J. Am. Chem. Soc.*, **62**, 269 (1940).

(4) J. C. Sheehan and P. A. Cruickshank, *J. Am. Chem. Soc.*, **78**, 3677 (1956).

(5) J. C. Sheehan and K. R. Henery-Logan, *J. Am. Chem. Soc.*, **79**, 1262 (1957).

(6) A. Bertho and J. Maier, *Ann. Chem.*, **498**, 50 (1932).

(7) H. Bretschneider, N. Karpitschka, and G. Piekarski, *Monatsh. Chem.*, **84**, 1084 (1953).

(8) *Org. Syntheses*, **34**, edit. W. S. Johnson, John Wiley & Sons, Inc., New York 1954, p. 26.

(9) E. Werle and R. Fried, *Biochem. Z.*, **322**, 507 (1952).

(10) E. Abderhalden and Sh. Suzuki, *Z. Physiol. Chem.*, **176**, 103 (1928).

(11) W. Th. J. Morgan, *J. Chem. Soc.*, 79 (1926).

(12) E. F. Mellon and S. R. Hoover, *J. Am. Chem. Soc.*, **73**, 3879 (1951).

(13) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen and Co., London 1958, p. 274.

(14) H. L. McMurray and V. Thornton, *Anal. Chem.*, **24**, 318 (1952).

(15) N. Sheppard and D. M. Simpson, *Quarterly Reviews*, **7**, 22 (1953).

(16) M. Gordon, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.*, **70**, 1946 (1948).

(17) M. Gordon, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.*, **71**, 1245 (1949).

(18) C. H. Bamford, A. Elliott, and W. E. Hanby, *Synthetic Polypeptides*, Academic Press Inc., New York, 1956, p. 17.

(19) E. Katchalski and M. Sela, *Advances in Protein Chemistry*, Vol. XIII, Academic Press Inc., New York 1958, p. 335.

TABLE I

PHYSICAL CONSTANTS AND ELEMENTARY ANALYSIS OF *t*-ALKYL ESTERS OF AMINO ACIDS AND RELATED COMPOUNDS

| | B.P./Mm. | $n_D^{25}$ | Yield, % | Formula | Analyses: Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| *sec*-Butyl bromoacetate[a] | 80.5/17 | 1.4450 | 72 | $C_6H_{11}BrO_2$ | 36.94 | 36.81 | 5.68 | 5.84 | | |
| *t*-Butyl bromoacetate[a] | 62–63/12 | 1.4425 | 78 | $C_6H_{11}BrO_2$ | [b] | | | | | |
| *t*-Amyl bromoacetate[a] | 84/16; 36/1 | 1.4486 | 74 | $C_7H_{13}BrO_2$ | 40.21 | 40.08 | 6.27 | 6.17 | | |
| *t*-Butyl α-bromopropionate | 62/13 | 1.4374 | 71 | $C_7H_{13}BrO_2$ | 40.21 | 40.00 | 6.27 | 6.31 | | |
| *t*-Amyl α-bromopropionate | 86–86/16; 36/1 | 1.4440 | 67 | $C_8H_{15}BrO_2$ | 43.06 | 43.11 | 6.77 | 6.57 | | |
| *sec*-Butyl azidoacetate | 89/17 | 1.4343 | 88 | $C_6H_{11}N_3O_2$ | 45.84 | 45.93 | 7.05 | 6.97 | 26.73 | 26.54 |
| *t*-Butyl azidoacetate | 72–73/13; 79–80/18 | 1.4332 | 95 | $C_6H_{11}N_3O_2$ | 45.84 | 45.56 | 7.05 | 7.04 | 26.73 | 26.49 |
| *t*-Amyl azidoacetate | 92/16; 44/1 | 1.4389 | 94 | $C_7H_{13}N_3O_2$ | 49.10 | 49.04 | 7.65 | 7.41 | 24.54 | 24.63 |
| *t*-Butyl α-azidopropionate | 73/14 | 1.4251 | 91 | $C_7H_{13}N_3O_2$ | 49.10 | 48.91 | 7.65 | 7.74 | 24.54 | 24.78 |
| *t*-Amyl α-azidopropionate | 92–93/17; 44/1 | 1.4327 | 93 | $C_8H_{15}N_3O_2$ | 51.87 | 51.96 | 8.16 | 7.98 | | |
| *sec*-Butyl glycine oxalate | 139° (m.p.) | | 71 | $C_{14}H_{28}N_2O_8$ | 47.71 | 47.59 | 8.01 | 7.95 | | |
| *t*-Butyl glycinate | 57/13; 68/21 | 1.4222 | 81 | $C_6H_{13}NO_2$ | 54.93 | 55.17 | 9.99 | 9.81 | 10.68 | 10.96 |
| *t*-Butyl glycinate hydrochloride | 136° (m.p.)[c] | | 89 | $C_6H_{14}ClNO_2$ | 42.98 | 42.92 | 8.41 | 8.38 | 8.35 | 8.47 |
| *t*-Butyl glycinate oxalate | 156° (m.p.) | | 76 | $C_{14}H_{28}N_2O_8$ | 47.71 | 47.93 | 8.01 | 7.98 | | |
| *t*-Amyl glycinate | 80.5/17; 35/1 | 1.4291 | 86 | $C_7H_{15}NO_2$ | 57.90 | 57.86 | 10.41 | 10.44 | 9.64 | 9.54 |
| *t*-Amyl glycinate hydrochloride | 121° (m.p.)[c] | | 88 | $C_7H_{16}ClNO_2$ | 46.28 | 46.24 | 8.87 | 8.71 | 7.71 | 7.91 |
| *t*-Butyl DL-alaninate | 58/13 | 1.4155 | 85 | $C_7H_{15}NO_2$ | 57.90 | 58.08 | 10.41 | 10.57 | 9.64 | 9.88 |
| *t*-Butyl DL-alaninate hydrochloride | 144° (m.p.)[c] | | 90 | $C_7H_{16}ClNO_2$ | 46.28 | 46.54 | 8.87 | 8.88 | 7.71 | 7.89 |
| *t*-Amyl DL-alaninate | 80.5/17 | 1.4235 | 83 | $C_8H_{17}NO_2$ | 60.34 | 60.21 | 10.76 | 10.70 | | |
| *t*-Amyl DL-alaninate hydrochloride | 135° (m.p.)[c] | | 89 | $C_8H_{18}ClNO_2$ | 49.09 | 48.95 | 9.27 | 9.17 | 7.16 | 7.37 |

[a] Lachramatory. [b] See ref. 21. [c] The ester hydrochloride melts with decomposition with liberation of alkene and formation of residual amino acid hydrochloride.

peptides were revealed by paper chromatography. On the other hand the index of refraction of glycine isobutyl ester increased appreciably in a few hours, and the peptides formed after two days approximated those observed for a sample of glycine *t*-butyl ester stored for four months.

## EXPERIMENTAL[20a]

*Reagents.* Bromoacetyl bromide, α-bromopropionyl bromide, *t*-butyl alcohol, *sec*-butyl alcohol, and *t*-amyl alcohol were Eastman's products. The alcohols were purified by fractional distillation. Dimethylaniline was dried over potassium hydroxide and distilled. Skelly B boiled at 60–70°.

*t-Butyl bromoacetate.* In a three-neck flask, fitted with a stirrer, a calcium chloride tube and a dropping funnel were placed 124 g. (1.02 mol.) dimethyl aniline, 74 g. (1 mol.) *t*-butyl alcohol and 165 ml. ether. A 200-g. sample (0.99 mol.) of bromoacetylbromide was run into the stirred solution within 1 hr. while the flask was cooled in an ice bath. Stirring was continued for 4 hr. at room temperature. The crystallized dimethylaniline hydrobromide was dissolved by addition of 150 ml. of water; the ether layer was treated with three 40-ml. portions of 10% sulfuric acid, then with sodium bicarbonate solution and water. The organic phase was dried over sodium sulfate and filtered. The ether was distilled through a Vigreux column and the ester was fractionated at reduced pressure. A 152-g. sample (78%) of colorless *t*-butyl bromoacetate, boiling at 69–70.5°/17–18 mm. was obtained. For the preparation of the *t*-amyl esters the ether was removed at slightly reduced pressure. The distillation of the *t*-amyl ester was carried out with the vacuum oil pump.

*t-Butyl azidoacetate.* To 39 g. (0.6 mol.) sodium azide in 150 ml. 60% (v/v) acetone were added 78 g. (0.4 mol.) *t*-butyl bromoacetate. Two phases were formed. The mixture was refluxed on a steam bath for 14 hr. The acetone was removed through a column. The oil was dissolved in 100 ml. ether and the aqueous phase was extracted with two 70-ml. portions of ether. The combined ether solutions were dried over anhydrous sodium sulfate and filtered. The ether was distilled through a column. Fractionation gave 60 g. (95%) azido ester, boiling at 79–80.5°/18 mm.

*Glycine t-butyl ester hydrochloride.* A 23.6-g. sample (0.15 mol.) of *t*-butyl azidoacetate, 200 ml. methanol, and 500 mg. palladium-charcoal (5% palladium) were placed in a 1 l. three-neck flask equipped with a condenser and a gas dispersion tube with fritted cylinder. Hydrogen was passed through the solution at room temperature for 10 hr., the mixture being stirred magnetically. The filtered solution was adjusted to *p*H 5.0 by slow addition of methanolic hydrogen chloride, the acidity being measured with a *p*H meter. The solution was evaporated under reduced pressure, 400 ml. ether added and the crystalline material stored overnight in the refrigerator. The product was filtered, washed with ether and dried over sulfuric acid in a desiccator; yield, 21.6 g. (90%). The hydrochloride can be recrystallized from cold chloroform-ether, chloroform-Skelly B or ethanol-ether.

*Glycine t-butyl ester.* A 16.7-g. sample (0.1 mol.) of glycine *t*-butyl ester hydrochloride was dissolved in 30 ml. methanol. Triethylamine 10.2 g. (0.1 mol.) and 400 ml. ether were added. After standing overnight in the refrigerator, the tri-

(20) (a) Each synthesis is typical of that used to prepare the compounds listed in Table I. (b) R. Grewe, *Chem. Ber.*, 76, 1081 (1943).

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.

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(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).

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[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.