Pd–C. The mixture was shaken with hydrogen (1.5 kg/cm²) until the theoretical amount had been taken up in 1 hr. The catalyst was removed by filtration and the filtrate was reduced *in vacuo* to yield a light red glass which was dissolved in 300 ml of ether and filtered to remove the insoluble material. The filtrate was treated with activated carbon and concentrated to yield 4.4 g (65.6%) of a white glass, mp 77° dec, λ_{max}^{Nujol} 2.98 μ.

Anal. Calcd for $C_{14}H_{19}NO_3$: N, 5.62. Found: N, 5.22.

α-Isopropyl-3,4-dihydroxyphenylacetamide (**4b**) was prepared from α-isopropyl-3,4-dibenzyloxyphenylacetamide as described above, mp 59° dec, in 93.8% yield.

Anal. Calcd for $C_{11}H_{15}NO_3$: N, 6.70. Found: N, 6.41.

β-(Cyclohexyl)-β-(3,4-dibenzyloxyphenyl)ethylamine Hydrochloride.—To a dispersion of 1.94 g (0.051 mole) of $LiAlH_4$ in 50 ml of ether was added 7 g (0.017 mole) of **3a** in 200 ml of ether in 15 min. The mixture was stirred at room temperature for 2 hr and refluxed for 8 hr. It was decomposed with 10 ml of water and the solids were removed by filtration. The filtrate was dried and adjusted to acidity by the addition of ethereal HCl. The precipitated solid was collected and recrystallized from methanol to yield 6.3 g (82.1%) of a light-textured white solid, mp 208–210°, λ_{max}^{EtOH} 281 mμ (ε 2810).

Anal. Calcd for $C_{28}H_{34}ClNO_2$: C, 74.40; H, 7.58; N, 3.10. Found: C, 74.40; H, 7.72; N, 2.98.

β-(Cyclohexyl)-β-(3,4-dihydroxyphenyl)ethylamine Hydrochloride (5).—To a solution of 3.05 g (0.0068 mole) of β-(cyclohexyl)-β-(3,4-dibenzyloxyphenyl)ethylamine hydrochloride in 200 ml of ethanol was added 0.5 g of 10% Pd–C. The mixture was shaken with hydrogen (2.81 kg/cm²) until the theoretical amount had been taken up in 5 hr. The catalyst was removed by filtration, and the filtrate was concentrated to yield a glassy solid which was dried thoroughly *in vacuo* at room temperature to yield 1.83 g (100%) of a gray-white powder, mp 71°, ν_{max}^{Nujol} 2.98 μ, λ_{max}^{EtOH} 283 mμ (ε 3330).

Anal. Calcd for $C_{14}H_{22}ClNO_2$: C, 61.86; H, 8.16; Cl, 13.05; N, 5.16. Found: C, 61.68; H, 8.07; Cl, 13.02; N, 4.85.

Acknowledgment.—The authors wish to thank Mr. E. Kluchesky, Mr. D. Dusterhoft, and the staff of our Analytical Department for many of the analyses and ultraviolet and infrared spectra.

Isomeric Mannich Bases Derived from Ethyl 5-Hydroxy-2-methylindole-3-carboxylate

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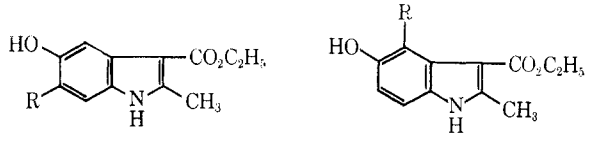
The condensation of ethyl 5-hydroxy-2-methylindole-3-carboxylate (I, R = H) with dimethylamine and formaldehyde is reported to yield a Mannich base in which the dimethylaminomethyl group has been assigned to the 6 position (Ia).[1] The discovery that this indole derivative exhibits hypoglycemic activity in rats led us to seek direct evidence for the position of the dimethylaminomethyl group, as the most likely alternative structure IIa cannot be excluded.



I

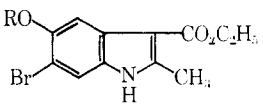
II

a, R = $CH_2N(CH_3)_2$; b, R = CH_3; c, R = CH_2N⟨⟩OH

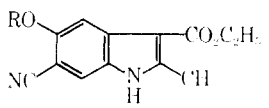
The dimethylaminomethyl side chain of the Mannich base was degraded to a methyl group by Raney nickel in refluxing alcohol to give an indole which must be the 4-methyl derivative IIb since it was different from the known 6-methyl isomer IIb.[2,3] Thus the Mannich base must be the product of substitution at the 4 and not the 6 position, a conclusion which is supported by the nmr spectra.[4]

The structure of the Mannich base does not resemble that of either major class of useful synthetic insulin substitutes, the sulfonylureas or the biguanides. Consequently a number of analogs were prepared by varying the amine component in the Mannich condensation in the hope of finding an improved insulin substitute. One member of this group, the 4-hydroxypiperidinomethyl derivative IIc, appeared to be as active in rats as the dimethylaminomethyl derivative and somewhat less toxic.

The original plan for synthesis of the corresponding 6-substituted derivatives, Ia and Ic, involved blocking the 4 position with a bromine atom followed by a Mannich reaction and removal of the blocking atom by a reduction process. Surprisingly, bromination of I (R = H), its O-acetate or O-benzyl ether in acetic acid led, in high yield, to the 6-bromo derivatives IIIa–c. The nmr spectra provided decisive evidence for these structures as the aromatic proton resonances appeared as two unsplit peaks. The reason for the contrasting courses of the bromination and Mannich reactions is not apparent. The 6-bromo derivatives were nevertheless useful since the bromine atom could be replaced by a nitrile group which in turn could be transformed to the desired dimethylaminomethyl function.



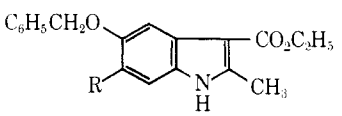
III



IV

a, R = H; b, R = $COCH_3$; c, R = $CH_2C_6H_5$

The benzyl ether IIIc was converted in high yield to the nitrile IVc by use of cuprous cyanide in a Rosenmund–von Braun reaction.[5,6] Hydrogenation catalyzed by platinum in acetic acid then yielded the 6-aminomethyl derivative Va. Methylation by the Eschweiler–Clarke procedure gave Vb which furnished the 6-dimethylaminomethyl-5-hydroxyindole Ia upon hydrogenation over palladium in alcohol.[7] This new



V

a, R = CH_2NH_2
b, R = $CH_2N(CH_3)_2$

(1) E. A. Steck, U. S. Patent 2,852,527 (June 1, 1956); *Chem. Abstr.*, **53**, 8163 (1959).

(2) R. J. S. Beer, K. Clarke, H. F. Davenport, and A. Robertson, *J. Chem. Soc.*, 2029 (1951).

(3) G. R. Allen, Jr., C. Pidacks, and M. J. Weiss, *J. Am. Chem. Soc.*, **88**, 2536 (1966).

(4) This finding was reached independently by S. A. Monti, O. Johnson, and H. White, *Tetrahedron Letters*, 4459 (1965).

(5) O. T. Mowry, *Chem. Rev.*, **42**, 207 (1948).

(6) L. Friedman and H. Shechter, *J. Org. Chem.*, **26**, 2522 (1961).

(7) Mr. A. E. Soria of our Development Laboratory reports that Ia may be prepared in good yield by hydrogenating an ethanol solution of the nitrile IVc and a large excess of dimethylamine in the presence of 10% Pd–C

Mannich base was degraded by Raney nickel in alcohol to the corresponding 6-methylindole Ib. The 4-hydroxypiperidinomethyl derivative Ic formed when Ia was heated with 4-hydroxypiperidine, an example of the Mannich base exchange reaction.[8]

Biological Activity.—The effects of these indole derivatives on rat blood glucose[9] may be seen in Table I.

TABLE I
EFFECT OF THE 4- AND 6-SUBSTITUTED ETHYL 5-HYDROXY-2-METHYLINDOLE-3-CARBOXYLATES ON BLOOD GLUCOSE IN THE RAT

Test agent	Single dose, mg/kg ig	Blood glucose, % of control — Postmedication, hr 1	2	3	5
Ia	100	0	0	0	0
Ic	100	0	0	0	0
IIa	50	−24	0	0	−26
IIc	50	0	0	−24	−35
	100	0	−27	−31	−40

Both 4-substituted indoles, IIa and IIc, were hypoglycemic when administered as a single oral dose of 50 mg/kg. The corresponding 6-substituted indoles Ia and Ic were inactive with respect to altering blood glucose levels when tested at a dose of 100 mg/kg orally.

Experimental Section[10]

Ethyl 5-Hydroxy-2-methylindole-3-carboxylate (I, R = H).—The product yield was improved by carrying out the condensation in acetic acid and using excess quinone.[11] To a stirred solution of 27 g (0.25 mole) of 1,4-benzoquinone in 450 ml of glacial acetic acid was added 16.2 g (0.125 mole) of ethyl 3-aminocrotonate during 10 min, the temperature being kept below 45° by external cooling. Stirring was continued at room temperature for 5 hr. The precipitated solid was washed with acetic acid and water to give 17 g (62%) of a gray crystalline solid, mp 203–205°. Recrystallization from pyridine raised the melting point to 207–208° (lit.[11] mp 205°).

Ethyl 4-[(dimethylamino)methyl]-5-hydroxy-2-methylindole-3-carboxylate (IIa) was prepared and isolated as the hydrochloride according to the literature procedure.[1] The identical product was formed in high yield when the Mannich condensation was carried out in hot acetic acid. The free base was generated by shaking a suspension of the hydrochloride in aqueous K_2CO_3 with CH_2Cl_2. Concentration of the dried CH_2Cl_2 phase and recrystallization of the residue from CCl_4 gave a yellow crystalline powder: mp 114.5–116.5°; nmr ($DCCl_3$), 404 and 422 cps (1 H each, doublets, J = 9 cps).

Anal. Calcd for $C_{15}H_{20}N_2O_3$: N_{AP},[12] 5.07. Found: N_{AP}, 4.9.

Ethyl 5-Hydroxy-2,4-dimethylindole-3-carboxylate (IIb).—A solution of 13 g of IIa in 1 l. of alcohol was refluxed 20 hr with 150 g of Raney nickel. The catalyst was removed by filtration, the filtrate was concentrated to dryness *in vacuo*, and the crystalline residue was washed (CH_2Cl_2, water) to give 7 g (64%) of a tan powder, mp 184–188°. The analytical sample melted at 187–189° after recrystallization from ethyl acetate; nmr (20% DMF-d_7), 408 and 422 cps (1 H each, doublets, J = 8 cps).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 67.25; H, 6.70; N, 5.81.

The infrared spectrum was entirely different from that of authentic ethyl 2,6-dimethyl-5-hydroxyindole-3-carboxylate (Ib), mp 229–230° (lit.[2] mp 230°): nmr (20% DMF-d_7), 427 and 453 cps (1 H each, singlets, J = <1 cps).

Ethyl 5-Hydroxy-4-[(4-hydroxypiperidino)methyl]-2-methylindole-3-carboxylate (IIc).—A solution of 5 g (0.0228 mole) of ethyl 5-hydroxy-2-methylindole-3-carboxylate (I, R = H), 2.05 g (0.0205 mole) of 4-hydroxypiperidine, and 1.82 ml (0.024 mole) of formalin (395 mg of formaldehyde/ml) in 20 ml of acetic acid and 5 ml of water was heated on the steam bath for 30 min, diluted with 200 ml of water, and filtered. The filtrate was made basic with solid K_2CO_3 and extracted (CH_2Cl_2). Concentration of the dried organic fractions left 6.5 g (96%) of the crude base best characterized as the hydrochloride[13] which melted at 204–205° dec following recrystallization from water: nmr (20% trifluoroacetic acid, external TMS), 419 and 447 cps (1 H each, doublets, J = 9 cps).

Anal. Calcd for $C_{18}H_{24}N_2O_4 \cdot HCl$: N, 7.59; Cl, 9.62. Found: N, 7.60; Cl, 9.78.

Ethyl 6-Bromo-5-hydroxy-2-methylindole-3-carboxylate (IIIa).—A stirred suspension of 44 g (0.2 mole) of I (R = H) in 400 ml of acetic acid was treated with 32 g (0.2 mole) of bromine during 20 min. The dark reaction mixture was stirred at room temperature 2 hr and then poured into 3 l. of water. Filtration afforded 60 g of purple crystals. The solid was recrystallized from ethyl acetate with charcoal treatment to give 48 g (80%) of off-white product, mp 196–198° dec. The analytical sample was obtained from another run as white needles, mp 201° dec, after recrystallization from ethyl acetate; nmr (20% DMF-d_7, external TMS), 445 and 456 cps (1 H each, singlets, J = <1 cps).

Anal. Calcd for $C_{12}H_{12}BrNO_3$: N, 4.69; Br, 26.81. Found: N, 4.66; Br, 27.21.

Ethyl 5-acetoxy-2-methylindole-3-carboxylate (I, O-acetate, R = H) was prepared by refluxing I (R = H) with acetic anhydride. It crystallized from benzene–hexane as white plates, mp 153–154.5°.

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.49; H, 5.91; N, 5.19.

Ethyl 5-Acetoxy-6-bromo-2-methylindole-3-carboxylate (IIIb).

A. By Acetylation of IIIa.—The bromophenol IIIa was refluxed 2 hr with acetic anhydride and the product was isolated as white crystals, mp 198.5–200°, when crystallized from ethyl acetate.

Anal. Calcd for $C_{14}H_{14}BrNO_4$: C, 49.41; H, 4.14; Br, 23.48; N, 4.11. Found: C, 49.63; H, 4.11; Br, 23.48; N, 4.49.

B. By Bromination of the O-Acetate of I (R = H).—The bromination of I O-acetate (R = H) was carried out in the same manner as the bromination of I (R = H). The yield was 68% of product, mp 195–196°, raised to 198–200° by further recrystallization. The infrared spectrum was identical with that of the product obtained by acetylation of IIIa.

Ethyl 5-Benzyloxy-6-bromo-2-methylindole-3-carboxylate (IIIc). A. By Bromination of I (O-benzyl ether, R = H).—The bromination of ethyl 5-benzyloxy-2-methylindole-3-carboxylate[14] was performed in the same manner as the bromination of I (R = H). The product crystallized from ethyl acetate in 74% yield as white needles, mp 204–205°.

Anal. Calcd for $C_{19}H_{18}BrNO_3$: C, 58.77; H, 4.67; N, 3.60; Br, 20.58. Found: C, 58.66; H, 4.56; N, 3.58; Br, 20.86.

B. By Benzylation of IIIa.—A stirred suspension of 90 g (0.302 mole) of ethyl 6-bromo-5-hydroxy-2-methylindole-3-carboxylate (IIIa), 58.3 g (0.460 mole) of benzyl chloride, and 250 g of anhydrous K_2CO_3 (dried 6 hr at 600°) in 900 ml of reagent grade acetone was refluxed 28 hr. The solvent was removed *in vacuo* and the residue was dissolved in a hot mixture of 2 l. of water and 2 l. of ethyl acetate. The aqueous phase was extracted with three 750-ml portions of ethyl acetate. The combined extracts were washed (water, brine), dried (Na_2SO_4), concentrated to about 1 l., and left at 0° to give 92 g (79%) of product, mp 202–204°. A recrystallized sample from an earlier run, mp 205–206°, did not depress the melting point of the product obtained by bromination of the benzyl ether of I (R = H).

Ethyl 5-Benzyloxy-6-cyano-2-methylindole-3-carboxylate (IVc).—The method employed was that described by Friedman

(8) H. R. Snyder and J. H. Brewster, *J. Am. Chem. Soc.*, **70**, 4230 (1948).

(9) R. M. Reinicke, *J. Biol. Chem.*, **143**, 351 (1942).

(10) Melting points were taken in capillary tubes in an oil bath. They are not corrected but are within one degree of the melting points of standards. Analyses were carried out under the supervision of Mr. K. D. Fleischer. Spectra were determined under the supervision of Dr. F. C. Nachod. Nmr spectra were determined with a Varian Model A-60 nmr spectrometer; TMS was used as the internal standard unless otherwise indicated. The ultraviolet and infrared spectra of most of the compounds were determined and are in accord with the structures written.

(11) (a) C. D. Nenitzescu, *Bul. Soc. Chim. Romania*, **11**, 37 (1929); *Chem. Abstr.*, **24**, 110 (1930); (b) G. Domschke and H. Fürst, *Chem. Ber.*, **92**, 3244 (1959).

(12) N_{AP} stands for perchloric acid titration in acetic acid for basic nitrogen.

(13) We are indebted to Dr. B. F. Tullar of our Development Laboratory for the characterization of the hydrochloride.

(14) J. H. Koehneke and M. E. Speeter, U. S. Patent 2,707,187 (April 26, 1955); *Chem. Abstr.*, **50**, 5035 (1956).

and Shechter.[6] A stirred solution of 53 g (0.136 mole) of IIIc and 37 g (0.410 mole) of CuCN in 180 ml of dimethylformamide was refluxed 5 hr in a nitrogen atmosphere. The hot, dark brown mixture was poured into a warm solution of 300 ml of ethylenediamine in 900 ml of water and shaken vigorously 5–10 min in order to dissolve the copper complexes. To the still warm mixture was added 750 ml of ethyl acetate and the organic phase separated after thorough shaking. The aqueous phase was extracted with four 500-ml portions of ethyl acetate. The combined extracts were washed with two 250-ml portions each of 30% aqueous ethylenediamine, water, and brine. The tan solution was dried (Na_2SO_4), concentrated to about 600 ml, and left at ice temperature to furnish 39 g (86%) of off-white product, mp 217–219°. Further recrystallization from ethyl acetate and then absolute ethanol provided the analytical sample, mp 219.5–220.5°.

Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.68; H, 5.48; N, 8.60.

Ethyl 6-Cyano-5-hydroxy-2-methylindole-3-carboxylate (IVa).—Compound IVc (18 g) was hydrogenated in 1300 ml of absolute ethanol in the presence of 2 g of 10% Pd-C. After absorption of 1 mole equiv of hydrogen the product was isolated and recrystallized from 2-propanol to give 12.5 g (94%), mp 282–284° dec. Further recrystallization furnished the analytical sample: mp 283.5–285° dec; infrared (KBr), 4.52 and 6.13 μ.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.83; H, 5.11; N, 11.56.

Ethyl 6-Aminomethyl-5-benzyloxy-2-methylindole-3-carboxylate (Va).—The benzyloxynitrile IVc (40 g) in 750 ml of acetic acid was hydrogenated in the presence of 2 g of PtO_2 at room temperature. In 24 hr 80% of the theoretical amount of hydrogen was absorbed. Fresh catalyst (2 g) was added to bring the reaction to completion (110% overreduction). The product was isolated and shaken with ethyl acetate and 10% NaOH. Concentration of the dried ethyl acetate extracts afforded 28 g (69%) of cream-colored needles, mp 150–153°. Recrystallization from 2-propanol gave 20.2 g (50%) of off-white crystals, mp 151.5–153°. The hydrochloride, mp 235.5–237° dec, was prepared by addition of alcoholic HCl to a solution of the free base in alcohol.

Anal. Calcd for $C_{20}H_{22}N_2O_3 \cdot HCl$: N, 7.47; Cl, 9.46. Found: N, 7.43; Cl, 9.40.

Ethyl 5-Benzyloxy-6-[(dimethylamino)methyl]-2-methylindole-3-carboxylate (Vb).—A mixture of 5 g (0.0148 mole) of the aminomethyl derivative Va, 3.4 g (0.074 mole) of formic acid, and 2.5 ml (0.0334 mole) of formalin was heated 12 hr on the steam bath. The brown solution was evaporated *in vacuo*, and the residue was treated with 10% NaOH and extracted with ethyl acetate. The dried extracts were concentrated, and the residue was chromatographed on 60 g of silica gel. Elution with ethyl acetate–methanol (3:1) furnished 4.5 g (83%) of off-white product, mp 152–155°. Recrystallization from aqueous ethanol produced 3.9 g of Vb (72%), mp 156–158°. This material contained a small amount of an impurity (thin layer chromatography) which could not be eliminated by crystallization or chromatography. The product was used in the next step without further purification.

Ethyl 6-[(Dimethylamino)methyl]-5-hydroxy-2-methylindole-3-carboxylate (Ia).—Compound Vb (5 g) was hydrogenated in 225 ml of ethanol in the presence of 500 mg of 10% Pd-C. The reduction was complete in 75 min. The product was isolated in good yield and characterized as the **hydrochloride**, mp 230–232° dec, after recrystallization from methanol–ether. The melting point was depressed on admixture with the 4-dimethylaminomethyl isomer IIa and their infrared spectra were different.

Anal. Calcd for $C_{13}H_{18}N_2O_3 \cdot HCl$: N, 8.96; Cl, 11.33. Found: N, 9.04; Cl, 11.52.

Compound Ia was degraded by Raney nickel in refluxing ethanol to ethyl 2,6-dimethyl-5-hydroxyindole-3-carboxylate (Ib) in 55% yield.

Ethyl 5-Hydroxy-6-[(4-hydroxypiperidino)methyl]-2-methylindole-3-carboxylate (Ic).—A mixture of 6.5 g of Ia and 25 g of 4-hydroxypiperidine was heated 24 hr at 115°. The reaction mixture was treated with 500 ml of water, and the dark insoluble solid was collected and washed thoroughly with water. Two recrystallizations from ethyl acetate with charcoal treatment yielded 2.6 g (38%) of product: mp 220–223° dec; nmr (20% DMF-d_7), 426 and 444 cps (1 H each, singlets, $J < 1$ cps).

Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 64.96; H, 7.33; N, 8.11.

Biological Methods. Male rats of the Charles River CD strain weighing 90–100 g were fasted 16 hr prior to test. Tail vein blood samples were assayed for blood glucose by the method of Reinicke.[9] The animals were divided into groups of five rats each on the basis of their fasting blood glucose levels. All rats were given 100 mg of glucose subcutaneously and then a single oral administration of the test agent. Blood glucose was monitored hourly from tail vein blood samples.

β-Phenoxyethylamines with Local Anesthetic and Antispasmodic Activity

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β-Phenoxyethylamine derivatives have many pharmacological activities. Bovet and Bovet-Nitti[1] who reviewed the subject until 1947 described for compounds of this type local anesthetic, adrenergic, adrenolytic, nicotinic, antihistaminic, curaremimetic, oxytocic, and antifibrillatory activities. More recently,[2–6] β-phenoxyethylamines with pronounced local anesthetic, antispasmodic, vasodilating, coronarodilating, and analgetic activities have been mentioned. For this reason an investigation was started in order to explore the pharmacological activities of β-phenoxyethylamines, N-disubstituted with different radicals in the benzene ring. Several compounds with a strong local anesthetic and with smooth muscle relaxing and antispasmodic activities were found. Particularly interesting for their local anesthetic and antispasmodic activity were 2-butyryl-β-(N,N-diisopropyl)phenoxyethylamine (**30**, ketocaine), 2-butyryl-6-amino-β-(N,N-diisopropyl)phenoxyethylamine (**34**), and 2-(α-hydroxybutyl-β-(N,N-diisopropyl)phenoxyethylamine (**36**), whose general pharmacological activities were described by Setnikar.[7] The synthesis of prototype compounds is to be found in the Experimental Section.

The results obtained in the pharmacological screening are summarized in Table I. The substances showed several pharmacological activities, but throughout, the most important in intensity were the local anesthetic and the antispasmodic activity.

Local Anesthetic Activity.—The attachment of different radicals to the phenoxyethylamino structure influenced the degree of the local anesthetic activity as follows.

(a) **Substituents in the Amino Group.**—The highest activity was obtained by substituting the hydrogens of the amino group with two isopropyl groups. The activity decreased with two ethyl and still more with two methyl groups. A further decrease of activity was

(1) D. Bovet and F. Bovet-Nitti, "Medicaments du Système Nerveux Vegetatif," Verlag S. Karger, Basel, 1948, p 229, 231.

(2) L. Beani and G. Fows, *Arch. Ital. Sci. Farmacol.*, **5**, 287 (1955).

(3) L. Turbanti and G. F. Di Paco, *Farmaco (Pavia), Ed. Sci.*, **17**, 651 (1962).

(4) S. Wiedling and C. Tegnér in "Progress in Medicinal Chemistry," A. P. Ellis and A. B. West, Ed., Butterworths and Co. (Publishers) Ltd., London, 1963, p 332.

(5) N. P. Buu-Hoï, P. Jacquignon, and M. Dufour, *Bull. Soc. Chim. France*, 23 (1964).

(6) N. P. Buu-Hoï, M. T. Richert, A. Krikorian, M. Dufour, and P. Jacquignon, *Bull. Chim. Thérap.*, **1**, 23 (1965).

(7) I. Setnikar, *Arzneimittel-Forsch.*, **16**, 1025 (1966).