[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORIES OF THE SCHERING CORPORATION]

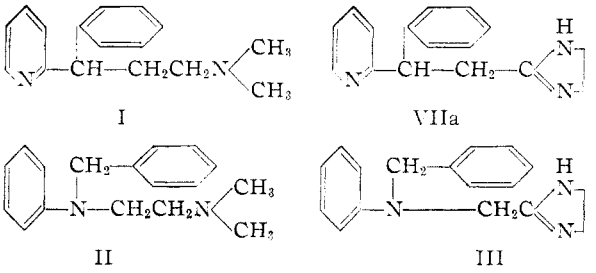
Cyclic Derivatives of α,α-Disubstituted Phenylacetonitriles[1]

BY NATHAN SPERBER AND ROSEMARIE FRICANO

RECEIVED JANUARY 2, 1953

α-Substituted-α-(ω-carbethoxyalkyl)-phenylacetonitriles, prepared by the alkylation of phenyl-2-pyridylacetonitrile or diphenylacetonitrile with ω-carbethoxyalkyl bromides and sodamide, were converted to imidazolines, pyrrolidones, pyrrolidines and dialkylaminoalkyl esters.

In continuation of studies on histamine antagonists unrelated to ethanolamine or ethylenediamine,[2] it was considered of interest to substitute a 2-methylimidazoline group VIIa for the N,N-dimethylaminoethyl moiety of γ-phenyl-γ-(2-pyridyl)-N,N-dimethylpropylamine (I),[3] since the replacement of the basic side chain of N′-phenyl-N′-benzyl-N,N-dimethylethylenediamine (II),[4] by a 2-methylimidazoline group III[5] gave a better tolerated antihistaminic agent.

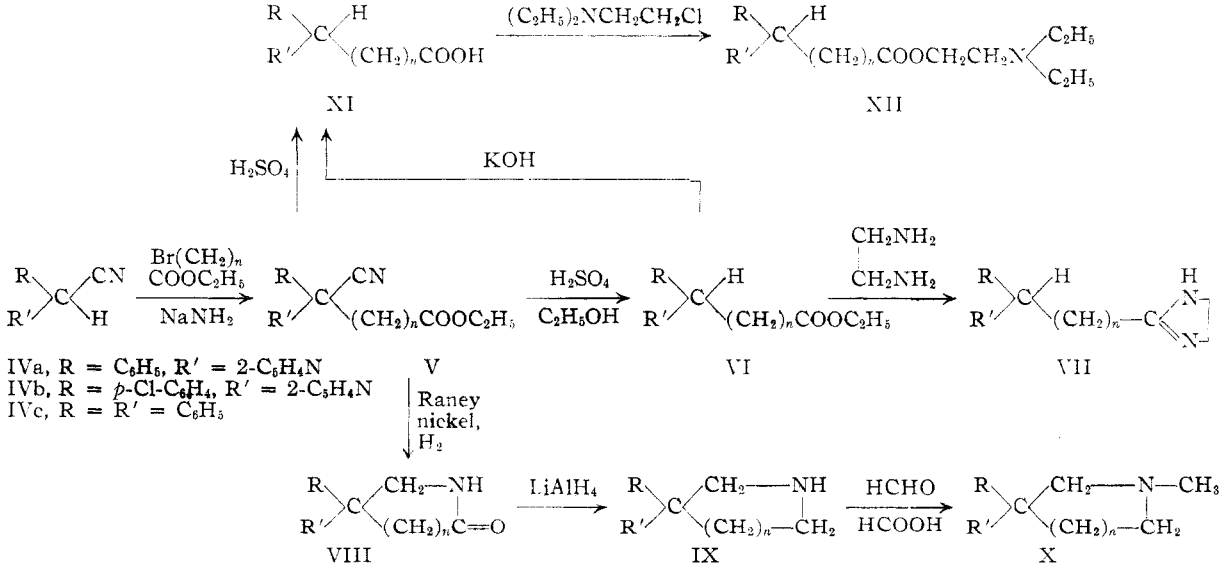


I VIIa

II III

The synthesis of the requisite α-substituted-α-(ω-carbethoxyalkyl)-phenylacetonitriles V was effected in good yields by the alkylation of α-phenyl- or α-(2-pyridyl)-phenylacetonitriles IV[6] with an ω-carbethoxyalkyl bromide[7] and sodamide. The esters (VIa, n = 1; VIa, n = 2; VIb, n = 2), were prepared from the corresponding cyano esters V by the removal of the cyano group with sulfuric acid and re-esterification of the carboxyl group of XI by the method of Eisleb[8] (Table I). VIa (n = 1) and VIb (n = 1) were converted to the corresponding imidazolines, VIIa and VIIb, by heating the esters with ethylenediamine followed by cyclization with magnesium powder.[9]

The α-substituted α-(ω-carbethoxyalkyl)-phenylacetonitriles served as useful intermediates for the preparation of several other cyclic derivatives and dialkylaminoalkyl esters of pharmacological interest. 4-Phenyl-4-(2-pyridyl)-pyrrolidone-2 (VIIIa, n = 1), 4,4-diphenylpyrrolidone-2 (VIIIc, n = 1) and 5-phenyl-5-(2-pyridyl)-piperidone-2 (VIIIa, n = 2) were prepared by the hydrogenation of the appropriate cyanoesters V with Raney nickel catalyst in ethanol.[10] The pyrrolidones



(1) Presented in part before the Division of Medicinal Chemistry, American Chemical Society, Atlantic City Meeting, September 15, 1952.

(2) N. Sperber, D. Papa, E. Schwenk, M. Sherlock and R. Fricano, THIS JOURNAL, **73**, 5752 (1951).

(3) J. O. Jílek and M. Protiva, *J. Chem. Soc.*, 188 (1950), have described the preparation of 2-(2,2-diphenylethyl)-imidazoline which is related similarly to γ,γ-diphenyl-N,N-dimethylpropylamine.

(4) B. N. Halpern, *Arch. intern. pharmacodynamie*, **68**, 339 (1942).

(5) R. Meier and K. Bucher, *Schweiz. med. Wochschr.*, **76**, 294 (1946).

(6) L. Pannizzon, *Helv. Chim. Acta*, **27**, 1748 (1944).

(7) F. Salmon-Legagneur, *Compt. rend.*, **208**, 1507 (1939). After this investigation had been completed, C. A. Miller and L. M. Long, THIS JOURNAL, **73**, 4895 (1951), reported on the preparation of ethyl β-cyano-β,β-diphenylpropionate by the alkylation of diphenylacetonitrile with ethyl bromoacetate and sodium ethoxide.

(8) O. Eisleb, *Ber.*, **74**, 1433 (1941).

(9) H. C. Chitwood and E. E. Reid, THIS JOURNAL, **57**, 2424 (1935); L. P. Kyrides, F. C. Meyer and F. B. Zienty, *ibid.*, **69**, 2239 (1947).

(10) (a) The procedure of C. F. Koelsch, *ibid.*, **65**, 2093 (1943), for the preparation of 5-phenylpiperidone-2 was followed with the exception that lower temperatures and pressures were employed to avoid reduction of the pyridine ring. (b) L. A. Walter and R. H. Barry, U. S. Patent 2,524,643 (1950), have described the synthesis of 3,3-diphenyl-2-piperidone by a similar process.

TABLE I

ESTERS, RR'R"—C—$(CH_2)_nCOOC_2H_5$

R	R'	R"	n	B.p. °C.	Mm.	M.p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Found
C_6H_5	2-C_5H_4N	CN	1			91–91.5[a]	80	$C_{17}H_{16}O_2N_2$	10.00	10.41
C_6H_5	2-C_5H_4N	CN	2	190–193	2.5		71	$C_{18}H_{18}O_2N_2$	9.52	9.68
p-ClC_6H_4	2-C_5H_4N	CN	1			67.5–68.5[b]	70	$C_{17}H_{15}O_2N_2Cl$	8.90	8.76
C_6H_5	C_6H_5	CN	1	180–184	1.5	107–107.5[c]	61	$C_{18}H_{17}O_2N$	5.02	5.25
C_6H_5	2-C_5H_4N	H	1	140–142[d]	1.5		70	$C_{16}H_{17}O_2N$	5.49	5.46
C_6H_5	2-C_5H_4N	H	2	149–152[e]	0.5		68	$C_{17}H_{19}O_2N$	5.20	5.61
p-ClC_6H_4	2-C_5H_4N	H	1	174–176[f]	1.0		57	$C_{16}H_{16}O_2NCl$	4.83	4.83

[a] Recrystallized from benzene–petroleum ether. [b] Recrystallized from alcohol–water. [c] Ref. 7, m.p. 102–105°. [d] $n^{24}D$ 1.5480. [e] $n^{25}D$ 1.5450. [f] $n^{24}D$ 1.5548.

were reduced with lithium aluminum hydride to the corresponding pyrrolidines,[11] IXa and IXc, and the latter methylated with formic acid and formaldehyde to yield Xa and Xc, respectively. The attempted reduction of 5-phenyl-5-(2-pyridyl)-piperidone-2 (VIIIa, $n = 2$) to 3-phenyl-3-(2-pyridyl)-piperidine (IXa, $n = 2$) with lithium aluminum hydride resulted only in the recovery of the unreacted piperidone.[12] However, an alternate synthesis of IXa ($n = 2$) was studied whereby α-phenyl-2-pyridylacetonitrile was alkylated with β-bromopropionitrile and sodamide and the resulting dinitrile, γ-phenyl-γ-(2-pyridyl)-γ-cyanobutyronitrile, was hydrogenated with Raney nickel catalyst in ethanol.[13] Although the analytical data for 3-phenyl-3-(2-pyridyl)-piperidine (IXa, $n = 2$) indicated contamination with uncyclized 2-phenyl-2-(2-pyridyl)-pentamethylenediamine, subsequent methylation of the impure piperidine yielded the desired 3-phenyl-3-(2-pyridyl)-1-methylpiperidine (Xa, $n = 2$). An attempt to prepare 3,3-diphenylpiperidine by the reduction and cyclization of γ,γ-diphenyl-γ-cyanobutyronitrile was unsuccessful.

Alkaline hydrolysis of the esters VIa ($n = 1$) and VIa ($n = 2$) yielded the corresponding acids XIa ($n = 1$) and XIa ($n = 2$). XIa ($n = 2$) was prepared more conveniently by the hydrolysis and decarboxylation of ethyl γ-cyano-γ-phenyl-γ-(2-pyridyl)-butyrate (Va, $n = 2$) with 70% sulfuric acid. The β-diethylaminoethyl esters, XIIa ($n = 1$) and XIIa ($n = 2$) were obtained by refluxing the appropriate acids with β-diethylaminoethyl chloride in isopropyl alcohol.[14]

Compounds VIIa ($n = 1$) and VIIb ($n = 1$) were tested as histamine antagonists by the method described previously[2] and were found to be inferior to γ-phenyl-γ-(2-pyridyl)-N,N-dimethyl propylamine. Compound XIIa ($n = 1$) was devoid of antispasmodic activity in the Magnus test. Compounds VIIIc ($n = 1$), Xc ($n = 1$), Xa ($n = 1$) and Xa ($n = 2$) possessed no significant antihistaminic or antispasmodic activity.

(11) A. L. Morrison, F. F. Lang and M. Konigstein, *J. Chem. Soc.*, 952 (1951), prepared 1-methyl-3,3-diphenylpyrrolidine by the reduction of 1-methyl-3,3-diphenylpyrrolidone-2 with lithium aluminum hydride.

(12) C. F. Koelsch (ref. 10a) prepared 3-phenylpiperidine in 57% yield by the reduction of 5-phenylpiperidone-2 with sodium and butyl alcohol. The presence of a pyridine group in VIIIa precluded the use of this procedure.

(13) Compare F. Bergel, A. L. Morrison and H. Rinderknecht, British Patent, 564,741. These investigators reductively cyclized α-phenyl-α-carbethoxyglutaronitrile to ethyl 3-phenylnipecotate with hydrogen and palladium–charcoal.

(14) H. Horenstein and H. Pählicke, *Ber.*, **71**, 1644 (1938).

Experimental[15]

Ethyl β-Cyano-β-phenyl-β-(2-pyridyl)-propionate (Va, $n = 1$).—To a hot, stirred solution of 97 g. (0.5 mole) of α-phenyl-2-pyridylacetonitrile[6] and 90 g. (0.54 mole) of redistilled ethyl bromoacetate in 600 ml. of dry toluene was added, portionwise, a stirred suspension of sodamide in 200 ml. of toluene (from 13 g. of sodium). The reaction mixture was refluxed and stirred for two hours, cooled and decomposed with water. The organic layer was concentrated to a residue and the latter either distilled *in vacuo* or crystallized from benzene–petroleum ether or alcohol–water.

Ethyl β-Phenyl-β-(2-pyridyl)-propionate (VIa, $n = 1$).—A solution of 21 g. (0.075 mole) of ethyl β-cyano-β-phenyl-β-(2-pyridyl)-propionate in 53 g. of 70% sulfuric acid was heated and stirred at 130° for nine hours. The acid solution of β-phenyl-β-(2-pyridyl)-propionic acid was re-esterified,[8] the ethanol removed *in vacuo*, the dark brown oil poured on ice, made basic with gaseous ammonia and the oil extracted with ether. The ether extracts were washed with water, dried, the ether removed and the residue distilled.

2-[β-(2-Pyridyl)-β-phenyl]-ethylimidazoline (VIIa, $n = 1$).—A mixture of 21 g. of ethyl β-phenyl-β-(2-pyridyl)-propionate and 50 g. of ethylenediamine was refluxed for 48 hours.[9] The ethanol and water were distilled off over a period of eight hours and the excess ethylenediamine was removed *in vacuo* on a steam-bath. The residue was transferred to a Claisen distilling flask which contained 2 g. of magnesium powder; the flask was heated at 280° for 30 minutes at 20 mm. and the residue was distilled; yield 15 g. (73%), b.p. 194–197° (1 mm.). The viscous yellow oil solidified and was recrystallized from benzene–petroleum ether, m.p. 122–123°.

Anal. Calcd. for $C_{16}H_{17}N_3$: C, 76.43; H, 6.81; N, 16.73. Found: C, 76.50; H, 6.78; N, 16.72.

2-[β-(2-Pyridyl)-β-p-chlorophenyl]-ethylimidazoline (VIIb, $n = 1$).—This compound was prepared by the above procedure from 25 g. of ethyl β-p-chlorophenyl-β-(2-pyridyl)-propionate, 50 g. of ethylenediamine and 2 g. of magnesium powder; yield 13.3 g. (54%), b.p. 215–218° (2.5 mm.).

Anal. Calcd. for $C_{16}H_{16}N_3Cl$: N, 14.72. Found: N, 14.73.

4-Phenyl-4-(2-pyridyl)-pyrrolidone-2 (VIIIa, $n = 1$).—A solution of 45 g. (0.16 mole) of ethyl β-cyano-β-phenyl-β-(2-pyridyl)-propionate in 700 ml. of absolute ethanol was hydrogenated for six hours with Raney nickel catalyst at 500 lb. p.s.i. and a temperature of 75°. The catalyst was removed by filtration, the filtrate concentrated to a residue *in vacuo* and the solid recrystallized from hot water; yield 24.5 g. (64%), m.p. 165–166°.

Anal. Calcd. for $C_{15}H_{14}ON_2$: C, 75.60; H, 5.92; N, 11.77. Found: C, 75.90; H, 6.19; N, 11.67.

4,4-Diphenylpyrrolidone-2 (VIIIc, $n = 1$) was prepared from 40 g. (0.143 mole) of ethyl β-cyano-β,β-diphenylpropionate by the procedure described for 4-phenyl-4-(2-pyridyl)-pyrrolidone-2; yield 30 g. (89%), m.p. 165–166° (from alcohol).

Anal. Calcd. for $C_{16}H_{15}ON$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.41; H, 6.12; N, 5.68.

3-Phenyl-3-(2-pyridyl)-pyrrolidine (IXa, $n = 1$).—4-Phenyl-4-(2-pyridyl)-pyrrolidone-2 (23.8 g., 0.1 mole) was

(15) All melting points are corrected.

extracted in a Soxhlet apparatus for 15 hours with a refluxing solution of 4.6 g. of lithium aluminum hydride in 600 ml. of dry ether. The undissolved pyrrolidone was taken up in 30 ml. of dry tetrahydrofuran and the solution added slowly to the reaction mixture. After refluxing and stirring for an additional hour, the reaction mixture was cooled and decomposed with 250 ml. of a 10% sodium hydroxide solution. The aqueous phase was extracted several times with ether, the combined ether extracts dried over sodium sulfate, the ether removed and the residue distilled; yield 10 g. (44%), b.p. 152–154° (1 mm.), $n^{27}D$ 1.5960.

Anal. Calcd. for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.50. Found: C, 80.67; H, 7.55; N, 12.28.

3,3-Diphenylpyrrolidine Hydrochloride (IXc, n = 1).—4,4-Diphenylpyrrolidone-2 (13.5 g., 0.057 mole) was reduced with 3.8 g. of lithium aluminum hydride in 500 ml. of absolute ether by the method described in the previous experiment; yield 9.5 g. (75%), b.p. 162–164° (2.5 mm.), $n^{26}D$ 1.5968. The compound formed a water insoluble hydrochloride which was recrystallized from alcohol–ether, m.p. 235–236°.

Anal. Calcd. for $C_{16}H_{18}NCl$: C, 73.95; H, 6.98; N, 5.39. Found: C, 73.70; H, 6.98; N, 5.12.

3-Phenyl-3-(2-pyridyl)-1-methylpyrrolidine (Xa, n = 1).—To 7 g. of cold 90% formic acid was added dropwise 8.8 g. (0.039 mole) of 3-phenyl-3-(2-pyridyl)-pyrrolidine followed by 6 ml. of a 37% formalin solution. After heating the solution for 18 hours, the formic acid and formaldehyde were removed *in vacuo*, the residue made basic with a 10% sodium carbonate solution and the oil extracted with ether. The ether extracts were washed with water, dried over potassium carbonate, filtered, the solvent removed and the residue distilled; yield 7.8 g. (83.5%), b.p. 143–144° (1 mm.), $n^{27}D$ 1.5815.

Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.60; H, 7.61; N, 11.76. Found: C, 80.10; H, 7.10; N, 11.67.

3,3-Diphenyl-1-methylpyrrolidine[11] **(Xc, n = 1).**—Fifteen grams (0.067 mole) of 3,3-diphenylpyrrolidine was added slowly to 8.5 g. of 90% formic acid followed by 7 ml. of 37% formalin solution. The conditions described in the previous experiment were employed; yield 11.5 g. (72%), b.p. 146–147° (2 mm.), $n^{25}D$ 1.5830 (lit.[11] b.p. 140–142° (1 mm.)).

Anal. Calcd. for $C_{17}H_{19}N$: C, 86.00; H, 8.07; N, 5.90. Found: C, 86.66; H, 8.04; N, 5.89.

5-Phenyl-5-(2-pyridyl)-piperidone-2 (VIIIa, n = 2).—This compound was prepared from 29.4 g. (0.1 mole) of ethyl γ-cyano-γ-phenyl-γ-(2-pyridyl)-butyrate by the method described for 4-phenyl-4-(2-pyridyl)-pyrrolidone-2; yield 18 g. (71.5%), m.p. 192.6–193.4°.

Anal. Calcd. for $C_{16}H_{16}ON_2$: C, 76.16; H, 6.39; N, 10.86. Found: C, 75.70; H, 6.78; N, 10.88.

Reduction of this compound with lithium aluminum hydride was unsuccessful.

γ-Phenyl-γ-(2-pyridyl)-γ-cyanobutyronitrile.—To a cooled, stirred suspension of sodamide (from 6 g. of sodium) was added in portions 48.5 g. (0.25 mole) of α-phenyl-2-pyridylacetonitrile and the reaction mixture was refluxed for three hours. β-Bromopropionitrile (35 g., 0.26 mole) was added dropwise, the suspension refluxed and stirred for an additional four hours, cooled and decomposed with ice-water. The toluene layer was concentrated *in vacuo* and the residue distilled; yield 45 g. (72%), b.p. 194–196° (1.5 mm.), yellow viscous oil which slowly crystallized. Upon recrystallization of the solid from ethanol, it melted at 82–83°.

Anal. Calcd. for $C_{16}H_{13}N_3$: C, 77.70; H, 5.30. Found: C, 77.73; H, 5.18.

γ,γ-Diphenyl-γ-cyanobutyronitrile was prepared by the alkylation of diphenylacetonitrile (97 g., 0.5 mole) in 650 ml. of toluene with β-bromopropionitrile (70 g., 0.52 mole) and sodamide (from 12.5 g. of sodium); yield 57%, b.p. 195–200° (1.5 mm.), viscous yellow oil which solidified. Upon recrystallization from benzene–petroleum ether the nitrile melted at 70–71°.

Anal. Calcd. for $C_{17}H_{14}N_2$: C, 82.89; H, 5.73; N, 11.39. Found: C, 82.61; H, 5.66; N, 11.28.

3-Phenyl-3-(2-pyridyl)-piperidine (IXa, n = 2).—γ-Phenyl-γ-(2-pyridyl)-γ-cyanobutyronitrile was hydrogenated in ethanol with Raney nickel catalyst at a temperature of 75–80° and 750 p.s.i. After processing the reaction mixture, a viscous, orange oil boiling at 168–171° (0.5 mm.) was obtained. The analysis corresponded to a mixture of the piperidine and the uncyclized diamine.

Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.60; H, 7.61; N, 11.76. Found: C, 78.72; H, 7.62; N, 13.30.

3-Phenyl-3-(2-pyridyl)-1-methylpiperidine (Xa, n = 2).—To 7 g. of formic acid was added slowly 11.9 g. (0.05 mole) of impure 3-phenyl-3-(2-pyridyl)-piperidine and 6 ml. of 37% formalin; yield 7.2 g., b.p. 170–175° (2.5 mm.), $n^{25}D$ 1.5680.

Anal. Calcd. for $C_{17}H_{20}N_2$: N, 11.11. Found: N, 11.33.

β-Phenyl-β-(2-pyridyl)-propionic Acid (XIa, n = 1).—A solution of 10 g. (0.039 mole) of ethyl β-phenyl-β-(2-pyridyl)-propionate and 20 g. of potassium hydroxide in 170 ml. of isopropyl alcohol was refluxed for 14 hours. The solvent was removed *in vacuo*, the residue dissolved in water and the aqueous solution extracted with ether. The alkaline layer was acidified with hydrochloric acid and the gelatinous precipitate was removed by filtration. The acid solution was saturated with sodium acetate, extracted with benzene, the benzene removed *in vacuo* and the residue crystallized from ethanol–water; yield 6.3 g. (71%), m.p. 110–111°.

Anal. Calcd. for $C_{14}H_{13}O_2N$: N, 6.16. Found: N, 6.26.

γ-Phenyl-γ-(2-pyridyl)-butyric Acid (XIa, n = 2) (a).—A solution of 10 g. (0.037 mole) of ethyl γ-phenyl-γ-(2-pyridyl)-butyrate and 20 g. of potassium hydroxide in 200 ml. of isopropyl alcohol was refluxed for 36 hours and processed as in the previous experiment; yield 4.7 g. (53%), m.p. 111–112° from ethanol–water.

Anal. Calcd. for $C_{15}H_{15}O_2N$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.91; H, 6.13; N, 5.75.

(b)—A solution of 72 g. (0.245 mole) of ethyl γ-cyano-γ-phenyl-γ-(2-pyridyl)-butyrate in 180 g. of 70% sulfuric acid was heated and stirred at 130–140° for nine hours. The reaction mixture was cooled, poured on ice and neutralized with a 25% sodium hydroxide solution. The brown oil was extracted with ether, the ether dried over sodium sulfate, the solvent removed and the solid residue crystallized from ethanol–water; yield 41 g. (70%), m.p. 110–112°. The melting point of a mixture of the two samples was not depressed.

β-Diethylaminoethyl β-Phenyl-β-(2-pyridyl)-propionate (XIIa, n = 1).—To a warm, stirred solution of 5 g. (0.022 mole) of XIa (n = 1) in 100 ml. of isopropyl alcohol was added dropwise 3 g. (0.022 mole) of β-diethylaminoethyl chloride in 25 ml. of isopropyl alcohol.[14] The reaction mixture was refluxed and stirred for 24 hours, concentrated *in vacuo* to a brown gum and made basic with a 10% sodium carbonate solution. The oil was extracted with ether, the ether dried over sodium sulfate, the solvent removed and the residue distilled; yield 3.2 g. (45%), b.p. 165–170° (2 mm.), $n^{30}D$ 1.5245.

Anal. Calcd. for $C_{20}H_{26}O_2N_2$: C, 73.57; H, 8.01. Found: C, 74.00; H, 8.03.

β-Diethylaminoethyl γ-Phenyl-γ-(2-pyridyl)-butyrate (XII, n = 2).—A solution of 4 g. (0.017 mole) of XIa (n = 2) and 2.3 g. (0.017 mole) of β-diethylaminoethyl chloride in 100 ml. of isopropyl alcohol was refluxed and stirred for 48 hours; yield 2.2 g. (38%), b.p. 183–185° (1 mm.), $n^{26}D$ 1.5290.

Anal. Calcd. for $C_{21}H_{28}O_2N_2$: C, 74.07; H, 8.29. Found: C, 74.28; H, 8.37.

BLOOMFIELD, N. J.