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Local Anesthetics. VII. Monoalkylamino-4-alkoxy-3-aminobenzoates and 3-Alkoxy-4-aminobenzoates[1]

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The preparation of some monoalkylaminoalkyl alkoxyaminobenzoates is reported. The use of the benzyl group and in one case the carbobenzoxy group as a blocking agent on the nitrogen of the alkylaminoalcohols prevented the formation of amides in the preparation of the intermediate nitro esters.

Recently there has been renewed interest in the dialkylaminoalkyl ester type of local anesthetics, particularly those highly potent ones containing both amino and alkoxy substituents on the ring.[2] Much earlier interest in these was evidenced by patents[3] in which claims cover all isomeric compounds containing both alkoxy and amino groups. Later work in this field included dialkylaminoalkyl esters of 2,4-[2b,c] and 3,4-[2a] substituted rings. Epstein and Meyer[2d] studied esters of 2-, 5- and 6-alkoxy substituted 3-aminobenzoic acids which included monoalkylaminoalkyl as well as dialkylaminoalkyl esters.

TABLE I

BENZYLIDENEAMINES, $C_6H_5CH{=}NR$

R	B.p. °C.	Mm.	$n^{25}D$	Yield, %
$-C_2H_5$	96–97	25	1.5378	83
$-C_3H_7$	105–112	23	1.5297	93.4
$-C_4H_9$	123–128	23	1.5232	91
$-CH_2CH(CH_3)_2$[a]				
$-C(CH_3)_3$	104–106	20	1.5180	85
$-C(CH_2)_2CH_2C(CH_3)_3$	150–152	20		91

[a] The undistilled product was used for hydrogenation.

TABLE II

BENZYLALKYLAMINES, $C_6H_5CH_2NHR$

R	B.p. °C.	Mm.	$n^{25}D$	Yield, %
$-C_2H_5$	93–95	21	1.5093	97
$-C_3H_7$	109–110	21	1.5043	83
$-C_4H_9$	124–126	21	1.5000	89
$-CH_2CH(CH_3)_2$	220–224	760	1.4942	66
$-C(CH_3)_3$[a]	107–108	22	1.4980	81
$-C(CH_3)_2CH_2C(CH_3)_3$[b]	156–157	21	1.4976	60

[a] *Anal.* Calcd. for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.58. Found: C, 80.51; H, 10.59; N, 8.60. [b] *Anal.* Calcd. for $C_{15}H_{25}N$: C, 82.10; H, 11.53; N, 6.38. Found: C, 82.12; H, 11.49; N, 6.39.

TABLE III

BENZYLAMINOALCOHOLS, $C_6H_5CH_2NHROH$

R	B.p. °C.	Mm.	$n^{25}D$	Yield, %
$-CH_2CH_2-$	164–166	22	1.5423	84.5
$-CH_2CH(CH_3)-$	144–149	11	1.5277	74
$-CH_2CH_2CH_2-$	161–163	11	1.5362	79.5
$-CH(C_2H_5)CH_2$[a]	155–156	11	[b]	68

[a] *Anal.* Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.97; H, 9.39; N, 8.02. [b] M.p. 55–60°.

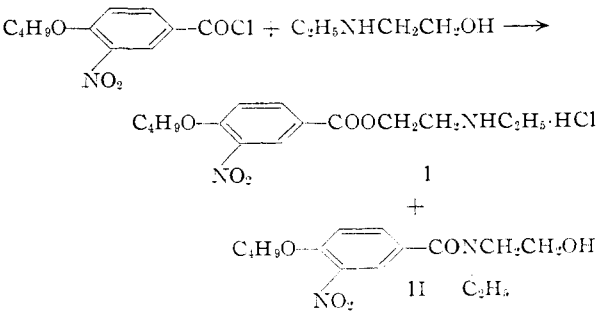
(1) Presented at the New York Meeting of the American Chemical Society, September, 1957.

(2) (a) J. Buchi, E. Stunzi, M. Flury, R. Hirt, P. Labhart and L. Rugay, *Helv. Chim. Acta*, **34**, 1002 (1951); (b) R. O. Clinton, U. J. Salvador, S. C. Laskowski and M. Wilson, THIS JOURNAL, **74**, 592 (1952); (c) W. Grimme and H. Schmitz, *Ber.*, **87**, 179 (1954); (d) E. Epstein and M. Meyer, THIS JOURNAL, **77**, 4059 (1955).

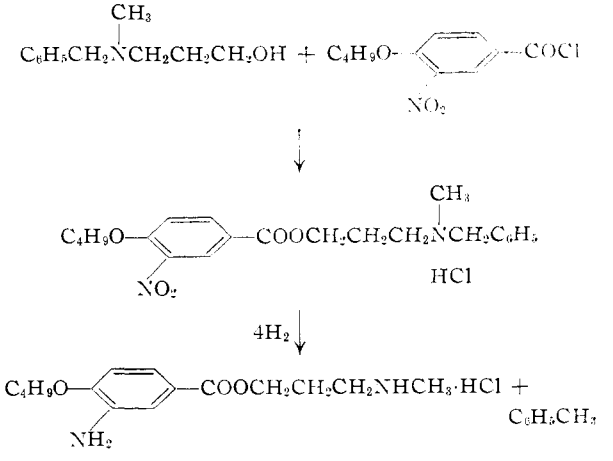
(3) Wildman, U. S. Patent 1,317,250, Sept. 30, 1919; Schering-Kahlbaum, German Patent 522,064, Aug. 11, 1928.

Our continuing interest in the field of local anesthetics led us to investigate some monoalkylaminoalkyl 4(3)-alkoxy-3(4)-aminobenzoates.

Following a modification of the method described by Cope and Hancock[4] several attempts were made to react 4-butoxy-3-nitrobenzoyl chloride with ethylaminoethanol. Each time a product was obtained which appeared to be a mixture of the hydrochloride of the substituted nitrobenzoate I and the N-ethyl-β-hydroxyethylamide II. In order to avoid formation of amides in the preparation of the intermediate monoalkylaminoalkyl alkoxynitrobenzoates N-benzylalkylaminoalcohols were used in



the synthesis instead of monoalkylaminoalcohols. In the course of catalytic hydrogenation of the hydrochloride salts of the nitro esters, hydrogenolysis was effected along with reduction of the nitro group. In one case, a carbobenzoxy group was substituted for benzyl. This blocking group was also easily removed; *e. g.*



(4) J. S. Pierce, J. M. Salsbury and J. M. Frederickson, THIS JOURNAL, **64**, 1961 (1942); A. C. Cope and E. M. Hancock, *ibid.*, **66**, 1448 (1944); J. R. Reasenberg and S. D. Goldberg, *ibid.*, **67**, 933 (1945).

TABLE IV

BENZYLALKYLAMINOALCOHOLS, $C_6H_5CH_2NR'OH$ (R on N)

R	R'	B.p. °C.	Mm.	$n^{25}D$	Yield, %	Method	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$-C_2H_5$	$-CH_2CH_2-$	148–156	20	1.5186	71	A[a]	$C_{11}H_{17}NO$	73.70	73.81	9.56	9.73	7.81	7.66
$-C_3H_7$	$-CH_2CH_2-$	143–155	11	1.5115	83	A[b]	$C_{12}H_{19}NO$	74.57	74.39	9.91	10.06	7.25	7.23
$-C_4H_9$	$-CH_2CH_2-$	172–183	21	1.5078	85	A	$C_{13}H_{21}NO$	75.31	75.96	10.21	10.38	6.76	6.73
$-C_4H_9$(iso)	$-CH_2CH_2-$	165–167	22	1.5030	71	A	$C_{13}H_{21}NO$	75.31	75.46	10.21	10.38	6.76	6.66
$-C(CH_3)_3$	$-CH_2CH_2-$	168–170	21	1.5130	13.6[c] 74[d]	A	$C_{13}H_{21}NO$	75.31	75.28	10.21	10.23	6.76	6.89
$-C_6H_{11}$[e]	$-CH_2CH_2-$	188–192	10	1.5103	45[f]	A	$C_{17}H_{29}NO$	77.51	77.12	11.10	11.19	5.32	5.40
$-CH_3$	$-CH_2CH(CH_3)-$	127–128	13	1.5087	86.5	B	$C_{11}H_{17}NO$	73.70	73.80	9.56	9.69	7.81	7.88
$-C_3H_7$	$-CH_2CH(CH_3)-$	141–143	11	1.5012	40	B	$C_{13}H_{21}NO$	75.31	75.12	10.21	10.17	6.76	6.62
$-C_3H_7$	$-CH(C_2H_5)CH_2-$	162–167	11	1.5052	56	B	$C_{14}H_{23}NO$	75.97	76.26	10.47	10.39	6.33	6.53
$-CH_3$	$-CH_2CH_2CH_2-$	148–147	11	1.5216	74	B	$C_{11}H_{17}NO$	73.70	73.91	9.56	9.26	7.81	7.67
$-C_6H_{11}$[g]	$-CH_2CH_2-$	207	22	1.5287	47.6	B	$C_{18}H_{23}NO$	77.20	77.34	9.93	10.01	6.00	5.99
$-CH(CH_3)_2$	$-CH_2CH_2-$	142–143	10	1.5110	17.5	C	$C_{12}H_{19}NO$	74.59	74.63	9.91	10.03	7.25	7.29

[a] Also prepared by method C in 63.5% yield. [b] Also prepared by method B in 76% yield. [c] Reaction with ethylene oxide carried out at 90–100° for 5 hours. [d] Reaction with ethylene oxide carried out at 125° for 24 hours. [e] $-C(CH_3)_2CH_2C(CH_3)_3$. [f] Reaction with ethylene oxide carried out at 150° for 28 hours. [g] Cyclohexyl.

TABLE V

BENZYLALKYLAMINOALKYL ALKOXYNITROBENZOATE HYDROCHLORIDES, RO(NO$_2$)C_6H_3COOZN(R')$CH_2C_6H_5$

R	Z	R'	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$-C_2H_5$	$-CH_2CH_2-$	$-C_3H_7$	175–176	66	$C_{21}H_{26}N_2O_5\cdot HCl$	59.64	59.64	6.44	6.57	6.62	6.56
$-C_2H_5$	$-CH_2CH_2-$	$-C_4H_9$	128–129	75	$C_{22}H_{28}N_2O_5\cdot HCl$	60.50	60.24	6.69	6.94	6.41	6.38
$-C_2H_5$	$-CH_2CH_2-$	$-C_4H_9$(iso)	126–128	94	$C_{22}H_{28}N_2O_5\cdot HCl$	60.50	60.58	6.69	6.83	6.41	6.44
$-C_2H_5$	$-CH_2CH(C_2H_5)-$	$-C_3H_7$	79–81	[a]	$C_{23}H_{30}N_2O_5\cdot HCl$	61.25	60.80	6.93	7.09	6.21	5.86
$-C_3H_7$	$-CH_2CH_2-$	$-C_2H_5$	166–167	91	$C_{21}H_{26}N_2O_5\cdot HCl$	59.64	59.48	6.44	6.49	6.62	6.37
$-C_3H_7$	$-CH_2CH_2-$	$-C_3H_7$	117–119	90	$C_{22}H_{28}N_2O_5\cdot HCl$	60.50	60.01	6.69	6.66	6.41	6.71
$-C_4H_9$	$-CH_2CH_2-$	$-C_2H_5$	139–141	82	$C_{22}H_{28}N_2O_5\cdot HCl$	60.50	60.69	6.69	6.68	6.41	6.23
$-C_4H_9$	$-CH_2CH_2-$	$-C_3H_7$(iso)	115–117	82	$C_{23}H_{30}N_2O_5\cdot HCl$	61.25	61.40	6.93	7.21	6.21	6.06
$-C_4H_9$	$-CH_2CH_2-$	$-C_6H_{11}$[b]	98–101	76	$C_{26}H_{34}N_2O_5\cdot HCl$	63.59	63.58	7.18	7.03	5.76	5.63
$-C_4H_9$	$-CH_2CH_2-$	$-C_3H_7$(iso)	130–132	89	$C_{23}H_{30}N_2O_5\cdot HCl$	61.25	61.15	6.93	6.74	6.21	5.99
$-C_4H_9$	$-CH_2CH_2CH_2-$	$-CH_3$	125–127	75	$C_{22}H_{28}N_2O_5\cdot HCl$	60.50	60.69	6.69	6.45	6.41	6.37
$-C_4H_9$	$-CH(CH_3)CH_2-$	$-CH_3$	78–83	[a]	$C_{22}H_{28}N_2O_5\cdot HCl$	60.50	59.02	6.69	6.63	6.41	6.23

[a] Adhering solvent made accurate calculation of yields difficult and interfered with analyses. [b] Cyclohexyl.

The benzylalkylaminoalcohols were prepared by several methods

(A) $C_6H_5CHO + RNH_2 \xrightarrow{-H_2O} C_6H_5CH{=}NR \xrightarrow{H_2} C_6H_5CH_2NHR \xrightarrow{CH_2CH_2O} C_6H_5CH_2N(R)CH_2CH_2OH$

(B) $C_6H_5CHO + NH_2(CH_2)_nCHOH \xrightarrow{H_2} C_6H_5CH_2NH(CH_2)_nCHOH \xrightarrow[H_2]{RCHO} C_6H_5CH_2N(CH_2)_nCHOH$ (R on N and on CHOH)

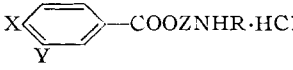
(C) $RNHCH_2CH_2OH + C_6H_5CHO \xrightarrow{H_2} C_6H_5CH_2N(R)CH_2CH_2OH$

Method A seems to be best for the preparation of benzylalkylaminoethanols. The Schiff bases (Table I) were isolated and distilled in most cases before hydrogenation. This led to higher over-all yields of benzylalkylamines (Table II). In method B, the intermediate benzylaminoalcohols were isolated and distilled (Table III) and then reductively alkylated with the appropriate aldehyde or ketone. In method C reductive benzylation of ethylaminoethanol and isopropylaminoethanol gave the respective tertiary aminoalcohols. Properties of the benzylaminoalcohols prepared by methods A, B and C are found in Table IV.

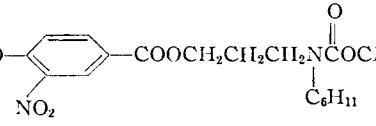
In the one example where a carbobenzoxy group was substituted for benzyl as the blocking agent, 3-cyclohexylaminopropanol was acylated with carbobenzoxy chloride. The product was then condensed with 4-butoxy-3-nitrobenzoyl chloride to yield an oily nitrobenzoate. This compound underwent catalytic reduction and hydrogenolysis to yield the desired compound (Table VI).

The alkoxynitrobenzoyl chlorides were prepared by refluxing the acids with excess thionyl chloride in toluene. It is interesting to note that when benzene was used as solvent conversion of the acids to acid chlorides was poor and incomplete. The acid chlorides were not isolated but, after removing excess thionyl chloride and some solvent, were

TABLE VI

ALKYLAMINOALKYL ALKOXYAMINOBENZOATE HYDROCHLORIDES 

X	Y	Z	R	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$-OC_4H_9$	NH_2	$-CH_2CH_2-$	$-CH_3$	204	28	$C_{14}H_{22}N_2O_3\cdot 2HCl$	49.56	49.36	7.13	7.22	8.26	8.13
$-OC_4H_9$	NH_2	$-CH_2CH_2-$	$-C_2H_5$	128–129	67	$C_{15}H_{24}N_2O_3\cdot HCl$	56.86	57.16	7.95	8.03	8.84	8.86
$-OC_4H_9$	NH_2	$-CH_2CH_2-$	$-C_3H_7$	141–142	78	$C_{16}H_{26}N_2O_3\cdot HCl$	58.08	57.67	8.23	7.90	8.46	8.01
$-OC_4H_9$	NH_2	$-CH_2CH_2-$	$-C_3H_7$(iso)	143–144	91	$C_{16}H_{26}N_2O_3\cdot HCl$	58.08	58.19	8.23	8.12	8.46	8.58
$-OC_4H_9$	NH_2	$-CH_2CH_2-$	$-C_4H_9$	140–141	63	$C_{17}H_{28}N_2O_3\cdot HCl$	59.20	59.02	8.48	8.69	8.12	8.12
$-OC_4H_9$	NH_2	$-CH_2CH_2-$	$-C_4H_9$(iso)	97–100	84	$C_{17}H_{28}N_2O_3\cdot HCl$	59.20	58.96	8.48	8.60	8.12	7.93
$-OC_4H_9$	NH_2	$-CH_2CH_2-$	$-C_4H_9$(tert.)	146–148	75	$C_{17}H_{28}N_2O_3\cdot HCl$	59.20	59.29	8.48	8.77	8.12	7.82
$-OC_4H_9$	NH_2	$-CH_2CH_2-$	$-C_6H_{11}$[a]	211–212	70	$C_{19}H_{30}N_2O_3\cdot 2HCl$	56.01	56.26	7.92	7.71	6.88	6.89
$-OC_4H_9$	NH_2	$-CH_2CH_2CH_2-$	$-CH_3$	156–158	63	$C_{15}H_{24}N_2O_3\cdot HCl$	56.86	56.72	7.95	7.75	8.84	8.78
$-OC_4H_9$	NH_2	$-CH_2CH_2CH_2-$	$-C_6H_{11}$[a,b]	216 dec.	60	$C_{20}H_{32}N_2O_3\cdot 2HCl$	57.00	57.40	8.13	7.97	6.65	6.78
$-OC_4H_9$	NH_2	$-CH(CH_3)CH_2-$	$-CH_3$	138–140	58	$C_{15}H_{24}N_2O_3\cdot HCl$	56.86	56.91	7.95	7.78	8.84	8.99
$-OC_4H_9$	NH_2	$-CH(CH_3)CH_2-$	$-C_3H_7$	144–146	55	$C_{17}H_{28}N_2O_3\cdot 2HCl$	53.53	53.58	7.90	7.91	7.35	7.12
$-OC_4H_9$	NH_2	$-CH_2CH(C_2H_5)-$	$-C_3H_7$	206–208	53	$C_{18}H_{30}N_2O_3\cdot 2HCl$	54.68	54.63	8.16	8.15	7.09	6.88
$-OC_2H_5$	NH_2	$-CH_2CH(C_2H_5)-$	$-C_3H_7$	168–170	77	$C_{16}H_{26}N_2O_3\cdot HCl$	58.08	58.15	8.23	8.27	8.46	8.29
$-OC_3H_7$	NH_2	$-CH_2CH_2-$	$-C_2H_5$	124–125	82	$C_{14}H_{22}N_2O_3\cdot HCl$	55.53	55.42	7.66	7.80	9.25	8.96
$-OC_3H_7$	NH_2	$-CH_2CH_2-$	$-C_3H_7$	140–142	87	$C_{15}H_{24}N_2O_3\cdot HCl$	56.86	56.73	7.95	8.16	8.84	8.65
$-OC_2H_5$	NH_2	$-CH_2CH_2-$	$-C_3H_7$	152–153	94	$C_{14}H_{22}N_2O_3\cdot HCl$	55.53	55.46	7.66	7.80	9.25	9.19
$-OC_2H_5$	NH_2	$-CH_2CH_2-$	$-C_4H_9$	136–137	92	$C_{15}H_{24}N_2O_3\cdot HCl$	56.86	56.89	7.95	8.18	8.84	8.82
$-OC_2H_5$	NH_2	$-CH_2CH_2-$	$-C_4H_9$(iso)	228 dec.[c]	54	$C_{15}H_{24}N_2O_3\cdot 2HCl$[d]$\cdot 1.5H_2O$	47.48	47.45	7.68	7.53	7.36	6.92
$-OC_2H_5$	NH_2	$-CH_2CH_2-$	$-C_8H_{17}$[e]	146–149	51	$C_{19}H_{32}N_2O_3\cdot 2HCl$	55.74	55.21	8.37	8.54	6.84	6.66
$-NH_2$	$-OC_3H_7$	$-CH_2CH_2-$	$-C_2H_5$	83–86	42	$C_{14}H_{22}N_2O_3\cdot HCl\cdot H_2O$	52.41	52.32	7.86	7.89	8.74	9.16
$-NH_2$	$-OC_3H_7$	$-CH_2CH_2-$	$-C_3H_7$	148	49	$C_{15}H_{24}N_2O_3\cdot 2HCl$	50.97	50.87	7.43	7.60	7.93	7.84
$-NH_2$	$-OC_2H_5$	$-CH_2CH_2-$	$-C_3H_7$	175–177[f]	10	$C_{14}H_{22}N_2O_3\cdot 2HCl\cdot H_2O$	47.06	47.24	7.34	7.36	7.84	7.56
$-NH_2$	$-OC_2H_5$	$-CH_2CH_2-$	$-C_4H_9$	196	25	$C_{15}H_{24}N_2O_3\cdot HCl$	56.86	57.05	7.95	7.82	8.84	8.93

[a] Cyclohexyl. [b] Prepared by hydrogenation of  . [c] Product appears to lose water of crystallization during heating. It resolidifies at 135°. [d] Calculated for anhydrous compound: C, 51.13; H, 7.44; N, 8.06. Found (after prolonged drying at 100°): C, 50.60; H, 7.32; N, 7.91. [e] $-C(CH_3)_2CH_2C(CH_3)_3$. [f] Loses water of crystallization at 100–105°.

mixed with the desired benzylalkylaminoalcohols in benzene to yield the hydrochloride salt of the corresponding nitroesters (Table V).

Not all of the hydrochlorides of the substituted nitrobenzoates could be characterized. Some were obtained as thick masses which resisted all attempts at crystallization. No difficulty was encountered in the hydrogenation of the compounds. The final products (Table VI) were obtained in good yields with a few exceptions.

Some of the monoalkylaminoalkyl alkoxyaminobenzoates showed good local anesthetic activity. These results will be published at some later date by Dr. John L. Schmidt of the Pharmacology Department of Abbott Laboratories.

Acknowledgment.—The authors are indebted to Mr. E. F. Shelberg and his staff for the microanalyses reported in this paper and to Mr. R. V. Johnson for the preparation of the alkoxynitrobenzoic acids.

Experimental

Method A. N-Benzyl-N-butylaminoethanol.—One mole of distilled benzaldehyde (106.1 g.) and 1.0 mole (73.0 g.) of *n*-butylamine were dissolved in a mixture of benzene and toluene and refluxed using a water separator. When separation of water was complete, the solvent was removed and the Schiff base distilled. This product was then hydrogenated at 80° under a pressure of 88 atm. in the presence of Raney nickel. When the reaction was complete, the reduction product was filtered and washed from the catalyst with some ethanol. The solvent was removed and the benzylbutylamine distilled.

A one-liter stainless steel bomb containing 81.6 g. (0.5 mole) of benzylbutylamine was cooled in an acetone–Dry Ice-bath. Ethylene oxide (22 g., 0.5 mole) was added and the bomb sealed. The reaction was warmed to room temperature and then heated at 90–100° for several hours. The oily aminoalcohol then was distilled.

Method B. 3-N-Benzyl-N-methylaminopropanol.—One mole (106.1 g.) of freshly distilled benzaldehyde was added to 1.0 mole (75.1 g.) of 3-aminopropanol in 100 cc. of thiophene-free benzene. The mixture became cloudy immediately and quite warm. It was refluxed about one hour using a water separator. The solvent was distilled and the residue was treated with 100 cc. of absolute ethanol. The solution was hydrogenated under 50 pounds pressure in the presence of 16 g. of 5% palladium-on-activated carbon. When the calculated amount of hydrogen was absorbed, the reaction mixture was filtered, concentrated and the residue was distilled. 3-Benzylaminopropanol (10.6 g., 0.0642 mole) was dissolved in 25 cc. of methanol and 15 g. (0.2 mole) of 40% formalin added. The mixture was allowed to stand overnight. Additional methanol (25 cc.) was added and the solution was hydrogenated in the presence of 0.9 g. of platinum oxide under 1.3 atm. pressure. When absorption was complete the mixture was filtered and concentrated under reduced pressure. The residue was distilled.

Method C. N-Benzyl-N-ethylaminoethanol.—A mixture of 44.5 g. (0.5 mole) of ethylaminoethanol and 58.3 g. (0.55 mole) of benzaldehyde in 200 cc. of dry benzene was allowed to stand for one hour. The solvent was distilled and the residue dissolved in 100 cc. of absolute alcohol and hydrogenated under 3 atm. pressure in the presence of 1.5 g. of platinum oxide catalyst. When uptake was complete (40 hr.), the solution was filtered, concentrated and the residue distilled.

3-N-Carbobenzoxy-N-cyclohexylaminopropanol.—One mole (98.1 g.) of cyclohexanone and 1.0 mole (75.1 g.) of 3-aminopropanol were mixed and allowed to stand overnight. Absolute alcohol (100 cc.) was added and the solution was hydrogenated under 3 atm. pressure in the presence of 10 g. of 5% palladium-on-activated carbon. When reduction was complete (15 hours), the solution was warmed and filtered. After the solvent was removed, the residue solidified and was dried. A crude yield of 150.4 g. (95.5%) of 3-cyclohexylaminopropanol melting at 61–67° was obtained. The product was later distilled and boiled at 122° (5 mm.). It solidified and melted at 71–73°. *Anal.* Calcd. for $C_9H_{19}NO$: N, 8.97. Found: N, 8.91.

A mixture of 20.2 g. (0.2 mole) of triethylamine and 31.4 g. (0.2 mole) of cyclohexylaminopropanol was dissolved in 500 cc. of warm benzene and 50 cc. of dry ether. Carbobenzoxy chloride (34.1 g., 0.2 mole) was added in portions. Triethylamine hydrochloride began to precipitate almost immediately. The reaction was warmed on the steam-bath for several hours and filtered. The solvent was removed and the residue distilled. The product weighed 17 g. and boiled at 200–207° (6–7 mm.), $n^{25}D$ 1.5243.

Anal. Calcd. for $C_{17}H_{25}NO_3$: C, 70.06; H, 8.65; N, 4.81. Found: C, 70.08; H, 8.80; N, 5.06.

2′-N-Benzyl-N-propylaminoethyl 4-Butoxy-3-nitrobenzoate Hydrochloride.—One-tenth mole (23.9 g.) of 4-butoxy-3-nitrobenzoic acid 0.2 mole (23.8 g.) of thionyl chloride and 200 cc. of dry toluene were mixed and refluxed for 18 hours. The excess thionyl chloride and some of the toluene were distilled off until the volume was about 100 cc. About 50 cc. of dry benzene was added and the mixture stirred and heated as 19.3 g. (0.1 mole) of 2-N-benzyl-N-propylaminoethanol in 100 cc. of dry benzene was added dropwise within 30 minutes. Stirring and heating were continued for about two hours and then the material was allowed to stand overnight at room temperature. The solvent was removed under reduced pressure and the light brown oily residue treated with anhydrous ether. After trituration and standing, a yellow crystalline solid was obtained. A sample of this was recrystallized from isopropyl alcohol and anhydrous ether for analysis.

2′-N-Propylaminoethyl 4-Butoxy-3-aminobenzoate Monohydrochloride.—Twenty-five grams (0.056 mole) of the above nitro ester hydrochloride was dissolved in 200 cc. of water and 25 cc. of ethanol and reduced catalytically in the presence of 3.0 g. of 5% palladium-on-carbon under 2 atm. pressure. After reduction was completed, the solution was filtered from the catalyst, made alkaline with sodium hydroxide (keep cool to prevent hydrolysis) and extracted with benzene. The benzene extract was washed with water to remove excess alkali and dried over anhydrous magnesium sulfate. After filtration from drying agent, the benzene solution was treated with 0.056 mole of alcoholic hydrogen chloride. The hydrochloride precipitated in a short time and was filtered and washed with dry ether. A sample was recrystallized from hot isopropyl alcohol for analysis.

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