[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

THIOCYANATION OF *p*-DIALKYLAMINOALKOXYANILINES

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The use of alkyl esters of *p*-aminobenzoic acid as local anesthetics is limited because of their insolubility (1). Introduction of a tertiary amino group into the ester portion of the molecule results in a more basic substance which forms soluble acid salts. For example, replacement of the ethyl group in ethyl *p*-aminobenzoate (benzocaine) by a diethylaminoethyl group yields the well-known local anesthetic procaine. For this reason it was thought desirable to prepare several 2-amino-6-dialkylaminoalkoxybenzothiazoles (III, A–F) in the expectation that these compounds might prove superior to 2-amino-6-ethoxybenzothiazole as local anesthetics. The latter has been described as being equal to novocaine in sensory and motor nerve blocking. Though inferior to cocaine in its effect upon human mucous membranes, its toxicity, upon both subcutaneous and intravenous injection in mammals, is less than either of these two substances (2, 3).

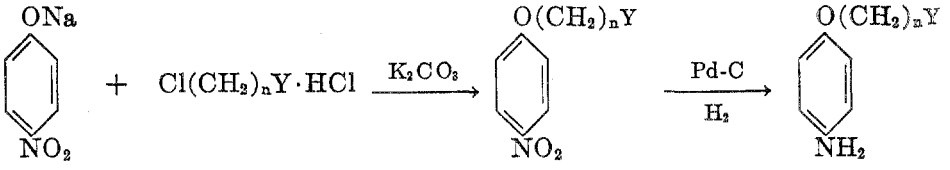
A similar series of compounds has been described recently, one of which is a commercially available fungistatic agent known as Asterol dihydrochloride (IV) (4).

The 2-amino-6-dialkylaminoalkoxybenzothiazoles were prepared by the thiocyanation of *p*-dialkylaminoalkoxyanilines (II, A–F) uxing the procedure of Kaufmann, Oehring, and Clauberg for the preparation of 2-amino-5-carbethoxybenzothiazole (5). The intermediate thiocyanates underwent spontaneous cyclization. In another investigation, excellent yields of dialkylaminoalkyl esters of 2-amino-6-carboxybenzothiazole had been obtained from dialkylaminoalkyl esters of *p*-aminobenzoic acid by the same thiocyanation procedure (6). However the products of this investigation (III, A–F) were formed, in very poor yield, as gums which were extremely difficult to purify, even as salts. All but one were characterized as picrates. These frequently could not be purified by recrystallization, since some decomposition occurred in the process, resulting in darkening of the compound and lowering of its melting point. Both the free bases, obtained by decomposing the picrate with ethanolamine (7), and their salts (in the form of 5% aqueous solutions kept in sealed ampoules at 5°) darkened on standing. In view of the apparent instability of these compounds, no attempt was made to study conditions for improving yields.

The *p*-dialkylaminoalkoxyanilines (II, A–F) were prepared by catalytic reduction of the corresponding *p*-dialkylaminoalkoxynitrobenzenes (I, A–F). Unlike the 2-amino-6-dialkylaminoalkoxybenzothiazoles, which are all new compounds, two of the *p*-dialkylaminoalkoxyanilines (II, A and B) had been prepared previously (8, 9) by reducing the corresponding nitro compounds with iron and hydrochloric acid in the presence of platinum as catalyst. They have been described as dark brown hygroscopic oils whose salts crystallized very poorly. In animal experiments II, B was found to show distinct local anesthetic action without causing irritation or disturbing the circulation (8).

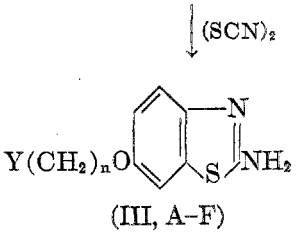
In contrast with the benzothiazoles, the intermediate anilines were prepared readily in 80–96% yield as colorless or pale yellow oils, some of which crystallized on standing. The free bases and their hydrochlorides darkened rapidly on exposure to air and were hygroscopic.

Of the nitro compounds, two (I, A and B) have been described in the literature (8, 9). Yields by the method of Rohman and Friedrich (8) were improved when the sodium salt of *p*-nitrophenol and the dialkylaminoalkyl chloride hydrochloride were refluxed in xylene, in the presence of potassium carbonate and water, for two hours. Refluxing, with simultaneous removal of the water from the reaction-mixture by azeotropic distillation, was then continued for 21–24 hours.

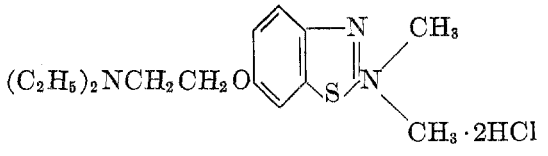


A; n = 2, Y = $N(CH_3)_2$
B; n = 2, Y = $N(C_2H_5)_2$
C; n = 2, Y = $N(CH_2C_6H_5)_2$
D; n = 2, Y = NC_4H_8O
E; n = 2, Y = NC_4H_8
F; n = 3, Y = $N(C_2H_5)_3$

(I, A–F) (II, A–F)



(III, A–F)



Asterol dihydrochloride, IV

Solutions of the salts of II and III, A–F have been prepared for pharmacological evaluation. It seems quite unlikely that these compounds will find any use as therapeutic agents since they are so unstable. The stable nitro compounds (I, A–F) may have interesting properties, since related compounds have been shown to be sweetening agents as well as local anesthetics (10, 11). The hydrochloride of I, B was found by Dr. Irwin H. Slater, at the School of Medicine and Dentistry of the University of Rochester, to cause clonic convulsions in mice. It showed no curariform activity in the cat and afforded no protection against electric shock, metrazole, or strychnine. Preliminary tests, conducted under the supervision of Dr. C. Chester Stock at the Sloan-Kettering Institute for Cancer Research, with the oxalate of III, E, revealed that it was ineffective in retarding the growth of sarcoma 180.

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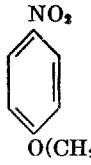
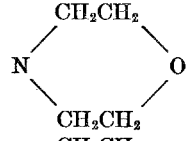
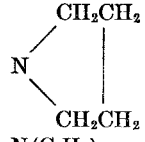
TABLE I

p-DIALKYLAMINOALKOXYNITROBENZENES,



No.	n	Y	B.P., °C.	MM.	YIELD, %	HCl SALT, M.P., °C.	FORMULA	NITROGEN	
								Calc'd	Found
I, A	2	$N(CH_3)_2$	116–117	0.4	38[a]	[b]	$C_{10}H_{14}N_2O_3$	13.32	12.81
I, B	2	$N(C_2H_5)_2$	143	.2	94	164–165[c]	$C_{12}H_{18}N_2O_3$	11.76	11.82
I, C	2	$N(CH_2C_6H_5)_2$	146–147	.15	92	186–188[d]	$C_{22}H_{22}N_2O_3 \cdot HCl$	7.02	6.80
I, D	2		89.5–90.5[e]		67	215–217[c]	$C_{12}H_{16}N_2O_4$	11.11	11.22
I, E	2		177–183[f]	2.0	75	190–191[c]	$C_{12}H_{16}N_2O_3$	11.86	12.15
I, F	3	$N(C_2H_5)_2$	144–146	0.4	79	177–177.5[c]	$C_{13}H_{20}N_2O_3 \cdot HCl$	9.70	9.75

[a] After the initial two-hour reflux period in the presence of water, the reaction mixture was refluxed for 24 hours longer. When this latter period was shortened to ten hours, the product was obtained in 16% yield. A 15-hour reflux period gave a 48% yield. [b] This salt was the only hygroscopic member of the series. [c] Recrystallized from propanol-2. [d] Recrystallized from methanol. [e] M.P. after two recrystallizations from hexane. The yield is based on the weight of crude product, m.p. 82–83°. [f] On redistillation the base crystallized, m.p. 57.5–58.5° after two recrystallizations from heptane.

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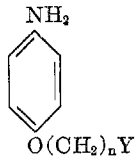
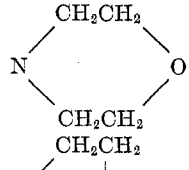
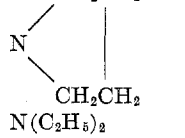
EXPERIMENTAL

All melting points are corrected; boiling points are not. The sodium salt of *p*-nitrophenol, *β*-dimethylaminoethyl chloride hydrochloride, and *β*-diethylaminoethyl chloride hydrochloride were commercial products. *β*-Dibenzylaminoethyl chloride hydrochloride (12), *γ*-diethylaminopropyl chloride hydrochloride (13), *β*-morpholinoethyl chloride hydrochloride (14), and *β*-(1-pyrrolidyl)ethyl chloride hydrochloride (15) were prepared by previously described methods. Nitrogen analyses were performed by the micro-Kjeldahl method.

TABLE II

p-DIALKYLAMINOALKOXYANILINES, 

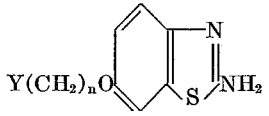
No.	n	Y	B.P., °C.	MM.	YIELD, %	FORMULA	NITROGEN	
							Calc'd	Found
II, A	2	$N(CH_3)_2$	115	0.35	89[a]	$C_{10}H_{16}N_2O$	15.54	15.18
II, B	2	$N(C_2H_5)_2$	114–116	.3	96	$C_{12}H_{20}N_2O$	208.3[b]	211.6
II, C	2	$N(CH_2C_6H_5)_2$	191–193	.02	83	$C_{22}H_{24}N_2O \cdot C_{12}H_6N_6O_{14}$[c, d]	14.19	14.47
II, D	2		147–150	.08	83[a]	$C_{12}H_{18}N_2O_2 \cdot C_6H_3N_3O_7$[c, e]	15.51	15.90
II, E	2		153–155	2.0	80	$C_{12}H_{18}N_2O$	13.58	13.50
II, F	3	$N(C_2H_5)_2$	125	0.06	95	$C_{13}H_{22}N_2O \cdot C_{12}H_6N_6O_{14}$[c, f]	15.49	15.30

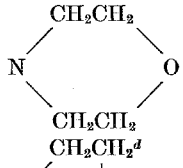
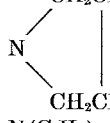
[a] The oil solidified in the receiver, but although it crystallized from propanol-2 as long needles, it was too hygroscopic to filter. [b] Acid equivalent, determined by the method of Fritz, *Anal. Chem.*, **22**, 578, 1028 (1950). [c] Picrate, recrystallized from propanol-2. [d] M.P. 161–161.5°. [e] M.P. 151.5–152°. [f] M.P. 97.5–99°.

p-Dialkylaminoalkoxynitrobenzenes (I, A–F). The commercial sample of the sodium salt of *p*-nitrophenol was found to contain 23.5% water. A mixture of 0.5 mole of the wet compound (corrected for its water content), 0.5 mole of the dialkylaminoalkyl chloride hydrochloride, 0.75 mole of potassium carbonate, 75 ml. of water, and 350 ml. of xylene was refluxed with stirring for two hours. Refluxing of the stirred mixture was then continued for 21–24 hours while the water in the reaction mixture was removed by azeotropic distillation The hot reaction mixture was filtered and the residue washed with hot xylene. The solvent was removed from the filtrate and the product obtained by distilling the residue *in vacuo*. In the case of I,D, the crude product solidified and was purified by recrystallization. Re-

TABLE III

PICRATES OF 2-AMINO-6-DIALKYLAMINOALKOXYBENZOTHIAZOLES,



No.	n	Y	M.P., °C.	RECRYSTN. SOLVENT	YIELD, %	FORMULA	NITROGEN	
							Calc'd	Found
III, A	2	$N(CH_3)_2$	248 d.	Propanol-2-acetone	4	$C_{11}H_{15}N_3OS \cdot C_{12}H_6N_6O_{14}$	18.13	17.20[a]
III, B	2	$N(C_2H_5)_2$	91.5–92[b]	Hexane	1	$C_{13}H_{19}N_3OS$	15.84	15.40
III, C	2	$N(CH_2C_6H_5)_2$	212–213	Acetone	1	$C_{23}H_{23}N_3OS \cdot C_{12}H_6N_6O_{14}$	15.23	14.44[a]
III, D	2		243.5–245	[c]	31	$C_{13}H_{17}N_3O_2S \cdot C_{12}H_6N_6O_{14}$	17.10	16.54[a]
III, E	2		250–252	Ethanol-water	5	$C_{13}H_{17}N_3OS \cdot C_{12}H_6N_6O_{14}$	17.47	17.30
III, F	3	$N(C_2H_5)_2$	216	Methanol	23	$C_{14}H_{21}N_3OS \cdot C_{12}H_6N_6O_{14}$	17.09	16.80

[a] Since the salt darkened on recrystallization, no attempt was made to purify the product further. [b] This is the only free base in this series which could be crystallized. [c] On recrystallization from propanol-2, the m.p. dropped to 237.5–238°. [d] A stable oxalate salt was also obtained and recrystallized from propanol-2, m.p. 170–170.5°.

sults are summarized in Table I. It is interesting to note that when I,B was prepared under anhydrous conditions, the yield dropped from 94% to 85%.

p-Dialkylaminoalkoxyanilines (II, A–F). The respective nitro compound (I, A–F) (0.1 mole), dissolved in 50 ml. of 95% ethanol was reduced at an initial pressure of 58 lbs. in the presence of one gram of 10% palladium-charcoal. Reductions were complete in about one hour. The products, isolated by distillation *in vacuo* after removal of the catalyst and solvent, are described in Table II.

2-Amino-6-dialkylaminoalkoxybenzothiazoles (III, A–F). To a stirred solution containing 0.48 mole of sodium or potassium thiocyanate and 0.11 mole of the *p*-dialkylaminoalkoxyaniline in 120 ml. of 96% acetic acid, was added 6.8 ml. of bromine dropwise. The temperature of the reaction mixture was maintained at −3° to 0° during the addition. The mixture was then refluxed for one-half hour and filtered. The filtrate was diluted with 500 ml. of water and neutralized with solid sodium carbonate. A brown gum separated at this point. In the case of III, B this material was dissolved in dilute hydrochloric acid and the solution decolorized with charcoal. The amorphous precipitate which appeared when the solution was made alkaline was recrystallized from hexane. In all other preparations, the gummy material was extracted repeatedly with ether and a picrate was prepared in ether. Yields (except III, B) were based on the weights of picrates. Results are given in Table III.

SUMMARY

A series of *p*-dialkylaminoalkoxyanilines (II, A–F), prepared by the catalytic hydrogenation of the corresponding *p*-dialkylaminoalkoxynitrobenzenes (I, A–F), was converted to 2-amino-6-dialkylaminoalkoxybenzothiazoles (III, A–F) with thiocyanogen. Compounds II, A–F and III, A–F were unstable both as free bases and salts. The nitrobenzenes (I, A–F) were stable substances which were prepared in good yield by heating a xylene solution of the sodium salt of *p*-nitrophenol with a dialkylaminoalkyl chloride hydrochloride in the presence of potassium carbonate.

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