[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

Dialkylaminoalkyl Esters of 2-Amino-6-carboxybenzothiazole

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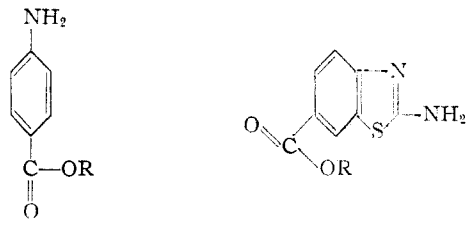
Several esters of 2-amino-6-carboxybenzothiazole were prepared as potential pharmaceuticals by the thiocyanation of the corresponding esters of *p*-aminobenzoic acid. One compound (IIC) was prepared also by an exchange reaction between diethylaminoethanol and 2-amino-6-carbethoxybenzothiazole. In the catalytic hydrogenation of three esters of *p*-nitrobenzoic acid in ethanol, an ester-exchange with the medium was observed.

Interest in the preparation of compounds containing the thiazole nucleus as chemotherapeutic agents has been stimulated by the successful application of several such compounds in the treatment of various diseases. The vitamin, thiamine, the only natural product which has thus far been found to contain the thiazole nucleus,[1] sulfathiazole, the most potent of the sulfa drugs in general use,[2] and promizole (4-aminophenyl-2′-aminothiazolyl-5′-sulfone),[3] a tuberculotherapeutic agent, are among the better-known thiazoles used in present-day medicine. The versatility of the thiazoles is further demonstrated by the fact that some of these compounds possess antimalarial activity,[4] that 2-(4-thiazolyl)-ethylamine has biological properties similar to those of histamine[5] and that 2-aminothiazole exhibits antithyroid activity.[6]

On the basis of the foregoing it seemed that the incorporation of the thiazole nucleus into the dialkylaminoalkyl *p*-aminobenzoate structure might potentiate the local anesthetic activity of this group of esters or result in a class of compounds having a more favorable therapeutic index. To test this hypothesis several esters of 2-amino-6-carboxy-benzothiazole, represented by II, were prepared. The structures of the two well-known local anesthetics, Procaine (IC) and Butyn (IE) are shown for comparison.



I II

A, R = C_2H_5
B, R = $CH_2CH_2N(CH_3)_2$
C, R = $CH_2CH_2N(C_2H_5)_2$
D, R = $CH_2CH_2N(n\text{-}C_4H_9)_2$
E, R = $CH_2CH_2CH_2N(n\text{-}C_4H_9)_2$
F, R = $CH_2CH_2NC_4H_8O$
G, R = $CH_2CH_2N(CH_2C_6H_5)_2$

Of the relatively few 2-amino-6-substituted-benzothiazoles described in the literature some have shown diverse biological properties. Both the 2-amino-6-nitro and the 2,6-diaminobenzothiazoles have exhibited antitubercular activity; the latter is said to be about three quarters as effective as streptomycin *in vitro* against human tubercle bacilli.[7] Asterol dihydrochloride [2-diethylamino-6-(β-diethylaminoethoxy)-benzothiazole dihydrochloride] is commercially available as a potent fungistatic agent.[8] A number of 2-amino-6-alkoxybenzothiazoles have been prepared[9] and tested for antimalarial activity.[10] One, 2-amino-6-ethoxybenzothiazole, has received some attention as it is a powerful local anesthetic.[11,12]

The intermediate *p*-aminobenzoic acid esters (I, B, D-G) were prepared by a modification of a previously described method,[22] from the corresponding *p*-nitrobenzoic acid esters. The latter, prepared from dialkylaminoalkanols and *p*-nitrobenzoyl chloride, were not isolated but reduced directly to the corresponding *p*-aminobenzoates. These esters have almost invariably been isolated and characterized as their salts. For the subsequent thiocyanation reaction, it seemed preferable to employ these intermediates as the free bases. Therefore, they were isolated in this form by distillation *in vacuo*, or by crystallization. One of these esters has not been described previously (I, G) while three others have been characterized only as salts (I, D, E and F).

This procedure is simple and convenient, giving high yields of pure products. However, difficulty was encountered in the preparation of three compounds (I, B, D and E) when the *p*-nitrobenzoic acid esters were hydrogenated in ethanol in the presence of either Raney nickel or palladium–charcoal. The reduction products were found to contain considerable amounts of lower boiling material and only small amounts, if any, of the expected *p*-aminobenzoates. The more volatile by-products were subsequently identified as aminoalcohols, derived from the alcoholic fragments of the esters, and ethyl *p*-aminobenzoate. When the reduction was conducted in benzene, rather than ethanol, the expected *p*-aminobenzoic acid esters were isolated in good yields, with neither of these by-products appearing. These results would seem to indicate that an ester-exchange reaction had occurred in the ethanolic medium. The reductions were run at elevated temperatures, since no attempt was made

(1) G. L. Jenkins and W. H. Hartung, "The Chemistry of Organic Medicinal Products," John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 617-621.

(2) E. H. Northey, "The Sulfonamides and Allied Compounds," Reinhold Publishing Corp., New York, N. Y., 1948, p. 34.

(3) L. L. Bambas, THIS JOURNAL, **67**, 671 (1945).

(4) F. Brody and M. T. Bogert, *ibid.*, **65**, 1080 (1943).

(5) H. Erlenmeyer and M. Muller, *Helv. Chim. Acta*, **28**, 922 (1945).

(6) D. Bovet, J. Bablet and J. Fournel, *Ann. inst. Pasteur*, **72**, Jan.-Feb. (1946); (b) **37**, Oct. 7 (1945).

(7) B. L. Freedlander and F. A. French, *Proc. Soc. Exptl. Biol. Med.*, **66**, 362 (1947).

(8) E. Grunberg, G. Soo-Hoo, E. Titsworth, D. Ressetar and R. J. Schnitzer, *Trans. N. Y. Acad. Sci.*, **13** [1], 22 (1950).

(9) C. G. Stuckwisch, THIS JOURNAL, **71**, 3417 (1949).

(10) "Survey of Antimalarial Drugs 1941–1945," F. Y. Wiselogle, Editor, Edwards Bros., Ann Arbor, Mich., 1946, Vol. II, Part I, pp. 938–939.

(11) K. Ballowitz, *Arch. expll. Path. Pharmakol.*, **163**, 687 (1931).

(12) C. L. Rose, H. A. Shonle and K. K. Chen, *Pharm. Arch.*, **11**, 81 (1940).

to dissipate the heat developed in hydrogenation. It appears unlikely that this would be responsible for the exchange reaction since similar results were obtained when the reductions were conducted at room temperature. No mention in the literature of similar exchange reactions occurring during hydrogenations of esters could be found.

The *p*-aminobenzoic acid esters were converted into the esters of 2-amino-6-carboxybenzothiazole by reaction with nascent thiocyanogen. In Method 1 this reagent, prepared by the thermal decomposition of cupric thiocyanate, formed *in situ* from cupric sulfate and potassium thiocyanate, reacted with the ester in an aqueous medium.[13] In Method 2 thiocyanogen was liberated by the action of bromine upon potassium thiocyanate in 96% acetic acid in the presence of the compound to be thiocyanated. The method of Kaufmann, Oehring and Clauberg[14] for the preparation of IIA, was used without significant modification. Compound IIC was prepared by both methods as well as a third (Method 3) wherein the ester grouping of IIA was exchanged for the diethylaminoethyl radical in the presence of aluminum amalgam. This was modeled after a method[15] patented for the preparation of procaine. Of the three, Method 2 was preferred since it was the least involved and gave highest yields.

Hydrochlorides of IG, IIC, IIF and IIG as well as the oxalate of dibenzylaminoethyl *p*-nitrobenzoate were inactive in retarding the growth of sarcoma 180.[16] Compound IIC caused convulsions in mice and afforded no protection against electric shock, metrazol or strychnine. It showed no curariform activity but did show a transient depression of multisynaptic reflex arcs in the spinal cord of the cat.[17] Further pharmacological tests are in progress, results of which will be reported elsewhere.

Experimental[18]

Dimethyl-,[19a] diethyl-[19a] and di-*n*-butylaminoethanols,[19b] γ-di-*n*-butylaminopropanol,[19b] N-(2-hydroxyethyl)-morpholine,[19a] *p*-nitrobenzoyl chloride, ethyl *p*-aminobenzoate (IA) and procaine hydrochloride (IB) were commercial products. The last three were used without further purification. Since the sample of dimethylaminoethanol was found to have a high water content which interfered in the subsequent esterification reaction, it was dried over anhydrous potassium carbonate and redistilled. The other amino-alcohols were redistilled before use without further purification. Dibenzylaminoethanol was prepared by the method of Rumpf and Kwass.[20]

Dibenzylaminoethyl *p*-Aminobenzoate (IG).—Seventy-seven grams (0.415 mole) of *p*-nitrobenzoyl chloride and 100 g. (0.415 mole) of 2-dibenzylaminoethanol in 800 ml. of dry thiophene-free benzene was refluxed for 1.5 hours. At the end of this time the solution had changed to a pale yellow semi-solid. The mixture was shaken thoroughly with dilute ammonia water. The precipitate which appeared at this point was removed by filtration and was washed well with dilute ammonia water, water and benzene. Twelve grams of material, which did not depress the melting point of an authentic sample of *p*-nitrobenzoic acid, remained. The benzene solution, after being washed several times with water and concentrated to a volume of about 250 ml., was hydrogenated, at an initial pressure of 58 lb., in the presence of 6.0 g. of 10% palladium–charcoal catalyst.[21] The orange oil remaining after removal of the catalyst and benzene crystallized readily from hexane as pale orange crystals which weighed 105.8 g., 81% yield (corrected for the *p*-nitrobenzoic acid recovered), m.p. 99–101°. Recrystallized to constant melting point from ethanol and then from hexane, the compound melted at 106.0–106.6°.

Anal. Calcd. for $C_{23}H_{24}N_2O_2$: N, 7.78. Found: N, 7.50.

The hydrochloride was prepared by passing hydrogen chloride into an ethereal solution of the free base. The salt, after washing with ether and drying in air, melted at 213–214°.

The same procedure was followed in the preparation of the other dialkylaminoalkyl esters of *p*-aminobenzoic acid. The results are summarized in Table I.

Ester-exchange Reactions in the Reduction of *p*-Nitrobenzoates.—The following is a description of one typical reaction. Others, involving different reactants, varying amounts of the same catalyst or Raney nickel, or a lower reaction temperature, gave qualitatively the same results. Using the same procedure described for the preparation of (IG) but starting with 105.5 g. (0.57 mole) of *p*-nitrobenzoyl chloride and 97.0 g. (0.56 mole) of di-*n*-butylaminoethanol, reducing the crude *p*-nitrobenzoic acid ester in 200 ml. of absolute ethanol in the presence of 2.0 g. of 10% palladium–charcoal, and distilling the products obtained in this manner, gave two main fractions. The first, b.p. 102–109° (15 mm.), $n^{20}D$ 1.4472, weighed 33.5 g. A commercial sample of di-*n*-butylaminoethanol, $n^{20}D$ 1.4444, had a b.p. of 117° at 20 mm. The *p*-nitrobenzoate of this fraction had a melting point of 90–93°, without purification, while that of di-*n*-butylaminoethanol is reported as melting at 92.5–93.5° after recrystallization.[22] The second fraction was collected over a broad temperature range, 119–170° (0.15–0.17 mm.) and weighed 82 g. It was recrystallized to constant melting point from dilute ethanol and then from hexane, m.p. 87.2–87.6°. Its melting point was not depressed when mixed with ethyl *p*-aminobenzoate.

Anal. Calcd. for $C_9H_{11}NO_2$: N, 8.48. Found: N, 8.42.

2-Amino-6-carbethoxybenzothiazole (IIA). Method 1.—A solution of 78 g. (0.47 mole) of ethyl *p*-aminobenzoate in 70 ml. of warm concentrated hydrochloric acid was diluted with water to 230 ml. This was added to 470 g. (4.8 moles) of potassium thiocyanate dissolved in 500 ml. of water. A solution of 625 g. (2.50 moles) of $CuSO_4 \cdot 5H_2O$ in 1500 ml. of water was added fairly rapidly, maintaining the reaction temperature at 40–41°. The mixture was heated to 75° and kept at this temperature with good stirring for 15 minutes after which a warm solution of one liter of concentrated hydrochloric acid in two liters of water was added. After heating to 90°, it was then filtered. The filter cake was washed with 2–3 liters of boiling water and the filtrate neutralized, while still hot, by the cautious addition of solid sodium carbonate. On cooling to room temperature, the precipitate which had formed was separated by filtration and washed well with cold water. The moist filter cake was added to 550 ml. of *ca.* 2 *N* hydrochloric acid and the mixture heated to boiling. Filtering the hot solution removed a red insoluble polymer. About 10–12 liters of water was added to the filtrate and the clear yellow solution was made alkaline by the slow addition, with cooling and stirring, of 1600 ml. of *ca.* 2 *N* sodium hydroxide.

The white precipitate was filtered and washed with cold water. After drying at 110°, it weighed 54 g. Recrys-

(13) "Organic Reactions," R. Adams, Editor-in-Chief, John Wiley and Sons, Inc., New York, N. Y., 1946, Vol. III, pp. 255–256.

(14) H. P. Kaufmann, W. Oehring and A. Clauberg, *Arch. Pharm.*, **266**, 215 (1928). This preparation of IIA is also described in "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p. 375, in the chapter by H. P. Kaufmann on "Methods for the Thiocyanation of Organic Compounds."

(15) W. Bader, U. S. Patent 1,396,913, November 15, 1921.

(16) These compounds were tested under the supervision of Dr. C. Chester Stock, at the Sloan–Kettering Institute for Cancer Research.

(17) The authors are grateful to Dr. Irwin H. Slater of The University of Rochester School of Medicine and Dentistry for this information.

(18) All melting points are corrected; boiling points are not.

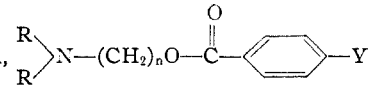
(19) Samples of these compounds were generously contributed by (a) the Carbide and Carbon Chemicals Corp. and (b) Sharples Chemical Corp.

(20) P. Rumpf and R. Kwass, *Bull. soc. chim.*, **10**, 347 (1943). A similar preparation of the compound has been described recently by W. S. Gump and E. J. Nikawitz, THIS JOURNAL, **72**, 1310 (1950).

(21) The catalyst was purchased from Baker and Co., Inc., Newark, N. J.

(22) W. B. Burnett, R. L. Jenkins, C. H. Peet, E. E. Dreger and R. Adams, THIS JOURNAL, **59**, 2248 (1937).

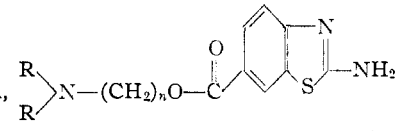
TABLE I

ESTERS OF FORMULA, 

No.	R	n	Y	Yield, %	B.p., °C.	B.p., Mm.	M.p., °C.	Nitrogen analyses, % Formula	Calcd.	Found
IB	CH_3	2	NH_2	84			114–117[a]			
ID	n-C_4H_9	2	NH_2	85	161–164[b]	0.01				
IE	n-C_4H_9	3	NH_2	91	178–182[b]	.11	157–158.5[c,d,e]			
							164–166[d,f]	$C_{18}H_{30}N_2O_2 \cdot H_2C_2O_4$	7.07	6.99
							138.5–139.5[g]	$C_{18}H_{30}N_2O_2 \cdot H_2SO_4$	6.93	6.94
IF	[h]	2	NH_2	93			117.5–118.5[i]	$C_{13}H_{18}N_2O_3$	11.20	11.03
IG	$C_6H_5CH_2$	2	NH_2	81			106–106.6	$C_{22}H_{24}N_2O_2$	7.78	7.50
	n-C_4H_9	3	NO_2	[i]			122–122.4[f,b,d]	$C_{18}H_{28}N_2O_4 \cdot H_2C_2O_4$	6.57	6.81
	$C_6H_5CH_2$	2	NO_2	[i]			148.5–151.5[f,d]	$C_{23}H_{22}N_2O_4$	7.17	7.15
							90.5–91.5[k]			

[a] Crude melting point after crystallization from ethanol. The purified ester has been reported as melting at 120–121° by A. Einhorn, K. Fiedler, C. Ladisch and E. Uhlfelder, *Ann.*, **371**, 142 (1909). [b] Described by W. B. Burnett, R. L. Jenkins, C. H. Peet, E. E. Dreger and R. Adams, THIS JOURNAL, **59**, 2248 (1937), as salts. [c] Hydrochloride. [d] Recrystallized from ethanol. [e] The hydrochloride of IE was found by R. Adams and E. H. Volwiler, U. S. Patent 1,676,470, July 10, 1928, to melt at 151–152° and the sulfate at 100°. [f] Oxalate. [g] Sulfate, prepared in *n*-propanol and recrystallized to constant melting point from the same solvent. [h] The morpholino radical replaces $-NR_2$. [i] The free base was recrystallized from heptane and then water. The hydrochloride was prepared by J. H. Gardner and E. O. Haenni, THIS JOURNAL, **53**, 2763 (1931). [j] Although these compounds were usually reduced directly to the corresponding amines without isolation, small amounts of these two compounds were removed and purified. [k] The free base was crystallized in ethanol and recrystallized from hexane.

TABLE II

ESTERS OF 2-AMINO-6-CARBOXYBENZOTHIAZOLE OF FORMULA, 

No.	R	n	Method	Yield, %	M.p., °C.	Nitrogen analyses, % Formula	Calcd.	Found
IIA	[a]		1(2)	44(99)	243.5–244.5[b,c]	$C_{10}H_{10}N_2O_2S$[d]	12.61	12.72
IIB	CH_3	2	2	81	186–187[e]	$C_{12}H_{15}N_3O_2S$	15.85	15.85
IIC	C_2H_5	2	1(2)(3)	45(80)(50)	152.5–153.5[f]	$C_{14}H_{19}N_3O_2S$[g]	14.32	14.09
IID	n-C_4H_9	2	2	85	164.5–165[e]	$C_{18}H_{27}N_3O_2S$	12.03	11.90
IIE	n-C_4H_9	3	2	89	150.5–152[e]	$C_{19}H_{29}N_3O_2S$	11.57	11.90
IIF	[h]	2	2	94	199.5–100.5[e]	$C_{14}H_{17}N_3O_3S$	13.68	13.64
IIG	$C_6H_5CH_2$	2	2	87	212.5–213.5[e]	$C_{24}H_{23}N_3O_2S$	10.07	9.91

[a] C_2H_5 replaces the dialkylaminoalkyl radical. [b] Recrystallized from ethanol. [c] The melting point of this compound has been given as 241°.[14] [d] The sulfate melted at 177–178°. [e] Recrystallized from isopropyl alcohol. [f] Recrystallized from acetone. [g] The hydrochloride was prepared in ethanol saturated with hydrogen chloride and recrystallized from aqueous isopropyl alcohol, m.p. 207.5–209°. [h] The morpholine radical replaces $-NR_2$.

tallized once from about 4 liters of 95% ethanol, the product weighed 46 g. (44%) and melted at 243.5–244.5°. Further recrystallization from the same solvent failed to raise the melting point.

Dialkylaminoalkyl Esters of 2-Amino-6-carboxybenzothiazoles. Method 2.—These compounds were prepared by the method of Kaufmann, *et al.*[14] Results are summarized in Table II.

Diethylaminoethyl Ester of 2-Amino-6-carboxybenzothiazole (IIC). Method 3.—A mixture of 66 g. (0.3 mole) of 2-amino-6-carbethoxybenzothiazole (IIA), 60.0 g. (0.47 mole) of diethylaminoethanol and 2.5 g. of aluminum amalgam[23] was stirred at a reaction temperature of 175–180° for 3 hours. During this time ethanol slowly distilled out of the reaction mixture. After cooling to room temperature, the mixture was distilled *in vacuo*. During the distillation, the temperature was raised until the temperature of the mixture reached 170° (at 40 mm.). The hot mixture was then poured onto ice and made strongly alkaline. The product was extracted with a benzene–ether mixture until the extracts were colorless. After removal of the solvents, the oily residue was dissolved in dilute hydrochloric acid. The yellow solution was decolorized with charcoal and made alkaline with dilute sodium hydroxide solution. The white precipitate which formed, after washing with water and air-drying, weighed 44.0 g. (50%) and melted at 149–152°. The melting point of IIC prepared by Method A, was not depressed when admixed with this product. Using the same directions, procaine was prepared in 55% yield.

(23) The aluminum amalgam was prepared by the method described by C. Weygand, "Organic Preparations," Interscience Publishers, Inc., New York, N. Y., 1945, p. 9.

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