Determination of Picric Acid.—Picric acid in solutions was determined with nitron[8] reagent by the following micromethod. Three to five ml. of picrate solution was pipetted into a porcelain crucible and diluted to 10 ml. One drop of 2:3 sulfuric acid was added and solution warmed in an oven to nearly boiling. One ml. of 10% nitron reagent[8] was added and the crucible heated at near the boiling point for fifteen to twenty minutes. The suspension was cooled for two hours and the solution removed from the crystalline precipitate with a porcelain filterstick. The precipitate was washed with 5 ml. of ice water and dried one hour at 105°. After cooling overnight the crucible and filterstick were weighed on a microbalance.

Summary

1. A new method of fractionating the allergenic protein picrate from cottonseed has been developed. The method is an application of the common ion effect of the mass action law.

2. Picric acid has been shown to combine with the active protein in true salt combination and to be adsorbed on the picrate.

3. A protein picrate fraction (CS-5RE) has been obtained which behaves essentially as a single component phase in solubility studies.

4. Chemical and clinical evidence is presented showing that the active picrate fraction CS-5 contains more than one allergenic component, probably very closely related structurally.

(8) Cope and Barab, THIS JOURNAL, **39**, 504 (1917).

WASHINGTON, D. C. RECEIVED JUNE 17, 1940

[CONTRIBUTION FROM THE ABBOTT LABORATORIES]

Esters of Brominated Aminobenzoic Acids

BY M. B. MOORE AND E. H. VOLWILER

The great majority of commercial synthetic local anesthetics belong to the class of esters of benzoic or aminobenzoic acids, and many such compounds have been described in the scientific literature. In contrast to this wealth of information is the scanty reference to alkamine esters of halogen-substituted benzoic acids, especially those containing exclusively bromine and amino groups in the ring. Only five such compounds were found described in the literature.

β-Diethylaminoethyl and β-piperidinoethyl 3,5-dibromo-4-aminobenzoates are described in a British patent[1] and the former is probably identical with the compound obtained by Morel, Leulier and Denoyel[2] by direct bromination of procaine in aqueous solution.

β-Diethylaminoethyl 2-bromo-4-aminobenzoate was prepared by Frejka and Vitha.[3] Two isomers of this, the β-diethylaminoethyl esters of 4-bromo-2-aminobenzoic acid and of 3-bromo-4-aminobenzoic acid, have been described,[4,5] the latter being formed by direct bromination of procaine in ether solution in sunlight.

The purpose of this communication is to report a number of brominated amino-benzoates and brominated alkylamino-benzoates which have been prepared in our laboratories during the past few years. The general formula for these compounds may be expressed as:

$$RNH(Br_m)C_6H_{(4-m)}COOR'\cdot HAc$$

R = H or alkyl R′ = dialkylaminoalkyl
HAc = acid used to form salt m = 1 or 2

Their properties are summarized in Table I.

These compounds were tested for local anesthetic efficiency and toxicity by Dr. C. C. Pfeiffer[6] and Dr. R. Kohn-Richards. All the monobrominated derivatives are quite efficient anesthetics and some have favorable efficiency/toxicity ratios. The water solubility of their common salts, however, is not very great, the hydrochlorides being so insoluble that a precipitate is formed when sulfates or acetates are used to produce corneal anesthesia. The dibrominated derivatives are, in general, less anesthetic and more convulsant.

Experimental Part

γ-Bromopropyl 2-Bromo-3-nitrobenzoate.—The potassium salt of 2-bromo-3-nitrobenzoic acid was prepared by the reactions: 3-nitrophthalic acid ⟶ anhydro-2-hydroxymercuri-3-nitrobenzoic acid ⟶ 2-bromo-3-nitrobenzoic acid as described in "Organic Syntheses."

The potassium salt of 2-bromo-3-nitrobenzoic acid (13.6 g.) was mixed with dry trimethylene bromide (47 g.) and a few drops of diethylamine and heated in a paraffin-bath at about 140° for twenty-four hours. The product was

(1) Schering-Kahlbaum A.-G., British Patent 321,968 (1928).

(2) Morel, Leulier and Denoyel, *Bull. soc. chim.*, [4] **45**, 457–463 (1929).

(3) Frejka and Vitha, *Pub. faculté sci. univ. Masaryk*, No. 48, 1–22 (1925); *C. A.*, **19**, 2332 (1925).

(4) Frejka and Vymetal, *Collection Czechoslov. Chem. Commun.*, **7**, 436–443 (1935); *C. A.*, **30**, 1370–1371 (1936).

(5) Frejka and Čižmář, *Chem. Listy*, **31**, 460–464 (1937); *C. A.*, **32**, 4967 (1938).

(6) University of Chicago.

TABLE I

RNH R (Position)	Br_m m number (Position)	R'	HAc	M. p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Bromine, % Calcd.	Bromine, % Found
H (3)	1 (2)	$(n\text{-}C_4H_9)_2NCH_2CH_2CH_2$—	HI	159–161	5.47	5.65	...	...
H (4)	1 (2)	$(n\text{-}C_4H_9)_2NCH_2CH_2CH_2$—	HI	149–150	5.47	5.35	...	...
H (4)	1 (3)	$(C_2H_5)_2NCH_2CH_2$—	HBr	165–166	7.08	7.22	...	...
H[5a] (4)	1 (3)	$(C_2H_5)_2NCH_2CH_2$—	HCl	154–155	7.97	8.10	...	...
H (4)	1 (3)	$(n\text{-}C_4H_9)_2NCH_2CH_2CH_2$—	$HC_2H_3O_2$	71- 72	6.29	6.41	17.94	18.58
H (4)	1 (3)	$(n\text{-}C_4H_9)_2NCH_2CH_2CH_2$—	HBr	129–130	...	...	...	...
$n\text{-}C_3H_7$ (4)	1 (3)	$(n\text{-}C_4H_9)_2NCH_2CH_2CH_2$—	HCl	146–148	6.04	6.00	...	...
$n\text{-}C_4H_9$ (4)	1 (3)	$(n\text{-}C_4H_9)_2NCH_2CH_2CH_2$—	HCl	116–117	5.86	5.90	...	...
$n\text{-}C_4H_9$ (3)	1 (2)	$(n\text{-}C_4H_9)_2NCH_2CH_2CH_2$—	HCl	169–171	5.86	5.77	...	...
H (4)	2 (3,5)	$(n\text{-}C_4H_9)_2NCH_2CH_2CH_2$—	HBr	162.5–163	5.14	4.80	43.98	43.74
$n\text{-}C_3H_7$ (4)	2 (3,5)	$(n\text{-}C_4H_9)_2NCH_2CH_2CH_2$—	HCl	117–118	5.16	5.10	...	...
H[1,2,a] (4)	2 (3,5)	$(C_2H_5)_2NCH_2CH_2$—	HBr	217–218	...	...	...	...

[a] The melting points of compounds given in footnotes (1), (2) and (5) agree with our values.

extracted with benzene, the solution dried by potassium carbonate and the solvent evaporated. The residue was extracted once by methyl alcohol and the residue after removal of this solvent further purified by another benzene extraction. The residue was an oil which did not crystallize; yield 14 g., 80%.

Anal. Calcd. for $C_{10}H_9NO_4Br_2$: N, 3.82. Found: N, 3.78.

γ-Di-*n*-butylaminopropyl 2-Bromo-3-aminobenzoate.—The bromoester (14 g.) was warmed on a steam-bath with 2 moles (12 g.) of di-*n*-butylamine. The product was extracted with benzene, the solution dried by sodium sulfate, and the hydrochloride precipitated by dry hydrogen chloride. This hydrochloride was quite hygroscopic.

The hydrochloride of the nitro base was reduced with iron. After benzene extraction, shaking out by dilute sulfuric acid, and further shaking out of the base in benzene, a liquid base was obtained. Crystallization, even of the salts, is difficult. The hydroiodide, after recrystallization from 12A absolute alcohol, alone and with pentane, finally melted at 157–158°. Another sample, recrystallized from 3A alcohol, after Norit treatment melted at 160–161°. Analysis was carried out on the former.

Anal. Calcd. for $C_{18}H_{29}N_2O_2Br\cdot HI$: N, 5.47. Found: N, 5.65.

γ-Di-*n*-butylaminopropyl 2-Bromo-4-aminobenzoate.—The 2-bromo-4-nitrobenzoic acid was prepared, starting with 4-nitrophthalic acid, in a manner analogous to that used for 2-bromo-3-nitrobenzoic acid. The potassium salt of the acid was converted to its γ-bromopropyl ester and its γ-dibutylaminopropyl ester by the same type of reactions. Iron reduction gave the ester of the aminoacid, an oil which did not crystallize. Its hydroiodide was obtained by recrystallization from aqueous alcohol and from water; m. p. 149–150°.

Anal. Calcd. for $C_{18}H_{29}N_2O_2Br\cdot HI$: N, 5.47. Found: N, 5.35.

β-Diethylaminoethyl 3-Bromo-4-aminobenzoate.—This compound had been made by Frejka and Čižmář[5] as the hydrochloride monohydrate; m. p. 157–158°. For the purpose of preparing the monobrominated derivative, several different methods of bromination of procaine were tried, but in none was a satisfactory yield obtained, as in the bromination of Butyn (see below).

(1) The method used by Leulier and Dinet[7] for bromination of alkyl esters of aminobenzoic acid was investigated. Bromination is carried out in aqueous solution with hydrobromic acid and hydrogen peroxide. From the reaction mixture only dibromoprocaine (m. p. 217–218°) and procaine were isolated.

(2) Bromination in glacial acetic acid, which gave a good yield of the monobromo derivative when applied to Butyn, gave more dibromo than monobromoprocaine.

(3) Bromine vapors were passed into an aqueous solution of procaine hydrochloride, with cooling. Heating the solution gives more highly brominated products. By this means, monobromoprocaine hydrochloride was obtained in sufficient quantity for purification and analysis; recrystallized from water, m. p. 154–155°.

Anal. Calcd. for $C_{13}H_{19}N_2O_2Br\cdot HCl$: N, 7.97. Found: N, 8.10.

(4) Procaine base in chloroform solution was brominated by bromine in chloroform. From this, the hydrobromide of monobromoprocaine was purified and analyzed; recrystallized from alcohol, m. p. 165–166°.

Anal. Calcd. for $C_{13}H_{19}N_2O_2Br\cdot HBr$: N, 7.08. Found: N, 7.22.

(5) Pyridine dibromide in glacial acetic acid gave a small yield of monobromoprocaine. It was isolated as the hydrochloride, from absolute alcohol; m. p. 153–155°.

γ-Di-*n*-butylaminopropyl 3-Bromo-4-aminobenzoate.—Butyn base, 30 g. (0.1 mole), was dissolved in 150 cc. of glacial acetic acid; bromine, 15.7 g. (0.2 atom) in 60 cc. of glacial acetic acid was dropped in with shaking or stirring, keeping cool by means of a water-bath. After the reaction was complete, the clear acetic acid solution was made alkaline to litmus by addition of ammonium hydroxide, with ice cooling during neutralization. The product was extracted by ether, the ether solution dried by sodium sulfate, and the ether evaporated. A low melting (71–72°) solid was left, which proved to be the acetate of the base; yield 37 g., 85%.

Anal. Calcd. for $C_{15}H_{29}N_2O_2Br\cdot C_2H_4O_2$: N, 6.29; Br, 17.94. Found: N, 6.41; Br, 18.58.

The hydrobromide was prepared and recrystallized from water; m. p. 129–130°.

(7) Leulier and Dinet, *J. pharm. chim.*, **8**, 57–61 (1928).

γ-Di-*n*-butylaminopropyl 3-Bromo-4-*n*-propylaminobenzoate.—γ-Di-*n*-butylaminopropyl 3-bromo-4-aminobenzoate, 26 g., was refluxed in *n*-propyl alcohol solution with 13 g. of *n*-propyl bromide until no longer alkaline to litmus, more bromide being added if necessary at the end of about twenty hours. The propyl alcohol was removed by vacuum distillation and the residue neutralized with alcoholic hydrochloric acid and placed in a desiccator, where it crystallized. The product was recrystallized three times from water; m. p. 146–148°.

Anal. Calcd. for $C_{21}H_{35}N_2O_2Br\cdot HCl$: N, 6.04. Found: N, 6.00.

γ-Di-*n*-butylaminopropyl 3-Bromo-4-*n*-butylaminobenzoate.—γ-Di-*n*-butylaminopropyl 3-bromo-4-aminobenzoate, 24.3 g., was refluxed in *n*-butyl alcohol solution with 15 g. of *n*-butyl bromide. The product was worked up in the same manner as the *n*-propyl analog. The hydrochloride was recrystallized from water; m. p. 116–117°.

Anal. Calcd. for $C_{22}H_{37}N_2O_2Br\cdot HCl$: N, 5.86. Found: N, 5.90.

γ-Di-*n*-butylaminopropyl 2-Bromo-3-*n*-butylaminobenzoate.—γ-Di-*n*-butylaminopropyl 2-bromo-3-aminobenzoate was alkylated by refluxing with *n*-butyl bromide in *n*-butyl alcohol solution. The hydrochloride was prepared and purified by leaching with acetone; m. p. 169–171°.

Anal. Calcd. for $C_{22}H_{37}N_2O_2Br\cdot HCl$: N, 5.86. Found: N, 5.77.

γ-Di-*n*-butylaminopropyl 3,5-Dibromo-4-aminobenzoate.—Butyn base, 10 g., was dissolved in chloroform and a solution of bromine in chloroform containing 0.75 g. of bromine per cc. was gradually added with cooling and stirring until no more bromine appeared to be absorbed. The flask became filled with crystals. After standing and cooling, these were filtered off and recrystallized from alcohol (four times); m. p. 162.5–163°; yield 8.5 g., 48%.

Anal. Calcd. for $C_{18}H_{28}N_2O_2Br_2\cdot HBr$: N, 5.14; Br, 43.98. Found: N, 4.80; Br, 43.74.

γ-Di-*n*-butylaminopropyl 3,5-Dibromo-4-*n*-propylaminobenzoate.—γ - Di - *n*-butylaminopropyl 3,5 - dibromo - 4-aminobenzoate, 6 g., was refluxed in *n*-propyl alcohol solution with a slight excess of *n*-propyl bromide in a total time of refluxing of eighteen hours. The product was made alkaline with sodium carbonate solution, shaken out in ether, the ether dried and evaporated. The residue in acetone solution was acidified with hydrochloric acid, and benzene added to precipitate the hydrochloride. This precipitate was twice recrystallized from alcohol; m. p. 117–118°; yield 2 g., 29%.

Anal. Calcd. for $C_{21}H_{34}N_2O_2Br_2\cdot HCl$: N, 5.16. Found: N, 5.10.

The authors wish to thank Mr. E. F. Shelberg for the microanalyses reported in this work.

Summary

For the purpose of testing as local anesthetics, a series of esters of aminobenzoic and N-alkylaminobenzoic acids containing one or two bromine atoms in the aromatic nucleus have been prepared.

The water insolubility of the hydrochlorides of these esters limits their usefulness as local anesthetics.

NORTH CHICAGO, ILLINOIS RECEIVED JULY 12, 1940

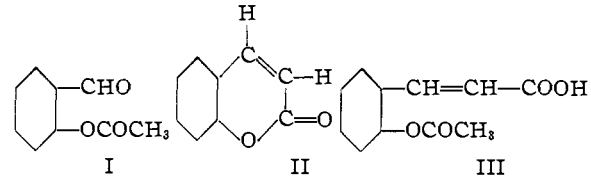
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF MARYLAND]

The Reactions of Ketene with Salicylaldehyde and *p*-Hydroxybenzaldehyde

BY JONATHAN W. WILLIAMS[1] AND ALEXANDER SADLE[2]

It has been shown by Hurd and Thomas[3] that ketene reacts with aromatic aldehydes in the presence of anhydrous potassium acetate to form β-aryl-substituted acrylic acids in a type of Perkin synthesis. It is shown in the present work that, although the same type of reaction may be accomplished with phenolic aldehydes, acetylation of the phenol group is the predominant reaction, and the substituted cinnamic acid obtained in small yield contains an acetylated phenol group.

Ketene and Salicylaldehyde.—The reaction of ketene with salicylaldehyde gives, under various conditions, acetylsalicylaldehyde (I), coumarin (II), and *o*-acetoxycinnamic acid (III). I may be obtained in 84% yield, along with a 9% yield



I II III

of II as a by-product, by the direct reaction of ketene and salicylaldehyde at room temperature in the absence of a catalyst. By running the reaction in the presence of a drop of sulfuric acid, the yield of II may be increased to 31%. III is obtained in the reaction products only when fused sodium or potassium acetate is present with the reactants, and then only in a 1–2% yield.

(1) Present address: Chemistry Department, University of North Carolina, Chapel Hill, North Carolina.

(2) Taken from the M.S. Thesis of Alexander Sadle.

(3) Hurd and Thomas, THIS JOURNAL, **55**, 275 (1933).