[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Basic-alkyl Esters of *p*-(Aminoalkyl)-benzoic Acids. I

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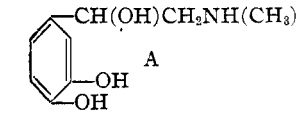
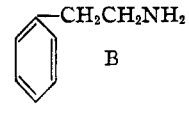
The clinical value of local anesthetics has been greatly enhanced by Braun's discovery[3] that the duration of anesthesia is prolonged to a very marked degree if epinephrine is added to the solution of the local anesthetic which is to be employed. By the use of epinephrine or one of its congeners, as an adjuvant, the anesthetic effect is prolonged, the desired degree of anesthesia can be produced with a much smaller amount of the anesthetic, and the danger of systemic toxicity and of hemorrhage is decreased.

The advantages gained by the use of epinephrine are due to its vasoconstrictor action. Cocaine exhibits the property of a strong local anesthetic as well as that of a weak vasoconstrictor; procaine does not constrict the capillary blood vessels. A few attempts[4] have been made to find a synthetic compound which would exhibit both types of activity but the fact that no potent pressor anesthetic has appeared on the market indicates that a suitable product of this kind has not yet been discovered.[5]

The characteristic activity of epinephrine (A), the most powerful vasoconstrictor known, is possessed also to some extent by its parent compound β-phenylethylamine (B). It seemed to us that it would be of considerable interest to prepare and determine the pharmacological properties of a compound which, at least as far as its structure was concerned, would bear a close resemblance to both β-phenylethylamine and procaine (C)[6]; formula D represents such a substance.



A



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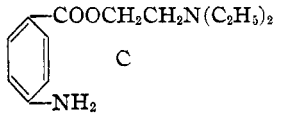
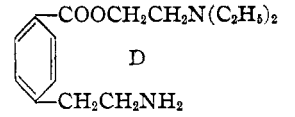
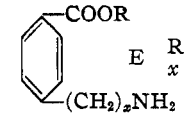


C



D



E R = basic alkyl
x = 1, 2 or 3

Unfortunately, we were not able to obtain the hydrochloride of the β-diethylaminoethyl ester of *p*-(β-aminoethyl)-benzoic acid (D) in a pure condition; however, we did prepare the pure, crystalline hydrochloride of the β-piperidinoethyl, γ-piperidinopropyl, γ-morpholinopropyl and the β,β-dimethyl-γ-piperidinopropyl esters of this acid.

In 1938 Slotta and Kethur[7] stated that they desired to synthesize compound D but they did not describe the substance. However, they did report the preparation of methyl and ethyl *p*-(β-aminoethyl)-benzoate, as well as of methyl and ethyl *m*-(β-aminoethyl)-benzoate. The two *para* substituted benzoates were said to be strong local anesthetics, while the *meta* substituted esters proved to be inactive. Unfortunately, they made no statement relative to pressor activity.

Barger[8] had *p*-(β-aminoethyl)-benzoic acid and ethyl *p*-(β-aminoethyl)-benzoate prepared; the acid was found to be devoid of pressor activity, while the ester was less active than β-phenylethylamine. Tainter,[9] who secured samples from Barger, stated that the acid exhibited $^1/_{30,000}$th and the ester $^1/_{900}$th of the pressor activity of epinephrine. Anesthetic activity was not reported.

In procaine the amino group is attached directly to the benzene ring. As far as we are aware, no study has been made hitherto to determine the extent to which local anesthetic activity of esters of the procaine type could be affected by the separation of the primary amino group from the benzene ring by one or more carbon atoms. However, in this connection, it is very interesting to note that Gilman and associates[10] have found β-diethylaminoethyl- and γ-diethylaminopropyl *p*-(diethylaminomethyl)-benzoate to be inactive as local anesthetics; the corresponding γ-dibutylaminopropyl ester possessed only slight activity. It has been shown[11] that, at least in some instances, a shift of the nitrogen atom of the amino group into the ring decreases the anesthetic activity of this type of product.[12] In order that

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by W. M. Lilienfeld in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) Parke, Davis & Company Fellow.

(3) Braun, *Arch. klin. Chir.*, **69**, 541 (1903).

(4) (a) Marvel and du Vigneaud, THIS JOURNAL, **46**, 2093 (1924); (b) Hartung, Munch and Kester, *ibid.*, **54**, 1526 (1932); (c) Slotta and Kethur, *Ber.*, **71**, 59 (1938).

(5) According to Hartung and co-workers (Ref. 4b) the hydrochloride of α-phenyl-β-aminopropyl benzoate ($C_6H_5COOCH(C_6H_5)CH(CH_3)NH_2 \cdot HCl$), which they prepared, seems to be the first synthetic substance ever described which possesses a demonstrated pressor and anesthetic action.

(6) The synthesis of a substance analogous to both epinephrine and procaine in structure presents experimental difficulties which are not easily overcome, hence at this stage of our investigation we prepared only products which contained neither an alcoholic nor phenolic group.

(7) Slotta and Kethur, *Ber.*, **71**, 59 (1938).

(8) Barger, "Some Applications of Organic Chemistry to Biology and Medicine," McGraw-Hill Book Company, Inc., New York, N. Y., 1930, pp. 95–96.

(9) Tainter, *Quart. J. Pharm. Pharmacol.*, **3**, 590 (1930).

(10) Gilman, Goodman, Thomas, Hahn and Prutting, *J. Pharmacol. Exptl. Therap.*, **74**, 290 (1942).

(11) Blicke and Jenner, THIS JOURNAL, **64**, 1721 (1942).

(12) The very high activity of the local anesthetic Nupercaine, an acid amide which contains the quinoline nucleus, shows that this is not universally true. The β-diethylaminoethyl ester of acridine-9-carboxylic acid is a very weak local anesthetic (Samdahl and Weider, *Bull. soc. chim.*, [5] **2**, 2008 (1935)).

some information might be obtained concerning this point, we prepared, in addition to the compounds mentioned (E, $x = 2$), basic-alkyl esters of the general formula E in which $x = 1$ or 3. It was to be expected that these latter products would be devoid of any pressor effect.[13]

The esters of *p*-(aminomethyl)- (E, $x = 1$), *p*-(β-aminoethyl)- (E, $x = 2$) and *p*-(γ-aminopropyl)-benzoic acid (E, $x = 3$) were obtained by conversion of the *p*-(aminoalkyl)-benzoic acid into the corresponding benzoyl chloride hydrochloride, and interaction of the latter with the required basic alcohol hydrochloride.

p-(Aminomethyl)-benzoic acid was synthesized by preparation of the following intermediates

$$p\text{-}CH_3—C_6H_4—CN \longrightarrow CH_3—C_6H_4—COOH \longrightarrow$$
$$CH_3—C_6H_4—COCl \longrightarrow ClCH_2—C_6H_4—COCl \longrightarrow$$
$$ClCH_2—C_6H_4—COOC_2H_5 \longrightarrow$$
$$ICH_2—C_6H_4—COOC_2H_5 \longrightarrow H_2NCH_2—C_6H_4—COOH$$

The following scheme illustrates the preparative procedure for *p*-(β-aminoethyl)-benzoic acid

$$BrCH_2CH_2—C_6H_5 \longrightarrow BrCH_2CH_2—C_6H_4—COCH_3 \longrightarrow$$
$$BrCH_2CH_2—C_6H_4—COOH \longrightarrow$$
$$BrCH_2CH_2—C_6H_4—COCl \longrightarrow$$
$$BrCH_2CH_2—C_6H_4—CONH_2 \longrightarrow$$
$$BrCH_2CH_2—C_6H_4—CN \longrightarrow ICH_2CH_2—C_6H_4—CN \longrightarrow$$
$$H_2NCH_2CH_2—C_6H_4—COOH$$

p-(γ-Aminopropyl)-benzoic acid was obtained by a process identical with the one indicated above except that γ-phenylpropyl bromide was employed in place of β-phenylethyl bromide.

We found that our *p*-(aminoalkyl)-benzoic acids behaved toward thionyl chloride similarly to *p*-aminobenzoic acid. Graf and Langer[14] showed that the latter acid yields, first, *p*-thionylaminobenzoyl chloride, and that this substance, when dissolved in ether and treated with hydrogen chloride, is converted into *p*-aminobenzoyl chloride hydrochloride.

The acid chloride hydrochlorides, $H_2N(CH_2)_x—C_6H_4—COCl \cdot HCl$, were obtained in very good yields, and our experience is in contrast to that of Slotta and Kethur,[7] who claimed that there is much decomposition when *m*- or *p*-(β-aminoethyl)-benzoic acid reacts with thionyl chloride.

Our products were examined pharmacologically by L. W. Rowe in the Parke, Davis & Company laboratories. The only compound which exhibited a definite pressor action was the hydrochloride of ethyl *p*-(β-aminoethyl)-benzoate. In 2% solution this substance produced no anesthesia on the rabbit's cornea. None of the basic-alkyl esters showed any appreciable local anesthetic activity either by topical application to the rabbit's cornea or by injection methods.

(13) Pressor activity is insignificant in compounds in which the amino group is separated from the benzene ring by only one or by more than two carbon atoms (Berger and Dale, *J. Physiol.*, **41**, 19 (1910); Pyman, *J. Chem. Soc.*, **111**, 1124 (1917)).

(14) Graf and Langer, *J. prakt. Chem.*, **148**, 161 (1937).

Experimental Part

***p*-(Aminomethyl)-benzoic Acid.**—*p*-Tolunitrile[15] (200 g.) was hydrolyzed with a mixture of 280 g. of sodium hydroxide, 1500 cc. of water and 300 cc. of alcohol, and the *p*-toluic acid (223 g., 96%) obtained was heated with 150 cc. of thionyl chloride; the *p*-toluyl chloride (232 g., 92%) boiled at 117–120° (24 mm.).[16]

A brisk stream of dry chlorine was passed into 262 g. of *p*-toluyl chloride, heated to 120–130°, for four hours while the material was illuminated with two 2-watt argon bulbs. Upon distillation there was obtained 286 g. (89%) of *p*-(chloromethyl)-benzoyl chloride[17]; b. p. 155–160° (35 mm.).

A mixture of 120 cc. of absolute alcohol and several drops of pyridine was kept at the boiling point, and 286 g. of *p*-(chloromethyl)-benzoyl chloride added dropwise. The material was refluxed for one-half hour, and poured into sodium carbonate solution. The ethyl *p*-(chloromethyl)-benzoate boiled at 140–150° (15 mm.); yield 262 g. (90%).[18]

To 262 g. of the ester there was added 201 g. of sodium iodide, dissolved in 500 cc. of dry acetone, the mixture was refluxed for fifteen minutes, cooled, the separated sodium chloride removed, and the solvent distilled from the filtrate. The residue was dissolved in benzene, the solution shaken with sodium thiosulfate solution, and the benzene removed from the organic layer. The solid, yellow residue, ethyl *p*-(iodomethyl)-benzoate, was not purified.

All of the crude iodomethyl compound was dissolved in 500 cc. of dry chloroform, and added slowly to a boiling solution prepared from 200 g. of hexamethylenetetramine and 1500 cc. of chloroform.[19] The crystalline complex began to precipitate almost immediately. The mixture was refluxed for one-half hour, cooled and filtered, washed with chloroform, and then with ether; the complex weighed 430 g. It was dissolved in 550 cc. of warm, concd. hydrochloric acid, 1350 cc. of 95% alcohol added, and the solution boiled for one hour. After twelve hours at room temperature, the precipitated ammonium salts were filtered, and the filtrate concentrated under reduced pressure until solid material began to separate. The mixture was then evaporated to dryness in an evaporating dish on a steam-bath. The solid residue was dissolved in the least possible amount of water, the solution filtered, and the filtrate extracted a number of times with ether to remove iodine. The solution was concentrated to a volume of 1 liter, and dilute sodium hydroxide added until the solution remained just acidic toward methyl red. The amino acid, which precipitated in the form of shining plates, was filtered, the filtrate concentrated to a volume of 400 cc., decolorized with Norite, and allowed to remain at room temperature until more amino acid precipitated. The acid was recrystallized from water, and the mother liquors concentrated in order to recover dissolved material; yield 112 g. (64% based on the chloromethyl compound). When heated the acid darkened above 270° but did not melt below 360°.[20]

Anal. Calcd. for $C_8H_9O_2N$: C, 63.56; H, 6.00; N 9.27. Found: C, 63.41; H, 6.15; N, 9.24.

We prepared a small amount of the acid by a second method. *p*-Tolunitrile was chlorinated with the aid of two 2-watt argon bulbs[21] at 120–130°. The *p*-(chloromethyl)-

(15) "Organic Syntheses," Coll. Vol. 1, p. 500 (first edition).

(16) Meyer (*Monatsh.*, **22**, 425 (1901)) found 225–227°.

(17) The side chain chlorination of *p*-toluyl chloride was mentioned in German Patents 239,331 (Frdl., **10**, 118) and 240,835 (Frdl., **10**, 140) but no experimental details were reported.

(18) The ester and acid chloride had been obtained previously by Einhorn and Papastavros (*Ann.*, **310**, 205 (1900)) in a rather impure state.

(19) Delépine reaction.

(20) Günther (*Ber.*, **23**, 2416 (1890)) prepared the acid by a different method.

(21) Barkenbus and Holtzclaw (THIS JOURNAL, **47**, 2190 (1925)) used a tungsten lamp, and obtained *p*-(chloromethyl)-benzonitrile in 58.7% yield.

benzonitrile was heated with hexamethylenetetramine in chloroform solution for two hours, and the complex treated in the manner described above; *p*-(aminomethyl)-benzoic acid was isolated in 50% yield.

p-(β-Aminoethyl)-benzoic Acid.—*p*-(β-Bromoethyl)-acetophenone[22] was obtained in 80% yield; b. p. 140–150° (3 mm.). Upon oxidation with hypobromite,[23] *p*-(β-bromoethyl)-benzoic acid (**X**) was formed in 80.5% yield. The acid was converted, through the acid chloride, into the amide[22] in 97% yield. The amide reacted with thionyl chloride to yield the nitrile in 68% yield; b. p. 148–151° (5 mm.); m. p. 49–50°.[24]

A mixture of 141 g. of the bromo nitrile, 122 g. of sodium iodide and 300 cc. of acetone was refluxed for fifteen minutes, the precipitated sodium bromide removed by filtration, and the solvent distilled from the filtrate on a steam-bath. The residue was dissolved in benzene, the solution shaken with thiosulfate solution, then with water, the benzene layer dried, and the benzene distilled under reduced pressure. The crystalline yellow residue, *p*-(β-iodoethyl)-benzonitrile, was not purified.

The crude iodo nitrile, dissolved in 300 cc. of chloroform, was mixed with 150 g. of finely powdered hexamethylenetetramine, dissolved in 700 cc. of the same solvent. The material was refluxed for three days on a steam-bath, and the precipitated complex filtered; yield 206 g. The latter was dissolved in 300 cc. of warm, concd. hydrochloric acid, 600 cc. of alcohol added, and the mixture heated until it began to boil. Ammonium chloride began to precipitate, and the application of heat was stopped. After twelve hours at room temperature, the ammonium chloride was filtered, and the alcohol and acetal distilled from the filtrate. The liquid residue was treated with 300 cc. of concd. hydrochloric acid, and the material refluxed for five hours. During this period some of the amino acid hydrochloride precipitated. The mixture was kept at 0° for some time, the precipitate filtered, washed with alcohol, dried and dissolved in water. Dilute sodium hydroxide solution was added until the mixture was only slightly acidic (methyl red). Any precipitation of the product at this stage should be disregarded. The mixture was heated to the boiling point, treated with Norite, filtered, and the filtrate cooled. After filtration of the product, more material can be obtained by concentration of the filtrate. The total yield of the amino acid was 45 g. (52%).

Anal. Calcd. for $C_9H_{11}O_2N$: C, 65.46; H, 6.72; N, 8.48. Found: C, 65.41; H, 6.91; N, 8.75.

p-(γ-Aminopropyl)-benzoic Acid.—In order to obtain *p*-(γ-bromopropyl)-acetophenone, 125 g. of aluminum chloride was suspended in a mixture of 68 cc. of acetyl chloride and 450 cc. of carbon disulfide. The material was cooled with ice, stirred and a mixture of 179 g. of γ-phenylpropyl bromide[25] and 140 cc. of acetyl chloride added. The aluminum chloride dissolved gradually, and a brown solution was obtained. The latter was cooled in an ice-bath, and stirred for three hours. It was then poured into a mixture of ice and hydrochloric acid, stirred for one-half hour, and treated as in a preceding experiment. The ketone distilled at 160–164° (7 mm.); yield 185 g. (85.5%).

Anal. Calcd. for $C_{11}H_{13}OBr$: Br, 33.14. Found: Br, 33.44.

By the same general procedure, employed before, 185 g. of the acetophenone was oxidized to yield 145 g. (78%) of *p*-(γ-bromopropyl)-benzoic acid; m. p. 118–120° after recrystallization from a mixture of benzene and petroleum ether (90–100°).

Anal. Calcd. for $C_{10}H_{11}O_2Br$: Br, 32.87. Found: Br, 33.01.

A mixture of 145 g. of the benzoic acid, 500 cc. of benzene and 125 cc. of thionyl chloride was refluxed for three hours, the solvent and excess thionyl chloride removed, and 100 cc. of dry acetone added to the residue. The acetone solution of the acid chloride was filtered, and added to 1000 cc. of 28% ammonia water which was cooled with ice, and stirred. The yield of acid amide was 139 g. (96.5%).

The amide (139 g.), 200 cc. of benzene and 150 cc. of thionyl chloride were refluxed for three hours, the solvent and excess thionyl chloride removed by distillation, 300 cc. of benzene added to the residue, the mixture filtered, the filtrate washed with sodium bicarbonate solution, dried, and the solvent removed. The *p*-(γ-bromopropyl)-benzonitrile boiled at 153–157° (4 mm.); yield 103 g. (80%).

Anal. Calcd. for $C_{10}H_{10}NBr$: Br, 35.66. Found: Br, 35.72.

A mixture of 103 g. of the bromo nitrile, 89 g. of sodium iodide and 300 cc. of acetone was refluxed for fifteen minutes, and the *p*-(γ-iodopropyl)-benzonitrile isolated in the same manner as the β-iodoethyl homolog.

To 110 g. of hexamethylenetetramine, dissolved in 400 cc. of chloroform, there was added all of the crude iodo nitrile, dissolved in 200 cc. of chloroform. The mixture was refluxed for eight hours, and the precipitated complex filtered; yield 166 g.

The complex was dissolved in 250 cc. of warm, concd. hydrochloric acid, 600 cc. of alcohol added, and the mixture heated until it began to boil whereupon ammonium chloride began to precipitate. The subsequent procedure was the same as that described above. The *p*-(γ-aminopropyl)-benzoic acid obtained weighed 38 g.; it decomposes above 290°.

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.05; H, 7.31; N, 7.82. Found: C, 66.96; H, 7.27; N, 7.94.

In order to prove that the acids were para substituted, a small portion of *p*-(β-acetylaminoethyl)- and of *p*-(γ-bromopropyl)-benzoic acid was oxidized to terephthalic acid. The latter was converted into dimethyl terephthalate for identification; m. p. 139–140°.[26]

Acid Chloride Hydrochlorides.—A mixture of 0.046 mole of the well-dried, finely-powdered amino acid and 25 cc. of thionyl chloride[27] was refluxed until all of the acid had dissolved,[28] and then for ten minutes longer.

To the solution of the *p*-(thionylaminoalkyl)-benzoyl chloride hydrochloride[29] there was added 150 cc. of absolute ether, and the mixture was then filtered through a Jena filter. The filtrate was refluxed on a steam-bath for one and one-half hours while a brisk stream of hydrogen chloride was passed into it. The precipitated *p*-(aminoalkyl)-benzoyl chloride hydrochloride was filtered on a Jena filter, washed thoroughly with absolute ether, and dried in a vacuum desiccator; yield 85–90%. The crude products were analyzed.

Hydrochloride of		Chlorine, % Calcd.	Found
p-(Aminomethyl)-benzoyl chloride	$C_8H_9ONCl_2$	34.25	33.63
p-(-Aminoethyl)-benzoyl chloride	$C_9H_{11}ONCl_2$	32.22	32.51
p-(-Aminopropyl)-benzoyl chloride	$C_{10}H_{13}ONCl_2$	30.29	29.66

Preparation of Esters

Ethyl *p*-(Aminomethyl)-benzoate and Hydrochloride.—A mixture of 71 g. of the ethyl *p*-(iodomethyl)-benzoate-hexamethylenetetramine complex and 250 cc. of absolute alcohol was refluxed for two hours while hydrogen chloride was passed into it. The mixture was cooled, saturated with hydrogen chloride and, after twelve hours at room temperature, evaporated to dryness. The solid residue was triturated with sodium hydroxide solution, extracted quickly with ether, the extract dried with magnesium

(22) Foreman and McElvain (THIS JOURNAL, **62**, 1436 (1940)).

(23) Ref. 22. The bromoform layer which forms should be separated and discarded.

(24) The same melting point has been reported (Ref. 22).

(25) Rupe and Bürgin, *Ber.*, **43**, 178 (1910).

(26) For procedure see Norris, "Experimental Organic Chemistry," first edition, McGraw-Hill Book Company, New York, N. Y., 1915, p. 168.

(27) Purified by distillation over linseed oil (Fieser, "Experiments in Organic Chemistry," 1941, p. 381).

(28) The time varied with the different acids from twenty minutes to two hours.

(29) Attempts were made to isolate these compounds but they decomposed spontaneously as soon as the excess thionyl chloride had been removed.

TABLE I

ESTER DIHYDROCHLORIDES

p-H_2N-$(CH_2)_x$-C_6H_4-COOR·2HCl

	R	M. p., °C.	Formula	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
	Esters of p-(Aminomethyl)-benzoic Acid (x = 1)						
1[a]	$CH_2CH_2N(C_2H_5)_2$	187–189	$C_{14}H_{24}O_2N_2Cl_2$	21.95	21.64		
2	$CH_2CH_2NC_5H_{10}$[a]	233–235	$C_{15}H_{24}O_2N_2Cl_2$	21.16	21.04		
3	$CH_2CH_2CH_2NC_5H_{10}$	228–230	$C_{16}H_{26}O_2N_2Cl_2$	20.31	20.38		
4	$CH_2CH_2CH_2NC_4H_8O$[b]	218–220[c]	$C_{15}H_{24}O_3N_2Cl_2$	20.19	19.98	7.98	7.94
	Esters of p-(β-Aminoethyl)-benzoic Acid (x = 2)						
5	$CH_2CH_2NC_5H_{10}$	222–225	$C_{16}H_{26}O_2N_2Cl_2$	20.31	20.06	8.02	7.85
6	$CH_2CH_2CH_2NC_5H_{10}$	188–190	$C_{17}H_{28}O_2N_2Cl_2$	19.53	19.32		
7	$CH_2CH_2CH_2NC_4H_8O$	190–192	$C_{16}H_{26}O_3N_2Cl_2$	19.41	19.64	7.67	7.47
8	$CH_2C(CH_3)_2CH_2NC_5H_{10}$	248–250[c]	$C_{19}H_{32}O_2N_2Cl_2$	18.13	18.13	7.16	7.00
	Esters of p-(γ-Aminopropyl)-benzoic Acid (x = 3)						
9	$CH_2CH_2CH_2N(C_4H_9)_2$	200–202	$C_{21}H_{38}O_2N_2Cl_2$	16.87	16.67		
10	$CH_2CH_2CH_2NC_5H_{10}$	168–170	$C_{17}H_{30}O_2N_2Cl_2$	18.80	18.72		
11	$CH_2CH_2CH_2NC_4H_8O$	193–195	$C_{17}H_{28}O_3N_2Cl_2$	18.70	18.88	7.47	7.39
12	$CH_2C(CH_3)_2CH_2NC_5H_{10}$	196–199	$C_{20}H_{34}O_2N_2Cl_2$	17.50	17.68	6.92	6.81

[a] NC_5H_{10} = piperidino. [b] NC_4H_8O = morpholino. [c] Decomposition. [d] Compounds 1 and 2 were recrystallized from a mixture of alcohol and ethyl acetate; compounds 3 and 4 from absolute alcohol; compounds 5, 9 and 12 from a mixture of alcohol and ether; compounds 6, 8, 10 and 11 from a mixture of alcohol and isopropyl ether; compound 7 from butyl alcohol.

sulfate, the solvent removed, and the ester distilled; b. p. 145–148°[30] (8 mm.); yield 19 g. (40% based on the amount of ethyl p-(iodomethyl)-benzoate employed).

When 4 g. of p-(aminomethyl)-benzoyl chloride hydrochloride, 10 cc. of absolute alcohol and 30 cc. of benzene were refluxed for one hour, and then cooled, the ester hydrochloride precipitated; m. p. 235–237° after recrystallization from a mixture of absolute alcohol and ether.

Anal. Calcd. for $C_{10}H_{14}O_2NCl$: Cl, 16.44. Found: Cl, 16.63.

Ethyl p-(β-Aminoethyl)-benzoate Hydrochloride.—This salt was obtained in 73% yield from the acid chloride hydrochloride; it melted at 178–180°[31] after recrystallization from a mixture of absolute alcohol and ethyl acetate.

Ethyl p-(γ-Aminopropyl)-benzoate Hydrochloride.—Prepared from the acid chloride hydrochloride, and recrystallized from a mixture of absolute alcohol and ether, the salt melted at 174–176°.

Anal. Calcd. for $C_{12}H_{18}O_2NCl$: Cl, 14.55. Found: Cl, 14.66.

Basic-Alkyl Ester Dihydrochlorides.—The general procedure is illustrated in the case of β-piperidinoethyl p-(aminoethyl)-benzoate dihydrochloride.

Ten grams (0.078 mole) of freshly distilled β-piperidinoethanol[32] was dissolved in a mixture of 40 cc. of dry tetrachloroethane and 8 cc. of dry toluene. Hydrogen chloride was passed into the solution until a white fog no longer appeared over the surface of the liquid; the alcohol hydrochloride did not precipitate. After the addition of 8.5 g. (0.41 mole) of the finely-powdered acid chloride hydrochloride, the mixture was heated on a steam-bath. Just before the boiling point was reached, a vigorous evolution of hydrogen chloride took place. The acid chloride dissolved gradually, and after about twenty minutes an oily layer had separated above the solution. The mixture was cooled, and 15 cc. of toluene added whereupon the oily layer sank to the bottom of the flask. The supernatant liquid was decanted, and the oily product washed thoroughly with a mixture of 20 cc. of tetrachloroethane and 5 cc. of toluene. The oily residue was dissolved in hot absolute alcohol, the solution boiled with Norite, filtered, the solvent removed from the filtrate, and the oily residue rubbed under dry ether until it became solid; the crude yield was practically quantitative.

The hydrochloride of γ-morpholinopropanol[33] and the acid chloride hydrochloride should be refluxed for forty minutes.

The esters prepared from γ-substituted propanols usually precipitated as solids.

Esters which did not solidify when rubbed under ether were obtained in crystalline form by recrystallization from a mixture of butanol and isopropyl ether (purified with sodium).

Summary

Satisfactory methods for the preparation of p-(aminomethyl)-, p-(β-aminoethyl)- and p-(γ-aminopropyl)-benzoic acids have been described. By interaction of the substituted benzoyl chloride hydrochloride with the required basic alcohol hydrochloride, basic-alkyl esters of the benzoic acids were obtained in the form of their dihydrochlorides. As local anesthetics the ester salts proved to be relatively inactive when compared with procaine or cocaine, and only ethyl p-(β-aminoethyl)-benzoate hydrochloride exhibited definite but weak pressor activity.

ANN ARBOR, MICHIGAN RECEIVED AUGUST 27, 1943

(30) Rupe and Bernstein (*Helv. Chim. Acta*, **13**, 457 (1930)) found 149–150° (10 mm.).

(31) Slotta and Kethur (ref. 7) found 178°.

(32) Vassiliades, *Bull. soc. chim.*, [5] **4**, 1132 (1937).

(33) This alcohol has been described by Cheney and Bywater (THIS JOURNAL, **64**, 970 (1942)), γ-piperidinopropanol by Barnes and Adams (*ibid.*, **49**, 1312 (1927)), β,β-dimethyl-γ-piperidinopropanol by Mannich, Lesser and Silten (*Ber.*, **65**, 381 (1932)); other alcohols were purchased from the Eastman Kodak Company.