total yield amounted to about 40–50%. The monopropionyl and mono-butyryl derivatives were prepared in a similar manner. The greater solubility of these derivatives in most organic solvents made them more difficult to purify. 4-Propionylamino-4'-aminodiphenyl sulfone melted at 201–202° (uncor.) and 4-butyrylamino-4'-aminodiphenyl sulfone melted at 192–193° (uncor.).

Preparation of 4-Acetylamino-4'-propionylaminodiphenyl Sulfone.—To 2.9 g. (0.01 mole) of 4-acetylaminodiphenyl sulfone dissolved in 15 cc. of pyridine was added slowly and with stirring 1 g. (0.01 mole) of propionyl chloride. The solution after standing for fifteen minutes was warmed to 80° on the water-bath for a few moments, then poured into 200 cc. of water containing 30 cc. of hydrochloric acid (sp. gr. 1.2), stirred well to induce crystallization and cooled for several hours in the refrigerator. The 4-acetylamino-4'-propionylaminodiphenyl sulfone after recrystallization from alcohol melted at 227–228° (uncor.). The yield of pure material was 90–95%. The other diacyl derivatives were prepared in the same manner. The melting points and analytical data are given in the table.

Summary

A series of twenty-one unsymmetrical diacyl derivatives of diaminodiphenyl sulfone has been prepared, and their effectiveness in streptococcus and pneumococcus infections in white mice has been compared to sulfanilamide and sulfapyridine.

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

BY F. F. BLICKE AND W. M. LILIENFELD[1,2]

The syntheses of p-(aminomethyl)-, p-(β-aminoethyl)- and p-(γ-aminopropyl)-benzoic acid, as well as of basic-alkyl esters of these acids, have been described in an earlier publication.[3] Subsequently we discovered another preparative procedure for p-(aminoalkyl)-benzoic acids, one which would seem to be applicable for the synthesis of any acid of this type. By means of this procedure we have prepared p-(β-aminoethyl)- and p-(β-aminopropyl)-benzoic acid.

β-Phenylethyl bromide (I) was transformed into the corresponding amine (II) with the aid of the Gabriel synthesis. The amine was acetylated, and the acetyl derivative (III) reacted with acetyl bromide and aluminum chloride to produce p-(β-acetylaminoethyl)-acetophenone (IV).[4] The latter was oxidized with hypobromite to p-(β-acetylaminoethyl)-benzoic acid (V)[5] which, upon hydrolysis, yielded p-(β-aminoethyl)-benzoic acid (VI).

I	$BrCH_2CH_2—C_6H_5$
II	$NH_2CH_2CH_2—C_6H_5$
III	$CH_3CONHCH_2CH_2—C_6H_5$
IV	$CH_3CONHCH_2CH_2—C_6H_4—COCH_3$
V	$CH_3CONHCH_2CH_2—C_6H_4—COOH$
VI	$NH_2CH_2CH_2—C_6H_4—COOH$

The procedure for p-(β-aminopropyl)-benzoic acid (XI) is entirely analogous to the one described above; in this instance it was possible to begin the synthesis with the use of benzedrine (VII).

VII	$NH_2CH(CH_3)CH_2—C_6H_5$
VIII	$CH_3CONHCH(CH_3)CH_2—C_6H_5$
IX	$CH_3CONHCH(CH_3)CH_2—C_6H_4—COCH_3$
X	$CH_3CONHCH(CH_3)CH_2—C_6H_4—COOH$
XI	$NH_2CH(CH_3)CH_2—C_6H_4—COOH$

The hydrochlorides of the ethyl ester and of the four basic-alkyl esters of p-(β-aminopropyl)-benzoic acid—the β-piperidinoethyl, γ-piperidinopropyl, γ-morpholinopropyl and the β,β-dimethyl-γ-piperidinopropyl—were prepared by interaction of the aminoalkylbenzoyl chloride hydrochloride with the required basic alcohol hydrochloride in the same manner described previously.[3]

The esters were examined for local anesthetic and pressor activity by L. W. Rowe in the Parke, Davis and Company laboratories. In 2% solution none of the esters produced anesthesia when applied to the rabbit's cornea; only slight anesthesia was obtained by injection. Ethyl p-(β-aminopropyl)-benzoate dihydrochloride brought about only a very moderate rise in blood pressure, while the effect of the other esters was negligible.[6]

Experimental Part

β-Phenylethyl bromide[7] (I), β-phenylethylamine[8] (II) and its acetyl derivative (III)[9] (b. p. 160–162° (3 mm.)) were prepared according to published methods.

p-(β-Acetylaminoethyl)-acetophenone (IV).—To 41 g. of the acetylated amine, dissolved in 100 cc. of dry tetrachloroethane, there was added 48 cc. of acetyl bromide. The solution was cooled to 0° and maintained at that temperature while it was stirred, and 110 g. of aluminum chloride added in small portions. After complete addition, the material was heated on a steam-bath for one-half hour,

(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 and Company Fellow.

(3) Blicke and Lilienfeld, THIS JOURNAL, **65**, 2281 (1943).

(4) Kunckell (*Ber.*, **33**, 2641 (1900)) showed that acetanilide, acetyl bromide and aluminum chloride react to form p-acetylaminoacetophenone.

(5) The fact that this substance was a *para* substituted compound was proven by oxidation of compound V to terephthalic acid, and identification of the latter through its dimethyl ester (see Norris, "Experimental Organic Chemistry," McGraw-Hill Book Company, New York, N. Y., first edition, 1915, p. 168).

(6) In this connection, it is interesting to note that Allewelt and Day (*J. Org. Chem.*, **6**, 384 (1941)) stated that certain basic alcohols which they prepared exhibit both local anesthetic and pressor activity.

(7) Norris, Watt and Thomas, THIS JOURNAL, **38**, 1078 (1916).

(8) Ing and Manske, *J. Chem. Soc.*, 2350 (1926).

(9) Bischler and Napieralski, *Ber.*, **26**, 1905 (1893).

TABLE I

DIHYDROCHLORIDES OF ESTERS OF *p*-(β-AMINOPROPYL)-BENZOIC ACID, *p*-$NH_2CH(CH_3)CH_2—C_6H_4—COOR \cdot 2HCl$

Compound 1 was recrystallized from a mixture of alcohol and ether; compounds 2 and 5 from a mixture of butyl alcohol and isopropyl ether; compounds 3 and 4 from absolute alcohol.

	R	M. p., °C.	Formula	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	CH_2CH_3[a]	140–142	$C_{12}H_{18}O_2NCl$	14.55	14.71	5.75	5.89
2	$CH_2CH_2NC_5H_{10}$[b]	218–220	$C_{17}H_{28}O_2N_2Cl_2$	19.53	19.36	7.72	7.82
3	$CH_2CH_2CH_2NC_5H_{10}$[b]	255–257	$C_{18}H_{30}O_2N_2Cl_2$	18.80	19.08	7.43	7.47
4	$CH_2CH_2CH_2NC_4H_8O$[c]	251–253	$C_{17}H_{28}O_3N_2Cl_2$	18.70	18.89	7.39	7.64
5	$CH_2C(CH_3)_2CH_2NC_5H_{10}$	223–226	$C_{20}H_{34}O_2N_2Cl_2$	17.50	17.32	6.92	6.72

[a] Monohydrochloride. [b] NC_5H_{10} = Piperidino. [c] NC_4H_8O = Morpholino.

poured over ice, stirred and the organic layer separated; the aqueous layer was extracted with tetrachloroethane. The solution of the product was shaken with water, the solvent removed and the residue distilled; the acetophenone boiled at 214–216° (3 mm.); yield 38 g. (74%); m. p. 99–101° after recrystallization from xylene.

Anal. Calcd. for $C_{12}H_{15}O_2N$: N, 6.67. Found: N, 6.81.

***p*-(β-Acetylaminoethyl)-benzoic Acid (V).**—A hypobromite solution, prepared from 31 cc. of bromine, 66 g. of sodium hydroxide and 500 cc. of water, was cooled in an ice-bath, stirred, and 38 g. of the acetophenone, dissolved in 100 cc. of technical dioxane, was added slowly. The cold mixture was stirred for three hours, most of the alkali neutralized with hydrochloric acid, the bromoform layer separated and discarded. After the aqueous layer had been shaken with chloroform, hydrochloric acid was added to it until it was just acidic to congo red whereupon the acetylamino acid began to precipitate. The mixture was cooled for several hours, the product filtered and washed with water; yield 30 g. (78%). A sample was recrystallized from water for analysis; m. p. 173–175°.

Anal. Calcd. for $C_{11}H_{13}O_3N$: N, 6.61. Found: N, 6.75.

***p*-(β-Aminoethyl)-benzoic Acid (VI).**—Thirty grams of the acetylamino compound was refluxed with 75 cc. of concd. hydrochloric acid for five hours. The mixture should be heated very carefully since it foams as soon as the reaction begins. After the addition of 15 cc. of alcohol to the cold mixture, it was placed in an ice-bath for some time. The precipitated amino acid hydrochloride was filtered, washed with alcohol, then with ether; yield 28 g.

The hydrochloride was dissolved in 100 cc. of hot water, treated with Norite, filtered and sodium hydroxide solution added to the filtrate until it was neutral to methyl red. The solution was concentrated until crystals of the amino acid began to separate. After some time at room temperature, the acid was filtered; a further amount of acid was obtained by concentration of the mother liquor; yield 15 g. (62%).

In order to prove that this acid was identical with the one which we obtained previously[3] by the Delépine reaction, it was converted into the ethyl ester hydrochloride[3]; the latter melted at 178–180°.

1-Phenylacetylisopropylamine (VIII).—A mixture of 33.2 g. of benzedrine (VII) and 28 cc. of acetic anhydride was refluxed for thirty minutes, the excess acetic anhydride and acetic acid removed by distillation, and the residue fractionated; the acetylated amine boiled at 144–145° (2 mm.); m. p. 88–91°[10]; yield 42.5 g. (96%).

***p*-(β-Acetylaminopropyl)-acetophenone (IX).**—Prepared in the same manner as compound IV, we obtained 38 g. (77%) of the acetophenone from 40 g. of the acetylated amine, 100 cc. of tetrachloroethane, 45 cc. of acetyl bromide and 110 g. of aluminum chloride; however, in this instance, the reaction mixture was heated on a steam-bath for only fifteen minutes. The product boiled at 206–208° (3 mm.). The distillate solidified very slowly; after the crystalline material had been washed with absolute ether, it melted at 97–99°.

Anal. Calcd. for $C_{13}H_{17}O_2N$: N, 6.39. Found: N, 6.64.

***p*-(β-Acetylaminopropyl)-benzoic Acid (X).**—To a hypobromite solution, obtained from 96 g. of bromine, 66 g. of sodium hydroxide and 500 cc. of water, there was added 38 g. of the acetophenone, dissolved in 100 cc. of dioxane. The procedure was the same as that described under compound V. The benzoic acid obtained weighed 32.5 g. (84.5%). A portion was recrystallized from 25% alcohol for analysis; m. p. 208–210°.

Anal. Calcd. for $C_{12}H_{15}O_3N$: C, 65.17; H, 6.84; N, 6.33. Found: C, 65.65; H, 6.97; N, 6.40.

***p*-(β-Aminopropyl)-benzoic Acid (XI).**—When 32.5 g. of the crude acetylamino acid was hydrolyzed with 75 cc. of concd. hydrochloric acid in the manner described above, we obtained 27.5 g. of the amino acid hydrochloride. The latter was converted into the amino acid; yield 15.5 g. (59%). When heated, the acid begins to decompose about 290°.

Anal. Calcd. for $C_{10}H_{13}O_2N$: N, 7.82. Found: N, 7.34.

***p*-(β-Aminopropyl)-benzoyl Chloride Hydrochloride.**—A mixture of 8.2 g. of well-dried, finely powdered *p*-(β-aminopropyl)-benzoic acid and 25 cc. of pure thionyl chloride was refluxed on a steam-bath for one hour, and the product then isolated in the manner described previously.[3]

The crude hydrochloride was analyzed.

Anal. Calcd. for $C_{10}H_{13}ONCl_2$: Cl, 30.29. Found: Cl, 30.08.

Summary

A relatively simple procedure, which appears to be a general one for the preparation of a *p*-(aminoalkyl)-benzoic acid, has been utilized for the synthesis of *p*-(β-aminoethyl)- and *p*-(β-aminopropyl)-benzoic acid.

The ethyl ester, as well as several basic-alkyl esters, of *p*-(β-aminopropyl)-benzoic acid have been described. These products were found to be of no significance as local anesthetics or as pressor agents.

(10) Hey (*J. Chem. Soc.*, 18 (1930)) found 93°.

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