[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF TEMPLE UNIVERSITY]

The Synthesis of Certain Local Anesthetics of the Biphenyl Series

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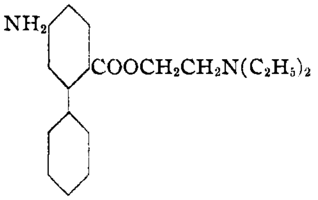
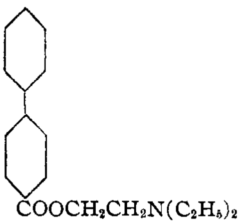
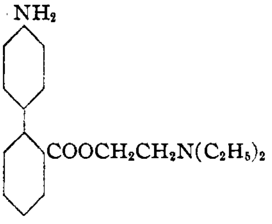
In 1935 Braker and Christiansen[1] synthesized a series of local anesthetics containing the biphenyl nucleus, of which those shown below are of particular interest in connection with the present work



I



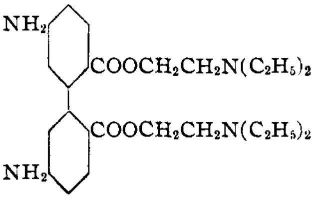
II



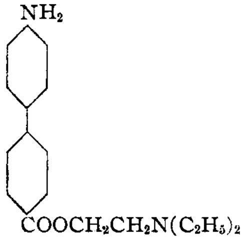
III

Compound I was found by these authors to be more active than procaine or cocaine, II was too acid, while III was weak in its action.

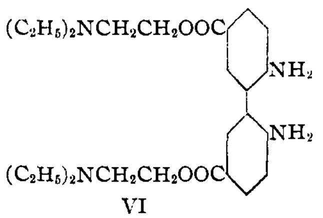
In this Laboratory the following three compounds have been synthesized with the idea of examining their local anesthetic properties



IV



V



VI

The similarity of IV to I and also to the local anesthetic β-diethylaminoethyl diphenate[2] would indicate pronounced anesthetic possibilities. In compound V the introduction of the amino group should lessen the acidity found in II. Furthermore, the position of the ester group may be more favorable than in III.

A strong argument for the possible anesthetic power of VI is found in the observation of Chierici[3] that 2,2′-diaminobiphenyl has about one-fourth the activity of cocaine.

The synthesis of 4-nitro-4′-biphenylcarboxylic acid (intermediate in the preparation of V) was accomplished through the following series of reactions: *p*-toluidine → 4-methylbiphenyl[4] → 4-methyl-4′-nitrobiphenyl → 4-nitro-4′-biphenylcarboxylic acid.[5]

The preparation of 5,5′-dinitrodiphenic acid (used in the preparation of IV) was first effected by Pufahl[6] in the following manner: 4-nitro-2-aminobenzoic acid → 4-nitro-2-iodobenzoic acid → methyl ester $\xrightarrow{\text{Cu}}$ dimethyl-5,5′-dinitrodiphenate → 5,5′-dinitrodiphenic acid. In this Laboratory we first attempted to couple 4-nitro-2-iodotoluene[7] according to the directions of Pummerer, Puttfarcken and Schopflocher,[8] with the intention of oxidizing later the resulting 5,5′-dinitro-2,2′-dimethylbiphenyl to the desired acid. The yields in the coupling reaction, however, were found to be very poor. A more satisfactory method of synthesis was found by us to be a modification of Pufahl's method in which the 4-nitro-2-iodobenzoic acid was prepared by a permanganate oxidation of 4-nitro-2-iodotoluene. The best and most direct method of preparation, however, was found to involve the coupling of diazotized 4-nitro-2-aminobenzoic acid in an ammoniacal solution of cuprous oxide according to the general procedure of Vorländer and Meyer.[9]

The preparation of di-(β-diethylaminoethyl) 5,5′-diaminodiphenate was effected by esterification of the nitro acid, followed by catalytic reduction.

The synthesis of 2,2′-dinitro-5,5′-biphenyl-di-

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(1) Braker and Christiansen, *J. Am. Pharm. Assoc.*, **24**, 358 (1935).

(2) Roberts and Johnson, THIS JOURNAL, **47**, 1396 (1925).

(3) Chierici, *Ann. chim. farmac.*, 48 (1938).

(4) Gomberg and Pernert, THIS JOURNAL, **48**, 1372 (1926).

(5) Grieve and Hay, *J. Chem. Soc.*, 1888 (1932).

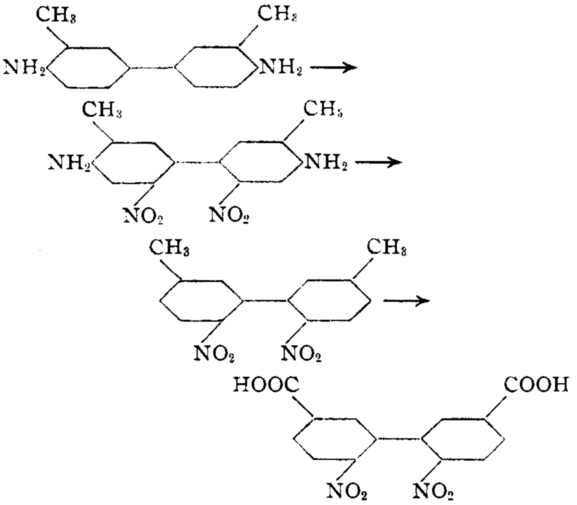
(6) Pufahl, *Ber.*, **62**, 2817 (1929).

(7) Willgerodt and Kok, *ibid.*, **41**, 2077 (1908).

(8) Pummerer, Puttfarcken and Schopflocher, *ibid.*, **58**, 1816 (1925).

(9) Vorländer and Meyer, *Ann.*, **320**, 138 (1902).

carboxylic acid was accomplished in the following manner



Improved methods were worked out for the nitration[10] and subsequent deamination of *o*-tolidine.[11]

The purification of the di-(β-diethylaminoethyl) ester of 2,2′-dinitro-5,5′-biphenyldicarboxylic acid was best effected by crystallization of its monohydrate from aqueous acetone. It was found that this hydrated ester on attempted crystallization from methanol was quickly converted into the dimethyl ester. Due to this ready interchange of alkyl radicals, catalytic reduction in alcoholic solutions was impracticable and in other solvents proved unsuccessful. The reduction was finally effected with tin and hydrochloric acid.

The conversion of all the nitro acids mentioned into their acid chlorides was brought about by means of phosphorus pentachloride, since these acids are not readily attacked by thionyl chloride at its boiling point.

Pharmacological tests on the three compounds whose preparation is described in this paper have been completed by Dr. E. J. Fellows in collaboration with Dr. A. E. Livingston, Department of Pharmacology, Temple Medical School. The results, which indicate in each case strong anesthetic power with varying degrees of toxicity, will be published in detail elsewhere.

Experimental

β - Diethylaminoethyl 4 - Nitro - 4′ - biphenylcarboxylate.—The crude acid chloride obtained by the action of 22 g. of phosphorus pentachloride on 25 g. of 4-nitrobiphenyl-4′-carboxylic acid at 180°, and freed from $POCl_3$, was treated in a cold dry toluene solution with an excess of diethylaminoethanol, and then refluxed for five hours. The free base, after liberation by means of 5% sodium carbonate solution, was crystallized from petroleum ether; m. p. 52–53°.

Anal. Calcd. for $C_{19}H_{22}O_4N_2$: N 8.19. Found: N, 8.13.

The hydrochloride obtained by the action of dry hydrogen chloride on an ether solution of the base melts at 186–188°.

Anal. Calcd. for $C_{19}H_{23}O_4N_2Cl$: Cl, 9.36. Found: Cl, 9.41.

β - Diethylaminoethyl 4 - Amino - 4′ - biphenylcarboxylate.—This was prepared by the catalytic reduction of the corresponding nitro ester in ethanol, followed by liberation of the free base. It crystallizes from a benzene–petroleum ether mixture, m. p. 78–79°.

Anal. Calcd. for $C_{19}H_{24}O_2N_2$: C, 73.03; H, 7.75. Found: C, 72.98; H, 7.94.

Preparation of 5,5′-Dinitrodiphenic Acid.—A suspension of the sodium salt of 4-nitro-2-aminobenzoic acid was prepared by dissolving 28.5 g. of the acid in 400 cc. of hot water containing 30 cc. of 6 *N* sodium hydroxide, and allowing the mixture to cool. This suspension, after the addition of a saturated solution of 13 g. of sodium nitrite, was added gradually to a solution of 130 cc. of 6 *N* hydrochloric acid in 60 cc. of water, the temperature being kept below 10° by the addition of ice. The diazotized solution was then added gradually (temperature 15–20°) to one prepared by mixing a solution of 22 g. of hydroxylamine hydrochloride and 17.5 g. of potassium hydroxide in 50 cc. of water with one made by dissolving 54 g. of hydrated copper sulfate in 200 cc. of water and adding 100 cc. of 28% ammonium hydroxide. On the addition of concentrated hydrochloric acid, the resulting 5,5′-dinitrodiphenic acid precipitated out, and after several hours' standing, was crystallized from glacial acetic acid; yield 16 g.; m. p. 288°.

Di-(β-diethylaminoethyl 5,5′-Dinitrodiphenate.—This was obtained by the action of diethylaminoethanol on the crude acid chloride as previously described in the case of β-diethylaminoethyl 4-nitro-4′-biphenylcarboxylate. It crystallizes from petroleum ether; m. p. 67–68°.

Anal. Calcd. for $C_{26}H_{34}N_4O_8$: C, 58.83; H, 6.46. Found: C, 59.06; H, 6.42.

Di-(β-diethylaminoethyl) 5,5′-Diaminodiphenate.—This was prepared by the catalytic reduction of the above nitro ester in ethanol. It crystallizes from ether–petroleum ether; m. p. 64–65°.

Anal. Calcd. for $C_{26}H_{38}N_4O_4$: C, 66.33; H, 8.14. Found: C, 66.20; H, 8.19.

Preparation of 3,3′-Dimethyl-4,4′-diamino-6,6′-dinitrobiphenyl.—To a well-stirred solution of 42 g. of *o*-tolidine, dissolved in a mixture of 72 cc. of 15% oleum and 280 cc. of concentrated sulfuric acid, was added in small portions 40 g. of finely powdered potassium nitrate, keeping the temperature below 6°. After the mixture had been allowed to warm to room temperature it was poured into

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(10) Loewenherz, *Ber.*, **25**, 1032 (1892).

(11) Tauber and Loewenherz, *ibid.*, **24**, 2597 (1891); Gerber, Dissertation, Basel, 1889.

5 liters of ice water, and the precipitated sulfate filtered off. The red base, precipitated by the addition of sodium hydroxide to a suspension of the sulfate in water, was dried and recrystallized from a mixture of alcohol and acetone; yield, 37 g.; m. p. 214–215°. In some cases (especially where larger amounts were used) the nitro base obtained using the above procedure was low-melting and could not be purified by crystallization. In these instances the crude dried product was acetylated by dissolving it in five times its weight of glacial acetic acid and adding once its weight of acetic anhydride and a few drops of concentrated sulfuric acid. The acetylated base, which is insoluble in most solvents, was extracted twice with hot alcohol to remove impurities, and hydrolyzed with hot dilute sulfuric acid. The pure base thus obtained melted at 220–221°.

Preparation of 2,2′-Dinitro-5,5′-dimethylbiphenyl.—The paste obtained by cooling a hot solution of 40 g. of 3,3′-dimethyl-4,4′-diamino-6,6′-dinitrobiphenyl in 164 cc. of concentrated sulfuric acid and 150 cc. of water was diazotized by the addition of 40 g. of solid sodium nitrite (a few small pieces of ice may be added). To the diazotized solution was added 150 cc. of 20% oleum, keeping the temperature below 30°. The resulting solution was then poured into 2 liters of boiling alcohol, and refluxed for two hours. After removal of most of the alcohol on the steam-bath by means of an aspirator, the solution was poured into water, and the brown precipitate dried and crystallized from alcohol; yield, 19 g.; m. p. 158–159°.

2,2′-Dinitro-5,5′-biphenyldicarboxylic Acid.—To a solution of 20 g. of the above dinitrodimethylbiphenyl in 180 cc. of hot glacial acetic acid was added 20 g. of chromic anhydride in small portions, keeping the mixture at the boiling point. After ten hours of refluxing the solution was poured into a large volume of water and the precipitated acid filtered and dried; yield, 15 g. of crude acid of low melting point which could not be purified by crystallization. It was reoxidized by dissolving in 180 cc. of glacial acetic acid, and adding 8 g. of chromic anhydride. After crystallization from glacial acetic acid, 7.5 g. of acid, m. p. 323°, was obtained. The pure acid melts with decomposition at 327–328°.

Anal. Calcd. for $C_{14}H_8N_2O_8$: C, 50.59; H, 2.43. Found: C, 50.75; H, 2.40.

The dimethyl ester, prepared by refluxing the acid with methanol in presence of concentrated sulfuric acid, crystallizes from methanol; m. p. 167–168°.

Anal. Calcd. for $C_{16}H_{12}N_2O_8$: C, 53.32; H, 3.36. Found: C, 53.24; H, 3.70.

Di-(β-diethylaminoethyl) 2,2′-Dinitro-5,5′-biphenyldicarboxylate.—A mixture of 20 g. of 2,2′-dinitro-5,5′-biphenyldicarboxylic acid and 27 g. of phosphorus pentachloride was heated under reflux for four hours at 130–140°. After removal of the resulting $POCl_3$ by means of an aspirator, the crude acid chloride was dissolved in 110 cc. of dry toluene and treated with 36 g. of β-diethylaminoethanol. After refluxing for six hours, the mixture was washed with dilute sodium carbonate solution, dried, freed from toluene and unchanged diethylaminoethanol, and extracted repeatedly with petroleum ether. The spontaneous evaporation of the solvent left yellow crystals which were washed with petroleum ether and crystallized from aqueous acetone; yield, 14.5 g.; m. p. 79–80°. The melting point of the pure product is 80–81° (with turbidity). The crystals proved to be the monohydrate of the dinitro ester.

Anal. Calcd. for $C_{26}H_{34}N_4O_8 \cdot H_2O$: C, 56.90; H, 6.62; H_2O(hydration), 3.29. Found: C, 57.25; H, 7.02; H_2O, 3.44.

The anhydrous free base is a liquid.

Dihydrochloride.—This crystallizes from an absolute alcohol–petroleum ether mixture; m. p. 215–216° (with decomposition).

Anal. Calcd. for $C_{26}H_{36}N_4O_8Cl_2$: Cl, 11.76. Found: Cl, 11.38.

Di-(β-diethylaminoethyl) 2,2′-Diamino-5,5′-biphenyldicarboxylate.—Nine grams of the corresponding nitro ester hydrate dissolved in concentrated hydrochloric acid was reduced with an excess of tin, the temperature being kept below 45°. After solution of the tin, the mixture was diluted and the tin removed by hydrogen sulfide. The base, liberated by solid sodium carbonate, was extracted with ether and crystallized from benzene–petroleum ether; yield, 4 g.; m. p. 91–92°.

Anal. Calcd. for $C_{26}H_{38}N_4O_4$: C, 66.33; H, 8.14. Found: C, 66.58; H, 8.50.

Summary

1. The synthesis of the following compounds has been described: di-(β-diethylaminoethyl) 5,5′-diaminodiphenate (IV), β-diethylaminoethyl 4-amino-4′-biphenylcarboxylate (V), di-(β-diethylaminoethyl) 2,2′-diamino-5,5′-biphenyldicarboxylate (VI).

2. Pharmacological tests have shown them to be powerful anesthetics.

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