TABLE I

PHYSICAL AND ANALYTICAL DATA FOR α,β-DIAMINO TERTIARY CARBINOLS

Compound	No.	M. p., °C.	Yield, %	Formula	Percentage composition: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
3-Piperidino-4-tetrahydroisoquinolino-butanol-2										
2-Methyl-4-phenyl	(I)	141–143	14	$C_{25}H_{34}N_2O$	79.32	78.92	9.05	9.09	7.41	7.35
2,4-Diphenyl	(II)	194–197	47	$C_{30}H_{36}N_2O$	81.77	81.69	8.24	8.01	6.36	6.57
2,4-Diphenyl	(III)	206–209	20	$C_{30}H_{36}N_2O$	81.77	81.94	8.24	8.33	6.36	6.09
2,4-Diphenyl-3,4-dipiperidinobutanol-2	(IV)	145–147	13	$C_{26}H_{36}N_2O$	79.54	79.66	9.26	9.32	..	..

Experimental

Reaction of Grignard Reagents with the Ketones.—Four equivalents of the corresponding Grignard reagent were prepared in dry ether solution in the usual manner. To these solutions, one equivalent of the corresponding α,β-diamino ketone dissolved in the minimum amount of dry benzene was added all at once. The reaction mixtures were refluxed for two hours, cooled, and then decomposed with ice and ammonium chloride. The benzene-ether layer was washed several times with water, dried and evaporated to give the crude oily products. Recrystallization of these products from 95% ethanol gave as a first crop, mainly unchanged starting material. The second crop contained most of the carbinol product. These crude carbinol products were purified further by boiling with 5% sulfuric acid to destroy by hydrolysis any remaining unchanged α,β-diamino ketone.[9] Neutralization of the acid solutions with sodium hydroxide precipitated the diamino carbinols, which were again recrystallized from a chloroform-alcohol mixture and finally from a benzene-petroleum ether mixture, see Table I.

(9) Cromwell, THIS JOURNAL, **62**, 2897 (1940).

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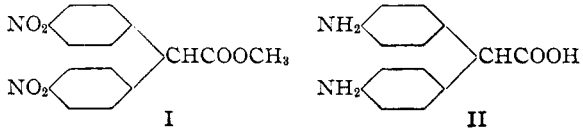
4,4′-Diaminodiphenylacetic Acid

BY L. HASKELBERG AND D. LAVIE

The interesting therapeutical properties of 1,1-di-(*p*-aminophenyl)-2,2,2-trichloroethane, of di-(*p*-aminophenyl)-sulfone and of di-(*p*-aminophenyl) ketone[1] led us to an investigation in the series of di-(*p*-aminophenyl)-acetic acid (II). Heller's[2] method, the condensation of dichloroacetic acid with aniline, gave no reliable results. The easily available diphenylacetic acid[3] was, therefore, selected as starting material. Whilst the products of its direct nitration could neither be crystallized nor purified by vacuum distillation, the methyl ester gave a crystalline dinitro-derivative, if only in 23% yield.[4] Formula (I) for the nitration product could be derived from the observation that, upon treatment with alkali, not only hydrolysis, but also decarboxylation took place, leading in quantitative yield to the known 4,4′-dinitrodiphenylmethane of m. p. 187°, which was oxidized to 4,4′-dinitrobenzophenone of the same melting point.[5] Hydrolysis of (I) could only be effected (in 95% yield) in acid medium, and both the free acid and the methyl ester (I) could be hydrogenated catalytically without difficulty. The 4,4′-diaminodiphenylacetic acid (II) (yield, 71%) had the melting point (204.5°) indicated by Heller[2]; its methyl ester was oily, but could be characterized by its dihydrochloride, its diacetyl derivative and by the hydrolysis to (II).



I II

Experimental

Methyl 4,4′-Dinitrodiphenylacetate (I).—At a temperature of −15°, 20 g. of methyl diphenylacetate was slowly added to 130 cc. of fuming nitric acid, with vigorous stirring. The clear solution was poured onto crushed ice and the solid which separated triturated with water and sodium carbonate solution and finally with alcohol. From glacial acetic acid, one obtained transparent platelets of m. p. 162°; yield, 23%. *Anal.* Calcd. for $C_{15}H_{12}O_6N_2$: C, 56.9; H, 3.8. Found: C, 57.2; H, 3.5.

4,4′-Dinitrodiphenylmethane.—To a solution of 1.6 g. of (I) in 7 cc. of methanol, one added gradually a solution of 0.2 g. of sodium hydroxide in 7 cc. of water. The violet solution (aci- salt) was refluxed for two hours, whereupon the color disappeared and crystals separated which were filtered, washed with dilute hydrochloric acid and water and recrystallized from petroleum ether: m. p. 187°; yield, quantitative.[6] Oxidation of 1 g. with 1.5 g. of chromic acid in boiling glacial acetic acid gave, after recrystallization from the same solvent, pure 4,4′-dinitrobenzophenone which was identified by mixed melting point with an authentic specimen.

Methyl 4,4′-Diaminodiphenylacetate.—When 4.7 g. of (I) in 100 cc. of ethyl acetate was shaken with hydrogen in presence of 0.5 g. of Raney nickel, the theoretical quantity of hydrogen was absorbed in two hours. The reaction product distilled without substantial decomposition at 252–258° under 1.5 mm. pressure; it was converted into its **dihydrochloride** by treatment of its ethereal solution with gaseous hydrogen chloride. The crude product which separated, was triturated with light petroleum ether and several times suspended in anhydrous methanol and brought to dryness. From alcohol, one obtained slightly pinkish crystals of m. p. 245° (dec.). *Anal.* Calcd. for $C_{15}H_{18}O_2N_2Cl_2$: C, 54.7; H, 5.5. Found: C, 54.7; H, 5.8. **Diacetyl derivative.** The mixture of 1 g. of the oily diamino-ester and 5 cc. of acetic anhydride was refluxed

(1) R. Kuhn, *et al.*, *Ber.*, **75**, 711 (1942).

(2) Heller, *Ann.*, **375**, 261 (1910).

(3) "Organic Syntheses," Coll. Vol. I, 2nd Edition, New York, N. Y., 1944, p. 224.

(4) Werner (*Ber.*, **39**, 1290 (1906)) described the tetra-nitration of *ethyl* diphenylacetate.

(5) The facile decarboxylation of similar substances has been reported before: 2,4-dinitrophenylacetic acid (Radiszewski, *Ber.*, **3**, 648 (1870)); 5-bromo-2,4-dinitro-phenylacetic acid (Jackson and Robinson, *Am. Chem. J.*, **11**, 549 (1889)); 2,4,6-trinitrophenylacetic acid (Jackson and Phinney, *ibid.*, **21**, 430 (1899); *Ber.*, **28**, 3067 (1895)).

(6) Staedel, *Ber.*, **27**, 2110 (1894).

for thirty minutes and the solid product filtered—after cooling—washed with water and recrystallized from glacial acetic acid; m. p. 293.5° (dec.). *Anal.* Calcd. for $C_{19}H_{20}O_4N_2$: C, 67.0; H, 5.8; N, 8.2. Found: C, 66.7; H, 5.5; N, 8.1.

4,4'-Dinitrodiphenylacetic Acid.—A mixture of 31 g. of the ester (I), 150 cc. of glacial acetic acid and 15 cc. of 25% sulfuric acid was refluxed for four hours. After dilution with water, the free acid crystallized upon standing. Recrystallization from 50% acetic acid gave transparent prisms, m. p. 174° (dec.); yield 95%. *Anal.* Calcd. for $C_{14}H_{10}O_8N_2$: mol. wt., 302. Found: mol. wt., 301 (by titration). The crystalline **acid chloride** was obtained in quantitative yield, when the acid (6.5 g.) was refluxed (six hours) with thionyl chloride (25 cc.); recrystallized from a mixture of benzene and petroleum ether, it melted at 142–143°. *Anal.* Calcd. for $C_{14}H_9O_8N_2Cl$: C, 52.5; H, 2.8; N, 8.7. Found: C, 52.5; H, 2.6; N, 9.0.

4,4'-Diaminodiphenylacetic Acid (II).—(a) A solution of 3 g. of 4,4'-dinitrodiphenylacetic acid in 50 cc. of glacial acetic acid was hydrogenated in presence of a palladium-barium sulfate catalyst; the required amount of hydrogen was absorbed in fifteen minutes. The filtered solution was evaporated and the oily residue triturated with isopropyl alcohol; from butanol, yellowish prisms of m. p. 204.5° (dec.); yield, 71%.

(b) A solution of 0.5 g. of the diamino ester in a mixture of 10 cc. of water and 3 cc. of glacial acetic acid was refluxed for twelve hours and then brought to dryness. Recrystallization of the residue from butyl alcohol gave crystals of m. p. 204.5° (dec.), which were identical with the above product.

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REHOVOTH, ISRAEL RECEIVED JANUARY 31, 1949

The Bromination of ε-Benzoylaminocaproic Acid

BY E. E. HOWE AND E. W. PIETRUSZA

One of the most acceptable syntheses of lysine is that of Eck and Marvel[1] which involves the bromination of ε-benzoylaminocaproic acid with bromine and red phosphorus. In a recent communication Galat[2] has observed that this bromination is not easily effected and that the yields are extremely erratic. He has circumvented this undesirable reaction and improved the synthesis of lysine by chlorinating ε-benzoylaminocaproic acid with sulfuryl chloride. The excellent yield of α-chloro-ε-benzoylaminocaproic acid more than compensates for the somewhat lower yield obtained in the subsequent amination step.

Although Eck and Marvel[1] insist on the use of dry reagents and take precautionary measures to prevent access of moisture to the bromination mixture, we have found that in the presence of a small amount of water the reaction proceeds smoothly with yields consistently above 95%. This innovation leads to the preparation of a compound of sufficiently high purity that it may be used in the succeeding step of the lysine synthesis without the additional recrystallization used by Eck and Marvel. It is our hope that this information may be of value to others who wish to brominate similar compounds.

(1) Eck and Marvel, "Org. Syn." Coll. Vol. II (1943), pp. 74, 76, 374.

(2) Galat, THIS JOURNAL, 69, 86 (1947).

Experimental

An intimate mixture of 37.5 g. (0.16 mole) of ε-benzoylaminocaproic acid and 5.45 g. (0.176 mole) of red phosphorus was placed in a 250-cc. 3-necked flask fitted with a dropping funnel, a mechanical stirrer and a reflux condenser. In addition, a thermometer was suspended in the flask through the condenser. To the contents of the flask were added 100 cc. of carbon tetrachloride and 1.16 cc. of distilled water. The mixture was agitated for a short time after which 70.4 g. (0.44 mole) of bromine was slowly added (seventy-five minutes) while the temperature was maintained below 50° by means of an ice-bath. The resultant dark red solution was stirred vigorously for one hour after which the solvent was removed by attaching a down condenser and heating the mixture under reduced pressure.

To the red, viscous mass 25.6 g. (0.16 mole) of bromine was added in thirty minutes with agitation. Again the temperature was kept below 50° during this addition but immediately afterward it was gradually raised to and maintained at 100° for one hour. After the reaction mixture had cooled to 70°, an additional 4.8 g. (0.03 mole) of bromine was added followed by a thirty-minute heating period at 100°.

The contents of the flask were cooled to 50°, whereupon with vigorous agitation and with cooling to maintain the temperature below 50°, 100 cc. of water was added to the acyl halide in the course of one and one-half hours. This reaction is extremely exothermic, consequently it must be carried out with great caution. The mixture was cooled to 0° and transferred to a mortar where the crystalline product was pulverized and stirred with small amounts of sodium bisulfite to remove unreacted bromine. The acid was removed by filtration and was treated in 50 cc. of water with bisulfite until it assumed a yellowish-white color. It was then collected on a funnel, washed three times with ice water, and dried at 50–60°. The yield was 47.4 g. (95%) of α-bromo-ε-benzoylaminocaproic acid melting at 153–161°.

By the procedure of Eck and Marvel[1] 42.3 g. of the acid obtained as described above was aminated to yield 25.6 g. (76%) of benzoyllysine which melted as did that prepared by the earlier workers at 265–270°.

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RESEARCH LABORATORIES
MERCK & CO., INC.
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2-Nitro-4-furaldehyde Semicarbazone, an Isomer of Furacin[1]

BY KENYON HAYES

The general *in vitro* antibacterial activity of α-nitrofuran derivatives has been reported previously from these Laboratories.[2,3] For *in vivo* activity it has been found that a negatively substituted hydrazone of an α' formyl or acyl group must also be present on the α-nitrofuran.[4,5] The compound of this class most thoroughly studied is 5-nitro-2-furaldehyde semicarbazone, Furacin (I). This compound is active against many gram-positive and gram-negative organisms

(1) Furacin is the Eaton Laboratories brand of nitrofurazone N. N. R.

(2) Dodd and Stillman, *J. Pharmacol. Exptl. Therap.*, **82**, 11 (1944).

(3) Stillman, Scott and Clampit, U. S. Patent 2,319,481 (1943).

(4) Stillman and Scott, U. S. Patents 2,416,233 through 2,416,239 (1947).

(5) Dodd, Cramer and Ward, to be published.