β-(4-Amino-3,5-diiodophenyl)-α-ethylpropionic Acid (Method B).—A solution of 87.4 g. of iodine monochloride in 150 ml. of 8 *N* hydrochloric acid and 300 ml. of chloroform was stirred and warmed to maintain a gentle reflux. A solution of β-(*p*-aminophenyl)-α-ethylpropionic acid in dilute hydrochloric acid prepared by acidifying the reduction mixture from 50 g. of α-ethyl-*p*-nitrocinnamic acid was added over a forty-minute period. After refluxing for forty minutes more the two-phase system was cooled and the layers separated. The aqueous portion was washed with chloroform. The combined organic layers were washed with two 150-ml. portions of water, two 120-ml. portions of 5% aqueous sodium hydrosulfite and again with water. The chloroform solution was dried over Drierite and diluted with petroleum ether. On standing 66.5 g. of the crude diiodo acid separated. After recrystallization from dilute methanol with the aid of Darco there was obtained 58.7 g. of pure product which melted at 114.2–115.1° (cor.).

Summary

1. The preparation of several β-(4-amino-3,5-diiodophenyl)-α-alkylpropionic acids has been described. These were obtained by iodination of the corresponding α-alkyl-β-(aminophenyl)-propionic acids which in turn were secured by catalytic reduction of the α-alkyl-*p*-nitrocinnamic acids.

2. α-Ethyl-β-(*m*-aminophenyl)-propionic acid gave a triiodo acid when treated with iodine monochloride.

RENSSELAER, NEW YORK RECEIVED MAY 10, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF LOUISVILLE, SCHOOL OF MEDICINE]

Reaction of Aliphatic Amines with 3-Nitro-4-chlorophenylarsonic Acid

BY ROBERT L. MCGEACHIN

In the study of the preparation of organic arsenicals of possible therapeutic use against protozoa and spirochetes, it has been found[1,2,3,4] that 3-nitro-4-chlorophenylarsonic and 3-nitro-4-bromophenylarsonic acids will react with certain amines and phenols to give 3-nitro-4-alkylaminophenylarsonic and 3-nitro-4-phenoxyphenylarsonic acids. There are a number of amines that have not been used in this type reaction, however, particularly the polyethylenepolyamines, so it was decided to investigate the preparation of these substituted 4-amino compounds.

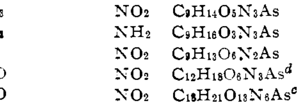
In all cases the products of these condensation reactions were yellow solids, soluble in dilute alkali giving blood-red solutions. The product obtained from tetraethylenepentamine, however, precipitated from solution as a heavy oil and resisted all attempts to crystallize it. For this reason it was isolated as the dipicrate. The products obtained from aminoethylethanolamine and aminoethylmorpholine were very soluble in water, probably due to the character of the side-chains, so that the yields here were low and the products were isolated as hydrates. In the condensation with dipropylenetriamine the product obtained constantly contained more arsenic than the theoretical amount for the product from one mole of amine and one mole of arsonic acid. Though several runs with increasing amounts of amine were tried, the desired product was not obtained.

The condensation of 2-amino-2-methyl-1-propanol with 3-nitro-4-chlorophenylarsonic acid did not proceed satisfactorily under standard conditions but was successful when an excess of the amine was heated with the arsonic acid at 160–170° for six hours. Apparently the amino group in 2-amino-2-methyl-1-propanol, which is linked to a tertiary carbon atom, is not reactive enough to allow condensation in aqueous solution at the lower temperatures. An attempt at a similar condensation using 2-amino-2-methyl-1,3-propanediol was unsuccessful.

Experimental

General Procedure for the Condensation of 3-Nitro-4-chlorophenylarsonic Acid with Amines in Aqueous Alkali.—Five grams of 3-nitro-4-chlorophenylarsonic acid, 15 ml. of 10% sodium hydroxide, 10 ml. of water and 3–5 ml. of the amine were heated, under reflux, at 135–140° for three to eight hours. The solution was cooled, made neutral to congo red with concd. hydrochloric acid. The product precipitated out as a yellow solid (except in the case of tetraethylenepentamine where the product was a thick brown oil). The product was redissolved in 5% sodium hydroxide, the solution charcoaled, filtered, and the yellow solid reprecipitated by addition of concd. hydrochloric acid to the congo red neutral point. The

TABLE I



R	R′	Formula	% Arsenic[a] Calcd.	% Arsenic[a] Found
$-CH_2CH_2NHCH_2CH_2NH_2$	NO_2	$C_{10}H_{17}O_5N_4As$	21.53	21.64
$-CH_2CH_2NHCH_2CH_2NH_2$	NH_2	$C_{10}H_{19}O_3N_4As$	23.57	23.48
$-(CH_2CH_2NH)_2CH_2CH_2NH_2$	NO_2	$C_{12}H_{22}O_5N_5As$	19.15	18.94
$-(CH_2CH_2NH)_2CH_2CH_2NH_2$	NH_2	$C_{12}H_{24}O_3N_5As$	20.77	20.98
$-(CH_2CH_2NH)_3CH_2CH_2NH_2$	NO_2	$C_{26}H_{33}O_{19}N_{12}As$[b]	8.41	8.60
$-CH_2CH_2NHCH_2CH_2OH$	NO_2	$C_{10}H_{16}O_6N_3As$[d]	20.41	20.29
$-CH_2CHNH_2CH_3$	NO_2	$C_9H_{14}O_5N_3As$	23.49	23.17
$-CH_2CHNH_2CH_3$	NH_2	$C_9H_{16}O_3N_3As$	25.95	25.61
$-CH_2CHOHCH_3$	NO_2	$C_9H_{13}O_6N_2As$	23.41	23.30
$-CH_2CH_2NC_4H_8O$	NO_2	$C_{12}H_{18}O_6N_3As$[d]	19.08	18.75
$-CH_2CH_2NC_4H_8O$	NO_2	$C_{18}H_{21}O_{13}N_6As$[c]	12.40	11.93
$-CH_2CH{=}CH_2$	NO_2	$C_9H_{11}O_5N_2As$	24.81	24.56
$-CH_2CH{=}CH_2$	NH_2	$C_9H_{13}O_3N_2As$	27.54	27.36
$-CH_2CHOHCH_2NH_2$	NO_2	$C_9H_{14}O_6N_3As$	22.37	21.98
$-C(CH_3)_2CH_2OH$	NO_2	$C_{10}H_{15}O_6N_2As$	22.45	22.39
$-C(CH_3)_2CH_2OH$	NH_2	$C_{10}H_{17}O_4N_2As$	24.67	24.17

[a] Arsenic was determined by a modification of the method of Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930). [b] Isolated as the dipicrate. [c] Isolated as the monopicrate. [d] Plus one molecule of water.

---

(1) Maclay and Hamilton, THIS JOURNAL, **54**, 3310 (1932).

(2) Fourneau and Funke, *Bull. soc. chim.*, **43**, 889 (1928).

(3) King, *J. Chem. Soc.*, 1094 (1927).

(4) Cragoe and Hamilton, THIS JOURNAL, **67**, 536 (1945).

product was dried overnight at 90° and then *in vacuo* over concd. sulfuric acid. Yield varied from 30–50%.

Condensation of 3-Nitro-4-chlorophenylarsonic Acid with 2-Amino-2-methyl-1-propanol.—Five grams of 3-nitro-4-chlorophenylarsonic acid and 10 cc. of 2-amino-2-methyl-1-propanol were heated, under reflux, on an oil-bath at 160–170° for six hours. During this time the mixture became almost black and was very viscous. The tarry residue was *dissolved* out in 50 ml. of hot water, the solution charcoaled, filtered and then made neutral to congo red with concd. hydrochloric acid. The yellow solid that separated was purified by reprecipitation from alkaline solution with concd. hydrochloric acid, dried at 90° in an oven overnight and then *in vacuo* over concd. sulfuric acid.

General Procedure for the Preparation of the 3-Amino Derivatives.—The nitro groups in the compounds described above were reduced to amino groups using the method of Jacobs, Heidelberger and Rolf.[5] The products obtained were light-red solids, which turned dark rapidly on exposure to air; yields, 10–30%.

Summary

The preparation of a number of 3-nitro-4-substituted aminophenylarsonic acids and the corresponding 3-amino compounds has been reported.

---

[5] Jacobs, Heidelberger and Rolf, THIS JOURNAL, **40**, 1581 (1918).

LOUISVILLE, KENTUCKY RECEIVED MAY 16, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGY AND VITAL ECONOMICS, UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY]

The Synthesis of 4,5-Diethyl-*o*-phenylenediamine through the Nitration of *o*-Diethylbenzene

BY JOHN P. LAMBOOY

Until relatively recently *o*-diethylbenzene has been available in such limited quantities that it has been used for synthetic purposes by no one but its discoverer. A. Voswinkel[1] first synthesized *o*-diethylbenzene in 1888 and along with it he reported the syntheses of barium *o*-diethylbenzenesulfonate, *o*-diethylbenzenesulfonamide and 1,2-diethyl-3,4,5,6-tetrabromobenzene. He was discouraged from more than preliminary efforts at nitration because of lack of starting material and the explosive nature of the product he obtained. The nature of this product as well as the position of the sulfonic acid group remain unknown.

Karabinos, Serijan and Gibbons[2] have introduced a method by which relatively large amounts of pure *o*-diethylbenzene are made available. Our need for compounds related to 4,5-diethyl-*o*-phenylenediamine made the prospect of obtaining it through successive nitrations of *o*-diethylbenzene attractive.

o-Diethylbenzene was nitrated and while it is probable that other products were produced, repeated vacuum fractional distillations yielded only one readily available product. This was shown by oxidation to the nitrophthalic acid to be exclusively 1,2-diethyl-4-nitrobenzene. The nitro compound was reduced catalytically to 3,4-diethylaniline. After carbethoxylation of the amino group the material was again subjected to nitration with the formation, for the most part, of 4,5-diethyl-2-nitrocarbethoxyaniline. Removal of the carbethoxy group to produce 4,5-diethyl-2-nitroaniline followed by deamination located the second nitro group by producing 1,2-diethyl-4-nitrobenzene. The 4,5-diethyl-2-nitroaniline was reduced catalytically to produce 4,5-diethyl-*o*-phenylenediamine.

Experimental

1,2-Diethyl-4-nitrobenzene.—A mixture of 175 ml. of fuming nitric acid (sp. gr. 1.59–1.60) and 87.5 ml. of glacial acetic acid was cooled to 10°. While this solution was stirred vigorously, 50 g. of *o*-diethylbenzene[3] was added at a rate to maintain the temperature between 10–20°. After the last of the *o*-diethylbenzene had been added the stirring was continued for forty-five minutes at the same temperature. The reaction mixture was then poured into one liter of ice-water. The crude nitro compounds were extracted with four 125-ml. portions of ether and the ether extract washed with three 50-ml. portions of water, with six 50-ml. portions (until the reaction has become alkaline) of 10% sodium hydroxide solution and again with three 50-ml. portions of water. The ether extract was dried over anhydrous sodium sulfate and the solvent removed. After preliminary studies the following procedure was used for the separation of the desired product. The combined nitration products obtained from the nitration of 422 g. of *o*-diethylbenzene were distilled from a Claisen flask at 10 mm. pressure. Only that material collected over the temperature range 130–150°, which amounted to 380 g. or 74% yield, was fractionated. The column used was 60 cm. long, 1.5 cm. i. d., and filled with small, single-turn glass helices. The fractionating head was designed so that any desired portion of the condensate could be returned to the column. The material was fractionated three consecutive times into three degree ranges between 120–141°. The material collected in the boiling point range 139–141° at 10 mm. weighed 230.5 g., which is 41% of the theoretical amount, and was identified as 1,2-diethyl-4-nitrobenzene; yellow oil, b. p. 139–141° at 10 mm. mercury pressure, d^{22} 1.0852, $n^{25}\text{D}$ 1.5440.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.22; H, 7.24; N, 8.10.

The 1,2-diethyl-4-nitrobenzene was characterized by permanganate and also nitric acid oxidation to the 4-nitrophthalic acid which was identified by the melting points of the acid, anhydride, the acid aniline salt and the anil. No evidence could be found for the presence of any of the 3-nitrophthalic acid.

3,4-Diethylaniline.—The 1,2-diethyl-4-nitrobenzene was reduced catalytically in a Parr hydrogenator at initial pressures of 60 p.s.i., using platinum oxide, platinum on zirconium or palladium on zirconium oxide. Seventeen and nine-tenths grams (0.1 mole) of 1,2-diethyl-4-nitrobenzene was dissolved in 150 ml. of absolute alcohol and

---

[1] Voswinkel, *Ber.*, **21**, 3499 (1888).

[2] Karabinos, Serijan and Gibbons, THIS JOURNAL, **68**, 2107 (1946).

[3] The *o*-diethylbenzene used in this study was generously furnished by the National Advisory Committee for Aeronautics.