[Contribution from the Department of Chemistry, Pomona College]

NITRATION OF *o*-ACETYLAMINOETHYLBENZENE[1]

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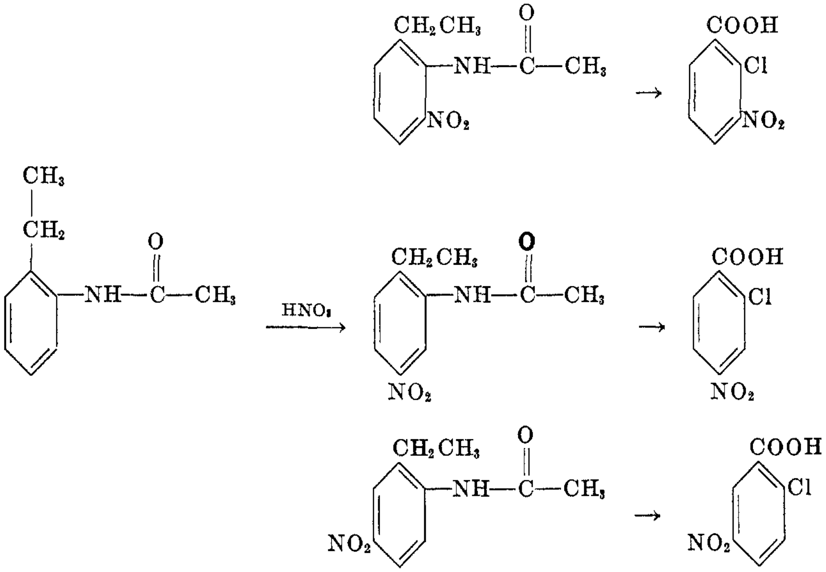
An intermediate needed for the synthesis of 2-mercapto-5-aminoethylbenzene is 2-amino-5-nitroethylbenzene. This paper describes its preparation by the nitration of *o*-acetylaminoethylbenzene, its proof of structure and that of two of its isomers. The products obtained in this nitration and their relation to known chlorobenzoic acids is illustrated in the following diagram:



Of the various nitrating agents investigated for the nitration of *o*-acetylaminoethylbenzene — nitric acid, nitric and sulfuric acids, nitric and acetic acids, nitric acid and acetic anhydride — fuming nitric and acetic acid gave the best yield of 5-nitro-2-acetylaminoethylbenzene. Carrying out this reaction at 50–55° gave about 80% crude 3-nitro- and 5-nitro-acetylaminoethylbenzene. The separation of these isomers is not easy. Attempts to separate the isomers by crystallization from common solvents gave poor separation and required many crystallizations. A useful method for separation of such isomers was developed by Witt and Utermann (1) and extended by Franzen and Helwert (2). These investigators found that many aromatic acetylamino compounds with an *o*-nitro group are soluble in cold aqueous-alcoholic potassium hydroxide solution while the corresponding *p*-isomers are insoluble. In a number of instances Witt's solution affords an easy and clean separation of such isomers,

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but in the present instance it was useless. The best procedure for the separation proved to be hydrolysis with sulfuric acid followed by steam-distillation of the acid solution. The 3-nitro-2-aminoethylbenzene steam-distilled slowly with small amounts of the 5-nitro-2-aminoethylbenzene. Pure 5-nitro-2-aminoethylbenzene could be obtained from the residue. To obtain pure 3-nitro-2-aminoethylbenzene from the crude material of the distillate it was necessary to chromatograph over alumina. It was observed that about 20% of the 5-nitro compound steam-distilled with the 3-nitro isomer.

Nitration of 2-acetylaminoethylbenzene in sulfuric acid solution, as would be expected, gave more of the 4-nitro isomer than the 3- or 5-nitro-2-acetylaminoethylbenzene. The 4-nitro-2-aminoethylbenzene steam-distilled along with the 3-nitro isomer, but the former could be easily separated from the latter because of its low water solubility.

EXPERIMENTAL[2]

o-Acetylaminoethylbenzene. To 60 g. of *o*-ethylaniline[3] was added 40 ml. of acetic acid and then 53 ml. of acetic anhydride. The mixture became quite hot and was held at the boiling point for 5 mins. After cooling somewhat it was poured into 750 ml. of cold water with stirring. The filtered, dried product melted at 110–111.5°. It was purified by heating to the boiling point with 100 ml. of ligroin and filtered while hot giving, on cooling, 72. g of product m.p. 111–111.8°. Paucksch reports m.p. of 110–112° (3).

Nitration of 2-acetylaminoethylbenzene in acetic acid. In 180 ml. of glacial acetic acid and 40 ml. of fuming nitric (*sp. gr.* 1.50) acid was dissolved 100 g. of 2-acetylaminoethylbenzene. The mixture was heated to 50–55° and held at this temperature while an additional 150 ml. fuming nitric acid was added in small portions. The mixture was stirred, carefully watched, and cooled from time to time in an ice-bath to keep the temperature below 55° in order to prevent the reaction from becoming too vigorous. About ½ hr. was required for the addition of the acid after which time the temperature was maintained at 55° for an additional 1½ hrs. Then it was poured into a large volume of ice-water, allowed to stand 1 hr., and filtered. The solid yellow product was suspended in bicarbonate solution to neutralize excess acid, filtered, and dried. Yield, 100 g. of a light yellow mixture of 3- and 5-nitro-2-acetylaminoethylbenzene.

Separation of 3- and 5-nitro-2-acetylaminoethylbenzene. The crude nitration product (100 g.) was refluxed for 2 hrs. with 250 ml. of water and 80 ml. of concentrated sulfuric acid. The resulting solution then was steam-distilled until no more oily product came over (40 liters of solution collected). The distillate was extracted with ether, the extracts were combined, and the ether was evaporated giving 27.8 g. of an orange oil. This oil then was chromatographed on 200 g. of alumina. The column was eluted with 100-ml. portions of solvent. The first two fractions, using 10% benzene-90% ligroin (30–60°), yielded on evaporation 1 g. of a yellow oil which did not solidify on seeding with 3-nitro-2-aminoethylbenzene, and was discarded. Elution with 90% ligroin-10% benzene (26 fractions) and then pure benzene (13 fractions) gave on evaporation 17.6 g. of 3-nitro-2-aminoethylbenzene, m.p. 29–31°. Elution with 50–50 ether-benzene (3 fractions) gave 0.5 g. of a mixture of 3-nitro- and 5-nitro-2-aminoethylbenzene. Elution with pure ether (8 fractions) gave 4 g. of 5-nitro-2-aminoethylbenzene, which after one recrystallization from benzene gave 3.65 g., m.p. 85–87°. The final two ether fractions contained 1.9 g. of dark liquid which did not crystallize on seeding or cooling.

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[2] The carbon-hydrogen analyses were made by C. F. Geiger, Chaffey College, Ontario, Calif.

[3] *o*-Ethylaniline was a gift of the Monsanto Chemical Company.

The aqueous layer remaining from the steam-distillation was decanted while hot from a dark oily mass. The dark oil was extracted three times with 200-ml. portions of boiling 10% sulfuric acid and these extracts were combined with the decanted aqueous layer. After cooling the combined fractions overnight in the ice box, orange crystals separated and were filtered, washed with bicarbonate solution, and then dried. Neutralization of the acid filtrate with bicarbonate gave an additional 1–2 g. Combining these fractions and recrystallizing from benzene gave 26.5 g. of light orange crystals m.p. 85–87°. This portion with that isolated by chromatography gave a total yield of 30.15 g. of 5-nitro-2-aminoethylbenzene.

Structure proof of 3-nitro-2-aminoethylbenzene. This substance was a bright orange solid of m.p. 31–32°.

Anal. Calc'd for $C_8H_{10}N_2O_2$: C, 57.80; H, 6.06.
Found: C, 57.71; H, 6.38.

The free amine was diazotized and converted with cuprous chloride to 2-chloro-3-nitroethylbenzene, a yellow liquid. This chloro compound then was oxidized to 2-chloro-3-nitrobenzoic acid with sodium dichromate in sulfuric acid. The resulting acid after recrystallization from water melted between 181 and 184°. Melting points of 181° (4) and 185° (5) have been reported.

2-Chloro-5-nitroethylbenzene. In 91 ml. of concentrated hydrochloric acid and 230 ml. of water was placed 42.5 g. of finely powdered 5-nitro-2-aminoethylbenzene. The mixture was cooled to below 5° and was diazotized with 25.6 g. of sodium nitrite in 45 ml. of water. The diazonium solution was poured into a solution of 61 g. of cuprous chloride in 230 ml. of hydrochloric acid and 75 ml. of water. After heating on the steam-bath for ½ hr. it was steam-distilled. The distillate was extracted with ether and the ether was washed with sodium hydroxide solution and then with water. After drying over calcium chloride the ether was evaporated and the product was distilled. Yield 36 g., b.p. 120°/7 mm. The product boiled at 263–265°/730 mm. with some decomposition.

Anal. Calc'd for $C_8H_8ClNO_2$: C, 51.76; H, 4.34.
Found: C, 51.90; H, 4.36.

Structure proof of 5-nitro-2-aminoethylbenzene. When pure this substance was bright yellow and melted at 86–87°.

Anal. Calc'd for $C_8H_{10}N_2O_2$: C, 57.80; H, 6.06.
Found: C, 57.94; H, 6.54.

A sample of the chloro compound made above was oxidized with potassium permanganate giving an acid of m.p. 165–167° which showed no depression when a mixture melting point was taken with an authentic sample of 2-chloro-5-nitrobenzoic acid.

3-Nitro-2-acetylaminoethylbenzene. 3-Nitro-2-aminoethylbenzene was converted to the acetyl derivative with acetic anhydride. After crystallization from benzene the product melted at 164–166°.

Anal. Calc'd for $C_{10}H_{12}N_2O_3$: C, 57.67; H, 5.81.
Found: C, 57.70; H, 6.07.

5-Nitro-2-acetylaminoethylbenzene. 5-Nitro-2-aminoethylbenzene was converted with acetic anhydride to the acetyl derivative and after crystallization from benzene the product melted at 154.5–156°.

Anal. Calc'd for $C_{10}H_{12}N_2O_3$: C, 57.67; H, 5.81.
Found: C, 57.99; H, 6.13.

Nitration of 2-acetylaminoethylbenzene in sulfuric acid. In 20 ml. of concentrated sulfuric acid was dissolved 10 g. of 2-acetylaminoethylbenzene. To this solution was added with cooling 10 ml. of concentrated nitric acid. During this addition the temperature was held between 0 and 5°. After the addition the mixture was allowed to rise to room temperature and then was poured over crushed ice. The resulting solid was filtered and dried. Yield, 11.8 g., m.p. 108–140°.

Separation of 4-nitro-2-aminoethylbenzene. The mixed amides from the above nitration were refluxed with 20 ml. of concentrated sulfuric acid and 40 ml. of water for 1½ hrs. and the resulting solution was steam-distilled until no more oil came over (15 liters of distillate collected). Cooling the distillate in the ice-box overnight caused 3.7 g. of yellow crystals of m.p. 60–61° to separate. Extraction of the filtrate with ether and evaporation of the ether gave 3.9 g. of a low-melting yellow solid which was apparently a mixture of 3- and 4-nitro-2-aminoethylbenzene. From the residue of the steam-distillation there was obtained 0.8 g. of 2-amino-5-nitroethylbenzene.

Structure proof of 4-nitro-2-aminoethylbenzene. This compound was best crystallized from benzene-ligroin or ethanol from which it separated as small yellow needles of m.p. 60.5–61.5°.

Anal. Calc'd for $C_8H_{10}N_2O_2$: C, 57.80; H, 6.06.
Found: C, 57.97; H, 6.26.

This amine was diazotized and converted with cuprous chloride to the corresponding chloro compound which was oxidized with potassium permanganate to an acid which, after recrystallization from water and then from benzene, melted at 139–142°. The melting point of 2-chloro-4-nitrobenzoic acid is reported as 142° (6).

4-Nitro-2-acetylaminoethylbenzene. 4-Nitro-2-aminoethylbenzene was converted to the acetyl derivative with acetic anhydride and then was recrystallized from benzene giving a product of m.p. 160.5–161.5°.

Anal. Calc'd for $C_{10}H_{12}N_2O_3$: C, 57.67; H, 5.81.
Found: C, 58.07; H, 6.09.

SUMMARY

The nitration of *o*-acetylaminoethylbenzene has been investigated and the structures of the three products resulting from this nitration have been established.

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