[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MISSISSIPPI STATE UNIVERSITY]

The *m*-Nitroazoxybenzenes

LYELL C. BEHR, EARL G. ALLEY, AND OSCAR LEVAND

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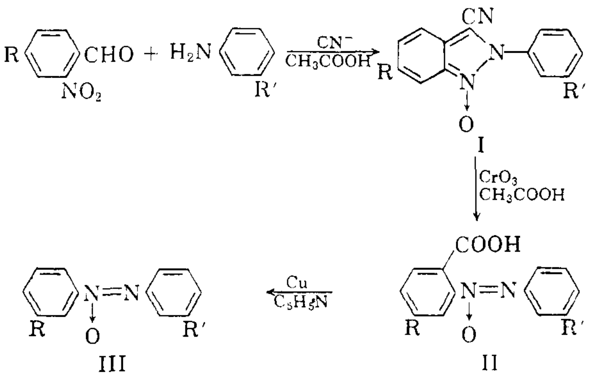
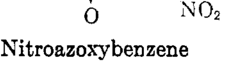
The position isomers 3-nitroazoxybenzene and 3'-nitroazoxybenzene have been synthesized by modification of a previously described method. No tendency for one isomer to rearrange to the other was observed. Both isomers yield the same compound, probably 3'-nitro-4-hydroxyazobenzene, when treated with sulfuric acid.

In continuation of our study of azoxy compounds, we have synthesized the two isomeric *m*-nitroazoxy benzenes by modification of a previously described procedure.[1] In the original sequence, the indazole oxide I was obtained by a several-step process. The Schiff base from the appropriate aldehyde and aniline was converted to its bisulfite addition product, which in turn was treated with sodium cyanide, which replaced the sulfonic acid group by the cyano group. The cyano compound sometimes yielded the indazole oxide spontaneously, but on other occasions had to be heated in solution with calcium carbon ate. In this work it was found possible to by-pass the intermediates and produce the indazole oxide directly by treatment of the aldehyde and aniline with sodium cyanide.[2,3] Thus, 3-cyano-2-(*m*-nitrophenyl)indazole 1-oxide (I. R = H; R' = NO_2) was produced in 54% yield by treating an acetic acid solution of *o*-nitrobenzaldehyde and *m*-nitroaniline with potassium cyanide. 3-Nitroazoxybenzene-2'-carboxylic acid (II. R = H; R' = NO_2) was obtained in 47% yield by treatment of the indazole oxide with chromium trioxide in acetic acid. Decarboxylation of the acid by cupric acetate in pyridine produced 3-nitroazoxybenzene (III. R = H; R' = NO_2) in 50% yield.

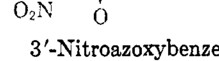


The position isomer 3'-nitroazoxybenzene was obtained similarly. Potassium cyanide added to a hot acetic acid solution of 2,4-dinitrobenzaldehyde and aniline furnished 3-cyano-2-phenyl-6-nitroindazole 1-oxide (I. R = NO_2; R' = H) in 36% yield. Oxidation yielded 5'-nitroazoxybenzene-2'-carboxylic acid (II. R = NO_2; R' = H) in 59% yield. The acid decarboxylated under the influence of copper powder and pyridine to give 3'-nitroazoxybenzene (III. R = NO_2, R' = H) in 59% yield.

Mixtures of the two *m*-nitroazoxybenzenes were obtained by the peracetic acid oxidation of *m*-nitroazobenzene[4] and by the condensation of *m*-dinitrobenzene and *N*-phenylhydroxylamine in the presence of alcoholic alkali.[5] In both methods of preparation, 3-nitroazoxybenzene predominated. Meisenheimer had previously separated the isomers by a tedious process of steam distillation, fractional recrystallization, or both.[5] In the earlier literature, the isomer which undergoes substitution more readily is referred to as the β-isomer. The lower-melting of the isomers (Meisenheimer gives 86–88°) qualified on this basis and was therefore referred to as β-*m*-nitroazoxybenzene. Meisenheimer reported 120–121° as the melting point of the α-isomer. In this work, the melting point of 3'-nitroazoxybenzene was found to be 91–91.5° and the 3-isomer, 121.5–122°. Thus it is established that the α-isomer is 3-nitroazoxybenzene, and the β-, the 3'-isomer. These structures would be predictable from a consideration of the comparative electron densities of the two rings and the fact that azoxybenzene undergoes substitution readily only in the 4-position.



3-Nitroazoxybenzene
α-Isomer
M.p. 121.5–122°



3'-Nitroazoxybenzene
β-Isomer
M.p. 91–91.5°

Attempts to improve the methods of separation used by Meisenheimer[5] were only moderately successful. Slow separation was effected by partition chromatography with a silicic acid column containing nitromethane, using a hexane solution saturated with nitromethane as the mobile solvent.

The *m*-nitroazoxybenzenes are of especial interest because it has been reported that 4'-nitroazoxybenzene is converted into 4-nitroazoxybenzene

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(1) L. C. Behr, *J. Am. Chem. Soc.*, **76**, 3672 (1954).

(2) G. Heller and G. Spielmeyer, *Ber.*, **58**, 834 (1925).

(3) K. Akashi, *Chem. Abstr.*, **43**, 7934 (1938); *Bull. Inst. Phys. Chem. Research (Tokyo)*, 20, 798 (1941).

(4) G. Leandri and A. Risalti, *Ann. Chim. (Rome)*, **44**, 1036 (1954).

(5) J. Meisenheimer, *Ber.*, **53**, 365 (1920).

by chromium trioxide in acetic acid.[6] No evidence for such a rearrangement of the *m*-isomer was found in this work.

A further point of interest with the two isomers is in connection with the Wallach transformation. In the archetype of this rearrangement, azoxybenzene is converted into 4-hydroxyazobenzene (among other products) by sulfuric acid.[7,8] When the two *m*-nitroazoxybenzenes were subjected to the conditions of the Wallach transformation, they yielded the same product, probably 4-hydroxy-3′-nitroazobenzene.

EXPERIMENTAL[9,10]

3-Cyano-2-(m-nitrophenyl)indazole 1-oxide. A solution of 5.0 g. of *o*-nitrobenzaldehyde and 4.6 g. of *m*-nitroaniline in 300 ml. of glacial acetic acid was obtained by gentle warning. It was cooled to 25° and 4.0 g. of potassium cyanide was added and the mixture allowed to stand for 12 hr. To the resulting dark brown solution there was added 200 ml. of water and the whole was placed in a refrigerator for 24 hr. The yellow precipitate which formed, after washing and drying, weighed 5.0 g. (54%) and melted at 205–208°. Recrystallization three times from ethanol raised the m.p. to 211–213°.

Anal. Calcd. for $C_{14}H_8N_4O_3$: C, 60.00; H, 2.88; N, 19.99. Found: C, 59.96; H, 2.78; N, 19.68.

3-Nitroazoxybenzene-2′-carboxylic acid. To a solution of 2.0 g. of crude 3-cyano-2-(*m*-nitrophenyl)indazole 1-oxide (m.p. 205–208°) in 75 ml. of glacial acetic acid (warmed to effect solution if necessary), there was added 1.5 g. of chromium trioxide in small portions. The solution was gently warmed until oxidation began and was then allowed to stand for 3 hr. Upon addition of the acetic acid solution to 225 ml. of cold water, a small amount of a yellow precipitate appeared. Removal by filtration was impractical, and the entire mixture was extracted with ether several times. The ether solution was washed by shaking with successive portions of cold water. The product was isolated by extraction of the ether with 5% aqueous sodium hydroxide and acidification with 15% phosphoric acid. The yellow acid weighed 1.0 g. (47%) and after recrystallization from benzene melted at 183–184.5°.

Anal. Calcd. for $C_{13}H_9N_3O_5$: C, 54.36; H, 3.15; N, 14.63. Found: C, 54.30; H, 3.56; N, 14.43.

3-Nitroazoxybenzene. A few crystals of copper acetate were added to a solution of 0.5 g. of crude 3-nitroazoxybenzene-2′-carboxylic acid dissolved in pyridine. The mixture was heated for 4.5 hr. at reflux, cooled, and diluted with 100 ml. of ether. It was washed successively four times with 10% hydrochloric acid, once with water, four times with 5% aqueous sodium hydroxide, and again with water. The ether solution was dried with anhydrous magnesium sulfate and the ether evaporated. A cream-colored solid remained which was recrystallized from ethanol. It melted at 121.5–122°. Meisenheimer[5] gives m.p. 120–121°.

Anal. Calcd. for $C_{12}H_9N_3O_3$: C, 59.25; H, 3.73; N, 17.28. Found: C, 59.06; H, 3.80; N, 17.60.

2,4-Dinitrobenzaldehyde.[11] Several methods were tried for the preparation of this aldehyde. The nitrone method of Kröhnke proved to be most reliable[12]; it is described, with some modifications, below.

(a) *2,4-Dinitrobenzyl bromide.* A solution of 15 ml. of bromine and 50 g. of 2,4-dinitrotoluene in 250 ml. of carbon tetrachloride was irradiated with a sun lamp and heated near the boiling point for 4.5 hr. The solution was cooled and filtered and the carbon tetrachloride evaporated with the aid of reduced pressure. The residual brown lachrymatory oil was used without further purification.

(b) *N-(2,4-Dinitrobenzyl)pyridinium bromide.* The dinitrobenzyl bromide (78 g.) was dissolved in a mixture of 150 ml. of pyridine and 260 ml. of ethanol and heated on a steam bath for 70 min. Cooling precipitated the salt, additional amounts of which could be obtained by adding diethyl ether to the filtrate.

(c) *N-(p-Dimethylaminophenyl)-α-2,4-dinitrophenyl nitrone.* A mixture of 22.0 g. of finely pulverized *N*,*N*-dimethyl-*p*-nitrosoaniline hydrochloride,[13] 8.0 g. of anhydrous sodium carbonate, and 300 ml. of ethanol was heated at the boiling point for 15 min. and filtered hot to remove sodium chloride and unchanged sodium carbonate. The filtrate, containing free *p*-nitrosodimethylaniline, was cooled and added to a solution of 36.0 g. of *N*-(2,4-dinitrobenzyl)pyridinium bromide in 300 ml. of ethanol. Piperidine (12 g.) was added gradually to the mixture with continual stirring. The green solution became reddish brown. It was allowed to stand for 1 hr. and was then poured into 2 l. of water which precipitated a mushy solid. It was removed by filtration and washed with water until the washings were colorless. The nitrone can be used without further purification.

(d) *2,4-Dinitrobenzaldehyde.* To 300 ml. of the still hot solution obtained by mixing equal volumes of sulfuric acid and water, there was added 30 g. of the nitrone. The mixture was shaken for 15 min., cooled in an ice bath, and filtered. The solid was treated again with sulfuric acid as described. A third treatment was found to be necessary if the product was dark. In various runs a total of 62.7 g. of 2,4-dinitrobenzaldehyde, m.p. 68–69°, was obtained from 200 g. of 2,4-dinitrotoluene. The yield, based upon 2,4-dinitrotoluene, was 29%.

3-Cyano-2-phenyl-6-nitroindazole 1-oxide. To a solution of 20.0 of g. 2,4-dinitrobenzaldehyde in 400 ml. of glacial acetic acid there was added 20.0 g. of aniline. A yellow precipitate appeared which redissolved on heating. Twenty grams of sodium cyanide was added in small portions and the mixture heated for 5 min. Three grams of acetic anhydride was then added and an additional 20.0 g. of sodium cyanide in portions. After 5 min. more of heating, the indazole oxide precipitated when the acetic acid solution was poured into 3 l. of water. The product was purified by leaching with 500 ml. of hot methanol and cooling. The yield of yellow 3-cyano-2-phenyl-6-nitroindazole 1-oxide melting at 235–237° was 10.2 g. (36%). A purer product (m.p. 242–243°) was obtained after three recrystallizations from methanol.

Anal. Calcd. for $C_{14}H_8N_4O_3$: C, 60.00; H, 2.88; N, 19.99. Found: C, 59.95; H, 2.92; N, 20.12.

5′-Nitroazoxybenzene-2′-carboxylic acid. A solution of 4 g. of 3-cyano-2-phenyl-6-nitroindazole 1-oxide, m.p. 235–237°, in 400 ml. of glacial acetic acid was prepared by heating. The solution was removed from the heat and 4 g. of chromium trioxide added during 10 min. When the reaction had slackened, the solution was heated for an additional 20 min.

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(6) A. Angeli and B. Valori, *Atti accad. naz. Lincei, Rend., Classe sci. fis. mat. e nat.*, [5], **21**, I, 729 (1912).

(7) O. Wallach and L. Belli, *Ber.*, **13**, 525 (1880).

(8) O. Wallach and L. Kiepenheur, *Ber.*, **14**, 2617 (1881).

(9) Melting points are uncorrected.

(10) Microanalyses by Micro-Tech Laboratories, Skokie, Ill.

(11) Several commercial samples of 2,4-dinitrobenzaldehyde were found actually to be 2,4-dinitrotoluene. The confusion apparently arises because the two compounds have approximately the same melting point (69°) and because the toluene is ordinarily used to prepare the aldehyde. It is strongly recommended that samples of 2,4-dinitrobenzaldehyde be checked either by a mixture melting point determination or by infrared examination. The aldehyde shows intense absorption at about 5.8 μ (1650 cm.$^{-1}$); the toluene shows none.

(12) F. Kröhnke and H. Schmeiss, *Ber.*, **72**, 440 (1939).

(13) G. M. Bennett and E. V. Bell, *Org. Syntheses*, **Coll. Vol. II**, 223 (1943).

at the boiling point and poured into a 3-l. beaker half full of crushed ice. After drying the precipitate was taken up in ether and the ether solution extracted three times with 5% sodium hydroxide solution. The sodium salt of the acid may precipitate but it can be dissolved by the addition of water. The combined alkaline extracts were acidified with 10% phosphoric acid to precipitate the azoxy acid. Additional amounts of the product can be obtained by extracting the filtrate from the oxidation with ether and isolating the acid as described. The total yield of crude product, 5′-nitroazoxybenzene-2′-carboxylic acid was 2.4 g. (59%), m.p. 165–175°. Satisfactory results were obtained using the crude acid in the decarboxylation reaction. Purification for analysis was effected by chromatography with a silicic acid column and 90% benzene-10% ether as the solvent. The pure acid melts at 191.5–193°.

Anal. Calcd. for $C_{13}H_9N_3O_5$: C, 54.36; H, 3.15; N, 14.63. Found: C, 54.30; H, 3.30; N, 14.43.

3′-Nitroazoxybenzene. To a solution of 0.2 g. of 5′-nitroazoxybenzene-2′-carboxylic acid in 20 ml. of pyridine there was added 0.5 g. of copper powder. The mixture was heated under reflux 14 hr., cooled, and the solution decanted from the copper. The solution was diluted with 100 ml. of ether and washed four times with 50-ml. portions of 10% hydrochloric acid, once with water, four times with 10% aqueous sodium hydroxide, and again with water. The solution was dried with anhydrous magnesium sulfate, filtered, and the ether evaporated. The residue was crystallized from hexane to yield 0.1 g. (59%) of yellow crystals, m.p. 91–91.5°. Meisenheimer[5] gives 86–88°.

Mixed m-nitroazoxybenzenes. Mixtures of the two isomers resulted when *m*-dinitrobenzene reacted with *N*-phenylhydroxylamine in the presence of alcoholic potassium hydroxide[5] and by the peracetic acid oxidation of *m*-nitroazobenzene.[4] The isomers in both instances were separated by chromatography with a silicic acid column saturated with nitromethane, using hexane saturated with nitromethane as the mobile solvent. Though quantitative data were not obtained, 3-nitroazoxybenzene was formed in the larger quantity.

Wallach transformation. A solution of 0.2 g. of 3-nitroazoxybenzene in 25 ml. of 82% sulfuric acid was heated near the boiling point for 15 min., at which time the solution gave no precipitate when a drop was added to 10% sodium hydroxide solution. The sulfuric acid solution was diluted and the resultant precipitate taken up in ether. The ether solution was extracted once with 2% sodium hydroxide and twice with 10% sodium hydroxide. The combined alkaline extracts were added to 25% phosphoric acid. The orange product melted at 159–161° and weighed 0.11 g. (65%).

When 3′-nitroazoxybenzene was treated similarly, the product melted at 161–162° and weighed 0.13 g. (77%). A mixture of the two products melted at 159–160.5°. They showed essentially the same infrared spectra. The substance is probably 4-hydroxy-3′-nitroazobenzene, which melts[14] at 159°, and would be an expected product of the rearrangement.

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STATE COLLEGE, MISS.

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[14] A. W. Smith and C . E. Boord, *J. Am. Chem. Soc.* **44**, 1451 (1922).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, AMERICAN UNIVERSITY OF BEIRUT]

Pentaerythritol Derivatives. V.[1] Preparation of Diethers of Pentaerythritol by Reduction of Acetals and Ketals[2]

ABDUL-RAHMAN ABDUN-NUR AND COSTAS H. ISSIDORIDES[3]

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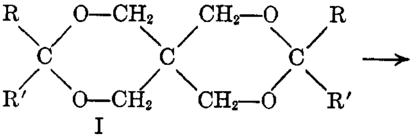
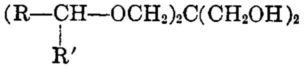
Diethers of pentaerythritol can be prepared in good yield from the corresponding cyclic diacetals and diketals by reduction with lithium aluminum hydride–boron fluoride etherate (or aluminum chloride). An improved method is described for the preparation of 2,6-dioxaspiro[3.3]heptane from pentaerythrityl dibromide.

Eliel and Rerick have described the reduction of acetals and ketals to ethers by lithium aluminum hydride–aluminum chloride ($LAH-AlCl_3$),[4] a method which was later extended to cyclic acetals, ketals and their hemithio analogs.[5]

As pentaerythritol forms cyclic diacetals and diketals readily, reduction by the "mixed hydride" offers a convenient route to the difficultly accessible diethers II.



I



$$(R\text{—}\underset{\displaystyle R'}{\underset{|}{CH}}\text{—}OCH_2)_2C(CH_2OH)_2$$

II

a. R = phenyl
   R′ = H
b. R, R′ = pentamethylene
c. R, R′ = tetramethylene
d. R = methyl
   R′ = H
e. R=R′ = H

During this study we have used lithium aluminum hydride–aluminum chloride as well as lithium aluminum hydride–boron trifluoride etherate (LAH $-BF_3$) as reducing agents, and found the latter to

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[1] For previous paper in this series see R. F. Nassar and C. H. Issidorides, *J. Org. Chem.*, **24**, 1832 (1959).

[2] Abstracted in part from the M.S. thesis of A. R. Abdun-Nur, American University of Beirut, June 1961.

[3] To whom requests for reprints should be addressed.

[4] E. L. Eliel and M. Rerick, *J. Org. Chem.*, **23**, 1088 (1958).

[5] E. L. Eliel and V. G. Badding, *J. Am. Chem. Soc.*, **81**, 6087 (1959).