Acta Chemica Scandinavica B 28 (1974) 645—649

Reactions of Nitrobenzyl Alcohol under Acidic Conditions. Possibilities of Intramolecular Nucleophilic Participation by the Nitro Group

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o-Nitrobenzyl alcohol was refluxed in toluene under acidic conditions. Three products were obtained: di-(*o*-nitrobenzyl) azoxybenzene-*o*,*o*′-dicarboxylate (*2*), 6*H*,12*H*-indazolo[2,1-*a*]indazole-6,12-dione (*3*), and benzidine-*m*,*m*′-dicarboxylic acid (*5*). *p*-Nitrobenzyl alcohol scarcely reacted under these reaction conditions. Possible reaction paths are discussed.

The study of the reactions of *ortho*-substituted nitrobenzene derivatives has revealed interesting interactions between the nitro group and the *ortho*-substituent.[1] These interactions often result in a reduction of the nitro group and an oxidation of the *ortho*-substituent.

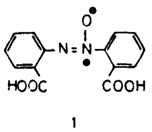
We have earlier studied the reactions between the nitro and methyl group in *o*-nitrotoluene under a variety of conditions,[2,3] and also the photochemical interaction between the nitro and hydroxyl group in 2-(*o*-nitrophenyl)ethanol.[4]

In continuation of our work on nitro group chemistry, some reactions of *o*-nitrobenzyl alcohol have been studied. Reactions under acidic conditions were believed to be particularly interesting. In the presence of strong acid, protonation of the hydroxyl group could be expected. However, the leaving of the water molecule would probably be assisted by the *o*-nitro group, thus providing interesting opportunities for reactions between the nitro group and the benzylic carbon atom.

The assistance by the nitro group was anticipated from the work of Noyce, Hartter and Miles [5] on acidic dehydration of 1,2-diarylethanols. They showed the reaction of 1-(*p*-nitrophenyl)-2-phenylethanol to be very slow, and indicated that this compound existed in solution as the protonated species. Further, the work of Spence and Tennant [6] and Sword [7] indicated that an *o*-nitro group assisted the ring opening of protonated epoxides.

o-Nitrobenzyl alcohol was accordingly treated with *p*-toluenesulfonic acid in refluxing toluene. After a few hours, the *o*-nitrobenzyl alcohol was consumed and three main products were obtained. Two of these were neutral and the third was slightly acidic. The structures of these substances were elucidated, mainly by spectroscopic methods.

One of the neutral compounds had an IR spectrum indicating ester groups (1725 and 1740 cm^{-1} together with a band at 1260 cm^{-1}) and nitro groups (1525 and 1340 cm^{-1}) to be present, but no NH or OH groups. The NMR spectrum suggested the compound to contain benzylic protons. The mass spectrum indicated an elemental formula of $C_{28}H_{24}N_4O_9$. The high molecular weight, the two ester carbonyls, and the benzylic protons would be explained by a dicarboxylic acid esterified with *o*-nitrobenzyl alcohol. The elemental formula of such an acid would be $(C_{12}H_8N_2O)(COOH)_2$. One possible structure would be azoxybenzene-*o*,*o*′-dicarboxylic acid (*1*). Saponification of the isolated compound gave an dicarboxylic acid identical to *1*, [10] together with *o*-nitrobenzyl alcohol as the neutral product. The structure of the isolated compound was thus the di-*o*-nitrobenzyl ester of azoxybenzene-*o*,*o*′-dicarboxylic acid (*2*).



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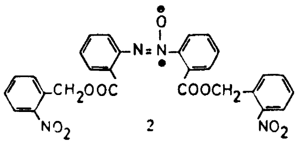

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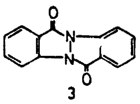
The other neutral compound gave an IR spectrum indicating carbonyl groups (1690 cm^{-1}) but no NH, OH, or NO_2 groups to be present in the molecule. The mass spectrum indicated an elemental formula of $C_{14}H_8N_2O_2$. The structure *3* (6*H*,12*H*-indazolo[2,1-*a*]indazole-6,12-dione) was in accordance with these data, and the isolated compound was identical to an authentic sample of *3*.[8]



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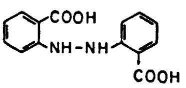
The isolated acidic product was almost insoluble in neutral solvents, and gave a rather indistinct melting point. The IR spectrum suggested the product to contain primary amino groups together with carboxylic acid groups.

The structure of *2* showed the formation of a compound with a nitrogen-nitrogen bridge between the aromatic rings. One could thus imagine that compounds with more reduced nitrogen-nitrogen bridges could have been formed, for instance of the hydrazobenzene type. Under the acidic reaction conditions, a hydrazobenzene would probably undergo a benzidine rearrangement to give products with primary amino groups. From these considerations and from the IR spectrum, a possible structure for the acidic product would be benzidine-*m*,*m*′-dicarboxylic acid (*5*). Reaction of hydrazobenzene-*o*,*o*′-dicarboxylic acid (*4*) with *p*-toluenesulfonic acid gave a product identical to the one isolated from *o*-nitrobenzyl alcohol. This path of formation, the IR spectrum and m.p. properties [9] identified the compound as *5*, and also indicated that *4* was the primary product in the reaction of *o*-nitrobenzyl alcohol.



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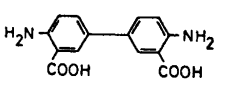

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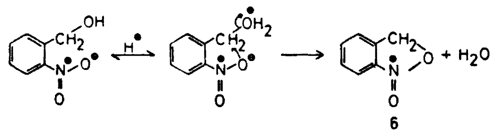
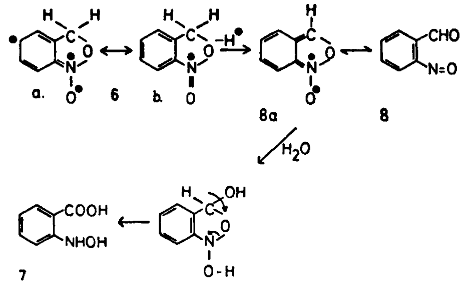
The structures of the isolated compounds (*2*, *3*, *5*) from the reaction of *o*-nitrobenzyl alcohol show a variety of reductions and oxidations to have taken place. From the products, it is obvious that intermolecular reactions have taken place, as neither *2*, *3* nor *5* are at the same oxidation stage as *o*-nitrobenzyl alcohol. However, the reactions have probably not taken place solely by intermolecular processes, as *p*-nitrobenzyl alcohol was shown to react only with difficulty under the conditions used in the reaction of *o*-nitrobenzyl alcohol. The initial reaction of *o*-nitrobenzyl alcohol is therefore probably of intramolecular nature.

An intramolecular reaction might have started with a protonation of the hydroxyl group, followed by internal substitution reaction to give the cyclic intermediate *6*. Similar intermediates have been postulated both in the ring opening of *o*-nitrophenylethylene oxides,[6,7] in the reactions of *o*-nitrobenzhydrol,[11] and in the solvolysis of *o*-nitrobenzhydryl bromide.[12] The intermediate *6* may then undergo internal electron shifts, for instance by the reactions postulated in Scheme 1, to produce *o*-hydroxylaminobenzoic acid (*7*) and *o*-nitrosobenzaldehyde (*8*) or the cyclic form *8a*. Compounds *7* and *8* would probably be rather unstable under the reaction conditions, both towards oxidations and reductions, and towards condensation reactions. From the resonance formula *a* of





Scheme 1.

compound *6*, a nucleophilic attack on the aromatic ring seemed possible. Such attacks have indeed been observed with analogous structures when nucleophiles like chloride ions have been present in the reaction.[6,7,11,12] In the present reaction, with *p*-tosylate ions as the predominant nucleophile, such attack was neither expected nor found.

It should also be noticed that bimolecular formulas analogous to *6* can be written, and that the reaction of *o*-nitrobenzyl alcohol is not proven to be intramolecular.

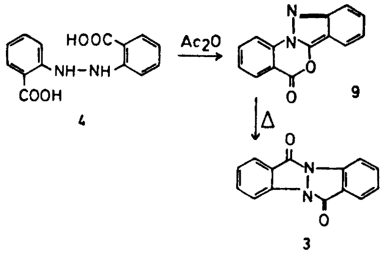
By further oxidation-reductions of compounds *7* and *8*, molecules with different combinations of oxidized benzylic carbon and reduced nitrogen atoms would be obtained, and by condensations of these molecules compounds *2*, *3*, and *5* could arise.

Benzidine-*m*,*m'*-dicarboxylic acid (*5*) is believed to originate from hydrazobenzene-*o*,*o'*-dicarboxylic acid (*4*). Both compounds *2* and *4* have been produced by condensation reactions between two nitrogen atoms. Azoxy- and hydrazobenzenes are interconvertible by various reduction and oxidation reactions.[13] If such interconversions have been important in their formation in the present reactions, or if they have been partly or solely formed by condensation reactions is not known at present.

Condensation products from the reduction of nitro compounds are usually formed under basic and not under acidic conditions.[13] However, the non-polar solvent used in the present reaction may explain the observed condensation reactions. In toluene, the protonation of the amines and hydroxylamines formed would be slow as compared to the reaction in more polar (*e.g.* aqueous) solvents, and the amines and hydroxylamines would therefore be more accessible to condensation reactions.

Of the two dicarboxylic acids formed by the reaction (*1*,*5*), only azoxybenzene-*o*,*o'*-dicarboxylic acid (*1*) was esterified by *o*-nitrobenzyl alcohol. Benzidine-*m*,*m'*-dicarboxylic acid (*5*) is hardly soluble in toluene and was therefore probably removed from the reaction before esterification could take place.

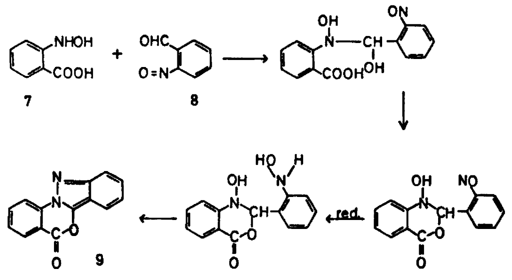
Several formation paths for compound *3* may be envisaged. Formally, the substance could be formed by condensation of *o*-hydroxylaminobenzoic acid (*7*) with *o*-aminobenzoic acid. However, not suprisingly, an experiment showed *o*-aminobenzoic acid to be precipitated as the *p*-toluenesulfonate under the reaction conditions, and substances *2* and *3* to be formed in the same ratio as when *o*-aminobenzoic acid was not added to the reaction. Compound *3* has earlier been made by heating of hydrazobenzene-*o*,*o'*-dicarboxylic acid (*4*) in acetic anhydride, followed by heating of the initially formed lactone (*9*).[8,14]



Under the present reaction conditions, hydrazobenzene-*o*,*o'*-dicarboxylic acid (*4*) gave benzidine-*m*,*m'*-dicarboxylic acid (*5*) as the major reaction product, with only traces of a substance which could have been *3*. The major part of *3* is therefore not formed from *4*.

However, lactone *9* was transformed to compound *3* when refluxed with *p*-toluenesulfonic acid in toluene, and the IR spectrum of a reaction mixture from *o*-nitrobenzyl alcohol indicated traces of lactone *9* to be present. The results thus indicate that compound *3* may have been formed from lactone *9*, but that hydrazobenzene *o*,*o'*-dicarboxylic acid (*4*) was not a precursor for *9*.

One possibility for the formation of *9* would be the reaction between one molecule of *o*-hydroxylaminobenzoic acid (*7*) and one of *o*-nitrosobenzaldehyde (*8*) (or the cyclic form *8*a).



Further investigations are necessary to determine the exact path of formation of the products *2*, *3* and *5*. Two points seem nevertheless to be clear from the present investigation. First, as *p*-nitrobenzyl alcohol reacted only slightly under the applied conditions, the *ortho* position of the nitro and hydroxymethyl groups is necessary for the reaction. Second, intermolecular reactions take place as the products are at different oxidation stages from *o*-nitrobenzyl alcohol.

One hypothesis fitting these two points is the one presented above: The reaction starts as an intramolecular reaction resulting in products with oxidized carbon atom and reduced nitrogen atom. Further intermolecular red-ox and condensation reactions then give the isolated products.

EXPERIMENTAL

The IR spectra were recorded on a Perkin-Elmer infrared spectrophotometer, Model 457. NMR spectra were recorded on a Varian A 60 spectrometer with TMS as in internal standard. The chemical shifts are given in δ-units. Mass spectra were recorded on an A.E.I. M.S. 902 mass spectrometer. The elemental formulas were obtained by peak matchings which gave *m/e* within ± 0.0006 mass units from the calculated values. Melting points are uncorrected.

Reaction of o-*nitrobenzyl alcohol with* p-*toluenesulfonic acid.* *p*-Toluenesulfonic acid (0.6 g) and toluene (*p.a.*) (35 ml) were refluxed with a water separator at the condenser. A toluene/water mixture (5 ml) was separated. *o*-Nitrobenzyl alcohol (0.3 g) was added to the solution and the mixture refluxed for 5 h. TLC indicated *o*-nitrobenzyl alcohol to diminish and two new compounds with $R_F > R_F$-nitrobenzyl alcohol and one with $R_F = 0$ (eluted with 10 % ether/chloroform) to be formed. After 5 h all of the nitrobenzyl alcohol had reacted. The mixture was left at 25 °C overnight and then filtered. The toluene solution contained 0.2 g which TLC indicated to consist of the two compounds with $R_F > R_F$-nitrobenzyl alcohol. Compound *3* (15 mg) crystallized from a chloroform solution of this mixture.

Attempts to separate the two compounds by dry column chromatography on silica gel or alumina were unsuccessful, and compound *2* was finally obtained pure by crystallization from chloroform/light petroleum. The 200 mg obtained from the toluene solution was estimated by TLC chromatography to contain *ca.* 150 mg of di-(*o*-nitrobenzyl)*o*,*o*′-azoxybenzene dicarboxylate (*2*) and *ca.* 50 mg of 6*H*,12*H*-indazolo[2,1-*a*]indazole-6,12-dione (*3*). More accurate estimations have not yet been possible.

Di-(*o*-nitrobenzyl)*o*,*o*′-azoxybenzenedicarboxylate (*2*) had m.p. 177 – 178 °C, IR (KBr): 1740, 1725, 1525, 1480, 1340, 1260, 1140, 1090, 1080, 865, 795, 770, 760, 740, 730, 720 cm^{-1}. NMR ($CDCl_3$): 16 protons with signals 7.15 – 8.20 (complex), 4 protons at 5.7 (singlet). Mass spectrum; *m/e* 556.1233 (2 %, $C_{28}H_{20}N_4O_9$), 540.1278 (2 %, $C_{28}H_{20}N_4O_8$), 420.0833 (2 %, $C_{21}H_{14}N_3O_7$), 404.0877 (2 %, $C_{21}H_{14}N_3O_6$), 376.0931 (50 %, $C_{20}H_{14}N_3O_5$), 136 (55 %), 78 (100 %).

Compound *3* had m.p. 296 – 297 °C (lit.[8] 300 – 300.8 °C), IR (KBr): 1690, 1620, 1480, 1470, 1365, 1320, 1210, 1150, 1130, 755, 670 cm^{-1}. Mass spectrum, *m/e* 236.0587 (100 %, $C_{14}H_8N_2O_2$), 208.0635 (21 %, $C_{13}H_8N_2O$, loss of CO from *m/e* 236 verified by m^* 183.32), 179.0612 (9 %, $C_{12}H_7N_2$), 118.0295 (11 %, C_7H_4NO).

In a new experiment, *o*-nitrobenzyl alcohol (8 g) and *p*-toluenesulfonic acid (16 g) in toluene (800 ml) were refluxed for 5 h. Substances *2* and *3* were obtained by crystallization of the toluene dissolved material (8.6 g).

The black material not dissolved in toluene was washed with water to remove *p*-toluenesulfonic acid. The undissolved material (1.3 g) had IR almost identical to benzidine-*m*,*m*-dicarboxylic acid (see below) and m.p. at 265 °C when the m.p. tube was put into the preheated (250 °C) m.p. apparatus. 1.1 g of the solid was dissolved on extraction with ethanol (2 × 100 ml) and 0.13 g of black powder remained. The undissolved black powder had an undistinguished IR and gave no indications of melting below 320 °C. This material is believed to be a polymer. The substance dissolved in ethanol (1.1 g) was refluxed with chloroform (25 ml), 0.25 g of it was dissolved. The undissolved material (0.8 g, 11 %) had IR and m.p. behaviour identical with benzidine-*m*,*m*′-dicarboxylic acid (see below). The chloroform-dissolved material consisted of at least seven compounds as judged by TLC. Two of these were compounds *2* and *3*, and one may have been azobenzene carboxylic acid. The chloroform fraction was not investigated further.

*Saponification of di-(*o-*nitrobenzyl)* o,o′-*azoxybenzenedicarboxylate* (*2*). *2* (50 mg) from the reaction of *o*-nitrobenzyl alcohol was dispersed in ethanol (10 ml) and sodium hydroxide (1 M, 1 ml) added. After stirring overnight at 25 °C, the reaction was complete. The neutral product (15 mg) was identical with *o*-nitrobenzyl alcohol and the acidic product (15 mg) with *o*,*o*′-azoxybenzenedicarboxylic acid m.p. 250 °C (decomp.) and IR (KBr): 3500 – 2000, 1690, 1610, 1490, 1420, 1310, 1290, 1280, 1090, 940, 800, 770, 755, 660, cm^{-1}. Mass spectrum *m/e*: 286.0584 (1 %, $C_{14}H_{10}N_2O_5$), 270.0636 (2 %, $C_{14}H_{10}N_2O_4$), 241.0616 (100 %, $C_{13}H_9N_2O_3$), 197.0709 (13 %, $C_{12}H_9N_2O$), 165 (13 %), 159 (13 %), 121 (68 %), 115 (29 %), 93 (58 %), 77 (32 %), 65 (65 %).

Reaction of o*-nitrobenzyl alcohol in the presence of* o*-aminobenzoic acid.* *o*-Nitrobenzyl alcohol (0.3 g), *o*-aminobenzoic acid (0.3 g), and *p*-toluenesulfonic acid (0.6 g) were refluxed in toluene (30 ml) for 5 h. A precipitate formed at once, and TLC indicated the reaction to be slower than the one without *o*-aminobenzoic acid; the ratio between products *2* and *3* was the same as before.

*Reaction of hydrazobenzene-*o,o′*-dicarboxylic acid* (*4*). *4* (1 g) and *p*-toluenesulfonic acid (2 g) were refluxed in toluene (100 ml) for 3 h. The toluene phase contained 15 mg which TLC indicated to consist partly of compound *3*. The crystalline part of the reaction mixture was washed with water to remove *p*-toluenesulfonic acid, and the residue dried. This compound had IR (KBr): 3510, 3400, 3400 – 2700, 1680, 1630, 1590, 1560, 1240, 815, 690 cm^{-1} and m.p. 275 °C when the m.p. tube was put into a preheated (250 °C) m.p. apparatus.

The result from the reaction was the same when *4* (0.1 g) was dissolved in refluxing toluene (100 ml) and added to a refluxing solution of *p*-toluenesulfonic acid (100 mg) in toluene (100 ml) and then refluxed for 3½ h.

Reaction of p*-nitrobenzyl alcohol with* p*-toluenesulfonic acid.* *p*-Toluenesulfonic acid (2 g) in toluene (100 ml) was refluxed with a water separator at the condenser. A toluene/water mixture (5 ml) was removed, and *p*-nitrobenzyl alcohol (1 g) added. The mixture was refluxed for 5 h. TLC of the product indicated only a slight reaction with trace of one product with $R_F > R_F$-nitrobenzyl alcohol to have been formed.

Reaction of the lactone 9. *p*-Toluenesulfonic acid (140 mg) and *9* [8] (25 mg) were refluxed in toluene (7 ml) for 5 h. IR and TLC showed *9* to have been transformed almost completely to *3*.

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Received August 23, 1973.