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Intramolecular Participation by the Nitro Group. Reactions of Nitrophenylethanols under Acidic Conditions

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The reaction of 2-(*o*-nitrophenyl)-1-phenylethanol, 1-(*p*-nitrophenyl)-2-phenylethanol, and 1-(*o*-nitrophenyl)-2-phenylethanol (*1*) were studied under acidic conditions. The two first alcohols gave *o*-nitrostilbene (95 % *trans*, 5 % *trans*, 5 % *cis*) and *p*-nitrostilbene (91 % *trans*, 9 % *cis*), respectively. 1-(*o*-Nitrophenyl)-2-phenylethanol gave *o*-nitrostilbene, 50 % *cis* and 50 % *trans*, together with 3-benzoylanthranil (*3*) and traces of 2-phenylisatogen (*4*). The results from *1* may be explained by neighbouring group participation of the *o*-nitro group in the reaction.

The interactions between a nitro group and an *ortho* benzyl carbon in aromatic systems have interested us for some time.[1] Recently, the reaction between the nitro group and the hydroxymethyl group in *o*-nitrobenzyl alcohol was reported.[2] The results from that reaction and from several others [3] can be explained by nucleophilic attack of the nitro group oxygens on the *ortho* carbon atom.

We have now studied such interactions further. 1-(*o*-Nitrophenyl)-2-phenylethanol (*1*) was refluxed in toluene with *p*-toluenesulfonic acid, in analogy with the reaction of *o*-nitrobenzyl alcohol.[2] Two substances were isolated from the reaction, *o*-nitrostilbene (7 %) and 3-benzoylanthranil (3-benzoyl-2,1-benzisoxazol) (*3*) (15 %). In addition TLC of the reaction mixture indicated traces of 2-phenylisatogen (2-phenyl-*3H*-indole-3-one-1-oxide) (*4*) to be present.

Analysis of the *o*-nitrostilbene showed it to consist of 50 % *cis* and 50 % *trans*-*o*-nitrostilbene. This is in contrast to the results of dehydrations of the isomeric alcohols, 2-(*o*-nitrophenyl)-1-phenylethanol and 1-(*p*-nitrophenyl)-2-phenylethanol, which gave nitrostilbenes with high *trans*/*cis* ratios, 95/5 and 91/9, respectively.

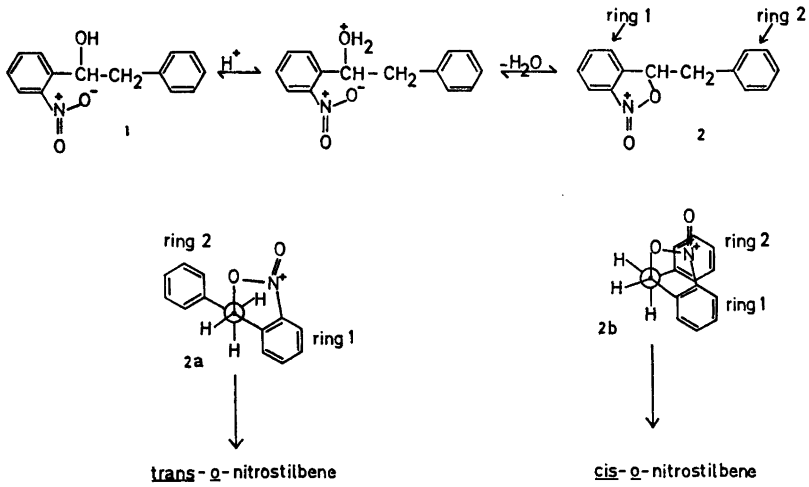
Control experiments showed *trans*-*o*-nitrostilbene to be stable under the reaction conditions, but the *cis* isomer to be slowly transformed to *trans*-*o*-nitrostilbene. Also, *cis*-*p*-nitrostilbene was transformed to the *trans* isomer.

The acidic dehydration of alcohols is generally assumed to proceed by an E1 mechanism. However, the details of the reaction are unknown, and subtle differences in structure may govern the results.[4,5]

The expected high yield of the *trans*-stilbenes in the dehydration of 2-(*o*-nitrophenyl)-1-phenylethanol and 1-(*p*-nitrophenyl)-2-phenylethanol may be explained by a *transoid* orientation of the aromatic rings during the reaction. A different mechanism may be operating in the case of 1-(*o*-nitrophenyl)-2-phenylethanol (*1*) as participation by the nitro group may give rise to the cyclic intermediate *2*. If *o*-nitrostilbene was formed from *2* by an E2-like mechanism, this may explain the high *cis*/*trans* ratio.

The conformer *2b* would be expected to be somewhat more favourable than the ones giving the *cis*-stilbenes from 2-(*o*-nitrophenyl)-1-phenylethanol and 1-(*p*-nitrophenyl)-2-phenylethanol, as ring 1 in *2b* can not rotate freely. Further, this conformer may be favoured by attraction between the positively charged ring system on carbon 1 and the phenyl ring on carbon 2.

The other substance isolated from the reaction of *1* was 3-benzoylanthranil (*3*). TLC of the

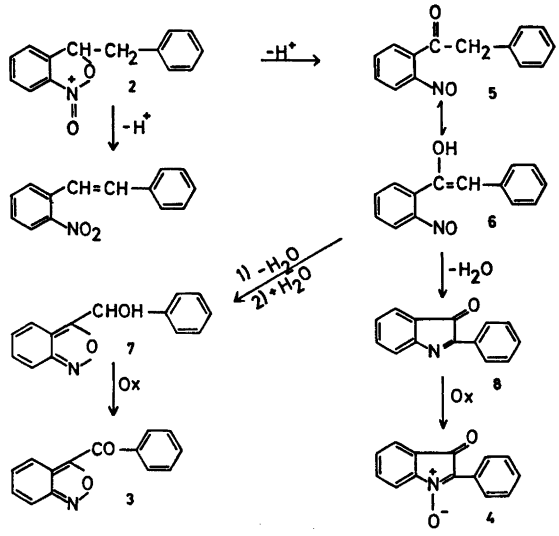


reaction mixture also indicated 2-phenylisatogen (*4*) to be a product. From the results of the investigation on nitrobenzyl alcohol [2] and of other *o*-nitroaryl compounds,[3] an intramolecular reaction was expected between the nitro and hydroxyl groups. However, both benzoylanthranil and phenylisatogen are at a higher oxidation level than 1-(*o*-nitrophenyl)-2-phenylethanol, showing part of the reaction paths of these compounds to be intermolecular.

Control experiments showed both *3* and *4* to be stable under the reaction conditions, and neither of them was therefore a precursor of the other in the studied reaction.

A reasonable way of formation of 3-benzoylanthranil and 2-phenylisatogen could start with the cyclic intermediate *2*, analogous to that proposed in the reaction of *o*-nitrobenzyl alcohol [2] and of several other *o*-nitro aromatic compounds.[3] The five membered ring of *2* could open to give benzyl *o*-nitrosophenyl ketone (*5*). Ring closure reactions of the enol form *6*, might give 3-(hydroxybenzyl)anthranil (*7*) and 3-oxo-2-phenylindolenine (*8*). Both *7* and *8* have to be oxidised if compounds *3* and *4* were formed by these paths.

Oxidation of 3-oxo-2-phenylindolenine (*8*) under slightly acidic conditions did not give



2-phenylisatogen (*4*).[6] However, *8* is reported to be unstable under strong acidic conditions,[6] and oxidation under the present conditions might have yielded *4*.

3-(Hydroxybenzyl)anthranil (*7*) seems not to have been reported earlier. It was readily made by sodium borohydride reduction of 3-benzoylanthranil and was refluxed with *p*-toluenesulfonic acid in toluene in the presence of nitrobenzene as an oxidant. The main product from the reaction was indeed 3-benzoylanthranil, together with several unidentified substances in low yields. Exlusion of oxygen was without effect on the reaction. 3-(Hydroxybenzyl)anthranil may thus be an intermediate in the studied reaction.

Further studies of the reactions of 3-(hydroxybenzyl)-anthranil showed that it was not oxidised by nitrobenzene in the absence of *p*-toluenesulfonic acid.

A rather different reaction path from benzyl *o*-nitrosophenyl ketone (*5*) to *3* and *4* would be by oxidation of the nitroso group to a nitro group. The resulting benzyl *o*-nitrophenyl ketone would be at the same oxidation level as *3* and *4* and the possibility of cyclisations to these compounds could not be excluded. However, an experiment with benzyl *o*-nitrophenyl ketone and *p*-toluenesulfonic acid showed it to be stable under the reaction conditions. Neither *3* nor *4* could be detected in the reaction mixture.

In photochemical reactions, 2-arylisatogens have been obtained from *o*-nitrostilbene.[7] Our own results show that neither *cis*- nor *trans*-*o*-nitrostilbene are transformed to 2-phenylisatogen or 3-benzoylanthranil under the acidic conditions in the present study.

In conclusion, the results from the reaction of 1-(*o*-nitrophenyl)-2-phenylethanol under acidic conditions can be explained by an intramolecular redox reaction occurring *via* the cyclic intermediate *2*. In addition, intermolecular redox reactions take place to give 3-benzoylanthranil and 2-phenylisatogen by oxidation.

EXPERIMENTAL

The general instrumentation has been described.[2] GLC were run on a Perkin-Elmer F-11 gas chromatograph, equipped with a 1.5 m column, 3 % OV-17. GLC-MS were run on the same GLC equipment, followed by a Hitachi-Perkin-Elmer, RMS-4 mass spectrometer. The syntheses of 1-(*o*-nitrophenyl)-2-phenylethanol (*1*)[8] and 2-(*o*-nitrophenyl)-1-phenylethanol[1] have been reported earlier.

Reaction of 1-(o-nitrophenyl)-2-phenylethanol (1). *p*-Toluenesulfonic acid (1 g), *1* (0.5 g), and toluene (50 ml) were refluxed. TLC showed *1* to react slowly and to have disappeared after 5 h. The reaction product consisted of a black powder (0.16 g) with an undistinguished IR spectrum, together with a toluene soluble mixture which was chromatographed on a dry column (silica gel, chloroform). Three products were obtained: *o*-nitrostilbene (32 mg), which GLC-MS showed to consist of 50 % *cis*-*o*-nitrostilbene (16 mg, 3.5 %) and 50 % *trans*-*o*-nitrostilbene (16 mg, 3.5 %), 3-benzoylanthranil (71 mg, 15 %) (IR, NMR, TLC), and 2-phenylisatogen (traces, TLC). This experiment was repeated twice with the same result.

Dehydration of 2-(o-nitrophenyl)-1-phenylethanol. *p*-Toluenesulfonic acid (0.6 g), 2-(*o*-nitrophenyl)-1-phenylethanol (0.3 g) and toluene (30 ml) were refluxed. After 15 min TLC showed the reaction to be complete. The reaction was followed by GC which showed the *trans*/*cis* ratio to be constant from 0.5 min throughout the reaction: 95 % *trans*- and 5 % *cis*-*o*-nitrostilbene. After work up and crystallisation *o*-nitrostilbene (0.19 g, 69 %), m.p. 71–72 °C (99 % *trans*, 1 % *cis*, GC) was obtained.

cis-o-*Nitrostilbene* was obtained by irradiation of a solution of *trans*-*o*-nitrostilbene (1 g) in benzene (170 ml) with a medium pressure Hg lamp. GC showed equilibration (65 % *cis*, 35 % *trans*) after 2.5 h irradiation. The *cis* isomer was isolated by preparative GC followed by crystallisation. The product (97 % *cis*- and 3 % *trans*-*o*-nitrostilbene) had m.p. 62.4–63.2 °C (lit.[9] *cis*-*o*-nitrostilbene 62 °C). IR (KBr): 3090, 3020, 1610, 1570, 1520, 1450, 1345, 865, 795, 780, 760, 710, 695 cm^{-1}. NMR ($CDCl_3$): 7.8–8.2 (1 H, *m*), 6.9–7.5 (8 H, *m*), 6.8 (1.5 H, *d*, *J* 3 Hz).

Stability of cis-o-*nitrostilbene.* *o*-Nitrostilbene (79 % *cis*, 21 % *trans*, 10 mg), *p*-toluenesulfonic acid (400 mg), and toluene (20 ml) were refluxed and the isomerisation followed by GLC. The results are given in Table 1.

Stability of trans-o-*nitrostilbene.* After 5 h reflux of *o*-nitrostilbene (98 % *trans*, 2 % *cis*) in toluene with *p*-toluenesulfonic acid, the composition was 99 % *trans* and 1 % *cis* isomer. TLC of this and of the preceding reaction mixture showed that neither 3-benzoylanthranil nor 2-phenylisatogen were formed in these reactions.

*Dehydration of 1-(*p-*nitrophenyl)-2-phenylethanol*[5] was performed by refluxing 50 mg with *p*-toluenesulfonic acid (100 mg) in toluene (5 ml). After 25 min TLC indicated the reaction to be complete, and *p*-nitrostilbene to be the major product. One more product (*ca.* 5 % from TLC) with R_F slightly smaller than nitrostilbene was

Table 1. Isomerisation of *cis*-*o*-nitrostilbene by reflux with *p*-toluenesulfonic acid.

Time (h)	Composition of *o*-nitrostilbene [a] % *cis*	% *trans*
0	79	21
0.5	44	56
1	30	70
2	36	64
3	25	75
5	28	72

[a] By GLC.

Table 2. Isomerisation of *cis*-*p*-nitrostilbene by reflux with *p*-toluenesulfonic acid.

Time (h)	Composition of *p*-nitrostilbene % *cis*	% *trans*
0	89	11
0.25	82	18
2	62	38
4	40	60
5	32	68

also present. The reaction was followed by GC, which showed the *trans*/*cis* ratio to be constant from 2 min throughout the reaction: 91 % *trans*, 9 % *cis*.

Stability of cis-p-*nitrostilbene*. *p*-Nitrostilbene (89 % *cis* and 11 % *trans*, from irradiation of *trans*-*p*-nitrostilbene) (20 mg) and *p*-toluenesulfonic acid (800 mg) in toluene (40 ml) were refluxed. The results of GC analyses at various times are given in Table 2.

Stability of 2-benzoylanthranil and 2-phenylisatogen. 3-Benzoylanthranil (10 mg), *p*-toluenesulfonic acid (400 mg), and toluene (20 ml) were refluxed for 5 h. TLC, GLC and IR showed no 2-phenylisatogen to be formed and 3-benzoylanthranil to have remained unchanged. An analogous experiment with 2-phenylisatogen showed that this compound too was stable under the reaction conditions.

3-(Hydroxybenzyl)anthranil (7). 3-Benzoylanthranil (40 mg) in methanol (20 ml) was cooled to 10 °C and sodium borohydride (30 mg) added. Water (30 ml) was added after 1 min and the mixture extracted twice with chloroform, the chloroform solution washed with water and evaporated to give a yellow oil (45 mg), showing one spot on TLC. UV ($CHCl_3$), λ_{max}: 303 (ε= 820 m^2 mol^{-1}), 272 (310), 265 (205), 258 (200), 252 (160), 247 (150). IR ($CHCl_3$, 5 %): 3610, 3360, 3080, 3010, 2940, 2860, 1650, 1550, 1500, 1660, 1160, 1145, 1075, 1020, 840 cm^{-1}. NMR ($CDCl_3$): δ 6.7–7.7 (9.5 H, *m*), 6.15 (1 H *s*), 4.1 (1 H, *s*, disappeared on shaking with D_2O). MS: *m/e* 225 (77 %), 208 (14 %), 207 (10 %), 196 (27 %), 180 (30 %), 179 (18 %), 120 (100 %), 118 (16 %), 107 (26 %), 105 (39 %), 92 (25 %), 79 (35 %), 77 (46 %).

Reactions of 3-(hydroxybenzyl)anthranil (7). (a) *With* p-*toluenesulfonic acid and nitrobenzene*. 3-(Hydroxybenzyl)anthranil (15 mg), *p*-toluenesulfonic acid (30 mg), and nitrobenzene (20 mg) were refluxed in toluene (5 ml). After 1 min, TLC showed all the alcohol to have reacted and to have given one product with R_F identical to that of 3-benzoylanthranil together with several other products with smaller R_F values, some of them fluorescing.

(b) *With only nitrobenzene*. The alcohol (8 mg) and nitrobenzene (12 mg) were refluxed in toluene (2.5 ml) for 5 min. TLC showed only starting material.

(c) *With only* p-*toluenesulfonic acid*. The alcohol (8 mg) and *p*-toluenesulfonic acid (15 mg) were refluxed in toluene (2.5 ml). After 1 min, the result, as judged by TLC, was similar to that of experiment a.

(d) *With only* p-*toluenesulfonic acid and exclusion of air*. A mixture of the alcohol (10 mg) and *p*-toluenesulfonic acid (18 mg) in toluene (3.3 ml) was degassed under vacuum by five cold (CO_2/acetone)/hot cycles with addition of N_2 for each cycle. The mixture was then refluxed for 1 min. The result was similar to that of experiments a and c. The reaction mixtures from experiments a, c, and d (from a total of 33 mg hydroxybenzylanthranil) were combined, concentrated and chromatographed. Yield 10 mg of a substance with TLC and IR spectrum identical to that of 3-benzoylanthranil.

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