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Electroörganic Preparations

XXVII. Electrochemical Preparation of Benzo-1,2,4-triazines

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Benzo-1,2,4-triazines may be prepared by electrolytic reduction at controlled cathode potential of suitable compounds followed by ring closure. 3-Phenylbenzo-1,2,4-triazine (IX) is formed (85–96 % yield) on reduction of *o*-nitrophenylazo phenylnitromethane (I), which may be prepared either by nitrosation of benzaldehyde-*o*-nitrophenylhydrazone or by coupling of phenylnitromethane with diazotized *o*-nitroaniline. IX is also formed in good yield by electrolytic reduction of *β*-thiobenzoyl-*o*-nitrophenylhydrazine. The mechanism of the reductions and ring closures are discussed.

Benzo-1,2,4,-triazines may be prepared by several methods,[1–9] but few are at the same time general and giving satisfactory yields, the best ones probably being those of Bamberger[2] or Fusco and Bianchetti.[6,7] Below is reported on the use of electrochemical methods in the preparation of 3-phenylbenzo-1,2,4-triazine.

Electrochemical reductions at controlled potential have the advantage that the starting material may be brought to the oxidation state suitable for the ring closure, thus avoiding overreduction of the intermediate or the product. A polarographic investigation of the relevant compounds reveals whether these compounds are reducible, at which potentials they are reduced, the pH-dependence of these potentials, and the number of electrons in the electrode reactions, and thus serves as a guide for the controlled potential reductions.

RESULTS AND DISCUSSION

o-Nitrophenylazo phenylnitromethane (I) gives in acid solution two polarographic waves with $E_{\frac{1}{2}} = -0.16$ V and $E_{\frac{1}{2}} = -0.42$ V (SCE), respectively, at pH 5. At pH<0 the two waves merge into a single wave. A detailed report

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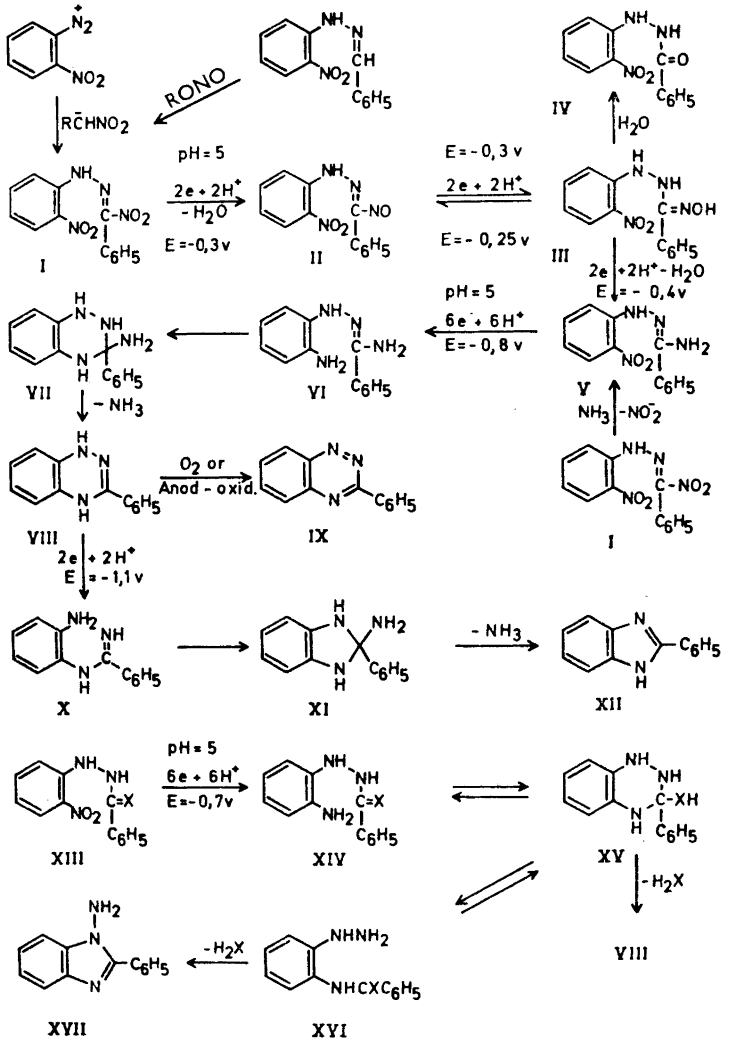
of the polarographic behaviour of the relevant compounds will be published elsewhere.

Controlled potential reduction of I at a mercury cathode at −0.80 V (SCE) in an acetate buffer containing 50 % DMF consumed 12 F/mole; after oxidation of the dihydrophenylbenzo-1,2,4-triazine (VIII) with oxygen the yield of 3-phenylbenzo-1,2,4-triazine (IX) was determined polarographically (85—96 %). The reaction is believed to follow the route indicated in Scheme 1.

Reduction of I at the potential of the first wave (−0.30 V (SCE)) in an acetate buffer consumed 4 F/mole; the product, the oxime hydrazine III, hydrolyzed easily and did so to a large extent during the reduction, but



its presence was indicated by its anodic polarographic wave observed during the reduction; isolated was its product of hydrolysis, β-benzoyl-*o*-nitrophenylhydrazine (IV).

From a reduction of I in N HCl at −0.05 V (SCE) some *o*-nitrophenylbenzamidrazone (V) besides IV was isolated, indicating that III is reduced to V before the reduction of the aromatic nitro group takes place. The reduction of III to V might not be expected from the fact that the unsubstituted oximehydrazine, $C_6H_5NHNHC(=NOH)C_6H_5$, is not further reducible;[10] however, the reduction of I (and of the *p*-nitro isomer) consumes 12 F/mole corresponding to a six-electron reduction of each nitro group to an amino group which suggests V as an intermediate; furthermore, it was not possible to detect hydroxylamine in the reaction mixture after the reduction of I to IX.

Dihydro-3-phenylbenzo-1,2,4-triazine (VIII), which is the product obtained by ring closure, may be determined by its anodic polarographic wave; anodic oxidation of VIII gives IX. VIII and IX form a reversible redox system.

The value of a control of the electrode potential in the electrochemical preparation of IX is seen from the fact that VIII is further reducible to 2-phenylbenzimidazole [11] at about −1.1 V at pH 4. In analogy with the reduction of phenylhydrazones in acid solution the reduction is formulated with an initial cleavage of the nitrogen-nitrogen bond followed by ring closure by attack on the azomethine group by the amine; loss of ammonia gives 2 -phenylbenzimidazole.

I may be prepared by reaction between benzaldehyde *o*-nitrophenylhydrazone and sodium or amyl nitrite; this is a convenient synthesis for benzo-1,2,4-triazines with different aromatic substituents in the 3-position.

o-Nitrophenylhydrazinobenzaldoxime (III), prepared in solution by reaction between *o*-nitrophenylhydrazine and benzhydroxamic chloride,[12] shows a cathodic wave corresponding to the reduction of the nitro groups and a smaller prewave from the reduction of the hydroxylamino (oxime) group; III gives further an anodic wave corresponding to an oxidation to II. III is easily hydrolyzed to IV.

o-Nitrophenylbenzamidrazone (V) gives IX on reduction at −0.7 V (pH∼4) in about 95 % yield; this is in accordance with the other data indicating V as an intermediate in the reduction of I. V was here obtained by reaction of I with ammonia; a more convenient synthesis of V, *e.g.* by reaction between *o*-nitrophenylhydrazine and an iminoether or its equivalent, would make V a useful starting material for the preparation of IX.

o-Nitrophenylazonitromethane (XVIIIa), *o*-nitrophenylazonitroethane (XVIII b), and *o*-nitrophenylazonitropropane (XVIII c) were reduced analogously to the reduction of I, and the yield of benzotriazine (XIX a), 3-methylbenzotriazine (XIX b), and 3-ethylbenzotriazine (XIX c) was determined polarographically (85—90 %).

β-Thiobenzoyl-*o*-nitrophenylhydrazine (XIII, X=S) shows in acid solution two polarographic waves, the first one corresponding to a six-electron reduction of the nitro group (pH=5; $E_{\frac{1}{2}}=-0.48$ V (SCE)) and the other one to the reduction of the thiobenzoyl group (pH=5; $E_{\frac{1}{2}}=-1.22$ V (SCE)).

Reduction of XIII (X=S) in an acetate buffer at −0.7 V (SCE) yielded β-thiobenzoyl-*o*-aminophenylhydrazine (XIV, X=S,) which could be isolated;

if the solution of XIV (X=S) was allowed to stand, ring closure through XV (X=S) to VIII took place in good yield (73 %) with loss of hydrogen sulfide. This ring closure is, however, much slower than the reaction VI → VII → VIII.

Reduction of β-benzoyl-*o*-nitrophenylhydrazine (XIII; X=O) in 4N HCl at −0.3 V or in acetate buffer at −0.7 V (SCE) yielded XIV (X=O). When the solution was allowed to stand, a small yield (15−19 %) of IX was detected polarographically. In a similar reaction acyl migration and formation of benzimidazoles have been reported.[3]

In many compounds it is possible to reduce a nitro group to a hydroxylamino group; however, an attempt to reduce the nitro group in benzaldehyde *o*-nitrophenylhydrazone to a hydroxylamino group, which, in principle, might make a ring closure and, after loss of water, form VIII, was unsuccessful, as it in this case was impossible to stop the reduction at the hydroxylamino stage. In this respect the *o*-nitrophenylhydrazine derivatives behave as *o*-nitroanilines.

From the above data it can be concluded that the starting material for the preparation of benzo-1,2,4-triazines must have the carbon atom, which becomes C-3 in the benzotriazine, in the oxidation state of a carboxylic acid; it must furthermore be substituted with a group which as such or after reduction can act as good leaving group (from VII or XV). In this respect I and V are equally good, XIII (X=S) is acceptable, but IV is a bad choice. The inapplicability of IV is a.o. caused by the poor properties of the hydroxyl group as a leaving group.

The results from the ring closure of IV explains why only a rather poor yield of benzo-1,2,4-triazines is obtained from the condensation of acid derivatives with *o*-aminophenylhydrazine [13] in which a mixture of benzo-1,2,4-triazines and benzimidazoles is obtained. The yield of benzotriazines, determined polarographically, was generally 15−50 %.

EXPERIMENTAL

The potential control was made with a fully transistorized potentiostat (Tage Juhl electronics, Copenhagen); the cell has been described previously.[14] The amount of electricity consumed was measured with an electromechanical integrator.

Materials. *o*-Nitrophenylazophenylnitromethane I. *Method A.* 1.0 g of benzaldehyde *o*-nitrophenylhydrazone was dissolved in hot glacial acetic acid (10 ml). To the cooled solution was added a large excess of amyl nitrite (15 ml) and the mixture stirred and heated gently until a clear solution resulted. The solution was left overnight at room temperature. The excess of amyl nitrite and the acetic acid was removed *in vacuo*; the oily residue crystallized on addition of ether and cooling. The product was recrystallized from ethanol, 1.0 g. (84 %), m.p. 138−140° (138−147°).[15] Found: C 53.94; H 3.38; N 19.25. Calc. for $C_{13}H_{10}N_4O_4$: C 54.55; H 3.52; N 19.57.

Instead of amyl nitrite a similar amount of sodium nitrite may be employed with somewhat lower yield of I (60 %).

Method B. *o*-Nitroaniline (14.0 g) in 6 N HCl was diazotized with an aqueous solution of 7.0 g sodium nitrite; pH of the diazonium solution was raised to 4−5 by addition of sodium acetate and sodium hydroxide while the temperature was kept at −5 to −2°C. The solution was then slowly poured into a cold solution of 14 g phenylnitromethane and 4 g NaOH in a mixture of 25 ml water and 50 ml ethanol. The resulting mixture was stirred at 0° for 1 h and left overnight at room temperature. The precipitate (I) was

then filtered off, washed with water and recrystallized from ethanol, yield 25 g (90 %) m.p. 140–142°. Found: C 54.36; H 3.38; N 19.43. Calc. for $C_{13}H_{10}N_4O_4$: C 54.55; H 3.52; N 19.57.

Similarly were prepared XVIII a, b, and c.

o-Nitrophenylbenzamidrazone (V) was prepared according to Corsi.[8]

Electrochemical reductions. Reduction of I (second wave). I (2.5 g) was reduced at −0.80 V (SCE) in a deaerated and prereduced acetate buffer containing 50 % DMF and KCl as supporting electrolyte. The reaction consumed 12 F/mole; the reduced solution was left in contact with air overnight, and the yield of IX determined polarographically (85–96 %). The solution was then neutralized with sodium bicarbonate and extracted continuously with ether for 3 h. The ether was dried (K_2CO_3), evaporated, and the residue recrystallized from ethanol-water, yielding 1.2 g IX, m.p. 122–123° (123° [3]). The identity of IX was further proved from the IR-spectrum identical with that obtained from an independently prepared [3] sample. (Found: C 74.4; H 4.45; N 19.94. Calc. for $C_{13}H_9N_3$: C 75.35; H 4.38; N 20.28).

XVIII a was reduced in an acetate buffer at −0.9 V (SCE). The yield of benzotriazine was determined polarographically (85–90 %). Similarly XVIII b and c were reduced with a similar yield of methyl-, resp. ethylbenzotriazine.

Reduction of I (first wave). I (0.5 g) was reduced in an acetate buffer containing 70 % ethanol at −0.30 V (SCE) with the consumption of 4 F/mole. The reduction completed, the solvent was removed *in vacuo*, and the residue extracted with chloroform. The dissolved material was chromatographed on silica with a 2:3 mixture of ether and light petrol as eluent. Isolated was β-benzoyl-*o*-nitrophenylhydrazine (IV) (300 g), m.p. 168–170° (166° [3]) and further identified from the IR-spectrum, identical with that of an authentic sample.

When I was reduced in N HCl containing 70 % ethanol at −0.05 V (SCE) and the reaction mixture treated as above, another chromatographic fraction could be isolated besides IV. This fraction consisted of *o*-nitrophenylbenzamidrazone (V), 50 mg, m.p. 170° (178° [15]), identified from its IR-spectrum.

Reduction of V. V (0.5 g) was reduced in N HCl (50 % ethanol) at −0.5 V (SCE) with consumption of 6 F/mole. Yield of IX, determined polarographically, 75 %; isolated were 320 mg. When V was reduced in an acetate buffer (50 % DMF) at −0.70 V (SCE) the yield of IX was, similarly determined, 95 %.

Reduction of XIII (X=S). XIII (X=S) (0.5 g) was reduced in an acetate buffer (50 % ethanol) at −0.7 V (SCE) with consumption of 6 F/mole. The reduction completed, the catholyte was neutralized with $NaHCO_3$ and extracted with chloroform, which was then dried and evaporated. The residue was recrystallized from benzene/light petrol; obtained was XIV (X=S) m.p. 115–118° (200 mg) and a small amount of IX (50 mg). (Found: C 64.6; H 3.96; N 16.6. Calc. for $C_{13}H_{13}N_3S$: C 64.20; H 5.39; N 17.27).

When, in a similar reduction, the reduced solution was allowed to stand in contact with air for several days after completion of the reduction, the yield of IX, determined polarographically, was 73 %. A similar yield of IX was obtained when XIII (X=S) was reduced in N HCl (50 % alcohol) or in an acetate buffer (50 % DMF).

Reduction of IV. IV (0.3 g) was reduced in an acetate buffer (50 % ethanol) at −0.70 V (SCE) with consumption of 6 F/mole. The reduction completed, the catholyte was neutralized with $NaHCO_3$ and extracted with chloroform, which was then dried and evaporated. The residue was recrystallized from ethyl acetate; isolated was β-benzoyl-*o*-aminophenylhydrazine, 160 mg, m.p. 163° (163–164° [3]). (Found: C 67.09; H 6.05; N 18.05. Calc. for $C_{13}H_{13}N_3O$: C 68.77; H 5.77; N 18.49).

In a similar reduction of 0.5 g IV the catholyte was allowed to stand for two days at room temperature after the reduction. The yield of IX, determined polarographically, was 19 %; 50 mg IX was isolated. In a reduction in 5 N HCl (50 % ethanol) the yield of IX was negligible, whereas in an acetate buffer (50 % DMF) the yield of IX, determined polarographically, was 15 %.

Preparation of benzo-1,2,4-triazine (XIX a). 20 ml of anhydrous formic acid was deaerated with nitrogen, 4.0 g of *o*-aminophenylhydrazine dihydrochloride [13] and 4.3 g Na_2CO_3 added, and the mixture refluxed under nitrogen for 2 h. After standing overnight a polarographic determination showed the presence of XIX a in 20 % yield. The solution was neutralized and extracted with benzene; after drying (K_2CO_3) of the benzene, ligth petrol was added. The precipitate was filtered off and

recrystallized from ethanol, 150 mg, which was identified as benzimidazole from its m.p. and IR-spectrum. The filtrate was evaporated and the residue, 500 mg, m.p. 71—72° (76—77°[3]) was identified as XIX a from the m.p. and analysis. (Found C 63.96; H 3.99. Calc. for $C_7H_5N_3$: C 64.11; H 3.84).

When triethyl orthoformate was used instead of formic acid the yield of XIX a, determined polarographically, varied between 20 and 50 %.

3-Methylbenzo-1,2,4-triazine (XIX b) was prepared similarly from *o*-aminophenylhydrazine dihydrochloride and acetic anhydride. Isolated were XIX b, m.p. 89—90° (92—94°)[3] in 15 % yield and 2-methylbenzimidazole, m.p. 173—174° (174—176°[3]) in 10 % yield.

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