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DIMERIC REDOX PRODUCTS FORMED FROM 4-NITROPHENYLACETATE ION IN BASIC SOLUTION

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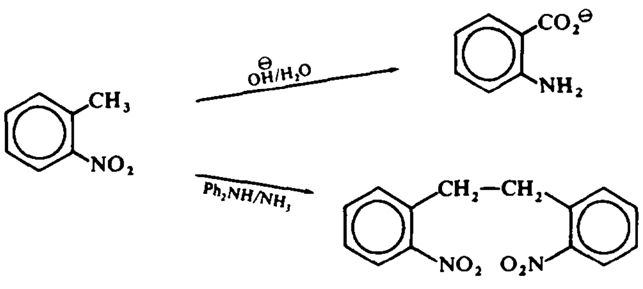
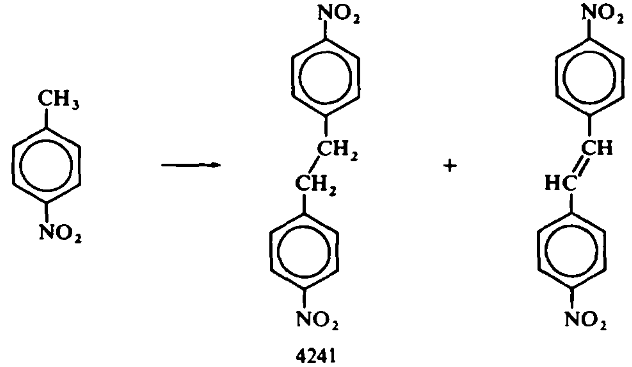
Abstract—4-Nitrophenylacetic acid, when dissolved in aqueous methanolic alkali, undergoes a redox-type dimerization leading to the formation of 4,4′-dioxaloazobenzene and the corresponding azoxy-compound. Structures are proven by interconversion and synthesis. The relative amounts of products are closely dependent upon solvent composition.

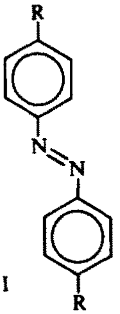
THE formation of azo- and azoxybenzene derivatives from nitroaromatics under mildly reducing conditions has been known for many decades.[1,2] However, the *type* of dimeric product can vary, not only with change of substituent in the aromatic ring, but also with relatively minor changes in the reaction conditions. Thus, in aqueous alkali, 2-nitrotoluene yields a salt of anthranilic acid[3,4] whereas, in the presence of diphenylamine in liquid ammonia, 2,2′-dinitrobibenzyl is formed.[5]

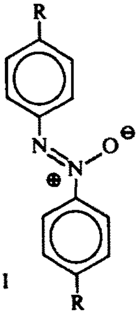


With 4-nitrotoluene in methanolic alkali the reaction course alters, 4,4-dinitrobibenzyl being accompanied by 4,4′-dinitrostilbene.[6–8] The precise nature of the product depends upon the presence or absence of aerial oxygen,[9,10] radical anions having been detected[11] as intermediates in this reaction.



We wish to report that 4-nitrophenylacetic acid, when heated in solution in aqueous methanolic alkali, gives rise to a mixture of dimeric products, viz., the dioxaloazo- and azoxybenzenes (I, II, $R = CO \cdot CO_2H$), the relative proportions depending upon the water : methanol ratio. Somewhat surprisingly, with sodium methoxide in *anhydrous* methanol, 4-nitrophenylacetate ion proved to be stable.


I

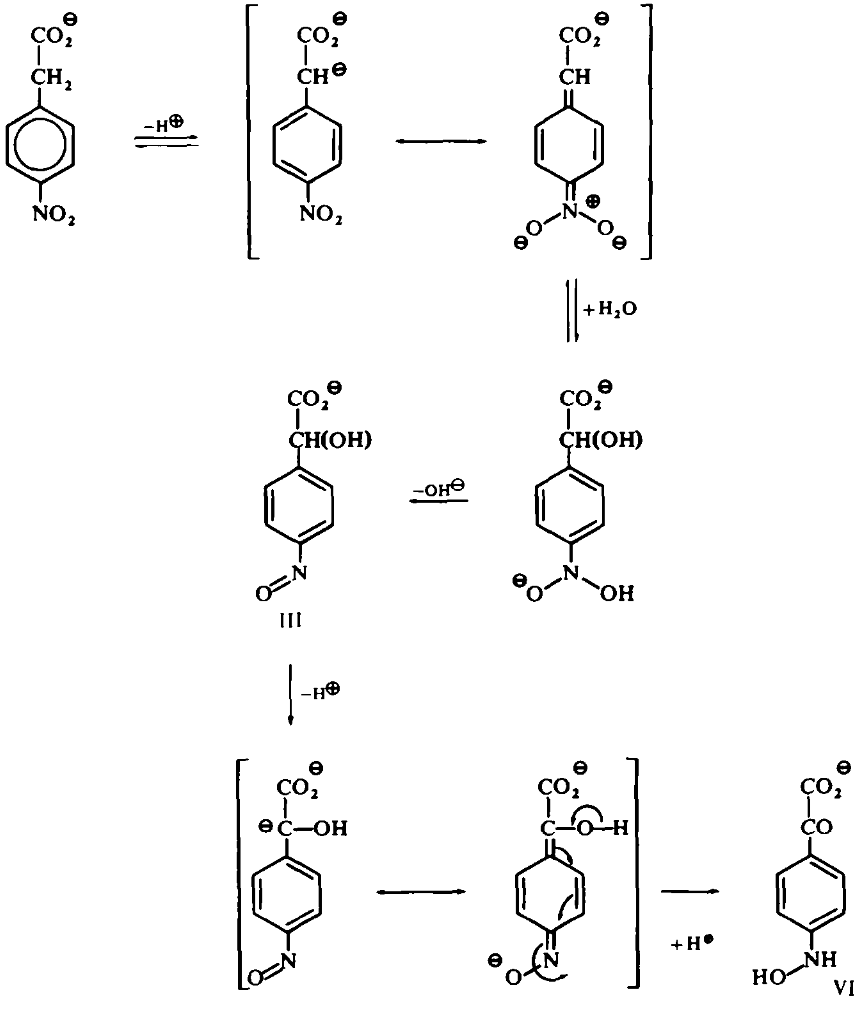

II

In aqueous methanolic sodium hydroxide, 4-nitrophenylacetate ion yielded an orange-yellow precipitate, this being a mixture of the sodium salts of I and II ($R = CO \cdot CO_2H$) whose colour varied according to the proportions of red azo- and yellow azoxy-compound formed. Treatment of the mixed sodium salts with hydrochloric acid gave the mixed acids whose separation proved to be extremely difficult. However, esterification using methanol and either sulphuric acid or dicyclohexylcarbodiimide gave an orange microcrystalline mixture of esters which was separated by preparative TLC on silica into a yellow and a red component. The mass spectrum of the yellow product (II, $R = CO \cdot CO_2Me$) indicated a molecular formula $C_{18}H_{14}N_2O_7$, the breakdown pattern (loss of CO_2Me followed by loss of CO) being consistent with that of a bis-α-keto ester. The IR spectrum indicated two different CO functions, absorbing at 1730 and 1692 cm^{-1}: in addition, a band at 1223 cm^{-1} supported the azoxy-formulation. The PMR spectrum was consistent with II ($R = CO \cdot CO_2Me$), there being an 8-proton multiplet in the aromatic region and a 6-proton singlet at approximately 6 τ as expected of the two ester Me groups.

The red dimethyl ester (I, $R = CO \cdot CO_2Me$) had a mass spectrometric molecular formula, $C_{18}H_{14}N_2O_6$, the breakdown pattern again being consistent with the presence of α-keto ester functions. As with II ($R = CO \cdot CO_2Me$) the IR spectrum exhibited two bands in the CO region, at 1732 and 1679 cm^{-1}, but there was *no* absorption in the region of 1230 cm^{-1}, i.e. the azoxy group was absent. The PMR spectrum showed an 8-proton AB quartet in the aromatic region and a 6-proton singlet at 6 τ, as required by I ($R = CO \cdot CO_2Me$).

Both the red α-keto acid (I, $R = CO \cdot CO_2H$) and the yellow α-keto acid (II, $R = CO \cdot CO_2H$) could be degraded by alkaline hydrogen peroxide to the corresponding decarbonylated acid (I, II, $R = CO_2H$)[12] and furthermore, II ($R = CO \cdot CO_2Me$) could be converted into I ($R = CO \cdot CO_2Me$) by deoxygenation using triphenyl phosphine in chloroform.

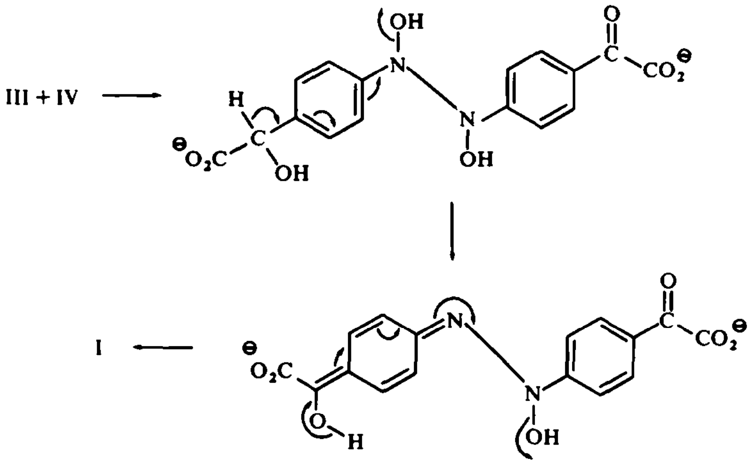
The structure of II ($R = CO \cdot CO_2Me$) indicated by the above observations was confirmed by synthesis as follows. The ethylene ketal of 4-nitroacetophenone was converted into 4,4′-diacetylazoxybenzene (II, $R = CO \cdot Me$) by treatment with zinc dust in aqueous methanolic alkali followed by acid hydrolysis of the ketal. Oxidation



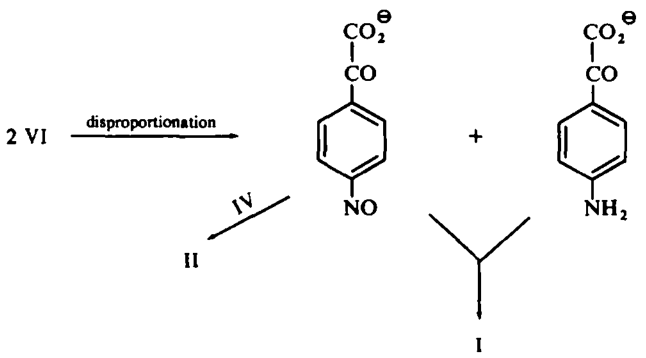
of the keto-Me group to the corresponding α-keto-carboxylic acid (using selenium dioxide in pyridine)[13] followed by esterification using methanol and sulphuric acid gave II ($R = CO \cdot CO_2Me$) identical in all respects with the product of esterification of the azoxy-component of the 4-nitrophenylacetate dimerization.

The relative amounts of I and II ($R = CO \cdot CO_2H$) formed in the reaction varied with the composition of the solvent mixture. For pure water, the ratio I/II was 10; in 75% methanol (by volume) the ratio was 0·1. In pure methanol, no reaction occurred.

This last observation is consistent with the prototropy necessitated in the redox formation of IV from III and its precursors, as exemplified in the scheme:



As the ratio of I/II varies with solvent composition, the disproportionation of IV[2,14] and its reaction with III[2,15] are presumably solvent dependent.



EXPERIMENTAL

Proton NMR spectra were recorded at 60 MHz using a Perkin–Elmer R10 spectrometer. Mass spectra were recorded on an AEI MS902 instrument. M.ps are uncorrected.

Reaction of 4-nitrophenylacetic acid with methanolic alkali

To a soln of 4-nitrophenylacetic acid (2 g) in MeOH (20 ml) 2N NaOH (20 ml) was added. The red soln was heated on a water bath for 2½ hr and then left overnight at room temp. The orange-yellow ppt (1·48 g) was collected, dissolved in water, and the soln acidified (2N HCl). An orange acid (1·12 g) was precipitated and showed IR absorption bands at 3517, 1718, and 1677 cm^{-1}. The mass spectrum indicated what appeared to be two products with molecular ions at *m/e* 326 and 342.

Acid-catalysed esterification of the orange acidic material

Conc H_2SO_4 (0·3 ml) was added to a soln of the orange material (1·71 g) in MeOH (60 ml) and the soln heated under reflux for 90 min. After cooling it was poured into water. The ppt (1·61 g) was filtered off and crystallized from acetone.

TLC on silica (1/1. v/v; $CHCl_3/CCl_4$) revealed the presence of two compounds, a yellow material having R_f 0·2 and a red one, R_f 0·25. The ester mixture was separated into its two components by preparative TLC using repeated development to give (a) *4,4′-dioxaloazoxybenzene dimethyl ester* (II. $R=CO\cdot CO_2Me$), yellow needles m.p. 182–183°. (Found: C, 58·1; H, 4·0; N, 7·7. $C_{18}H_{14}N_2O_7$ requires: C, 58·4; H. 3·8; N, 7·6%); λ_{max} nm (ε in $CHCl_3$) 276 (11,100), 351 (18,000); ν_{max} cm^{-1} 1730. 1692, 1598, 1462, 1223, 1210; NMR ($CDCl_3$) τ 1·2–1·75 m |8H|, 5·93 s |6H|; mass spectrum (M^+) Found: 370·0799. $C_{18}H_{14}N_2O_7$ requires: 370·0801; *m/e* (M^+) 370, (M^+ —O) 354, (M^+ —CO_2Me) 295. 283, 208, 196, 163, 135, 104, 76 and (b) *4,4′-dioxaloazobenzene dimethyl ester* (I, $R=CO\cdot CO_2Me$), red needles m.p. 207–208°. (Found: C, 61·0; H, 4·0; N. 7·7. $C_{18}H_{14}N_2O_6$ requires: C, 61·0; H, 4·0; N. 7·9%); λ_{max} nm (ε in $CHCl_3$). 341 (35,600), 474 (950); ν_{max} cm^{-1} 1732, 1679, 1596, 1202; NMR ($CDCl_3$) τ 1·61. 1·78 (AB quartet. $J_{AB}=9\cdot6$ c/s) [8H], 5·96 s [6H]; mass spectrum (M^+) Found 354·0848. $C_{18}H_{14}N_2O_6$ requires: 354·0852, *m/e* (M^+) 354, 309, (M^+ —CO_2Me) 295, 267, 208, 163, 135, 120, 104. 76.

Esterification of the acid mixture using dicyclohexylcarbodiimide

To a saturated soln of the acid mixture in dioxan (50 ml) MeOH (10 ml) dicyclohexylcarbodiimide (1 g) was added; the resulting suspension was heated overnight on a steam bath. After cooling the mixture was filtered and the solvent removed *in vacuo*. Chromatography of the chloroform-soluble residue on silica plates ($CHCl_3/CCl_4$: 1/1. v/v) showed the presence of I ($R=CO\cdot CO_2Me$) and II ($R=CO\cdot CO_2Me$).

Variation in composition of the reaction product with change in the reaction medium

Aliquots of 4-nitrophenylacetic acid (2 g) were heated for 2½ hr on a steam bath with a constant quantity of NaOH in solns of varying MeOH/water content. The precipitated Na salts were converted into the acid mixture and esterified with $MeOH/H_2SO_4$. The ratio of I ($R=CO\cdot CO_2Me$) to II ($R=CO\cdot CO_2Me$) was determined spectrophotometrically using chloroform solutions, the former absorbing at 341 nm and the latter at 276 nm. The results are given in the accompanying Table.

TABLE. VARIATION IN PRODUCT RATIO WITH SOLVENT COMPOSITION

Vol. 2N NaOH used (ml)	Vol. H_2O used (ml)	Vol. MeOH used (ml)	Wt. of mixed salts obtained (g)	% (II, $R=CO\cdot CO_2Me$) in ester mixture
20	20	—	1·23	10
20	10	10	1·39	51
20	—	20	1·12	81
*10	—	30	0·39	91
0·92 g sodium in		40	—	—

* 4N NaOH.

4,4′-Dicarboxyazoxybenzene (II, R = CO_2H) was prepared by the method of Reid and Pritchett[12] in 45% yield, and recrystallized from dimethylformamide, m.p. >360°. (Found: C, 58·75; H, 3·5; N, 9·9. Calc. for $C_{14}H_{10}N_2O_5$: C, 58·7; H, 3·5; N, 9·8%); ν_{max} cm^{-1} 2665, 2550, 1692, 1292; λ_{max} nm (ε in 0·1N NaOH) 262 (10,200), 334 (17,700). NMR (in d^6-DMSO) τ 1·54, 1·74 (AB quartet J_{AB} = 9·3 c/s) |4H| 1·70 s |4H|; mass spectrum *m/e*, (M^+) 286, 270, 258, 149, 121, 109, 93, 76, 65.

4,4′-Dicarboxyazobenzene (I, $R=CO_2H$) was prepared by the method of Reid and Pritchett[12] in 45% yield, and recrystallized from dimethylformamide, m.p. >360°. (Found: C, 61·8; H, 3·9; N, 10·5. Calc. for $C_{14}H_{10}N_2O_4$: C, 62·2; H, 3·7; N, 10·4%); ν_{max} cm^{-1} 2670, 2550, 1684, 1295; λ_{max} nm (ε in 0·1N NaOH) 233 (11,900), 332 (25,800), 435 (1,250); NMR (in d^6-DMSO) τ 1·62, 1·78 (AB quartet $J_{AB}=9\cdot3$ c/s) [8H]; mass spectrum *m/e* (M^+) 270, 149, 121, 104, 93, 76, 65.

Peroxide oxidation of II ($R=CO\cdot CO_2H$) *using hydrogen peroxide*

The salt (727 mg) from the reaction between 4-nitrophenylacetic acid and MeOH/4N NaOH (see Table above) was dissolved in water and the acid precipitated with 2N HCl. The ppt was dissolved in dil $NaHCO_3$, aq, H_2O_2 (100 vol., 20 ml) added, and the mixture left overnight at room temp. Subsequent acidification with 2N HCl produced a ppt which was filtered off (316 mg, 62%). Recrystallization from dimethylformamide gave a product identical with the synthetic II ($R = CO_2H$) obtained in the preceding experiment.

Conversion of II ($R = CO \cdot CO_2Me$) *into* I ($R = CO \cdot CO_2Me$)

A soln of II ($R = CO \cdot CO_2Me$) (11 mg) and triphenylphosphine (37 mg) in chloroform (5 ml) was heated under reflux in the dark for 5 days. Evaporation of solvent followed by TLC on silica (using $CHCl_3/CCl_4$: 1/1, v/v) indicated the presence of I ($R = CO \cdot CO_2Me$) in addition to unchanged II ($R = CO \cdot CO_2Me$).

Ethylene ketal of 4-*nitroacetophenone*

This was prepared from 4-nitroacetophenone by the general method of Salmi[16] in 95% yield, m.p. 74–75°. (Found: C, 57·8; H, 5·45; N, 6·6. Calc. for $C_{10}H_{11}NO_4$: C, 57·4; H, 5·25; N, 6·7%); ν_{max} cm^{-1} 1512, 1380, 1348; NMR (CCl_4) τ 1·71, 2·24 (AB quartet, $J_{AB} = 9 \cdot 0$ c/s). [4H], 5·74–6·40 m [4H] 8·40 s [3H].

The diethylene ketal of 4,4′-*diacetylazoxybenzene*

4-Nitroacetophenone ethylene ketal (5·5 g) was dissolved in MeOH (50 ml) and NaOH aq (6·5 g in 45 ml water). Zn dust (5·3 g) was added, and the mixture heated under reflux with stirring for 10 hr, and then filtered hot. The solid residue was washed with hot MeOH and the washings added to the filtrate. On cooling, yellow crystals of the diethylene ketal of II ($R = COMe$) were deposited: these were recrystallized from MeOH (2·95 g, 61%) m.p. 124°. (Found: C, 64·9; H, 5·8; N, 7·5. $C_{20}H_{22}N_2O_5$ requires: C, 64·9; H, 5·95; N, 7·6%); ν_{max} cm^{-1} 1455, 1237, 1034; λ_{max} nm (ε in $CHCl_3$) 267 (10,000), 330 (21,600); NMR ($CDCl_3$) τ 1·57, 2·22 (AB quartet $J_{AB} = 9 \cdot 0$ c/s) [4H], 1·69, 2·24 (AB quartet $J_{AB} = 8 \cdot 7$ c/s) [4H], 5·64–6·41 m [8H], 8·30 s [6H].

4,4′-*Diacetylazoxybenzene*

To a soln of the ethylene ketal of II ($R = COMe$; 2 g) in hot MeOH (100 ml) 2N HCl (16 ml) was added. On cooling, a yellow-orange crystalline material was deposited (1·45 g, 97%), which was recrystallized from acetone. The material contained a trace of a red impurity but was used in the next stage without further purification. A sample was purified for analysis by chromatography on Florisil giving pale yellow needles, m.p. 192–194° (lit.[17] 195·5°). (Found: C, 67·7; H, 5·15; N, 10·1. Calc. for $C_{16}H_{14}N_2O_3$: C, 68·1; H, 4·95; N, 9·9%); ν_{max} cm^{-1} 1688, 1677, 1266; λ_{max} nm (ε in $CHCl_3$) 272 (12,100) 342 (20,400); NMR ($CDCl_3$) τ 1·42, 1·70 (AB quartet, $J_{AB} = 9 \cdot 0$ c/s) |4H|, 1·61, 1·74 (AB quartet, $J_{AB} = 9 \cdot 3$ c/s) |4H|, 7·30 s |6H|; mass spectrum *m/e* (M^+) 282, 267, 254, 239, 212, 169, 147, 119, 104, 91, 77, 43.

4,4′-*Dioxaloazoxybenzene dimethyl ester*

Freshly sublimed selenium dioxide (500 mg) was added to a soln of II ($R = COMe$; 350 mg) in pyridine (25 ml) and the mixture stirred overnight at 100°. The hot mixture was filtered and the pyridine removed *in vacuo*. The residue was dissolved in aq $NaHCO_3$, the soln filtered and the filtrate acidified (2N HCl) and extracted with ether (3 x 120 ml). The ethereal layer was dried (Na_2SO_4), evaporated, and the residue dissolved in MeOH to which a few drops of conc H_2SO_4 had been added. The soln was heated under reflux for 6 hr then poured into water. The ppt (172 mg) was filtered off and purified by preparative TLC on silica, giving yellow needles, m.p. 182–183°, undepressed on admixture with a sample of II ($R = CO \cdot CO_2Me$) derived from the dimerization of 4-nitrophenyl acetate. The IR, UV and mass spectra of the two samples were superposable.

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