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Catalytic Hydrogenation of Some Derivatives of 2-Nitrophenylpyruvic Acid

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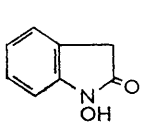
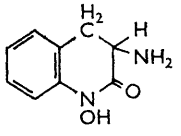
Catalytic hydrogenation of the oxime, semicarbazone, and phenylhydrazone of 2-nitrophenylpyruvic acid yields indole-2-carboxylic acid and 1-hydroxyindole-2-carboxylic acid. Similar reduction of the oxime of ethyl 2-nitrophenylpyruvate yields a mixture of ethyl indole-2-carboxylate and 3-amino-1-hydroxy-1*H*-quinolin-2-one.

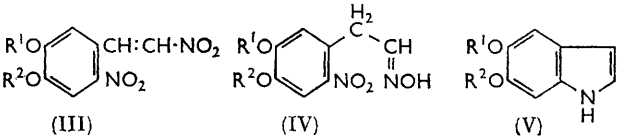
CATALYTIC hydrogenation of aromatic nitro-compounds normally yields amines or their derivatives. However, a few examples of the trapping of the hydroxyamino-group, an intermediate in the formation of an amine from a nitro-compound during catalytic reduction have been reported. Catalytic reduction of 2-nitrophenylacetic acid gave in addition to oxindole a small amount


(I)


(II)

of 1-hydroxyoxindole (I).[1] 2-Nitrophenylalanine is converted into the quinoline (II) when hydrogenated in acid solution.[2] More recently the trapping of the hydroxyamino-group by carboxy-, methoxycarbonyl-, and carbamoyl-groups in the biphenyl series has been described.[3]

In connection with other work it was found that 2-nitrophenylacetaldehyde oximes (IV), conveniently prepared from 2,β-dinitrostyrenes (III) by catalytic reduction over 5% rhodium–alumina, were reduced over


(III) (IV) (V)

a; $R^1 = R^2 = Me$ b; $R^1 = Me$, $R^2 = CH_2Ph$

[1] F. J. Di Carlo, *J. Amer. Chem. Soc.*, 1944, **66**, 1420.
[2] R. Weichert, *Annalen*, 1963, **662**, 160.
[3] C. W. Muth, J. R. Elkins, M. L. De Matte, and S. T. Chiang, *J. Org. Chem.*, 1967, **32**, 1106.

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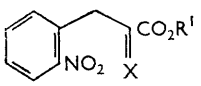
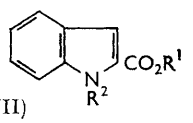
platinum to indoles (V) in low yield. It was of interest therefore to study the hydrogenation of the oximes of 2-nitrophenylpyruvic acid (VIa) and its ethyl ester (VIb) with a view to preparing derivatives of indole-2-carboxylic acid (VIIa). Catalytic hydrogenation of acid



(VI)

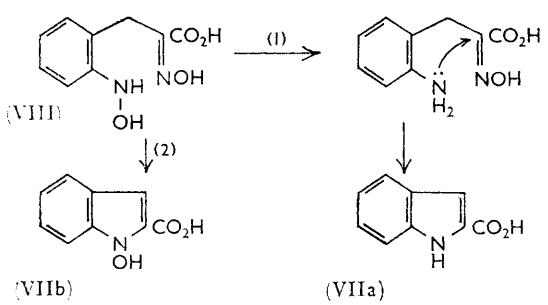
a; $R^1 = H$, X = N·OH
b; $R^1 = Et$, X = N·OH
c; $R^1 = H$, X = O
d; $R^1 = H$, X = N·NH·CO·NH_2
e; $R^1 = H$, X = N·NHPh
f; $R^1 = Et$, X = O



(VII)

a; $R^1 = H$, $R^2 = H$
b; $R^1 = H$, $R^2 = OH$
c; $R^1 = Me$, $R^2 = H$
d; $R^1 = Me$, $R^2 = OH$
e; $R^1 = Et$, $R^2 = H$
f; $R^1 = Me$, $R^2 = OAc$

(VIa) over either platinum or palladium gave a mixture of indole-2-carboxylic acid (VIIa) and 1-hydroxyindole-2-carboxylic acid (VIIb). The crude product consisted of a mixture of the ammonium salts of the two acids and separation was most easily achieved by treatment of the crude product with methanolic hydrogen chloride and chromatography of the resulting methyl esters (VIIc) and (VIId). The ratio of the two products (VIIc) and (VIId) was approximately 2 : 3. The hydroxy-acid (VIIb) was not converted into (VIIa) by hydrogen and platinum. This reaction presumably involves the acid (VIII) as an intermediate which may either undergo

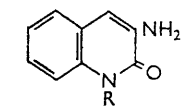


(VIII) (VIIb) (VIIa)

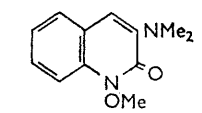
further reduction to the amino-compound followed by cyclisation (route 1) to indole-2-carboxylic acid or cyclise immediately with the formation of acid (VIIb) (Route 2). The failure of the intermediate (VIII) to cyclise to any great extent on to the carboxy-group may be due to the fact that the latter group will be ionised, owing to the presence of ammonia produced during the reaction, and consequently less susceptible to attack from either a hydroxyamino- or amino-group.[3]

Reduction of 2-nitrophenylpyruvic acid (VIc) with ferrous sulphate and ammonium hydroxide is a standard procedure for the preparation of indole-2-carboxylic acid.[4] When the reduction was performed catalytically over platinum the hydrogen uptake ceased at approximately two molar equivalents and 1-hydroxyindole-2-carboxylic acid (VIIb) was isolated in about 50% yield. This acid has been obtained by treatment of diethyl 2-nitrobenzylmalonate with aqueous sodium hydroxide solution,[5] and also by treatment of both 2-nitrophenylpyruvic acid (40%) and its methyl ester (64%) with sodium borohydride in the presence of palladium–charcoal.[6]

Similarly catalytic reduction of the semicarbazone (VId) and phenylhydrazone (VIe) gave the hydroxy-acid (VIIb) in 21 and 44% yield, respectively.

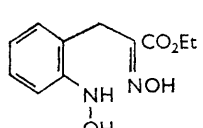


(IX) a; R = OH
b; R = H

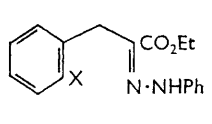


(X)

The hydrogenation of ethyl 2-nitrophenylpyruvate oxime (VIb) over platinum in ethanolic solution gave a mixture of ethyl indole-2-carboxylate (VIIe) and an amphoteric substance $C_9H_8N_2O_2$ which has been assigned structure (IXa) for the following reasons. The ^1H n.m.r. spectrum showed the presence of five aromatic protons and broad absorption corresponding to three protons which was readily removed by exchange with deuterium oxide. The base peak in the mass spectrum was $(M - 16)^+$ and loss of 16 mass units from the molecular ion has been shown to be characteristic of *N*-oxides or *N*-hydroxy-compounds in the quinoline series.[7] The presence of the quinoline nucleus suggested by the i.r. and u.v. spectra was confirmed by the formation of 3-amino-1*H*-quinolin-2-one (IXb) on reduction of (IXa) with Raney nickel alloy in aqueous sodium hydroxide. Methylation of (IXa) gave a mixture of products from which a small quantity of an alkali-insoluble trimethyl derivative, presumably (X), was isolated as its picrate. The molar ratio of the ester (VIIe) and quinolinone (IXa) produced by hydrogenation was approximately 2 : 1. The quinolinone (IXa) was unaffected by treatment with hydrogen and platinum but the ester (VIId) was converted into methyl indole-2-carboxylate (VIIc). Once again an intermediate of type (XI) can be expected to be involved and presumably the relative susceptibility of the C=N bond and the C=O bond



(XI)



(XII) a; X = NO_2
b; X = NH_2

in the ester to nucleophilic attack controls the nature of the products. The isolation of 3-amino-1*H*-quinolin-2-one (IXb) together with the ester (VIIe) from the hydrogenation of the ester (VIb) over palladium–charcoal has been reported.[8]

[4] W. O. Kermack, W. H. Perkin, jun., and R. Robinson, *J. Chem. Soc.*, 1921, **119**, 1602.
[5] A. Reissert, *Ber.*, 1896, **29**, 639.
[6] R. T. Coutts and D. G. Wibberley, *J. Chem. Soc.*, 1963, 4610.
[7] T. A. Bryce and J. R. Maxwell, *Chem. Comm.*, 1965, 206.
[8] R. E. Bowman, P. J. Islip, I. M. Lockhart, K. E. Richards, and M. Wright, *J. Chem. Soc.*, 1965, 1080.

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Reduction of the ester (VIf) gave ethyl indole-2-carboxylate (VIIe) as the sole product. The phenylhydrazone (XIIa) was rapidly reduced exclusively to the amino-ester (XIIb) which underwent cyclisation to the ester (VIIe) on heating. The fact that ester (XIIb) does not undergo spontaneous cyclisation to either an indole or a quinoline must be due to steric hinderance.

EXPERIMENTAL

Light petroleum refers to the fraction having b. p. 60—80°. The i.r. spectra were measured as KBr discs and the u.v. spectra in 95% ethanol. N.m.r. spectra were measured at 60 Mc./sec. in deuteriochloroform (unless otherwise stated) using tetramethylsilane as internal reference. Mass spectra were determined on an AEI. MS 9 mass spectrometer by the direct insertion technique.

4,5-Dimethoxy-2,β-dinitrostyrene (IIIa).—To a suspension of 3,4-dimethoxy-β-nitrostyrene (7·5 g.) in glacial acetic acid (48 ml.) was added a mixture of fuming nitric acid (24 ml.) and acetic acid (24 ml.). The solid dissolved initially but on standing a precipitate separated which was filtered off. The filtrate was diluted with water and a further quantity of solid was collected. Recrystallisation of the total solid from ethyl acetate–ethanol gave the nitro-styrene (7·1 g.), m. p. 172—173° (lit.,[9] 173°), $\lambda_{max.}$ 240, 291, and 355 mμ (log ε 4·02, 4·13, and 3·90).

4-Benzyloxy-5-methoxy-2,β-dinitrostyrene (IIIb).— This was prepared from 4-benzyloxy-3-methoxy-β-nitrostyrene [10] as above. It crystallised from ethanol in needles, m. p. 171° (lit.,[11] 167°).

4,5-Dimethoxy-2-nitrophenylacetaldehyde Oxime (IVa).—The nitro-styrene (IIIa) (1·0 g.), 5% rhodium–alumina (0·12 g.), ethanol (1·25 ml.), acetic acid (1·5 ml.), and ethyl acetate (20 ml.) were stirred under hydrogen at 3·2 atmos. for 45 min. The catalyst was filtered off and the excess of acetic acid neutralised with sodium hydrogen carbonate. The dried organic liquid was concentrated and cooled whereupon a cream coloured solid was deposited. Recrystallisation from ethyl acetate gave the *oxime* (0·24 g.), m. p. 182°, $\lambda_{max.}$ 240, 295, and 340 mμ (log ε 3·89, 3·67, and 3·69) (Found: C, 50·2; H, 5·2; N, 11·9. $C_{10}H_{12}N_2O_5$ requires C, 50·0; H, 5·05; N, 11·65%). Chromatography of the original mother-liquor on silica gave the starting material (0·11 g.).

4-Benzyloxy-5-methoxy-2-nitrophenylacetaldehyde Oxime (IV).—The nitro-styrene (IIIb) (2·5 g.) was hydrogenated in the presence of 5% rhodium–alumina (0·3 g.) as above. The *oxime* crystallised from ethyl acetate, m. p. 177°, $\lambda_{max.}$ 247, 300, and 338 mμ (log ε 4·15, 3·73, and 3·71), $\nu_{max.}$ 3260 (hydroxy), 747, and 696 cm.$^{-1}$ (benzyl group) (Found: C, 60·95; H, 5·3. $C_{16}H_{16}N_2O_5$ requires C, 60·75; H, 5·1%).

5,6-Dimethoxyindole (Va).—The oxime (IVa) (40 mg.) was hydrogenated over platinum oxide (7 mg.) in ethanol (5 ml.) at atmospheric pressure. The catalyst was filtered off and the filtrate evaporated to dryness under reduced pressure. Recrystallisation of the crude product from benzene–light petroleum gave the indole (15 mg.), m. p. 150—151° (lit.,[12] 154—155°).

6-Benzyloxy-5-methyoxyindole (Vb).—The oxime (IVb) (0·18 g.) was hydrogenated over platinum oxide (0·02 g.) as above. The crude product was chromatographed on neutral alumina. The indole (0·03 g.) crystallised from benzene–light petroleum, m. p. 155° (lit.,[11] 146°) (Found: C, 76·15; H, 6·05; N, 5·3. Calc. for $C_{16}H_{15}NO_2$: C, 76·0; H, 5·9; N, 5·5%).

2-Nitrophenylpyruvic Acid (VIc).—This was prepared as described by Di Carlo,[1] as needles, m. p. 117° (lit.,[1] 119—120°). The oxime (VIa) crystallised from ethanol, m. p. 161° (lit.,[13] 161°). The phenylhydrazone (VIe) had m. p. 152° (decomp.) (lit.,[14] 153·5°). The *semicarbazone* (VId) separated from methanol, m. p. 190—192° (decomp.) (Found: C, 45·05; H, 4·05. $C_{10}H_{10}N_4O_5$ requires C, 45·1; H, 3·8%).

Ethyl 2-Nitrophenylpyruvate (VIf).—This was prepared by esterification of the acid (VIc).[15] The oxime [8] (VIb) crystallised from ethanol in needles, m. p. 124° (lit.,[15] 121—122°); $\nu_{max.}$ 1738 cm.$^{-1}$; τ 8·73 (3, triplet, J = 7 c./sec., CH_3–CH_2), 5·75 (2, quartet, J = 7 c./sec., CH_3–CH_2), 5·70 (2, singlet, $ArCH_2$), *ca.* 2·6 (4, complex, aromatic protons), and 2·19 (1, broad, O*H*). The phenylhydrazone (XIIa) crystallised from ethanol, m. p. 103° (lit.,[15] 103·5°), τ 8·56 (3, triplet, J = 7 c./sec., CH_3–CH_2), 5·50 (2, quartet, J = 7 c./sec., CH_3–CH_2), 5·66 (2, singlet, $ArCH_2$), 2·3—3·0 (9, complex, aromatic), and 0·65 (1, broad, N*H*).

Catalytic Hydrogenations.—All hydrogenations were performed at room temperature and atmospheric pressure using Adams catalyst in ethanol.

(a) *Acid* (VIa). The acid (1·40 g.) was hydrogenated over Adams catalyst (0·10 g.) until uptake ceased (*ca.* 3 mol.). The catalyst was filtered off and the filtrate evaporated to dryness under reduced pressure. The residue (1·01 g.) separated from ethanol, m. p. 203—205° (decomp.). Spectral and chromatographic evidence indicated that this substance was a mixture of the ammonium salts of two acids. The substance (0·50 g.) was refluxed with 5% methanolic hydrogen chloride (40 ml.) for 1·5 hr. and the solution evaporated to dryness. Chromatography of the residue on neutral alumina gave methyl indole-2-carboxylate (VIIc) (0·13 g.), m. p. 151° (lit.,[16] 151—152°) and methyl 1-hydroxyindole-2-carboxylate (VIId) (0·20 g.), m. p. 102° (lit.,[5] 100—101°) (Found: C, 62·7; H, 4·7; N, 7·5. Calc. for $C_{10}H_9NO_3$: C, 62·8; H, 4·7; N, 7·35%); $\lambda_{max.}$ 230 and 296 mμ (log ε 4·32 and 4·13). The O-*acetate* (VIIf) crystallised from methanol in needles, m. p. 101° (Found: C, 62·05; H, 4·7. $C_{12}H_{11}NO_4$ requires C, 61·8; H, 4·75%); $\nu_{max.}$ 1802 (*O*-acetyl) [17] and 1704 cm.$^{-1}$ (methyl ester); τ 6·10 (3, singlet, methyl ester), 7·45 (3, singlet, CH_3CO_2), and 2·75 (1, singlet, β-indolic proton).

(b) *Acid* (VIc). The acid (1·00 g.) was reduced over platinum oxide (0·10 g.). The crude product crystallised from benzene to give 1-hydroxyindole-2-carboxylic acid (0·40 g.), m. p. 170° (decomp.) [lit.,[5] 159·5° (decomp.)] (Found: C, 61·15; H, 4·25; N, 8·4. Calc. for $C_9H_7NO_3$: C, 61·1; H, 3·95; N, 7·9%), $\lambda_{max.}$ 237 and 296 mμ (log ε 4·42 and 4·16) and on addition of 0·1N-sodium hydroxide $\lambda_{max.}$ 243, 298, and 306 mμ (log ε 4·67, 4·11, and 4·11); *M* (mass spectrum), 177. Alkaline hydrolysis of the ester (VIId) under nitrogen gave 1-hydroxyindole-2-carboxylic

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acid identical with the material obtained above. Treatment of the acid (VIIb) with ethereal diazomethane gave an oil which on chromatography on silica gave methyl 1-methoxyindole-2-carboxylate, m. p. 59° (lit.,[18] 63—64°); $\nu_{max.}$ 1720 cm.$^{-1}$ (methyl ester); τ (CCl_4) 6·07 (3, singlet, methyl ester), 5·80 (3, singlet, CH_3O), and 3·02 (1, singlet, β-indolic proton).

(c) *Phenylhydrazone* (VIe).—The acid (0·116 g.) gave 1-hydroxyindole-2-carboxylic acid (0·030 g.), m. p. 170° (decomp.).

(d) *Semicarbazone* (VId). The acid (0·423 g.) gave 1-hydroxyindole-2-carboxylic acid (0·058 g.), m. p. 170° (decomp.).

(e) *Ester* (VIb). The ester (0·80 g.) was reduced over Adams catalyst (0·08 g.) in ethanol (80 ml.). After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure, whereupon a solid separated. This solid was collected and recrystallised from a large volume of ethanol. On cooling, *3-amino-1-hydroxy-1H-quinolin-2-one* (IXa) (0·17 g.) separated as a cream coloured solid, m. p. >320° (Found: C, 60·7; H, 4·7; N, 15·3. $C_9H_8N_2O_2$ requires C, 61·3; H, 4·6, N, 15·9%), *M* (mass spectrum), 176; $\lambda_{max.}$ 228, 326, and 340 mμ (log ε 4·46, 4·18, and 4·11), $\lambda_{infl.}$ 245 and 300 mμ (log ε 4·03 and 3·94); on addition of 0·1N-sodium hydroxide solution $\lambda_{max.}$ 285, 325, and 340 mμ (log ε 4·20, 3·94, and 3·87); $\nu_{max.}$ 3320, 1665, 1620, and 1580 cm.$^{-1}$, τ [$(D_3C)_2SO$] 5·6—6·6 (2, broad, NH_2), 2·1—2·7 (5, complex, aromatic protons), and 1·76 (1, broad, O*H*). On shaking with deuterium oxide the peaks at τ 1·76 and 5·6—6·6 disappeared. Compound (IXa) gave a blue-green colour with neutral ferric chloride, as does 1-hydroxy-3-methyl-4-phenyl-Δ^3-pyrrolin-2-one.[19]

Evaporation of the original filtrate to dryness gave a solid which when recrystallised from benzene gave ethyl indole-2-carboxylate (VIIe) (0·40 g.), m. p. 121° (lit.,[20] 121—122°).

(f) *Ester* (VIf). The ester (1·08 g.) gave ethyl indole-2-carboxylate (0·75 g.), m. p. 121°.

(g) *Ester* (XIIa). The ester (0·376 g.) was hydrogenated over Adams catalyst (0·050 g.) in ethanol (100 ml.). After filtration, the solution was concentrated to 30 ml. and cooled. The white solid which was deposited was recrystallised from ethanol to give *ethyl 3-(2-aminophenyl)-2-(phenylhydrazono)-propionate* (XIIb) (0·250 g.), m. p. 159° (Found: C, 68·9; H, 6·55; N, 13·75. $C_{17}H_{19}N_3O_2$ requires C, 68·7; H, 6·4; N, 14·5%), *M* (mass spectrum), 297; $\lambda_{max.}$ 230, 295, and 332 mμ (log ε 4·00, 3·72, and 4·00); τ [$(D_3C)_2CO$] 8·65 (3, triplet, J = 7 c./sec., CH_3–CH_2), 5·62 (2, quartet, J = 7 c./sec., CH_3–CH_2), 7·18 (2, singlet, NH_2), 6·07 (2, singlet, $ArCH_2$), 5·05 (1, broad, N*H*), and 2·6—3·2 (9, complex aromatic protons). On shaking the solution with deuterium oxide the peaks at τ 7·18 and 5·05 disappeared.

When heated to above its melting point in the absence of solvent, the ester (XIIb) readily underwent loss of phenylhydrazine to give ethyl indole-2-carboxylate, m. p. 121° (from ethanol).

(h) *Ester* (VIId). The ester (0·10 g.) in methanol was shaken with Adams catalyst (0·01 g.) for 2 hr. The filtered solution was evaporated to dryness under reduced pressure and the residue recrystallised from methanol, giving the ester (VIIc) (0·04 g.) as needles, m. p. 151°.

3-Amino-1H-quinolin-2-one (IXb).—To a stirred solution of the quinoline (IXa) (85 mg.) in 10% aqueous sodium hydroxide (10 ml.) was added Raney nickel alloy (250 mg.) during the course of 1 hr. The mixture was stirred for a further 15 min., filtered, and extracted with methylene dichloride. The dried extract (Na_2SO_4) was evaporated and the residue recrystallised from ethanol to give the quinolinone (25 mg.) as needles, m. p. 211—213° (lit.,[21] 211—213°). $\lambda_{max.}$ 223, 247, 326, and 340 mμ (log ε 4·49, 4·07, 4·17, and 4·12), $\lambda_{infl.}$ 293 and 303 mμ (log ε 3·79 and 3·82).

Methylation of 3-Amino-1-hydroxy-1H-quinolin-2-one.—The quinolinone (80 mg.) in 2N-sodium hydroxide (2 ml.) was heated on a water-bath for 2 hr. with dimethyl sulphate (0·2 ml.). The cooled mixture was extracted with methylene dichloride, the extract dried (Na_2SO_4), and evaporated to give an oil (40 mg.). T.l.c. investigation of the oil showed the presence of three compounds. Chromatography of the oil on an alumina column and elution with chloroform gave a yellow oil which failed to crystallise but which gave a picrate. Recrystallisation of this from acetone, gave, presumably, *3-dimethylamino-1-methoxy-1H-quinolin-2-one picrate* (X) (10 mg.), m. p. 178° (Found: C, 48·25; H, 3·8; N, 15·6. $C_{12}H_{14}N_2O_2,C_6H_3N_3O_7$ requires C, 48·35; H, 3·85; N, 15·65%). The oily base had $\lambda_{max.}$ 274 and 330 mμ and *M* (mass spectrum), 218.

This work was supported by the U.S. Public Health Service *via* a grant from the National Cancer Institute. Part of the work was carried out at The University Chemical Laboratory, Lensfield Road, Cambridge, during the tenure of an S.R.C. Fellowship by I. B.

[7/699 *Received, June 7th,* 1967]

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