Reductive Cyclisation of Some Derivatives of Methyl *o*-Nitrophenylpyruvate and Other Keto-esters by Catalysed Sodium Borohydride

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3-Amino-1-hydroxyquinolin-2(1*H*)-one (Va) is one of the products when the oxime of methyl *o*-nitrophenylpyruvate is reduced with sodium borohydride and palladium–charcoal. The claim that the same quinolone is one of the products of the catalytic hydrogenation of ethyl *o*-nitrophenylpyruvate oxime is shown to be erroneous. Reduction of the oximino-, benzylidene, and other derivatives of selected keto-esters with sodium borohydride and palladium–charcoal is described.

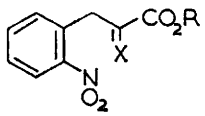
A CONTINUED interest in cyclic hydroxamic acids with antimicrobial properties prompted us to investigate further the preparation of 3- and 4-monosubstituted and 3,4-disubstituted quinoline hydroxamic acids from appropriate aromatic *o*-nitro-esters, by reductive cyclisation of the latter with sodium borohydride and palladium–charcoal. An earlier investigation [1] revealed that when keto-esters such as methyl *o*-nitrophenylpyruvate (Ia) or methyl *o*-nitrobenzoylacetoacetate (IIa) were so reduced, the nitro-group was converted into the hydroxyamino-function which then attacked the carbonyl but not the ester group, and gave an *N*-hydroxy-compound (III) or an *N*-oxide (IV).

The effect of blocking the ketone group prior to reduction, by forming the oxime (Ib) and then reducing it with sodium borohydride and palladium–charcoal was studied. While this study was in progress, Baxter and Swan [2] reported that catalytic hydrogenation of ethyl *o*-nitrophenylpyruvate oxime (Ic) over platinum gave ethyl indole-2-carboxylate and another product, m.p. >320°, to which the structure 3-amino-1-hydroxyquinolin-2(1*H*)-one (Va) was assigned.

Reduction of (Ib) with sodium borohydride and palladium–charcoal gave two products, A and B. The relative amounts varied considerably in what were apparently identical reactions. Product A, $C_9H_8N_2O_2$, was a yellow solid, m.p. 190—192°, insoluble in water but soluble both in sodium carbonate solution and in dilute hydrochloric acid. It gave a magenta colour with alcoholic ferric chloride. This and the solubility in aqueous sodium carbonate are properties of cyclic hydroxamic acids.[1] The i.r. spectrum showed two sharp bands at 3370 and 3475 cm.$^{-1}$ (NH_2); two carbonyl bands at 1665 and 1610 cm.$^{-1}$, and broad hydroxy-stretching from 2000 to 3200 cm.$^{-1}$, typical of quinoline

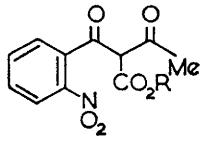
[1] R. T. Coutts and D. G. Wibberley, *J. Chem. Soc.*, 1963, 4610.
[2] I. Baxter and G. A. Swan, *J. Chem. Soc.*, 1967, 2446.

hydroxamic acids.[3,4] The base peak in the mass spectrum was the molecular ion, *m/e* 176. Both $M - 16$ and $M - 17$ ions were also present. Quinoline hydroxamic acids have been observed[4,5] to expel an oxygen atom



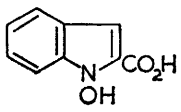
(I)

a; R = Me, X = O
b; R = Me, X = NOH
c; R = Et, X = NOH
d; R = Et, X = O

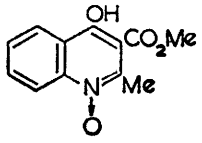


(II)

a; R = Me
b; R = Et



(III)



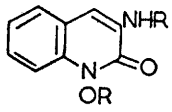
(IV)

and a hydroxy-radical from the molecular ion on electron impact.

Product A readily formed a hydrochloride which had an i.r. spectrum typical of a primary amine salt,[6] the two bands at 3370 and 3475 cm.$^{-1}$ in the base having been replaced by a series of weak peaks and inflections between 2540 and 2730 cm.$^{-1}$ and a broad weak band at 1946 cm.$^{-1}$. Acetylation of A gave a diacetate, $C_{13}H_{12}N_2O_4$, which no longer gave a magenta colour with ferric chloride. Its i.r. spectrum showed a single NH stretching band at 3320 cm.$^{-1}$ as well as a strong band at 1804 cm.$^{-1}$, characteristic of a cyclic *N*-acetoxy group.[7] Product A is thus 3-amino-1-hydroxyquinolin-2(1*H*)-one (Va), and the diacetate is (Vb).

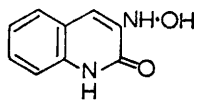
The compound, $C_9H_8N_2O_2$, thought[2] to possess structure (Va) is a cream coloured amphoteric solid. Its ^{1}H n.m.r., i.r., u.v., and mass spectra were all consistent with the proposed structure.[2] Reduction over Raney nickel to 3-aminoquinolin-2(1*H*)-one and methylation to a trimethyl derivative appeared to confirm this. Three observations are, however, inconsistent with this conclusion. The compound gives[2] a blue-green colour with neutral ferric chloride; its i.r. spectrum shows only one band in the NH stretching region; and its m.p. (>320°) differs considerably from that of the corresponding lactam [3-aminoquinolin-2(1*H*)-one], m.p. 211—213°. Aromatic cyclic hydroxamic acids usually give[8] blood red to violet colours with ferric chloride and the m.p.s of lactams are invariably higher than those of the related hydroxamates. A sample of Baxter and Swan's compound was prepared as reported;[2] it did give a blue-green colour with ferric chloride, although the colour developed only slowly. Attempts to acetylate the compound were unsuccessful.

Baxter and Swan's compound must therefore be an isomer of (Va). Structure (VI) would explain most of the reported observations. The i.r. spectrum of 3-aminoquinolin-2(1*H*)-one shows three strong bands of characteristic shape at 1663, 1620, and 1580 cm.$^{-1}$. Similar strong bands at 1665, 1620, and 1580 cm.$^{-1}$

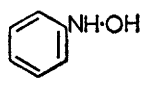


(V)

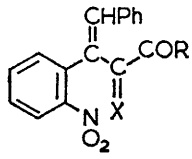
a; R = H
b; R = Ac



(VI)



(VII)



(VIII)

a; R = OEt, X = O
b; R = OEt, X = NOH
c; R = NHOH, X = O
d; R = NHOH, X = NOH

were exhibited by Baxter and Swan's compound. Structure (VI) is also consistent with the observation[2] that the base peak in the mass spectrum was the $M - 16$ ion. Phenylhydroxylamine (VII) and other aromatic hydroxylamines give strong $M - 16$ ions and weak $M - 2$ ions on electron impact.[9] A sample of Baxter and Swan's compound prepared by us showed weak M^+ and $M - 2$ ions, and a strong $M - 16$ ion.

Attempts to prepare an authentic sample of (VI) were unsuccessful. Reduction of 3-nitroquinolin-2-ol with hydrogen over Adams catalyst gave only 3-aminoquinolin-2(1*H*)-one. Reduction with zinc and ammonium chloride also gave the same lactam and another product, m.p. >300°, which could not be freed from inorganic material. The i.r. spectrum of this solid was different from that of the compound isolated by Baxter and Swan.

The second product (B) isolated by us has not been identified. It was an orange solid, m.p. >330°, not identical to Baxter and Swan's high-melting solid. That it was a hydroxamic acid was inferred from the observations that it is acidic, gives a positive ferric chloride test, and forms an acetate, m.p. >300°, $\nu_{max.}$ 1805 cm.$^{-1}$ (C=O). Owing to their non-volatility, both product B and its acetate gave uninformative mass spectra.

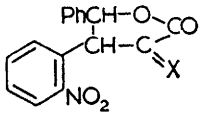
Treatment of ethyl *o*-nitrophenylpyruvate (Id) with

[3] R. T. Coutts, K. W. Hindmarsh, S. J. Powell, J. L. Pound, and E. M. Smith, *Canad. J. Pharm. Sci.*, 1968, **3**, 49.
[4] R. T. Coutts, *J. Chem. Soc.*, 1969, 713.
[5] R. T. Coutts and K. W. Hindmarsh, *Org. Mass Spectrometry*, 1969, **2**, 681.
[6] W. E. Thompson, R. J. Warren, I. B. Eisdorfer, and J. E. Zarembo, *J. Pharm. Sci.*, 1965, **54**, 1819.
[7] J. D. Loudon and I. Wellings, *J. Chem. Soc.*, 1960, 3462.
[8] R. T. Coutts, *Canad. J. Pharm. Sci.*, 1967, **2**, 27, and references contained therein.
[9] R. T. Coutts and G. Mukherjee, *Org. Mass Spectrometry*, in the press.

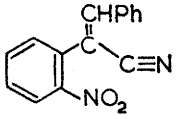
benzaldehyde in the presence of a catalytic quantity of piperidine gave ethyl 3-benzylidene-3-(*o*-nitrophenyl)-pyruvate (VIIIa). All attempts to prepare the oxime of this compound failed. When methyl *o*-nitrophenylpyruvate (Ia) was treated with hydroxylamine, the oxime (Ib) was the readily obtained product. When, however, the pyruvate (VIIIa) was treated with hydroxylamine, the hydroxamate (VIIIc) or the oximino-hydroxamate (VIIId) could be obtained, depending on the conditions. Structures (VIIIc) and (VIIId) were assigned to these products as a result of i.r. and mass spectral evidence, colour reaction of each with ferric chloride solution, and appropriate elemental analyses.

4-*o*-Nitrophenyl-5-phenyltetrahydrofuran-2,3-dione (IXa) is obtained when *o*-nitrophenylpyruvic acid reacts with benzaldehyde.[10] An attempt to prepare the oxime (IXb) resulted, instead, in spontaneous decarboxylation and dehydration of the oxime to α-(*o*-nitrophenyl)-cinnamonitrile (X) in good yield. This reaction was base-catalysed but was reminiscent of the acid-catalysed formation of *o*-nitrophenylacetonitrile from the oxime of *o*-nitrophenylpyruvic acid by the action of aqueous acetic acid.[11] Treatment of the oximino-ester (Ic) with benzaldehyde gave only starting materials.

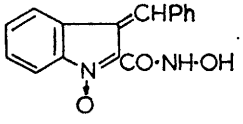
Reduction of the keto-hydroxamic acid (VIIIc) with sodium borohydride and palladium–charcoal gave a product, $C_{16}H_{12}N_2O_3$, m.p. 147°. Its mass spectrum showed a molecular ion and an $M - 16$ ion, each of significant abundance, and its i.r. spectrum and



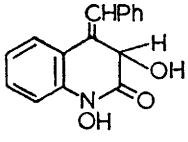
(IX)
a; X = O
b; X = NOH



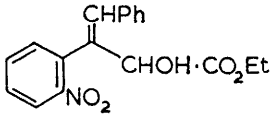
(X)



(XI)



(XII)



(XIII)

colour reaction with ferric chloride solution were consistent with it being 3-benzylidene-3*H*-indole-2-carbohydroxamic acid *N*-oxide (XI). In contrast, a similar reduction of the related ester (VIIIa) did not yield an indole derivative. The two products isolated from the reduction of (VIIIa) were the cyclic hydroxamic acid, 4-benzylidene-3,4-dihydro-1,3-dihydroxyquinolin-2(1*H*)-one (XII), and what was concluded to be ethyl 3-benzylidene-3-(*o*-nitrophenyl)lactate (XIII), since the same ester was also obtained when the sodium borohydride reduction of (VIIIa) was performed in the absence of the palladium catalyst. The formation of (XII) and (XIII) from (VIIIa) indicates that the ketone group is more susceptible to reduction than the nitro-group, in contrast to the reduction of methyl *o*-nitrophenylpyruvate (Ia) with sodium borohydride and palladium–charcoal.[1] Structure (XII) was assigned for the following reasons. The compound gave the correct analysis for $C_{16}H_{13}NO_3$ and gave the expected violet colour with ferric chloride. The mass spectrum showed an abundant ion of *m/e* 267 as well as strong $M - 16$ and $M - 17$ ions, typical of many cyclic hydroxamates,[4] and the i.r. spectrum displayed carbonyl and broad hydroxy-group stretching bands at frequencies which were also typical of cyclic hydroxamic acids;[3] the ester and ketone carbonyl stretching bands (1740 and 1675 cm.$^{-1}$) in the spectrum of (VIIIa), were absent from the spectrum of (XII), which showed a sharp OH stretching band at 3400 cm.$^{-1}$.

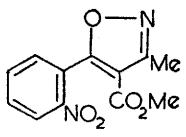
Methyl α-hydroxyimino-β-(*o*-nitrophenyl)propionate (Ib) was readily prepared from the ketone (Ia) and hydroxylamine hydrochloride in aqueous sodium hydroxide. Treatment of ethyl or methyl *o*-nitrobenzoylacetoacetate (II) with hydroxylamine in the same way resulted in ready hydrolysis of the acetyl group, however, and gave ethyl or methyl *o*-nitrobenzoylacetate in up to 80% yield. This method of preparing *o*-nitrobenzoylacetates is simpler and more efficient than the one reported.[12]

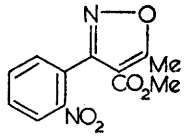
Treatment of the methyl ester (IIa) with hydroxylamine hydrochloride in the presence of pyridine gave a product, $C_{12}H_{10}N_2O_3$. Since the isoxazole ring system is commonly prepared by the interaction of hydroxylamine and a 1,3-dicarbonyl compound,[13] this product could be either (XIV) or (XV). Mass spectral analysis indicated the former structure. The molecular ion was present at *m/e* 262 and abundant ions of *m/e* 150 and 104 ($C_7H_4NO_3^+$ and $C_7H_4O^+$ respectively) were observed and are identified as the ions (XVI) and (XVII) respectively. Ions of *m/e* 148 and 102 were absent.

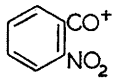
Reduction of (XIV) with sodium borohydride and palladium–charcoal gave 5-hydroxy-3-methylisoxazolo-[4,5-*c*]quinolin-4(5*H*)-one (XVIII), the structure of which was confirmed by elemental analysis, mass and i.r. spectra, its acidic properties, and its ability to give a violet colour with ferric chloride solution. When ethyl *o*-nitrobenzoylacetoacetate (IIb) was treated with hydroxylamine hydrochloride and pyridine, two products were obtained. The product which was insoluble in sodium hydrogen carbonate solution was the ethyl

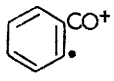
[10] W. Wislicenus and E. Thoma, *Annalen*, 1924, **436**, 42.
[11] H. Rinderknecht, H. Koechlin, and C. Niemann, *J. Org. Chem.*, 1953, **18**, 971.
[12] R. T. Coutts, M. Hooper, and D. G. Wibberley, *J. Chem. Soc.*, 1961, 5058.
[13] R. A. Barnes, in 'Heterocyclic Compounds,' vol. 5, ed. R. C. Elderfield, Wiley, New York, 1957, pp. 452, 472.

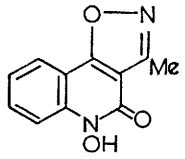
ester (XIX), which on reduction gave (XVIII). The product, $C_9H_6N_2O_4$, was acidic. It was reprecipitated from sodium hydrogen carbonate solution on acidification


(XIV)

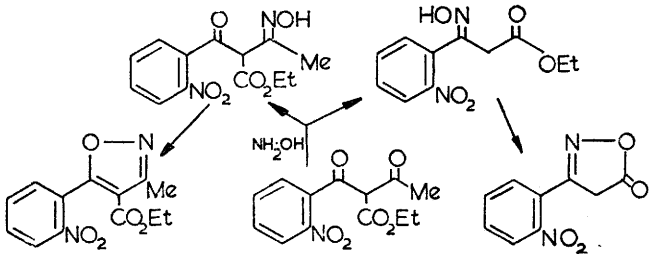

(XV)


(XVI)


(XVII)

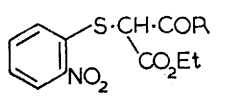

(XVIII)

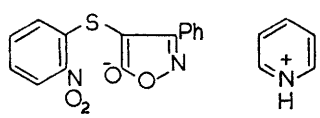
of the alkaline filtrate. The absence of an ester group and the presence of a lactone group (i.r. spectrum) confirmed the structure 3-*o*-nitrophenyl-5-isoxazolone (XX), a compound previously prepared by a less direct route.[14]


(XIX) (IIb) (XX)

An attempt was made to extend this study to the preparation of 2*H*-1,4-benzothiazine derivatives. Ethyl α-(*o*-nitrophenylthio)benzoylacetate (XXIa) was treated with hydroxylamine hydrochloride in sodium hydroxide solution. The ketonic side-chain was eliminated and ethyl (*o*-nitrophenylthio)acetate was isolated. When the reaction was repeated in pyridine, the product was 4-(*o*-nitrophenylthio)-3-phenyl-5-isoxazolone (XXIIa). On one occasion, the isoxazolone (XXIIa) was isolated as its pyridine salt (XXIII). This was an orange solid, $C_{20}H_{15}N_3O_4S$, soluble in sodium carbonate solution; acidification of this solution gave (XXIIa).

In the same way, 3-methyl-4-(*o*-nitrophenylthio)-5-isoxazolone (XXIIb) was obtained when ethyl


(XXI)


(XXIII)

a; R = Ph, b; R = Me

α-(*o*-nitrophenylthio)acetoacetate (XXIb) was treated with hydroxylamine hydrochloride in pyridine. The i.r. spectra of (XXIIa) and (XXIIb) in conjunction with the findings of Katritsky and Boulton [15] lead to the conclusion that these two compounds are isoxazolones which, in the solid state, exist as a mixture of the NH and OH forms as shown (XXII). The absence of carbonyl absorption near 1800 $cm.^{-1}$ excludes the possibility of any contribution due to the CH form (XXIV).

Attempts were made to reduce the isoxazolones (XXIIa and b) with various systems (sodium borohydride, palladium–charcoal; iron and iron(II) ammonium sulphate; hydrogen and palladium catalyst; and tin(II) chloride reagent) but only in one instance was a product isolated, and in poor yield. Reductive cyclisation of 4-(*o*-nitrophenylthio)-3-phenyl-5-isoxazolone (XXIIa) with iron and iron(II) ammonium sulphate gave 3-phenyl-2*H*-1,4-benzothiazine (XXV), the identity of which was confirmed by comparison with an authentic sample.

EXPERIMENTAL

I.r. spectra were measured for potassium bromide discs and u.v. spectra for solutions in 95% ethanol. Mass spectra were measured with an A.E.I. MS 9 spectrometer by the direct insertion technique. 10% Palladium–charcoal was used. Ethanolic solutions of all the hydroxamic acids prepared gave a violet or magenta colour when treated with aqueous ferric chloride.

Ethyl 3-Benzylidene-3-(o-nitrophenyl)pyruvate (VIIIa).—A solution of ethyl *o*-nitrophenylpyruvate (4·97 g.), benzaldehyde (2·21 g.), and piperidine (0·2 ml.) in benzene (40 ml.) was boiled under reflux for 18 hr. with use of a Dean-Stark apparatus. The cooled solution was extracted successively with dilute hydrochloric acid, water, 5% sodium hydrogen sulphite solution, and water. It was then concentrated; the material (4·48 g.) deposited gave pale brown crystals of the *pyruvate*, m.p. 103·5—105° (from absolute ethanol) (Found: C, 66·4; H, 4·65; N, 4·5. $C_{18}H_{15}NO_5$ requires C, 66·5; H, 4·65; N, 4·3%); $\nu_{max.}$ 1732 (ester C=O), 1668 (ketone C=O), and 1525 and 1350 (NO_2) $cm.^{-1}$.

Ethyl α-(o-Nitrophenylthio)benzoylacetate (XXIa).—A solution of *o*-nitrobenzenesulphenyl chloride (17·0 g.) and ethyl benzoylacetate (25·5 g.) in acetonitrile (150 ml.) was boiled under reflux for 4 hr. Acetonitrile (100 ml.) was then removed under reduced pressure. The concentrated solution was cooled whereupon the *title compound* (24·9 g.), m.p. 123—125°, was deposited as yellow crystals (Found: C, 59·2; H, 4·4; N, 4·0; S, 9·3. $C_{17}H_{15}NO_5S$ requires C, 59·1; H, 4·4; N, 4·1; S, 9·3%), $\nu_{max.}$ 1625 (β-keto-ester) and 1525 and 1342 (NO_2) $cm.^{-1}$.

Reactions with Hydroxylamine.—(*A*) The ketone (1 g.) was added to a solution of hydroxylamine hydrochloride (1 g.) in 5% sodium hydroxide (8 ml.) and sufficient methanol or ethanol was added to give a homogeneous solution. The mixture was boiled under reflux for 0·5 hr., cooled, and diluted with water. If the product did not precipitate at this stage, the aqueous solution was extracted with ether. Evaporation of the ether yielded the product.

(*B*) A solution of the ketone (1 g.), hydroxylamine hydrochloride (1 g.), and pyridine (5 ml.) in absolute

[14] G. Gaudiano, A. Ricca, and L. Merlini, *Gazzetta*, 1959, **89**, 2466.

[15] A. R. Katritsky and A. J. Boulton, *Tetrahedron*, 1961, **12**, 41.

ethanol (5 ml.) was heated under reflux for 2 hr. The solvent was removed and the residue was triturated first with water (discarded) then with ethanol to yield the product.

(a) *Methyl* o-*Nitrophenylpyruvate* (Ia). Reaction of the pyruvate by method *A* on a three-fold scale gave *methyl* α-*hydroxyimino*-β-(o-*nitrophenyl*)*propionate* (Ib) (1·89 g.), which gave buff-coloured crystals, m.p. 126—128° (from aqueous ethanol) (Found: C, 50·4; H, 4·2; N, 12·0. $C_{10}H_{10}N_2O_5$ requires C, 50·4; H, 4·2; N, 11·8%), $\nu_{max.}$ 1718 (ester C=O) and 1530 and 1330 (NO_2) cm.$^{-1}$.

In the same way, the oxime (Ic) (2·1 g.), m.p. 121—122° (lit.,[10] 121—122°), was obtained from ethyl *o*-nitrophenylpyruvate (3·5 g.).

(b) *Pyruvate* (VIIIa). (i) A solution of the pyruvate (0·5 g.) and hydroxylamine hydrochloride (0·44 g.) in pyridine (5 ml.) was boiled under reflux for 2 hr. then evaporated to give a thick yellow oil which was dissolved in ether. The ether solution was extracted with dilute hydrochloric acid and then water. Evaporation of the ether gave a yellow oil from which a colourless solid (0·25 g.) was obtained by trituration with dry ether. Crystallisation from benzene gave 2-*hydroxyimino*-3-o-*nitrophenyl*-4-*phenylbut*-3-*enohydroxamic acid* (VIIId), m.p. 212·5—214° (Found: C, 59·0; H, 3·9; N, 12·7. $C_{16}H_{13}N_3O_5$ requires C, 58·6; H, 4·3; N, 12·8%), $\nu_{max.}$ 3515 (OH), 1692 (C=O), 1660 (C=N), and 1530 and 1360 (NO_2) cm.$^{-1}$.

(ii) Reaction (i) was repeated with the pyruvate (1·6 g.) and hydroxylamine hydrochloride (0·37 g.) in pyridine (15 ml.). This yielded a solid (0·85 g.) which gave 3-*o*-*nitrophenyl*-2-*oxo*-4-*phenylbut*-3-*enohydroxamic acid* (VIIIc) (0·41 g.), m.p. 186—188° (from benzene), as pale yellow needles (Found: C, 61·0; H, 3·95. $C_{16}H_{12}N_2O_5$ requires C, 61·5; H, 3·85%), *M* (mass spectrum) 312, $\nu_{max.}$ 2500—3610 (OH), 1712 and 1680 (C=O), and 1530 and 1350 (NO_2) cm.$^{-1}$.

(c) *Lactone* (IXa). The lactone[10] (1 g.) was treated with hydroxylamine for 2 hr. by method *A*. The product (0·7 g.) from the ether solution gave α-(*o*-nitrophenyl)-cinnamonitrile (X) as yellow plates (0·52 g.), m.p. 122—123° (from aqueous ethanol) (lit.,[16] 115°) (Found: C, 72·1; H, 4·15; N, 11·0. Calc. for $C_{15}H_{10}N_2O_2$: C, 72·0; H, 4·0; N, 11·2%), *M* (mass spectrum) 250, $\nu_{max.}$ 2210 (C≡N) and 1525 and 1340 (NO_2) cm.$^{-1}$.

(d) *Ester* (IIa). (i) Reaction of the ester by method *A* on a four-fold scale gave methyl *o*-nitrobenzoylacetate (60—80%) as a yellow oil. A portion of the oil (0·63 g.) when slowly added with stirring to a solution of potassium hydroxide (0·28 g.) in ethanol (10 ml.) gave the potassium derivative (0·60 g.) (Found: C, 45·55; H, 3·1; N, 5·2. Calc. for $C_{10}H_8KNO_5$: C, 46·0; H, 3·1; N, 5·4%).

(ii) Reaction of the ester (1·03 g.) by method *B* gave an orange solid (0·42 g.). Crystallisation from aqueous ethanol gave *methyl* 3-*methyl*-5-(o-*nitrophenyl*)*isoxazole*-4-*carboxylate* (XIV) as a colourless solid, m.p. 98—100° (Found: C, 55·2; H, 3·8; N, 10·5. $C_{12}H_{10}N_2O_5$ requires C, 55·0; H, 3·8; N, 10·7%), *m/e* 262 (M^+), 216, 150, 134, 130, 120, 104, 88, 76, 42, 30, and 28, $\nu_{max.}$ 1723 (ester C=O) and 1535 and 1353 (NO_2) cm.$^{-1}$.

(e) *Keto-ester* (IIb). When this ester[17] (1·1 g.) was treated with hydroxylamine by method *B*, a buff-coloured solid (0·47 g.) was obtained. This was stirred into sodium hydrogen carbonate solution. The insoluble portion when crystallised from aqueous ethanol gave ethyl 3-methyl-5-(*o*-nitrophenyl)isoxazole-4-carboxylate (XIX) (0·28 g.), m.p. 71—73° (lit.,[18] 73·5—74·5°) (Found: C, 56·8; H, 4·5; N, 10·2. Calc. for $C_{13}H_{12}N_2O_5$: C, 56·5; H, 4·8; N, 10·1%) The alkaline filtrate when treated with dilute hydrochloric acid gave a pale pink solid (0·10 g.). Crystallisation from benzene gave colourless 3-*o*-nitrophenyl-5-isoxazolone (XX), m.p. 178—179° (lit.,[14] 172—174°) (Found: C, 52·0; H, 2·9. Calc. for $C_9H_6N_2O_4$: C, 52·4; H, 2·9%), $\nu_{max.}$ 1796 (C=O) and 1525 and 1345 (NO_2) cm.$^{-1}$.

(f) *Keto-ester* (XXIa). (i) The ester (1·53 g.) was treated with hydroxylamine by method *B*. The yellow solid (1·05 g.) isolated was dissolved in sodium hydrogen carbonate solution. The insoluble portion (0·48 g.) was discarded. Acidification of the filtrate gave 4-(o-*nitrophenylthio*)-3-*phenyl*-5-*isoxazolone* (XXIIa) as yellow crystals, m.p. 168—170° (from ethanol) (Found: C, 57·7; H, 3·2; N, 8·9. $C_{15}H_{10}N_2O_4S$ requires C, 57·3; H, 3·2; N, 8·9%), $\nu_{max.}$ 1910—3220 (NH and OH), 1690 and 1680 (C=O), 1563 (C=N), 1450, 1282, 1252, and 1190 (isoxazolone ring),[15] and 1515 and 1340 (NO_2) cm.$^{-1}$.

(ii) When the keto-ester was treated with hydroxylamine by method *B* on a four-fold scale, dark orange crystals of the *pyridinium salt* (XXIII) (0·81 g.), m.p. 160—165°, separated when the mixture was cooled (Found: C, 61·3; H, 3·9; N, 11·1. $C_{20}H_{15}N_3O_4S$ requires C, 61·1; H, 3·8; N, 10·7%). Acidification of a solution of the salt in sodium carbonate solution gave the lactone (XXIIa).

(iii) The ester (4·02 g.) was treated with hydroxylamine by method *A*. The crude product gave ethyl (*o*-nitrophenylthio)acetate as a yellow solid (1·79 g.), m.p. 49—50° (from ethanol) (lit.,[19] 46—48°) (Found: C, 50·5; H, 4·6; N, 5·6. Calc. for $C_{10}H_{11}NO_4S$: C, 50·0; H, 4·2; N, 5·8%).

(g) *Keto-ester* (XXIb). This ester[20] (1·84 g.) was treated as in reaction (f), method (i). The acidic product, 3-methyl 4-(o-*nitrophenylthio*)-5-*isoxazolone* (0·73 g.) was a yellow solid, m.p. 172—173° (Found: C, 47·8; H, 3·3; N, 11·0. $C_{10}H_8N_2O_4S$ requires C, 47·6; H, 3·2; N, 11·1%), $\nu_{max.}$ 2000—3220 (NH and OH), 1675 and 1660 (C=O), 1565 (C=N), 1450, 1250, and 1170 (isoxazolone ring),[15] and 1516 and 1339 (NO_2) cm.$^{-1}$.

Reductions with Sodium Borohydride and Palladium–Charcoal: Typical Reduction.—A solution of the nitro-compound (0·01 mol.) in dioxan (50 ml.) was added during 15 min. to a stirred suspension of palladium–charcoal (0·15 g.) in 50% aqueous dioxan (25 ml.) containing sodium borohydride (1·5 g.). A slow stream of nitrogen was passed through the mixture during the addition and for a further 30 min. The mixture was filtered, concentrated, and then acidified with dilute hydrochloric acid. If the product did not separate at this stage, the aqueous solution was extracted with ether. Evaporation of the dried ether extract yielded the product.

(a) *Propionate* (Ib). The filtrate obtained from the reduction of the ester (1·51 g.) was acidified to pH 6 with dilute hydrochloric acid and diluted with water. A solid (0·905 g.) separated. A portion (0·42 g.) (product B) was insoluble in 50% aqueous ethanol. The soluble portion (product A) was 3-*amino*-1-*hydroxyquinolin*-2(1H)-*one* (Va), which gave pale yellow crystals, m.p. 190—192° (from

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ethanol) (Found: C, 61·65; H, 4·6; N, 15·6. $C_9H_8N_2O_2$ requires C, 61·4; H, 4·6; N, 15·9%), $\nu_{max.}$ 3475 and 3370 (NH_2), 3200—2000 (hydroxamate OH),[3] and 1665 and 1610 (hydroxamate C=O) [3] cm.$^{-1}$, *m/e* 176 (M^+, 100%), 160 (10), and 159 (11). The product (Va) was soluble in aqueous sodium carbonate and in hydrochloric acid.

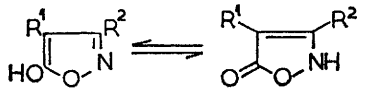
Addition of hydrogen chloride to an ether solution of (Va) gave the *hydrochloride* as a pale yellow solid, m.p. 238—240° (decomp.) (Found: N, 13·0. $C_9H_9ClN_2O_2$ requires N, 13·2%), $\nu_{max.}$ 3300—2050 (hydroxamate OH and NH_3^+), 1946 (NH_3^+), and 1663 and 1624 (hydroxamate C=O) cm.$^{-1}$.

Acetylation of (Va) with acetic anhydride gave 3-*acetamido*-1-*acetoxyquinolin*-2(1H)-*one* (Vb) as a colourless solid, m.p. 223—225°, insoluble in both sodium hydroxide solution and dilute hydrochloric acid. In contrast with (Va), the diacetate (Vb) did not give a violet colour with ethanolic ferric chloride (Found: C, 59·75; H, 4·8; N, 10·8. $C_{13}H_{12}N_2O_4$ requires C, 60·0; H, 4·65; N, 10·8%), $\nu_{max.}$ 3320 (NH), 1804 (NOAc),[7] 1695 (amide C=O), and 1650 (lactam C=O) cm.$^{-1}$.

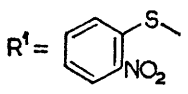
Product B gave an orange solid, m.p. >330° (from benzene then ethanol) (Found: C, 53·9; H, 3·3; N, 13·4%), $\nu_{max.}$ 3420br (OH) and 1638 (hydroxamate C=O) cm.$^{-1}$. The acetate was a pale orange solid, m.p. >300°, $\nu_{max.}$ 1805 (NOAc) [7] and 1708 (C=O) cm.$^{-1}$.

(b) *Hydroxamic Acid* (VIIIc). Evaporation of the ether extract obtained from the reduction of the acid (0·3 g.) gave 3-*benzylidene*-3H-*indole*-2-*carbohydroxamic acid* N-*oxide* (XI) (0·102 g.), m.p. 147—150° (from ethanol) (Found: C, 68·6; H, 4·6. $C_{16}H_{12}N_2O_3$ requires C, 68·6; H, 4·3%), *m/e* 280 (M^+, 14%), 264 (13), 263 (10) and 262 (11), $\nu_{max.}$ 3640—2500 (hydroxamate OH), 1686br (C=O), and 1240 (*N*-oxide) cm.$^{-1}$.

(c) *Pyruvate* (VIIIa). (i) Reduction of the pyruvate (2·0 g.) in methanol (120 ml.) was followed by ether extraction of the aqueous filtrate. The extract was shaken with sodium carbonate solution. The aqueous extract was acidified and re-extracted with ether. Evaporation of the dried ether solution gave 4-*benzylidene*-3,4-*dihydro*-1,3-*dihydroxyquinolin*-2(1H)-*one* (XII) (0·91 g.), m.p. 244—245°



(XXII)



a; R^2 = Ph
b; R^2 = Me

(from benzene–light petroleum) (Found: C, 71·8; H, 5·2; N, 5·1. $C_{16}H_{13}NO_3$ requires C, 71·9; H, 4·9; N, 5·2%), *m/e* 267 (M^+, 71%), 251 (100), and 250 (92), $\nu_{max.}$ 3640—2400 [broad with max. at 3400 and 3260 (OH and hydroxamate OH)] and 1641 (hydroxamate C=O) cm.$^{-1}$.

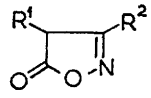
Evaporation of the ether solution which remained after sodium carbonate extraction gave *ethyl* 3-*benzylidene*-3-(o-*nitrophenyl*) *lactate* (XIII) as a viscous brown oil (0·35 g.) which could not be distilled (Found: C, 66·0; H, 5·0; N, 4·5. $C_{18}H_{17}NO_5$ requires C, 66·0; H, 5·1; N, 4·3%), *M* (mass spectrum) 327, $\nu_{max.}$ 3440br (OH), 1740 (ester C=O), and 1528 and 1348 (NO_2) cm.$^{-1}$.

(ii) Reduction of the pyruvate (1 g.) in dioxan (30 ml.) with sodium borohydride (0·3 g.) in water (5 ml.), and in the absence of palladium–charcoal, gave a product (0·8 g.), the i.r. spectrum and mass spectrum of which were identical with those for (XIII).

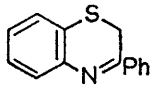
(d) *Isoxazole* (XIV). When the filtrate from the reduction of this isoxazole (0·283 g.) was acidified, 5-*hydroxy*-3-*methylisoxazolo*[4,5-c]*quinolin*-4(5H)-*one* (XVIII) (0·104 g.) was isolated as a colourless solid, m.p. 244—245° (from aqueous ethanol) (Found: C, 61·2; H, 3·65; N, 13·0. $C_{11}H_8N_2O_3$ requires C, 61·1; H, 3·7; N, 13·0%), $\nu_{max.}$ 3300—2500 (hydroxamate OH) and 1662 (C=O) cm.$^{-1}$, *m/e* 216 (M^+, 100%), 200 (18), and 199 (11).

Reduction of the corresponding ethyl ester (XIX) (0·278 g.) gave the same product (XVIII) (0·124 g.).

Reduction of 4-(o-*Nitrophenylthio*)-3-*phenyl*-5-*isoxazolone* (XXIIa).—The title compound (0·30 g.), iron(II) ammonium sulphate (0·16 g.), iron powder (0·60 g.), and dilute hydrochloric acid (0·1 ml.) were added to ethanol (10 ml.) and the mixture was boiled under reflux for 1 hr. The filtrate was concentrated to give an oil which was extracted with 10% sodium hydroxide. The insoluble portion was triturated with ethanol to give a cream-coloured solid which yielded 3-phenyl-2*H*-1,4-benzothiazine (XXV) (0·017 g.) as a bright



(XXIV)



(XXV)

yellow solid, m.p. 235° (from ethanol–benzene) (lit.,[21] 233°) (Found: N, 6·15. Calc. for $C_{14}H_{11}NS$: N, 6·2%). The i.r. spectrum was identical with that of an authentic sample [21] of (XXV).

Reduction of 3-*Nitroquinolin*-2-*ol*.—(*a*) The title compound [22] (0·05 g.) was hydrogenated over Adams catalyst (0·025 g.) at room temperature and atmospheric pressure until uptake ceased. The crude product (0·02 g.) separated when the filtrate was concentrated. Crystallisation from methanol gave 3-aminoquinolin-2(1*H*)-one, m.p. 210—212° (lit.,[2] 211—213°), *M* (mass spectrum) 160, $\lambda_{max.}$ 222, 245, 325, and 339 mμ (log ε 4·47, 4·05, 4·15, and 4·10).

(*b*) A solution of the title compound (0·119 g.) in ethanol (10 ml.) was added to a solution of ammonium chloride (0·14 g.) in water (2 ml.). Zinc dust (0·14 g.) was added in small portions to the stirred mixture. After 1 hr. the mixture was filtered and evaporated to dryness under reduced pressure. Trituration of the residue with methanol gave 3-aminoquinolin-2(1*H*)-one (0·025 g.), m.p. 210°, the u.v. spectrum of which was identical with that of the product from (*a*).

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