Hydroxyiminoisoquinolin-3(2*H*)-ones. Part 4.[1] Synthesis and Reactions of Isoquinoline-3,4-diones

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Deoximation of the 4-hydroxyimino-1-phenyl-1,4-dihydroisoquinolin-3(2*H*)-ones (**1**), (**2**), and (**3**) with formaldehyde gave isoquinoline-3,4-diones; this reaction of the *N*-unsubstituted lactams (**1**) and (**2**) was found to be accompanied by hydroxymethylation of the amide group to yield compounds (**4**) and (**5**). In the presence of sodium acetate and hydroxylamine, the product from (**4**) was not the oxime but 3,4-dihydroxy-1-phenylisoquinoline (**14**). Reduction of the dioxo derivatives (**4**) and (**6**) led to the 4-hydroxy-3-ones (**7**) and (**8**) and the 4-hydroxy-1,2,3,4-tetrahydroisoquinolines (**9**) and (**10**). The stereochemistry of the products was determined by n.m.r. spectroscopy.

α-Keto amides occur in several ring systems[2] and the isoquinoline-3,4-dione structural unit can also be found in 4,5-dioxoaporphines.[3]

Some 4-hydroxyimino-1,4-dihydroisoquinolin-3(2*H*)-ones prepared earlier[4] were referred to as the oximes of isoquinoline-3,4-diones in *Chemical Abstracts*; however, the corresponding isoquinoline-3,4-diones have not been found previously, since the C-1 methylene group is sensitive to oxidation[5] giving 1,3,4-trioxo derivatives on exposure to air. Therefore, in the present investigation 1-phenylisoquinolines were used.

Of the several methods of deoximation tried, that using formaldehyde proved to be the best (Scheme 1). It was found that hydroxymethylation of the *N*-unsubstituted lactams (**1**) and (**2**) also took place under the conditions employed to give (**4**) and (**5**) while the oximes (**3a**) and (**3b**) yielded the expected isoquinolinedione (**6**). The oxime with the chelate structure (**3b**) reacted more slowly than the corresponding (*E*)-isomer (**3a**).

The possibility of preparing the starting hydroxyimino compounds from the 4-oxo derivatives was also investigated. It was found that the dione (**6**) yielded compound (**3b**) which was interesting since the nitrosation[4] of 1-phenyl-1,4-dihydroisoquinoline-3(2*H*)-one had given predominantly isomer (**3a**). On the other hand, the reaction of the dione (**4**) with hydroxylamine in the presence of sodium acetate failed to give the 4-hydroxyimino compound (**1**). 3,4-Dihydroxy-1-phenylisoquinoline (**14**) formed in this reaction can also be prepared in the absence of hydroxylamine from (**4**), by treatment with sodium acetate. Acetylation of (**14**) gave the corresponding *O,O*-diacetyl compound (**15**).

In acidic media, 2,4-dinitrophenylhydrazine reacted with both the 2-hydroxymethyl and the 2-methyl derivatives to yield the corresponding hydrazones (**12**) and (**13**).

The reactions of the isoquinoline-3,4-diones with lithium tetrahydridoaluminate(III) and the sodium tetrahydridoborate-(III) were studied (Scheme 2).

In the literature, the synthesis[6] and determination of stereochemistry[7] of various 4-hydroxy-1,2,3,4-tetrahydroisoquinolines are reported, several of which are biologically active. The common feature in these syntheses is that there is always a substituent on the homoaromatic ring, usually located at the 6- and/or 7-position, which promotes the isoquinoline formation.

In contrast, the methods developed for the synthesis of 1,4-dihydroisoquinolin-3(2*H*)-ones,[8,9] which are the starting compounds for the 4-hydroxyimino derivatives, are also suitable for the preparation of isoquinoline derivatives containing a non-substituted homoaromatic ring.

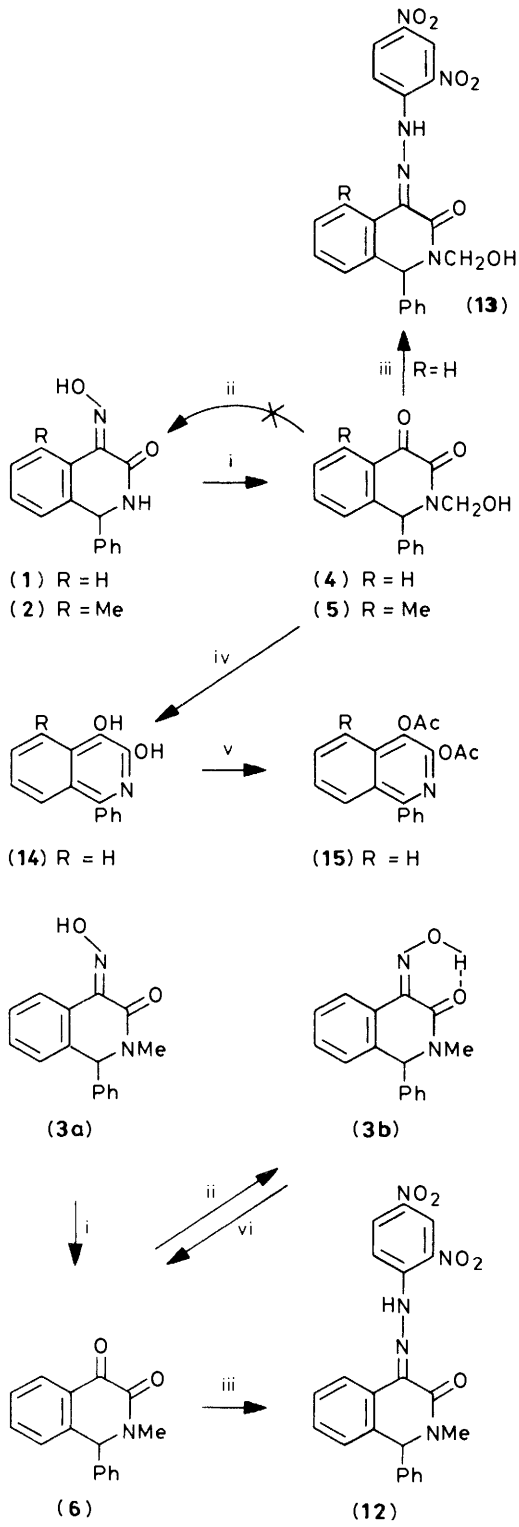
The reduction with sodium tetrahydridoborate(III) of the C-4 oxo group in compounds (**4**) and (**6**) gave a mixture of the *cis*- and *trans*-4-hydroxy-1,4-dihydroisoquinolin-3(2*H*)-ones (**7**) and (**8**), and the reduction of (**4**) was also accompanied by the hydrogenolysis of the hydroxymethyl side chain. Reduction of compound (**7**) with lithium tetrahydridoaluminate(III) yielded *trans*- (**9a**) and *cis*- (**9b**) 4-hydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline. The *trans* derivative (**9a**) was acylated with acetic anhydride in acetic acid to give *trans*-2-acetyl-4-hydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**11**).

The product obtained on reduction of compounds (**4**), (**6**), and (**8**) with lithium tetrahydridoaluminate(III) was found, after purification by column chromatography, to be the 4-hydroxy-2-methyl derivative (**10**). It is interesting that the reduction of (**4**) also yielded (**10**); thus the 4-oxo group is converted into a hydroxy group, the C-3 lactam carbonyl into a methylene group, and the hydroxymethyl group reduced to a methyl substituent all in one step.

In the ^{1}H n.m.r. spectra of the products obtained from the *N*-unsubstituted compounds (**1**) and (**2**), two unexpected CH signals also appeared [in (**4**), at 4.16 and 5.57 p.p.m.; in (**5**), at 4.36 and 5.48 p.p.m.], with coupling constants of 11 Hz. In the ^{13}C n.m.r. spectra, however, only one unexpected signal was found [(**4**), δ 67.4 p.p.m.]: its multiplicity in the off-resonance spectrum and the chemical shift indicated that formation of an N–CH_2OH group had occurred simultaneously with the deoximation.

The large difference between the chemical shifts of the geminal N–CH_2 methylene protons [Δ δ = 1.41 p.p.m. in (**4**), 1.12 p.p.m. in (**5**)] could be due to their diastereoisotopic nature, and could also indicate that the predominant conformation atom along the N–C(H_2) bond is such that one of the methylene protons falls into the shielding cone of the neighbouring C=O group, causing deshielding.

The n.m.r. spectra of compounds (**7**) and (**8**) show that in both the *cis*-and *trans*-isomers the C-1 phenyl group is in a pseudoaxial position (Scheme 3), since in (**7**) the signal for 1-H is



Scheme 1. *Reagents:* i, HCHO, HCl; ii, H_2NOH, NaOAc; iii, dinitrophenylhydrazine; iv, NaOAc; v, Ac_2O, AcOH; vi, HCHO

found at 5.60 (40%) and 5.68 p.p.m. (60%), while in (**8**) it appears at 5.45 (82%) and 5.43 p.p.m. (18%). In each pair of isomers, the 1-H shifts are very similar and are in good agreement with the shift of the pseudoequatorial 1-H in the *trans*-isomer of 4-benzyl-1-phenyl-1,4-dihydroisoquinolin-3(2*H*)-ones [10] (δ 5.64 p.p.m.).

Accordingly, in the present case the *cis*- and *trans*-isomers are epimers of each other at the 4-position; this is in contrast with the 4-benzyl derivatives, where the 4-benzyl group is in the pseudoequatorial position in both isomers and 1-H is pseudoaxial in the *cis* derivatives (δ 4.48 p.p.m.), and pseudoequatorial in the *trans* pair (δ 5.64 p.p.m.).

In tetrahydroisoquinolines, the half-chair conformation of the saturated ring is the most stable one, and in this case the pseudoequatorial substitution at both C-1 and C-4 gives rise to a strain of type $A^{1,3}$ between the substituent and the fused ring. Owing to this, the energy difference between the conformers of compounds with pseudoaxial or pseudoequatorial substituents at the above two sites is reduced, and special care must be taken in the determination of the steric structures and conformational equilibrium.

Kametani *et al.*[7a] have shown in the analogous 6-methoxy-2-methyl derivatives that the phenyl group is in the pseudoequatorial position in both the *cis*- and *trans*-isomers. Thus it might be expected that the steric arrangement in (**9a**) and (**9b**) is similar. The multiplicity of the 4-H signals, however, indicates that this proton is pseudoequatorial in both isomers, and is *gauche* to the C-3 methylene proton, *i.e.* in this case the C(4)–OH is in the pseudoaxial position, and the steric position of the C(1)–phenyl is different in the two isomers. This is further confirmed by the non-identical chemical shifts of the 1-H signals [(**9a**):1-H_{eq} = 5.12 p.p.m., and (**9b**):1-H_{ax} = 4.95 p.p.m.]. This is in agreement with the observations made with 4-hydroxy-1-methyl-1,2,3,4-tetrahydroisoquinolines.[7b]

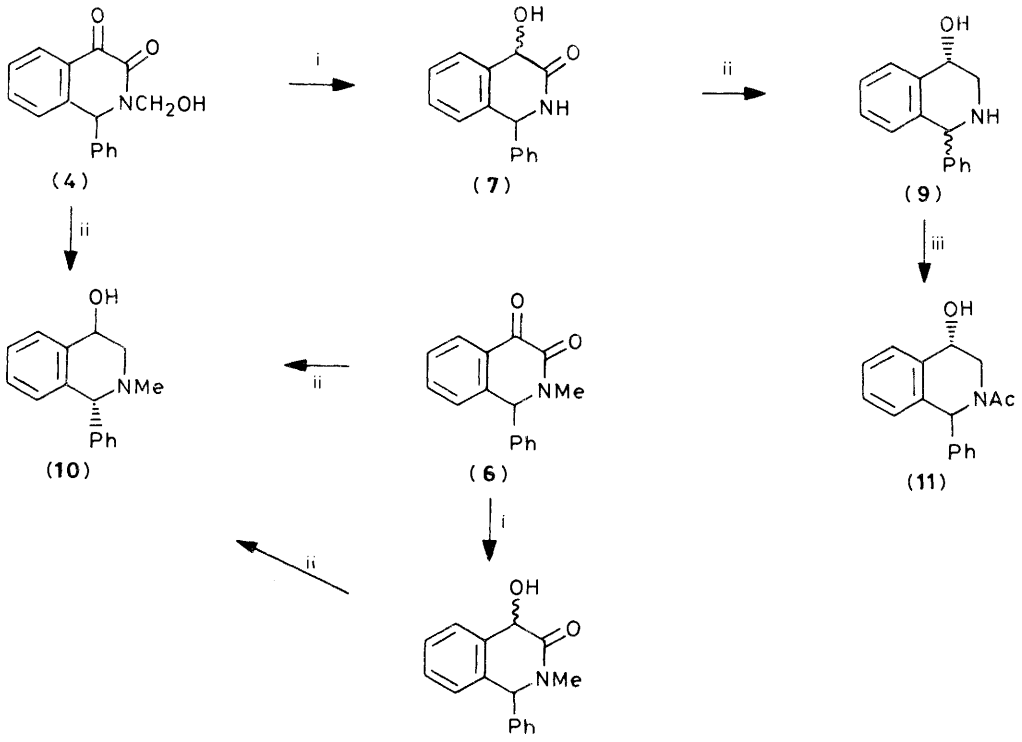
In the case of compound (**10**), the coupling constant of 7.1 Hz between 4-H and 3a-H is in good agreement with the value of 7.5 Hz measured for the analogous 6-methoxy derivatives, supporting the hypothesis that the above two hydrogen atoms are in an axial-axial orientation; hence C(4)–OH is in the pseudoequatorial position. As far as the steric position of 1-H is concerned, the following statement can be made: in the ^1H n.m.r. spectrum of (**10**), the 1-H signal is found at δ 4.32 p.p.m.; comparison with the value, δ 4.95 p.p.m., for 1-H in the spectrum of (**9b**) gives Δ δ 0.63 p.p.m. which is in agreement with the observation of Brossi *et al.*,[7b] who measured an upfield shift of Δ δ 0.63 p.p.m. in similar isoquinoline derivatives as a result of the NH ⟶ NMe exchange.

Experimental

M.p.s were determined on a Büchi-Tottoli apparatus and are uncorrected. I.r. spectra were recorded in KBr pellets on a Perkin-Elmer 457 instrument. The ^1H n.m.r. spectra were obtained with a JEOL FX–100 spectrometer and chemical shifts are given in p.p.m. relative to the internal standard tetramethylsilane. Mass spectra were run on a Varian MAT spectrometer at 70 eV. The microanalyses of the new compounds were in good agreement with the calculated values. Ether refers to diethyl ether.

Deoximation of 4-*Hydroxyimino*-1,4-*dihydroisoquinolin*-3(2*H*)-*ones. General Method.*—Oxime (**1**), (**2**), or (**3**) (0.04 mol) was heated in a mixture of water (200 ml), concentrated hydrochloric acid (100 ml), and 37% formaldehyde (200 ml) 70—75 °C, with vigorous stirring. After dissolution of the oxime, heating was discontinued and the solution was allowed to cool slowly. The crystals were filtered off, washed with water, and recrystallised from ethanol [Tables 1 and 2; (**4**), (**5**), and (**6**)].

Reduction of 1,2,3,4-*Tetrahydroisoquinoline*-3,4-*diones with Sodium Tetrahydridoborate*(III). *General Method.*—Compound (**4**) or (**6**) (13 mmol) was dissolved in anhydrous methanol (100 ml) and sodium tetrahydridoborate(III) (30 mmol) was added to



Scheme 2. *Reagents:* i, $NaBH_4$; ii, $LiAlH_4$; iii, Ac_2O, AcOH

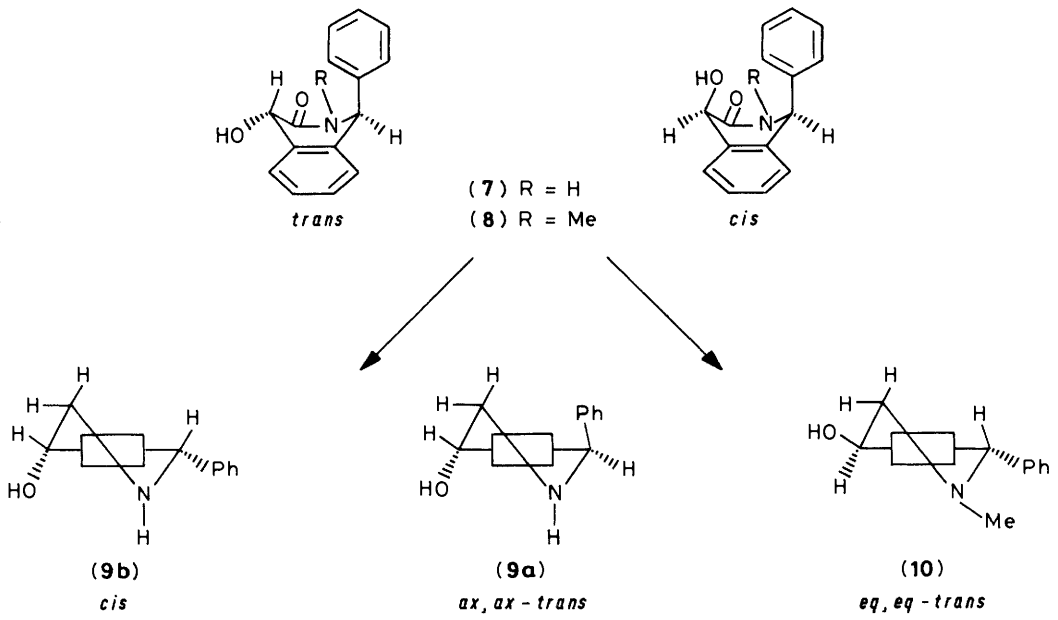
Table 1. Analytical data for the 4-hydroxy- and 4-oxo-isoquinolinones (**4**)—(**8**), (**12**), and (**13**)

Compound (formula)	Yield (%)	Solvent	M.p. (°C)	Found (%) (Required) C	H	N
(**4**)	66	EtOH	168—169	71.9	4.9	5.2
($C_{16}H_{13}NO_3$)				(72.3)	(5.1)	(5.2)
(**5**)	20	EtOH	168—170	72.5	6.9	5.0
($C_{17}H_{15}NO_3$)				(72.4)	(6.8)	(4.9)
(**6**)	71	EtOH	140—144	76.5	5.2	5.6
($C_{16}H_{13}NO_2$)				(76.6)	(5.3)	(5.7)
(**7**)	75	EtOH	190—193	75.3	5.5	5.9
($C_{15}H_{13}NO_2$)				(75.5)	(5.3)	(6.0)
(**8**)	75	Et_2O	116—118	75.9	6.0	5.5
($C_{16}H_{15}NO_2$)				(76.2)	(6.1)	(5.7)
(**12**)	30	EtAc	266—267	61.2	4.0	16.2
($C_{22}H_{17}N_5O_5$)				(61.2)	(4.2)	(16.4)
(**13**)	12	MeOH	193—195	59.1	3.8	15.6
($C_{22}H_{17}N_5O_6$)				(59.0)	(4.0)	(15.8)

Table 2. I.r. and ^1H n.m.r. data for the 4-hydroxy-and 4-oxo-isoquinolinones (**4**)—(**8**), (**12**), and (**13**)

Compound	$\nu_{max.}$(KBr)/cm^{-1}	δ_H($CDCl_3$)/p.p.m. (*J* in Hz)
(**4**)	3 310 (OH), 1 690, 1 655, 1 645 (CO)	4.44 and 5.46 (each 1 H, d, *J* 11, CH_2), 6.06 (1 H, s, 1-H)
(**5**)	3 300 (OH), 1 682, 1 658 (CO)	2.66 (3 H, s, Me), 4.36 and 5.48 (each 1 H, d, *J* 11 CH_2), 6.00 (1 H, s, 1-H)
(**6**)	1 698, 1 658 (CO)	3.03 (3 H, s, NMe), 5.68 (1 H, s, 1-H)
(**7**)	3 500—3 000br (OH), 1 662 (amide I)	5.02 (1 H, s, 1-H), 5.68 (1 H, d, *J* 5, 1-H)[a,b] 4.78 (1 H, s, 1-H), 5.60 (1 H, s, 1-H)[a,c]
(**8**)	3 420 (OH), 1 630 (amide I)	3.21 (3 H, 2, NMe), 5.00 (1 H, s, 4-H_{ax}), 5.45 (1 H, s, 1-H)[b] 2.83 (3 H, s, NMe), 5.13 (1 H, s, 4-H_{eq}), 5.43 (1 H, s, 1-H)[c]
(**12**)	1 610 (amide I)	
(**13**)	1 612 (amide I)	

[a] In $(CD_3)_2SO$. [b] *cis*-Isomer. [c] *trans*-Isomer.



Scheme 3.

Table 3. Analytical data for the 4-hydroxy-1,2,3,4-tetrahydroisoquinolines (**9**)—(**11**)

Compound (formula)	Yield (%)	Solvent	M.p. (°C)	Found (%) (Required) C	H	N
(**9**) ($C_{15}H_{15}NO$)	56	EtOH	180—181[a]	79.9 (79.6)	6.7 (6.8)	6.2 (6.5)
(**10**) ($C_{16}H_{17}NO$)	10	$CHCl_3$	134—135[a]	80.3 (80.2)	7.2 (7.0)	5.8 (6.0)
(**11**) ($C_{17}H_{17}NO_2$)	43	Et_2O	175—176[a]	76.4 (7615)	6.4 (6.2)	5.2 (5.5)

[a] *trans*-Isomer.

Table 4. I.r. and ^1H n.m.r. data for the 4-hydroxy-1,2,3,4-tetrahydroisoquinolines (**9**)—(**11**)

Compound	$\nu_{max.}$(KBr)/cm^{-1}	$\delta_H(CDCl_3)$/p.p.m. (*J* in Hz)
(**9**)	3 278 (OH)	*trans:* 2.95 (1 H, dd, J_{gem} 12.0, $J_{ax,eq}$ 4.5, 3-H_{ax}), 3.33 (1 H, dd, $J_{eq,eq}$ 4.0, 3-H_{eq}), 4.73 (1 H, dd, 4-H), 5.12 (1 H, s, 1 H) *cis:* 3.18 (1 H, dd, J_{gem} 12.0, $J_{ax,eq}$ 4.5, 3-H_{ax}), 3.35 (1 H, dd, $J_{eq,eq}$ 3.0, 3-H_{eq}), 4.58 (1 H dd, 4-H), 4.95 (1 H, s, 1-H)
(**10**)	3 300—3 200br (OH)	*trans:* 2.18 (3 H, s, NMe), 2.50 (1 H, dd, J_{gem} 11.5 11.5, *J* 7.1, 3-H_{ax}), 3.22 (1 H, dd, *J* 4.9, 3-H_{eq}), 4.95 (1 H, dd, 4-H), 4.32 (1 H, s, 1-H_{ax})
(**11**)	3 380 (OH)	*trans:* 2.15 (3 H, s, NAc), 3.17 (1 H, d, *J* 9.0, OH), 3.42 (1 H, dd, J_{gem} 14, *J* 3, 3-H_{ax}), 3.90 (1 H, dd, J_{gem} 14, *J* 3, 3-H_{eq}), 4.70 (1 H, dd, 4-H)

the solution. After being refluxed for 30 min, the solution was evaporated to dryness and the residue was dissolved in water and extracted with chloroform. The organic phase was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The remaining oil was treated with ether and crystallised, then recrystallised, from ethanol [Table 1; (**7**) and (**8**)].

Synthesis of 4-Hydroxy-1,2,3,4-tetrahydroisoquinolines. General Method.—Compound (**7**) (41 mmol) was added, in small portions, to a suspension of lithium tetrahydridoaluminate(III) (10 g) in anhydrous ether (400 ml), with vigorous stirring, in a stream of nitrogen, at a temperature between −2 and 0 °C. After completion of the addition, the mixture was allowed to warm to room temperature and it was stirred at this temperature for 1 h, and then cooled to 0 °C. Ethyl acetate (20 ml), water (10 ml), and ethyl acetate (100 ml) were then added dropwise to the ethereal suspension. The solution was decanted and evaporated. The product (**9**) was a 2:3 mixture of the *cis*- and *trans*-isomers (**9a**) and (**9b**) (Table 2). The precipitate was washed with chloroform, and the solvent evaporated to give the *trans*-isomer (**9a**). Reduction of compounds (**4**), (**6**), and (**8**) was effected in a similar manner and the product was subjected to chromatographic separation on a Kieselgel column using chloroform–methanol (9:1) as eluant to isolate 4-hydroxy-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**10**) (Tables 3 and 4).

Formation of 2',4'-Dinitrophenylhydrazones (**12**) *and* (**13**).—Compound (**4**) or (**6**) (0.8 mmol) was dissolved in hot ethanol (5.0 ml) and the solution was treated with 2,4-dinitrophenyl-

hydrazine (0.2 g, 1 mmol) dissolved in a mixture of water (5.0 ml) and 70% perchloric acid (5.0 ml). On cooling, red crystals separated, which were recrystallised from ethyl acetate (Table 1).

trans-2-*Acetyl*-4-*hydroxy*-1-*phenyl*-1,2,3,4-*tetrahydroisoquinoline* (**11**).—*trans*-4-Hydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**9a**) (0.2 g, 0.88 mmol) was refluxed in a mixture of acetic acid (5.0 ml) and acetic anhydride (0.5 ml) for 15 min. The solution was then poured onto ice, made alkaline (to pH 10) with 6M-sodium hydroxide solution, and extracted with chloroform. The organic phase was dried (Na_2SO_4), the solvent evaporated under reduced pressure, and the residual pale oil treated with ether to give the product (**11**) (0.1 g, 43%) (Table 3).

Reaction of the 1-*Phenylisoquinoline*-3,4-*diones* (**4**) *and* (**6**) *with Hydroxylamine*.—Compound (**6**) (1.0 g, 4.0 mmol) was refluxed in a mixture of hydroxylamine hydrochloride (1.0 g, 14.4 mmol), sodium acetate (2.0 g, 24.4 mmol), ethanol (25.0 ml), and water (15.0 ml). After 2.5 h, the solution was diluted with water to precipitate the *oxime* (**3b**) (1.0 g). It was recrystallised from benzene (0.5 g, 47%), m.p. 116—118 °C (lit.,[4] 118—119 °C) (Found: C, 71.9; H, 5.2; N, 10.8. $C_{16}H_{14}N_2O_2$ requires C, 72.17; H, 5.30; N, 10.52%); $\nu_{max.}$ 1 620 (Amide I), 1 050 (OH), and 960 cm^{-1} [N–O(H)].

Compound (**4**) (2.0 g, 7.4 mmol) was heated in a solution of hydroxylamine hydrochloride (2.0 g, 28 mmol) and sodium acetate (4.0 g, 48 mmol) in ethanol (50 ml) and water (25 ml) to 60—70 °C. On cooling, crystals separated (1.0 g, 56.6%). m.p. 238—240 °C. After being washed with ethanol, 3,4-dihydroxy-1-phenylisoquinoline (**14**) (0.9 g) was obtained, m.p. 244—246 °C.

The above reaction, effected in the absence of hydroxylamine, similarly gave the product (**14**).

3,4-*Diacetoxy*-1-*phenylisoquinoline* (**15**).—3,4-Dihydroxy-1-phenylisoquinoline (**14**) (1.5 g, 6.3 mmol) was dissolved in a mixture of acetic acid (50 ml) and acetic anhydride (25 ml) and stirred at 80—90 °C for 30 min. The solution was then clarified with carbon and the solvent evaporated. The residual oil (1.6 g, 80%) crystallised spontaneously. Recrystallisation from ethanol (10 ml) yielded the product (**15**) (1.3 g, 65%), m.p. 108—110 °C.

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