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3(2H)-ISOQUINOLONES—I

SYNTHESIS AND PROPERTIES OF SOME ALKOXY-3(2H)-ISOQUINOLONES

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Abstract—A general preparation of 6,7-dioxygenated 3(2H)-isoquinolones from 2-hydroxymethyl arylacetic acid lactones *via* 2-formimino-N,N-dimethyl arylacetamides is described and their properties discussed. Where carbinolimine–lactam tautomerism is possible, the equilibria can be studied by NMR and IR as well as by UV spectroscopy. 1,4-Dihydro derivatives and phthalonimides are obtained respectively by reduction and manganese dioxide oxidation of 3(2H)-isoquinolones, and these can readily be interconverted.

3(2H)-ISOQUINOLONES FORM a class of heterocycle whose chemistry until recently has been somewhat neglected.[1–6] One deterrent to more extensive study has been their relative inaccessibility. We here describe a convenient synthesis and the properties of some 6,7-dioxygenated 3(2H)-isoquinolones.

Synthesis of 3(2H)-*isoquinolones*

The key compounds in this synthesis (Chart 1) are the aldehydes VII and VIII which become readily available from the corresponding arylacetic acids I and II by a sequence involving conversion to the corresponding lactone (III and IV) followed by ring opening with dimethylamine and oxidation with MnO_2. Imino derivatives (IX and X) of these aldehydes undergo smooth cyclisation to the hydrochlorides of the corresponding N-substituted 3(2H)-isoquinolone (XI and XII) upon treatment with hot 6N HClaq. the time required varying from 1 min (*e.g.* for XII, R = Me. —CH_2Ph or —OH) to 20–30 min (*e.g.* for XII. R = —NH_2, or p-Br·C_6H_4—). The free bases. although sensitive in some cases to aerial oxidation. may be recovered as required using NH_4OH.

This cyclisation presumably involves attack upon the arylacetamide carbonyl group by the imino nitrogen atom (*cf.* Type A. Chart 1).[7] The cyclisation step in the previously reported syntheses of 3(2H)-isoquinolones from *ortho* acyl arylacetic acid derivatives[3,8] has been supposed to involve attack upon the acyl carbonyl group by arylacetamide nitrogen atom (Type B mechanism. Chart 1). although Type A cyclisation *via* an imino ester also seems possible. In the present work. the amide aldehydes VII and VIII were found to react with NH_4OH at room temperature to give the corresponding 3(2H)-isoquinolones XI and XII R = H and here cyclisation

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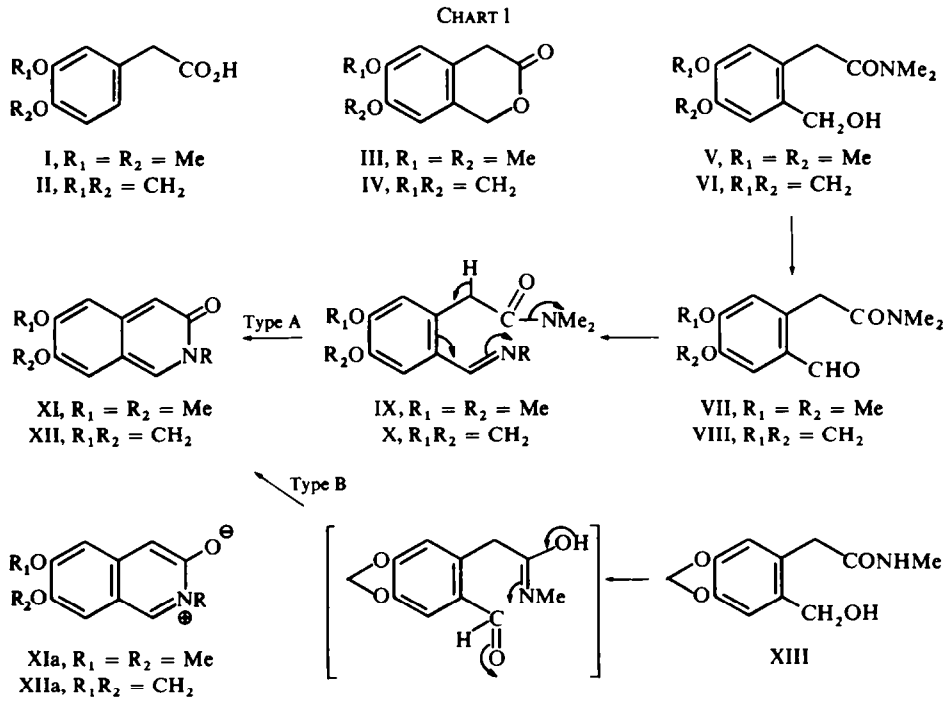
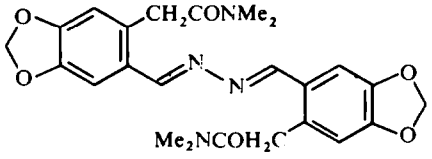
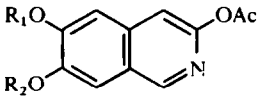
CHART 1



via the imine (Type A mechanism) seems more likely than transamidation and type B cyclisation. However, the type B mechanism seems to be involved in one reaction at least, namely that resulting in the formation of the N-methyl 3(2H)-isoquinolone (XH, R = Me) by MnO_2 oxidation of the amido alcohol XIII in pyridine. (This is a poor method for preparation of isoquinolones because of their susceptibility to further oxidation as discussed later).



XIV



XV, $R_1 = R_2 = Me$
XVI, $R_1R_2 = CH_2$

A side reaction which occurred in the preparation of the hydrazone X (R = NH_2) (highest λ_{max} 314 nm) was the formation of the benzalazine XIV (highest λ_{max} 354 nm) upon repeated crystallization or upon prep. TLC on silica, presumably by self-condensation and loss of hydrazine. Treatment of this compound with hot acid gave the N-amino-3(2H)-isoquinolone (XII. R = NH_2) (92% yield) together with the aldehyde VIII (72%). rather than the *bis*-quinolone which would arise from a double cyclization.

Tautomerism

3(2H)-Isoquinolones having a secondary nitrogen atom are capable of existing as the 3-hydroxyisoquinoline tautomer. Properties of such compounds which have been quoted as indicative of phenolic character are solubility in NaOHaq and a violet reaction with $FeCl_3$.[8] The isoquinolones XI (R = H) and XII (R = H) indeed formed O-acetyl derivatives (XV and XVI)[9] and gave salts merely by crystallization from aqueous solutions of alkali metal hydroxides. The sodium salt of XII (R = H). however. reacted with MeI to give the N–Me rather than O–Me derivative. (CH_2N_2. incidentally. did not appear to react with XII (R = H) in ether–MeOH solution). The $FeCl_3$ reaction cannot be taken as significant of phenolic character since the N-alkyl 3(2H)-isoquinolones XI (R = Me) and XII (R = Me) give similar reactions.

Reliable evidence about the 3(2H)-isoquinolone/isoquinoline-3-ol tautomerism has been provided from UV spectra.[1,3] We have attempted to correlate similar studies on the alkoxyquinolones prepared in the present work with results using IR and NMR spectroscopy.

TABLE 1. RATIO OF INTENSITIES OF ABSORPTION BANDS AT *ca* 400 nm AND *ca* 350 nm

XI. R = H	THF	0·01	$CHCl_3$	1·04
	Dioxan	0·01	$CHCl_3$ + 2% EtOH	1·16
	CCl_4	0·03	Dioxan + 5% H_2O	1·58
	DMSO	0·24	DMSO + 25% H_2O	1·67
	DMSO + 5% H_2O	0·37	EtOH	2·20
			H_2O	2·26
XII. R = H	Dioxan	0·02	EtOH	2·04
			Dioxan + 40% H_2O	2·17
XI. R = Me	Dioxan	2·08	Dioxan + 10% H_2O	2·17
			DMSO	1·43
XII. R = OH	Dioxan	2·14	DMSO	2·20
			EtOH	1·82

It may be seen from Table 1 that for the tautomerisable 3(2H)-isoquinolones. the intensity ratio of the ultraviolet absorptions at *ca.* 400 and at *ca.* 350 nm (usually a maximum or inflection) varies according to solvent, very low values (corresponding to predominance of hydroxyisoquinoline tautomer) being found in aprotic solvents and the highest values (corresponding to predominance of isoquinolone tautomer) being found in EtOH and water. The values for XII, R = OH suggest that this compound probably exists as the N-hydroxy-3(2H)-isoquinolone rather than as the 3-hydroxyisoquinoline N-oxide tautomer[10] even in dioxan.

It has been shown that H-1 appears in the NMR spectrum of 3-methyoxyisoquinoline and 2-methyl-3(2H)-isoquinolone at 1·05 and 1·72 τ respectively.[1,3] suggesting that this resonance might reflect the tautomeric composition of 3(2H)-isoquinolones. Indeed, the H-1 resonance value of XI (R = H) in dioxan or DMSO (1·5 τ) seems to be as might be expected for the dialkoxy-3-hydroxyisoquinolone tautomer. (H-1 in the O—Ac derivatives XV and XVI resonates at *ca.* 1·2 τ). Also the value in D_2O (2·28 τ) is close to that found for the N—Me analogues XI and XII.

Table 2. τ Values of olefinic protons of 6,7-dioxygenated 3(2H)-isoquinolones and related compounds

		H-1	H-4. H-5 and H-8		
XV	$CDCl_3$	1·15	2·98.	2·83.	2·72
XVI	$CDCl_3$	1·26	3·01.	2·87.	2·78
XI, R = H	DMSO	1·47	3·30.	3·00.	2·80
	Dioxan	1·50	3·27.	3·07.	2·91
	DMSO—D_2O (3:1)	1·63	3·32.	3·07.	2·85
	Dioxan—D_2O (4:1)	1·81	3·35.	3·22.	3·05
	Dioxan—D_2O (1:1)	1·86	3·35.	3·20.	3·03
	$CDCl_3$	1·75	3·27.	3·24.	3·14
	MeOH	1·70	3·20.	3·07.	2·88
	D_2O	2·13	3·53.	3·50.	3·35
XI, R = Me	$CDCl_3$	2·20	3·60.	3·50.	3·50
XII, R = Me	$CDCl_3$	2·20	3·45.	3·40.	3·40
	DMSO	1·56	3·51.	3·22.	3·07
	MeOH	1·70	3·33.	3·28.	3·13
XII, R = NH_2	DMSO or DMSO—D_2O	1·53	3·65.	3·37.	3·13
XII, R = OH	DMSO	1·32	3·39.	3·17.	3·02

R = Me, in $CDCl_3$ (2·2 τ). suggesting a preponderance of the 3(2H)-isoquinolone tautomer. Intermediate values are found in $CDCl_3$, MeOH or dioxan—D_2O, apparently reflecting intermediate tautomeric compositions (*cf.* Table 2). That the chemical shift differences may not, however, be entirely due to tautomerism is suggested by the low values for H-1 found for XI and XII, R = Me, in DMSO and MeOH where an increased contribution from the ionised species XIa and XIIa could be responsible.

Table 3. ε_a of some bands in the IR spectra of 3(2H)-isoquinolones

XI (R = H)	$\nu \pm 2\,cm^{-1}$	1653	1635	1611	1592	1581	1570
	THF		200	110		100	140
	Dioxan	80	200	110		80	110
	DMSO	320	340	140	180	170	190
	$CHCl_3$[a]	1020	580	160	130	150	170
	$CHBr_3$	1070	610		190	180	160
	EtOH	1100	700			240	220
XII (R = Me)	$\nu \pm 2\,cm^{-1}$	1664	1652	1620	1560–1580		
	THF	1510	490	170	500		
	$CHCl_3$	1050	900	320	790		

[a] Dilution studies were carried out in this case but no appreciable variation was found

The IR spectra of XI, R = H, also showed solvent dependence (*cf.* Table 3), variations in the band at 1653 cm^{-1} being particularly marked. Thus the predominance of hydroxyisoquinoline tautomer in THF or dioxan and of isoquinolone tautomer in

EtOH or $CHCl_3$ were reflected by low and high intensities respectively of this band.* These results from IR and NMR suggest that the variations in tautomer composition with solvent parallel those found in the more dilute solutions used in the determination of UV spectral data.

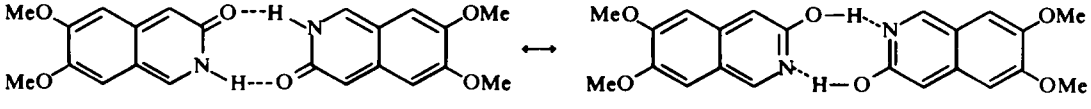
Oxidation and reduction products

While these secondary lactams were relatively stable compounds, their N-alkyl analogues were sensitive to light, in EtOH giving high melting insoluble dimers, presumably the 1,4-photodimers,[3,17] and readily undergoing aerial oxidation in $CHCl_3$. The latter was first appreciated after MnO_2 oxidation of the amido-alcohol XIII had been found to afford not the expected aldehyde but the phthalonimide XVIII (R = Me) (imide and keto groupings giving ν_{max} at 1730, 1700 and 1681 cm^{-1}, deshielding by *peri* carbonyl groups[14] giving two low field aryl protons, 2·30 and 2·44 τ). Briefer treatment allowed isolation of a second product identified as the isoquinolone XII (R = Me) and this was readily converted to the phthalonimide by further treatment with MnO_2 in $CHCl_3$ or, slightly less efficiently, merely by exposure of a $CHCl_3$ solution to air and light.[15]

3(2H)-Isoquinolones appear to be reacting towards oxygen as cisoid dienes. Support for the concept of an endoperoxide intermediate (*cf.* XIX) was recently provided by the reported[4] oxygenation of N-methyl-3(2H)-isoquinolone in boiling benzene, presumably in the presence of light to give a mixture of the phthalonimide and a hydroxy compound, assigned structure XX rather than the isomeric XXI on the basis of the chemical shift (4·2 τ in dry DMSO-d_6) of the methine proton geminal to the OH group. We suggest that this value is acceptable for the latter structure, which represents the more likely product of an ionic rearrangement of the hypothetical endoperoxide intermediate XIX. Comparison may be made with H-6 in 6-hydroxycrinamine and its C-6 epimer (XXII), which give rise to signals at 4·95 and 4·35 τ.[16]

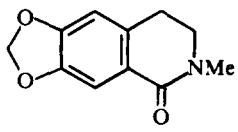
Reduction of alkoxy-3(2H)-isoquinolones was of particular interest in view of possible application to the synthesis of various alkaloidal systems. Catalytic reduction readily afforded colourless 1,4-dihydro derivatives (XXIII or XXIV) (showing UV spectra corresponding to the dialkoxybenzene and $\nu_{C=O}$ at 1650 cm^{-1}).† XXIV (R = Me) was also obtained in good yield by reduction of the isoquinolone with Zn/HCl and could also be obtained in fair yield by reduction with $NaBH_4$. The

* It may be noted that one complication in interpreting such IR results is the possible occurrence of strong intermolecular hydrogen bonds. The solid state IR spectra of XI and XII (R = H) showed broad absorption centred at 2600 cm^{-1}, indicative of strong intermolecular association[11] to which their greater solubility in organic solvents, relative to their N-substituted derivatives can be attributed.[12] Molecular weight estimations by isothermal distillation carried out on XI (R = H) over a series of concentrations in $CHCl_3$ gave results in the range 362–401, indicating almost complete self-association in this solvent to give the resonance stabilised dimer:

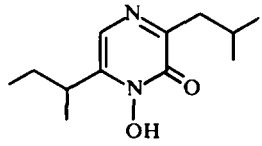


† More direct synthesis of 1,4-dihydro-3(2H)-isoquinolones from 2-hydroxymethylphenylacetic acid lactones may be possible in some cases[17]

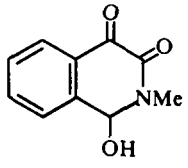
Chart 2



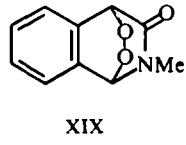
XXV



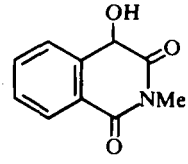
XXVII



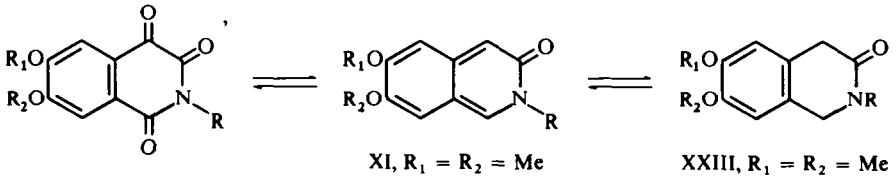
XXI



XIX



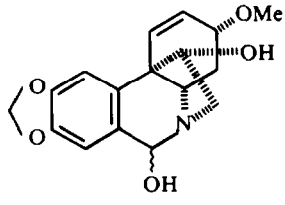
XX



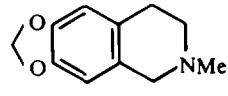
XVII, $R_1 = R_2 = Me$
XVIII, $R_1R_2 = CH_2$

XI, $R_1 = R_2 = Me$
XII, $R_1R_2 = CH_2$

XXIII, $R_1 = R_2 = Me$
XXIV, $R_1R_2 = CH_2$



XXII



XXVI

latter reaction could involve reduction of the iminium system in the dipolar form (XIIa. R = Me) of the isoquinolone (*cf*, reduction of *e.g.* papaverine methiodide[18]).

The carbinolimine tautomer is no longer resonance stabilised in the 1,4-dihydro derivatives. Thus acetylation of XXIII (R = H) occurs on the nitrogen atom (3H singlet at 7·41 τ, $\nu_{C=O}$ 1712, 1703 cm^{-1}. downfield shifts by 0·4 p.p.m. of the H-1 protons and by 0·15 p.p.m. of the H-4 protons) and the absence of strong intermolecular association in $CHCl_3$ is indicated by molecular weight measurements and by NH absorptions occurring at 3402 cm^{-1}.

It was observed that the colourless 1.4-dihydro derivative XXIV (R = Me) tended to turn yellow on standing. This was shown to be due to oxidation and it was found that treatment with MnO_2 in $CHCl_3$ gave the phthalonimide (12% yield) together with unreacted material and smaller amounts of isoquinolone (XII, R = Me). These lactams incorporate the system $Ar{\cdot}CH_2{\cdot}N$ (conceivably oxidisable by MnO_2) and 1-methyl-2(1H)-isoquinolone and oxyhydrastinine[19] (XXV) which lack this, are unaffected by these conditions. The reverse transformation was readily effected in

good yield using Zn/HCl, small quantities of the probable intermediate the isoquinolone (XII, R = Me), again being detected.

Preparation of the corresponding tetrahydroisoquinoline systems was readily completed by LAH reduction of the 1.4-dihydro-3(2H)-isoquinolones. The product obtained in this way from XXIV (R = Me) was shown to be hydrohydrastinine (XXVI), also preparable from oxyhydrastinine (XXV).[19] In view of the reactivity of 3(2H)-isoquinolones towards borohydride, the isoquinolone XII (R = Me) itself was treated with LAH and found to give a good yield of hydrohydrastinine, traces of presumed intermediate dihydroisoquinolone also being detected. However, it was evident that two-stage reduction of a 3(2H)-isoquinolone might be preferable in some cases since LAH reduction of XI (R = H) gave only tars. Application of the above results to the synthesis of a number of alkaloidal systems will be described in separate paper.

TABLE 4. % ABUNDANCE OF MAJOR IONS IN THE MASS SPECTRA OF SOME ALKOXY-3(2H)-ISOQUINOLONES

Losses[a]	—	15 Me	28 CO	43 CO Me	58 CO HCHO	68 CO Me CO	86 CO HCHO CO
XI. R = H	54	21	65	79	23	83	—
XII. R = H	100[b]	—	78[b]	—	8	—	34
XII. R = Me	100[b]	—	69[b]	5	8	—	24

[a] Interpretation of the transitions involved being supported by the presence of appropriate metastable ions

[b] Accompanied by doubly charged ions of *ca.* 10% abundance

Mass spectral breakdown of the 3(2H)-isoquinolones indicated in Table 4, proceeds by loss of 28 mass units (presumably CO) followed by further breakdown evidently involving the ether grouping (CH_3 and CO being eliminated from the dimethoxy compound and HCHO and CO from the methylenedioxy compounds).[20] The corresponding 1.4-dihydro derivatives show a predominant fragmentation involving loss of NR=C=O presumably by retro Diels–Alder type of mechanism. The lactone III analogously loses CO_2. The N-hydroxy-3(2H)-isoquinolones XI and XII (R = OH), were markedly different from those in Table 4 in that they gave only a very weak parent ion (or no parent ion if a heated inlet system was used). Facile loss of 16 mass units (oxygen) from the 3-hydroxyisoquinoline-N-oxide tautomer may be responsible N-oxides being known to undergo such facile cleavage.[21] In keeping with this, the remainder of the spectrum was essentially the same as that of the isoquinolone XI or XII (R = H).

Antibacterial properties have been associated with a number of cyclic hydroxamic acids[22] (*e.g.* aspergillic acid, XXVII[23]) and N-hydroxy-3(2H)-isoquinolones XI and XII (R = OH) were found to be active against *E. coli*, *S. aureus* and *B. subtilis*. Since the dihydro compound XXIII (R = OH) was inactive, the activity of the foregoing compounds may reflect their ability to exist as N-oxide tautomers.*

* In this connection, quinoline N-oxide was found to be active against *B. subtilis*. Also, amodiaquine N-oxide and related N-oxides have been found to be five times more potent as antimalarials than amodiaquine itself[24]

EXPERIMENTAL

M.ps are uncorrected. Unless otherwise stated. NMR spectra were determined at 60 MHz. Chemical shifts are given in τ using TMS as internal reference and coupling constants (J) in Hz.

4.5-*Dimethoxy-2-hydroxymethylphenylacetic acid lactone* III. A. Veratraldehyde azlactone.[25] under the conditions applied in the following preparation to its methylenedioxy analogue. gave the lactone III. which after crystallization from EtOH (charcoal) and C_6H_6-light petroleum (b.p. 60–80°) formed colourless leaflets (44·5 g. 33%). m.p. 110–112°. $\nu_{max}^{CCl_4}$ cm^{-1}: 1760; λ_{max}^{EtOH} 234 nm (ε 5600). 286 (3000): NMR ($CDCl_3$): two 1H s at 3·18 and 3·23 (H-3 and H-6). 4·72 (2H. s. $—CH_2CO·O—$). 6·10 (6H s. OMe). 6·35 (2H s. $Ar·CH_2O·CO—$). (Found: C. 63·5; H. 6·0. $C_{11}H_{12}O_4$ requires C. 63·5; H. 5·8%).

B. The lactone III was also readily prepared in *ca.* 70% yield by chloromethylation of 3.4-dimethoxyphenylacetic acid.[26]

2-Hydroxymethyl-4.5-methylenedioxyphenylacetic acid lactone IV. The mixture of benzoic acid and homopiperonylic acid obtained by hydrolysis and oxidative decomposition of piperonal azlactone (200 g).[25] was heated at 100° for one hr with glacial HOAc (500 ml). conc HCl aq (150 ml) and 40% HCHO aq (150 ml) and then poured into water (500 ml). The $CHCl_3$ extracts of the resulting solution were thoroughly washed with sat $NaHCO_3$ aq and water. Evaporation of the $CHCl_3$ and crystallization from EtOH (charcoal) gave the lactone as pale brown crystals (33 g. 25%). m.p. 125–130°. sufficiently pure for further reaction. Further purification was effected by filtration in 1:1 $CHCl_3$–MeOH through a short column of Al_2O_3 (Woelm. Grade I. neutral). followed by crystallization from EtOH giving colourless crystals. m.p. 132–135°. identical with authentic material (IR spectra. m.m.p.) ν_{max}^{Nujol} cm^{-1}: 1735; $\nu_{max}^{CCl_4}$ cm^{-1}: 1762. λ_{max}^{EtOH} 240 nm (ε 3100). 290 (4400). NMR ($CDCl_3$): 6·40 (2H. s. sharpened by irr at 4·80 or 3·31. $Ar·CH_2·CO·O—$). 4·80 (2H s. sharpened by irr at 6·40 or 3·29. $Ar·CH_2·O·CO—$). 3·31 (1H m. collapsing to s upon irr at 6·40. H-6). 3·29 (1H m. collapsing to s upon irr at 4·80. H-3).

2-(N.N-Dimethylcarboxamidomethyl)-4.5-dimethoxybenzyl alcohol (V). The lactone III (10 g). refluxed with 33% ethanolic Me_2NH (200 ml) for 3½ hr gave the *dimethoxybenzyl alcohol*. which crystallized from C_6H_6-light petroleum (b.p. 60–80°) in colourless prisms (10·3 g. 85%). m.p. 127–128°. ν_{max}^{Nujol} cm^{-1}: 3325 (OH). 1620 ($—CONR_2$); λ_{max}^{EtOH} 235 nm (ε 9100). 284 (2900); NMR ($CDCl_3$): 7·03 and 6·85 (two s. each 3H. NMe_2). 6·27 (2H. s $Ar·CH_2·CO—$). 6·15 and 6·13 (two s. each 3H. OMe). 5·50 (2H s. $Ar·CH_2O—$). 3·33 (1H s. H-3). 3·05 (1H s. H-6). (Found: C. 61·9; H. 7·6; N. 5·7. MW by isothermal distillation 267 ± 15. $C_{13}H_{19}NO_4$ requires: C. 61·7; H. 7·5; N. 5·5% M.W. 251).

2-(N.N-Dimethylcarboxamidomethyl)-4.5-methylenedioxybenzyl alcohol (VI). The lactone IV (14·8 g) was refluxed gently with 33% ethanolic Me_2NH (300 ml) for 3 hr. Evaporation and crystallization of the residue from C_6H_6-light petroleum (b.p. 60–80°) gave the *alcohol* VI as colourless needles (16·15 g. 88%). m.p. 98–99°. $\nu_{max}^{CCl_4}$ cm^{-1}: 3410. 1647; λ_{max}^{EtOH} 244 nm (ε 4700). 294 (4100); NMR ($CDCl_3$): 7·02 and 6·82 (two s. each 3H. $—NMe_2$). 6·28 (2H s. $Ar·CH_2·CO—$). 5·51 (2H s. $Ar·CH_2·O—$). 4·04 (2H s. $—OCH_2O—$). 3·37 (1H s. H-3). 3·10 (1H s. H-6). (Found: C. 61·0; H. 6·3; N. 5·9. $C_{12}H_{15}NO_4$ requires: C. 60·8; H. 6·4; N. 5·9%).

2-(N.N-Dimethylcarboxamidomethyl)-4.5-dimethoxybenzaldehyde VII. The alcohol V (11·8 g) was shaken with MnO_2 (100 g) in $CHCl_3$ (200 ml) for 48 hr. Filtration (glass paper) and evaporation of $CHCl_3$ gave the *dimethoxybenzaldehyde*. crystallized from light petroleum (charcoal) in colourless needles (10·04 g. 86%). m.p. 112·5–113°. $\nu_{max}^{CCl_4}$ cm^{-1}: 1693 (ε 720. —CHO). 1654 (ε 510. $—CONR_2$). 1604 (ε 330): λ_{max}^{EtOH} 236 nm (ε 22.900). 283 (10.000). 315 (6500); NMR ($CDCl_3$): 7·03 and 6·88 (two s. each 3H. $—NMe_2$). 6·07 (6H s. OMe). 5·93 (2H s. $Ar·CH_2·CO—$). 3·22 (1H s. H-3). 2·70 (1H s. H-6). 0·03 (1H s. —CHO). (Found: C. 62·2; H. 6·6; N. 5·4. $C_{13}H_{17}NO_4$ requires: C. 62·2; H. 6·8; N. 5·6%).

The corresponding *oxime* crystallized from EtOH in colourless needles. m.p. 175–178° decomp.. ν_{max}^{Nujol} cm^{-1}: 3250. 1640; λ_{max}^{EtOH} 217 nm (ε 18.600). 229 (20.400). 272 (11.500). 304 (4700). (Found: C. 58·5; H. 6·5; N. 10·6. $C_{13}H_{18}N_2O_4$ requires: C. 58·6; H. 6·8; N. 10·5%).

2-(N.N-Dimethylcarboxamidomethyl)-4.5-methylenedioxybenzaldehyde VIII. The alcohol VI (10·8 g) in $CHCl_3$ (250 ml) was shaken with MnO_2 (100 g) for 60 hr. The MnO_2 was removed by filtration through glass paper and washed with hot $CHCl_3$. Evaporation of the combined filtrates gave the *aldehyde* which crystallized from light petroleum as colourless needles (9·01 g. 85%). m.p. 130–131°: ν_{max}^{Nujol} cm^{-1}: 1690. 1645. 1610: λ_{max}^{EtOH} 236 nm (ε 24.600). 281 (5400). 316 (6000). The corresponding *semicarbazone* crystallized from 40% aqueous EtOH in colourless crystals. m.p. 226°; λ_{max}^{EtOH} 219 nm (ε 28.200). 292 (20.400). 322 (18.600) unchanged on acidification. (Found: C. 53·4; H. 5·3; N. 19·3. $C_{13}H_{16}N_4O_4$ requires: C. 53·4; H. 5·5; N. 19·2%).

The corresponding *oxime* crystallized from EtOH in colourless plates (slow crystallization gave needles).

double m.p. 173·5–174·5 and 257–264° decomp.; ν_{max}^{Nujol} cm^{-1}: 3250, 1620; λ_{max}^{EtOH} 212 nm (ε 22.400), 228 (15.500) inf., 273 (9800), 309 (5600). (Found: C, 57·7; H, 5·65; N, 11·0; MW by isothermal distillation 270 ± 15. $C_{12}H_{14}N_2O_4$ requires: C, 57·6; H, 5·60; N, 11·2% MW 250). The oxime was readily acetylated by heating at 100° with an excess Ac_2O for 5 min* and pouring on to crushed ice. The *oxime acetate* crystallized from C_6H_6-light petroleum (b.p. 60–80°) in colourless needles, m.p. varying with rate of heating 148–163°, but one spot by TLC. ν_{max}^{Nujol} cm^{-1} 1760, 1640. (Found: C, 57·9; H, 5·8; N, 9·8. $C_{14}H_{16}N_2O_5$ requires: C, 57·5; H, 5·5; N, 9·6%).

2-(N,N-*Dimethylcarboxamidomethyl*)-4,5-*methylenedioxybenzylidene methylamine* (X, R = Me). The aldehyde VIII (6·77 g) was refluxed with 33% ethanolic $MeNH_2$ (135 ml) for 90 min. Evaporation gave the *imine* which crystallized from C_6H_6-light petroleum (b.p. 60–80°) in pale yellow needles (6·38 g, 90%), m.p. 127–128·5°: ν_{max}^{Nujol} cm^{-1}: 1635 (—$CONR_2$); λ_{max}^{EtOH} 230 nm (ε 18.900), 274 (9000), 311 (7000); $\lambda_{max}^{EtOH\cdot HCl\,aq}$ 246 nm (ε 38.000), 305 (14.600), 355 (17.900), reverting upon basification to EtOH spectrum: NMR ($CDCl_3$): 7·01 and 6·94 (two s, each 3H, —CO·NMe_2), 6·52 (3H, d, J = 2, MeN=), 6·07 (2H, s, Ar·CH_2·$CONR_2$), 4·02 (2H, s, —O·CH_2·O—), 3·28 (1H, s, H-3), 2·66 (1H, s, H-6), 1·57 (1H, q, J = 2, Ar·CH=N—). (Found: C, 63·05; H, 6·75; N, 11·2. $C_{13}H_{16}N_2O_3$ requires: C, 62·9; H, 6·5; N, 11·3%).

2-(N,N-*Dimethylcarboxamidomethyl*)-4,5-*methylenedioxybenzylidene benzylamine* (X, R = CH_2·Ph). The aldehyde VIII (264 mg) in EtOH (20 ml) was refluxed with benzylamine (118 mg) for 3 hr. Evaporation gave the *imine* which crystallized from benzene-light petroleum (b.p. 60–80°) in pale yellow plates (285 mg, 78%), m.p. 86–87·5°: λ_{max}^{EtOH} 233 nm (ε 15.000), 278 (6100), 313 (4500); $\lambda_{max}^{EtOH-HCl\,aq}$ 251 nm (ε 10.400), 308 (4500), 360 (8200), reverting upon basification to EtOH spectrum. (Found: C, 70·6; H, 6·0; N, 8·4. $C_{19}H_{20}N_2O_3$ requires: C, 70·4; H, 6·2; N, 8·6%).

2-(N,N-*Dimethylcarboxamidomethyl*)-4,5-*methylenedioxybenzilidene* p-*bromoaniline*. (X, R = *p*Br × C_6H_4—). The aldehyde VIII (560 mg) in EtOH (40 ml) was refluxed with *p*-bromoaniline (400 mg) for 3 hr. Evaporation gave the *imine* which crystallized from EtOH in colourless needles (830 mg, 90%), m.p. 141–142·5°: λ_{max}^{EtOH} 237 nm (ε 20.000), 290 (10.000), 337 (14.800); $\lambda_{max}^{EtOH-HCl\,aq}$ 227 nm (ε 17.000), 236 (16.500), 285 (4.900), 318 (4.200). (Found: C, 55·8; H, 4·3; N, 7·1; Br, 20·3. $C_{18}H_{17}BrN_2O_3$ requires C, 55·6; H, 4·4; N, 7·2; Br, 20·6%).

6,7-*Dimethoxy*-2-*methyl*-3(2H)-*isoquinolone* (XI, R = Me). The aldehyde VII (1 g) was refluxed with 33% ethanolic $MeNH_2$ (50 ml) for 2 hr. Evaporation gave the imine as an orange gum: ν_{max}^{Nujol} cm^{-1}: 1640, 1600; λ_{max}^{EtOH} nm: 228, 238, 274, 308; $\lambda_{max}^{EtOH-HCl\,aq}$ nm: 220, 247, 312, 354. Treatment of the crude imine with warm 6N HCl aq (30 ml) for 1 min gave a precipitate of *isoquinolone hydrochloride* which crystallized from 6N HCl aq as pale yellow fluffy needles (842 mg, 73%), m.p. behaviour: subliming at *ca.* 190° to needles, m.p. 226–233° decomp: ν_{max}^{Nujol} cm^{-1}: 3400 (br), 1950, 1640, 1620, 1570, 1540; λ_{max}^{EtOH} 252 nm (ε 63.000), 288 (2.400), 303 (3.500), 314 (3.600), 394 (2.900); $\lambda_{max}^{EtOH-HCl\,aq}$ 249 nm (ε 57.800), 307 inf (7.500), 314 (7.100), 364 (3.600); NMR (CF_3CO_2H): Three 3H s at 5·81, 5·77 and 5·70 (NMe and two OMe), three 1H s at 2·70, 2·58, 2·37 (H-4, H-5, and H-8), 1·20 (1H s, H-1). (Found: C, 49·3; H, 6·0; N, 4·9. $C_{12}H_{13}NO_3$·HCl·HCl·H_2O requires C, 49·4; H, 6·2; N, 4·8%). Treatment of the isoquinolone hydrochloride with NH_4OH and extraction with $CHCl_3$ gave the isoquinolone as an unstable yellow solid which rapidly oxidised on exposure to air. NMR ($CDCl_3$): Three 3H s at 6·31, 6·18 and 6·10 (NMe and two OMe), 1H s at 3·60 and 2H s at 3·50 (H-4, H-5 and H-8), 2·2 (1H s, H-1).

6,7-*Dimethoxy*-2-*hydroxy*-3(2H)-*isoquinolone* (XI, R = OH). A. The oxime (285 mg) of the aldehyde VII, in warm EtOH (12 ml) was treated with 6N HCl aq (6 ml). After 12 hr at room temp. $CHCl_3$ extraction gave the isoquinolone hydrochloride which crystallized from 6N HCl aq in colourless needles (200 mg), m.p. behaviour: subliming above 165° to needles, m.p. 216·5–221° decomp. Sublimation at 140–200°/0·1 mm gave the free *N-hydroxyisoquinolone* as a bright yellow solid, m.p. behaviour: subliming above 190 to needles, m.p. 218–222·5 decomp: ν_{max}^{Nujol} cm^{-1}: 1655, 1635, 1580, 1550, 1525, 1510; λ_{max}^{EtOH} 251 nm (ε 43.700), 305 (4900), 390 (3000); $\lambda_{max}^{EtOH-HCl\,aq}$ 249 (ε 44.000), 306 (7400), 315 (8100), 364 (4000); NMR (CF_3CO_2H): two 3H s at 5·83 and 5·80 (OMe), three 1H s at 2·65, 2·55 and 2·30 (H-4, H-5 and H-8), 0·96 (1H s, H-1). (Found: C, 59·5; H, 4·9. M^+ at *m/e* 221. $C_{11}H_{11}NO_4$ requires: C, 59·7; H, 5·0% MW 221). The isoquinolone formed a bright red Ni complex. It discoloured upon exposure to air.

B. The aldehyde VII (880 mg) in warm EtOH (30 ml) was warmed with NH_2OH·HCl (1·25 g) in 50% EtOH-aq (40 ml) and allowed to stand for 4 hr. $CHCl_3$ extraction gave the isoquinolone (722 mg), m.p. behaviour and IR spectrum identical to that of a sample prepared as in A.

* Longer reaction with Ac_2O resulted in partial conversion to the corresponding nitrile as indicated by IR max at 2240 cm^{-1}, and by the isolation of the dihydroisoquinoline XXIV (R = OH) after catalytic reduction.

2-Amino-6.7-dimethoxy-3(2H)-isoquinolone (XI. R = NH_2). The hydrazone prepared from the aldehyde VII (1·43 g). was heated at 100° for 30 min with 6N HCl aq (50 ml). Cooling to 0° resulted in crystallization of the *isoquinolone hydrochloride* which recrystallized from 6N HCl aq in pale yellow needles. (1·17 g. 80%). m.p. 197–207° decomp; ν_{max}^{Nujol} cm^{-1}: 3400. 3200. 2540. 1880 br. 1640. 1625. 1575; $\lambda_{max}^{EtOH-NaOH}$ 251·5 nm (ε 69.000). 307 (4400). 317 (4300). 395 (3400); $\lambda_{max}^{EtOH-HCl}$ 249 nm (ε 60.000). 310 *inf* (7200). 317 (7900). 364 (3300); NMR (DMSO): two 3H s. at 6·13 and 6·05 (OMe). 1H s at 2·72 and 2H s at 2·60 (H-4. H-5. H-8). 0·97 (1H s. H-1); NMR (CF_3CO_2H): two 3H s at 5·78. 5·75 (OMe) three 1H s at 2·59. 2·48. 2·23 (H-4. H-5. H-8), 0·84. (1H s. H-1). (Found: C, 47·9: H, 5·7; N, 10·2. $C_{11}H_{12}N_2O_3 \cdot HCl \cdot H_2O$ requires: C, 48·1; H, 5·5; N. 10·2%).

Treatment of the hydrochloride with NH_4OH and extraction with $CHCl_3$ gave the free isoquinolone: ν_{max}^{Nujol} cm^{-1}: 3300. 3220. 1670. 1650. 1540. found to be very susceptible to aerial oxidation. and unable to be crystallized from common organic solvents.

2-Methyl-6.7-methylenedioxy-3(2H)-isoquinolone (XII. R = Me). A. The imine X (R = Me). prepared from aldehyde VIII. R = Me (8 g) was heated with 6N HCl aq (200 ml) for 1 min. The resulting ppt of *isoquinolone hydrochloride* crystallized from 6N HCl aq in colourless needles (6·88 g. 85%. based on aldehyde). m.p. 195–200° giving a sublimate m.p. 235–240°: ν_{max}^{Nujol} cm^{-1}: 3320. 2600. 2500. 2300. 1900. 1645, 1615, 1560: NMR (CD_3SOCD_3): 6·04 (3H s. $\overset{+}{N}H \cdot Me$), 3·73 (2H s. —O·CH_2·O—) 2H s. at 2·68 and 1H s. at 2·58 (H-4, H-5, H-8), 0·92 (1H s. H-1). (Found: C, 54·8; H, 4·6; N, 5·9. $C_{11}H_9NO_3 \cdot HCl$ requires: C. 55·1: H. 4·2: N. 5·8%).

Treatment of the crude hydrochloride with dilute NH_4OH and extraction with $CHCl_3$ gave the *isoquinolone* which crystallized from MeOH in yellow needles (*ca.* 85% yield. based on aldehyde). m.p. 251–253°: ν_{max}^{Nujol} cm^{-1}: 1662. 1648. 1618. 1566: $\nu_{max}^{CHBr_3}$ cm^{-1}: 1661. 1650. 1618. 1556: λ_{max}^{EtOH} 248 nm (ε 57.800). 290 inf (2700). 305·5 (3300). 317·5 (3500). 399 (4100): $\lambda_{max}^{EtOH-HCl\,aq}$ 246 nm (ε 47.200). 307 inf (8300). 315 (10.000). 358 (5000). 368 (5000). (the spectrum in EtOH–NaOH aq being the same as in EtOH): NMR ($CDCl_3$): 6·26 (3H s. NMe). 4·04 (2H s. —O·CH_2·O—). 1H s at 3·45 and 2H s at 3·40 (H-4. H-5. H-8). 2·20 (1H s. H-1): NMR (CD_3·SO·CD_3): 6·37 (3H s). 3·91 (2H s). four s each 1H at 3·51. 3·22. 3·07 and 1·56: NMR (CF_3CO_2H): 5·77 (3H s). 3·78 (2H s). four s each 1H at 2·87. 2·76. 2·54 and 1·38. (Found: C. 64·9: H. 4·3; N. 7·1; M^+ at *m/e* 203. $C_{11}H_9NO_3$ requires: C. 65·0; H. 4·5; N. 6·9% MW 203). The isoquinolone crystallized from MeOH aq as an almost colourless *dihydrate*. m.p. 232–238°: ν_{max}^{Nujol} cm^{-1}: 3250 br. 1665. 1620. 1540. (Found: C. 55·0; H. 5·4; N. 5·9. $C_{11}H_9NO_3 \cdot 2H_2O$ requires: C. 55·2: H. 5·5; N. 5·9%).

B. The sodium salt of the isoquinolone XII (R = H). was refluxed with excess MeI for 5 hr. Evaporation. extraction with $CHCl_3$ and sublimation of the product at 165°/0·07 mm gave the —Me analogue XII (R = Me) in 70% yield. Identity with a sample prepared as in A was established by TLC. m.m.p. and by comparison of IR and UV spectra (no base shift).

2-(N.N-Dimethylcarboxamidomethyl)-4.5-methylenedioxybenzaldehyde hydrazone (X. R = NH_2) *and the azine* XIV. The aldehyde VIII (360 mg) in EtOH (15 ml) was allowed to stand with 100% hydrazine hydrate (5 ml) for 1 hr. After addition of water (15 ml). $CHCl_3$ extraction gave the *hydrazone* which crystallized from EtOH at low temp to give pale yellow needles (303 mg. 79%). m.p. 143·5–145° resolidifying as yellow-orange needles. m.p. 254–259° *decomp*: ν_{max}^{Nujol} cm^{-1}: 3470. 3260. 1655 sh. 1630. 1580: λ_{max}^{EtOH} 217 nm (ε 23.500). 284 (14.100). 314 (9600): $\lambda_{max}^{EtOH-HCl\,aq}$ 206 nm (ε 20.900). 239 (17.400). 284 (6000). 316 (8700). 354 (7400): NMR ($CDCl_3$): two 3H s at 7·00. 6·97 (—NMe_2). 6·20 (2H s. Ar·CH_2·$CONR_2$). 4·50 (2H br m. NH_2). 4·02 (2H s. —O·CH_2·O—). 3·31 (1H s. H-3). 2·74 (1H s. H-6). 2·04 (1H s. Ar·CH=N—).

The hydrazone underwent self-condensation upon heating briefly in EtOH or upon prep. TLC giving the corresponding *azine* XIV. This crystallized from $CHCl_3$-light petroleum in bright yellow prisms. m.p. 249–253° decomp: ν_{max}^{Nujol} cm^{-1}: 1630. 1595: λ_{max}^{EtOH} 206 nm (ε 32.400). 220 inf (25.700). 246 (30.200). 307 inf (11.200). 352 (25.700): $\lambda_{max}^{EtOH-HCl\,aq}$ 206 nm (ε 33.900). 237 (36.300). 283 (10.000). 318 (13.500). 353 (11.000). 414 (4200): NMR ($CDCl_3$): 7·00 and 6·93 (each 6H s. —NMe_2). 6·08 (4H s. Ar·CH_2·$CONR_2$). 4·00 (4H s. —O·CH_2·O—). 3·25 (2H s. H-3). 2·50 (2H s. H-5). 1·28 (2H s. Ar·CH=N—). (Found: C. 61·5: H. 5·8: N. 12·2. $C_{24}H_{26}N_4O_6$ requires: C. 61·8; H. 5·6: N. 12·0%).

2-Benzyl-6.7-methylenedioxy-3(2H)-isoquinolone (XII. R = CH_2Ph). The crude imine X (R = CH_2Ph) prepared from aldehyde VIII (820 mg) was treated with 6N HCl aq (50 ml). The isoquinolone hydrochloride crystallized almost immediately as colourless needles. Addition of 4N NaOH aq and extraction with $CHCl_3$ gave the *isoquinolone* which crystallized from EtOH in yellow needles (810 mg. 83%. based on VIII). m.p. 210–213°. ν_{max}^{KCl} cm^{-1}: 1661. 1655. 1621. 1566; $\nu_{max}^{CHBr_3}$ cm^{-1}: 1660. 1651. 1619. 1559: λ_{max}^{EtOH} 252 nm (ε 69.000). 293 (3500). 307 (5000). 318·5 (5300). 401 (5200); $\lambda_{max}^{EtOH-HCl\,aq}$ 248 nm (ε 48.500). 308 (9800). 3200 (12.800). 360 (5000). 373 (4900): NMR ($CDCl_3$) 4·66 (2H s. —N·CH_2Ph). 4·08 (2H s. —O·CH_2·O—).

2H s at 3·48 and 1H s at 3·34 (H-4, H-5 and H-8), 2·66 (5H s, Ph), 2·26 (1H s, H-1): NMR (CF_3CO_2H): 4·24 (2H s, —N·CH_2Ph), 3·73 (2H s, —O·CH_2·O—) 2·78 and 2·73 (each 1H s, H-4 and H-5), 2·46 (6H, s, H-8 and Ph), 1·29 (1H s, H-1). (Found: C, 73·4; H, 4·8; N, 5·2. $C_{17}H_{13}NO_3$ requires: C, 73·1; H, 4·7; N, 5·0%).

2-(p-*Bromophenyl*)-6.7-*methylenedioxy*-3(2H)-*isoquinolone* (XII. R = p-Br·C_6H_4—). The *p*-bromoanil X (R = p-Br·C_6H_4—) (585 mg) was heated at 100° with 3·6N HClaq (25 ml) for 10 min. The isoquinolone hydrochloride (160 mg) which had crystallized from the hot solution was removed and heating continued for a further 25 min to give a further 255 mg of crystalline hydrochloride. The hydrochloride was dissolved in NH_4OH and the solution extracted with $CHCl_3$ until colourless. Evaporation gave the *isoquinolone* (371 mg) as a bright yellow solid, a sample of which was purified for analyses by subliming twice at 244°/0·01 mm. m.p. behaviour: subliming at *ca.* 250° to needles m.p. 310–315° decomp: ν_{max}^{KCl} cm^{-1}: 1663, 1655, 1620, 1590, 1563, 1554, 1488; λ_{max}^{EtOH} 252 nm (ε 60.500), 310 (6800), 321 (7300), 408 (4500); $\lambda_{max}^{EtOH-HCl\,aq}$ 251 nm (ε 58.500), 316 inf (13.300), 323 (13.800), 366 (4700); NMR (CF_3CO_2H): 3·64 (2H s, —O·CH_2·O—) three 1H s at 2·69, 2·63, 2·35 (H-4, H-5, H-8), two 2H d at 2·51 and 2·05 (AA'BB' system, J_{AB} = 9, p-Br·C_6H_4—), 1·30 (1H s, H-1). (Found: C, 55·9; H, 3·2; N, 4·0. MW by isothermal distillation 364 ± 20. $C_{16}H_{10}BrNO_3$ requires: C, 55·8; H, 2·9; N, 4·1% MW 344).

2-*Hydroxy*-6.7-*methylenedioxy*-3(2H)-*isoquinolone* (XII. R = OH). A. The aldehyde VIII (320 mg) in EtOH (5 ml) was treated with NH_2OH·HCl (400 mg) in EtOH (4 ml) at 100° for 1 min. The isoquinolone hydrochloride separated as pale brown crystals (235 mg), m.p. behaviour: subliming above 210° to yellow needles m.p. 277–279°: NMR (CH_3·SO·CH_3): 3·84 (2H s, —O·CH_2·O—), three 1H s at 3·04, 2·94, 2·83 (H-4, H-5, H-8), 1·08 (1H s, H-1).

When a solution of the hydrochloride in the minimum volume of hot dil. NH_4OH was allowed to cool, the free *isoquinolone* crystallized in yellow needles. Sublimation at 190°/0·01 mm gave analytical sample, m.p. 285–286°, bright yellow when hot and pale yellow when cold. ν_{max}^{KCl} cm^{-1}: 1647 br, 1617, 1554 sh, 1527 sh, 1510; λ_{max}^{EtOH} 246·5 nm (ε 60.000), 290 (4100), 303 (5700), 314·5 (5700), 393 (4200); $\lambda_{max}^{EtOH-HCl\,aq}$ 245 nm (ε 56.200), 306 (8000), 317 (8900), 354 inf (4800), 365 (5100): NMR (CH_3·SO·CH_3): 4·16 (1H s, OH), 3·94 (2H s, —O·CH_2·O—), three 1H s at 3·39, 3·17, 3·02 (H-4, H-5, H-8), 1·32 (1H s, H-1): NMR (CF_3CO_2H): 3·70 (2H s, —O·CH_2·O—), three 1H s at 2·75, 2·68, 2·39 (H-4, H-5, H-8), 1·07 (1H s, H-1). (Found: C, 58·7; H, 3·8; N, 7·0. $C_{10}H_7NO_4$ requires: C, 58·5; H, 3·4; N, 6·8%).

B. Treatment of ethanolic solutions of either the oxime or oxime acetate of the aldehyde VIII with a few drops of dil HClaq gave almost immediate pptn of the isoquinolone hydrochloride as needles, m.p. 274–279° (IR spectrum identical to that of a sample prepared as in A.).

2-*Amino*-6.7-*methylenedioxy*-3(2H)-*isoquinolone*. (XII. R = NH_2). A. The hydrazone prepared from the aldehyde VIII (1·32 g) was heated at 100° for 15 min with excess 6N HClaq. The clear solution obtained was allowed to cool and basified with dil NaOHaq. $CHCl_3$ extraction gave the *isoquinolone* which crystallized from EtOH in orange-yellow needles (0·97 g, 85%), m.p. 222–234° decomp: ν_{max}^{KCl} cm^{-1}: 1659, 1614, 1541; $\nu_{max}^{CHBr_3}$ cm^{-1}: 1662, 1652, 1610, 1546; λ_{max}^{EtOH} 250 nm (ε 64.900), 293 inf (3200), 307 (5200), 318·5 (5300), 400 (5100); $\lambda_{max}^{EtOH-HCl\,aq}$ 247 nm (ε 50.700), 310 inf (9900), 317 (10.900), 356 inf (4700), 367 (5200): NMR (DMSO): 3·95 (2H s, —O·CH_2·O—), three 1H s at 3·52, 3·24, 2·99 (H-4, H-5, H-8), 1·53 (1H s, H-1): NMR (CF_3CO_2H): 3·67 (2H s, —O·CH_2·O—), three 1H s at 2·74, 2·67, 2·40 (H-4, H-5, H-8), 1·04 (1H s, H-1). (Found: C, 59·0; H, 4·0; N, 13·3. $C_{10}H_8N_2O_3$ requires: C, 58·8; H, 3·9; N, 13·7%).

B. The azine XIV (52 mg) was heated at 100° with 6N HClaq (10 ml) for a few min. The neutral product, isolated by $CHCl_3$ extraction and prep. TLC as a colourless solid (19 mg, 72%), m.p. 128–131·5°, was shown to be identical with the aldehyde VIII (IR, UV and TLC). Basification with NH_4OH and $CHCl_3$ extraction now gave the aminoisoquinolone (92%), identity with a sample prepared as in A by IR, UV and TLC.

6.7-*Dimethoxy*-3(2H)-*isoquinolone*. (XI. R = H). The aldehyde VII (1·53 g) in EtOH (30 ml) was allowed to stand overnight with conc NH_4OH (50 ml). Extraction with $CHCl_3$ gave the *isoquino.one* as a pale yellow fluorescent solid (1·21 g, 97%), m.p. 235–245° decomp, sublimation at 175–180°/0·02 mm giving bright yellow prisms, m.p. 236–245° decomp: ν_{max}^{KCl} cm^{-1}: 1656, 1638, 1614, 1580, 1560; $\nu_{max}^{CHCl_3}$ cm^{-1}: 1653, 1637; λ_{max}^{EtOH} 251 nm (ε 46.500), 286 (2400), 300 (2300), 313 (2400), 393 (2900); $\lambda_{max}^{EtOH-HCl\,aq}$ 248 nm (ε 41.100), 305 (6800), 313 (7500), 362 (3600); $\lambda_{max}^{EtOH-NaOH\,aq}$ 246 nm (ε 43.800), 275 (6100), 285 (4400), 370 (3200): NMR ($CDCl_3$): two 3H s at 6·05 and 6·01 (OMe), three 1H s at 3·27, 3·24, 3·14 (H-4, H-5, H-8), 1·75 (1H s, H-1): NMR (CD_3·SO·CD_3): two 3H s at 6·14 and 6·10 (OMe), three 1H s, at 3·25, 2·96, 2·75 (H-4, H-5, H-8), 1·43 (1H s, H-1): NMR (CF_3CO_2H): two 3H s at 5·76 and 5·72 (OMe), three 1H s at 2·59, 2·41, 2·37 (H-4, H-5, H-8), 1·08 (1H d, J = 6, H-1). (Found: C, 64·7; H, 5·7; N, 7·1. M^+ at *m/e* 205. MW by isothermal

distillation 377 ± 20. $C_{11}H_{11}NO_3$ requires: C. 64·4: H. 5·4: N. 6·8% MW 205). The isoquinolone gave a hydrochloride and a sodium salt like the methylenedioxy analogue. The dimethoxy compound was rather susceptible to aerial oxidation. $CHCl_3$ solutions turning red upon shaking.

The O–Ac *derivative* crystallized from light petroleum (b.p. 60–80°) in colourless crystals m.p. 96–98·5°: ν_{max}^{Nujol} cm^{-1}: 1760: λ_{max}^{EtOH} 239 nm (ε 44.000). 268 (4700). 280 (4200). 291 (3700). 315 (2800). 327 (2900). reverting to the spectrum of the isoquinolone upon standing: NMR ($CDCl_3$): 7·65 (3H s. —O·CO·CH_3). 6·02 (6H s. two OMe). three 1H s at 2·98. 2·83. 2·72 (H-4. H-5. H-8). 1·15 (1H s. H-1).

6.7-*Methylenedioxy*-3(2H)-*isoquinolone* (XII. R = H). The aldehyde VII (1·45 g) in EtOH (10 ml) was allowed to stand overnight with conc NH_4OH (70 ml). to give a nearly quantitative yield of the *isoquinolone* as a bright yellow ppt. A sample sublimed at 180–185°/0·05 mm as prisms. m.p. 284–285°: ν_{max}^{KCl} cm^{-1}: 1644. 1606: λ_{max}^{EtOH} 246·5 nm (ε 37.500). 303 (2100). 316 (2400). 354 (1500). 394 (2200): $\lambda_{max}^{EtOH-HCl\,aq}$ 244 nm (ε 36.400). 305 inf (5000). 314 (5900). 356 (3100). 367 (3200): $\lambda_{max}^{EtOH-NaOH\,aq}$ 240 nm (ε 36.200). 248 (32.800). 277 (6100). 288 (4100). 372 (3200): NMR (CD_3·SO·CD_3): 3·91 (2H s. —O·CH_2·O—). three 1H s at 3·29. 2·99. 2·78 (H-4. H-5. H-8). 1·50 (1H s. H-1): NMR (CF_3CO_2H): 3·68 (2H s. —O·CH_2·O—). three 1H s at 2·72. 2·60. 2·47 (H-4. H-5. H-8). 1·24 (1H d. J = 6. H-1). (Found: C. 63·8: H. 3·9: N. 7·6. M^+ at *m/e* 189. $C_{10}H_7NO_3$ requires: C. 63·5: H. 3·7: N. 7·4% MW 189).

The *hydrochloride* (obtained by crystallization from 6N HCl aq) formed colourless needles (hydrated by IR). which on drying at 50–60° for 3 hr. turned pale yellow. m.p. 270–272°. NMR (CD_3·SO·CD_3): 3·75 2H s. —O·CH_2·O—). three 1H s. at 2·70. 2·68. 2·54 (H-4. H-5. H-8). 1·17 (1H s. H-1). 0·65 (1H. m. NH). (Found- C. 53·9: H. 4·20: N. 6·4. $C_{10}H_7NO_3$·HCl requires: C. 53·2: H. 3·6: N. 6·2%). Complete loss of HCl occurred upon heating at 60° under vacuum for 72 hr the isoquinolone. m.p. 285° being recovered.

The *sodium salt* (obtained by crystallization from 4N NaOH aq) formed pale yellow plates. m.p. not below 360°: ν_{max}^{Nujol} cm^{-1}: 1640 (weak). 1600 (strong). (Found: Na as Na_2CO_3. 10·4. $C_{10}H_6NO_3$·Na·H_2O requires: Na 10·0%).

The *O-Ac derivative* XVI (obtained from XII. (R = H) by 4 hr reflux with excess Ac_2O and evaporation) crystallized from EtOAc-light petroleum (charcoal). in colourless leaflets. m.p. 134–136 : ν_{max}^{KCl} cm^{-1}: 1758 sh. 1746. 1601. 1238: $\nu_{max}^{CHCl_3}$ cm^{-1}: 1767. 1752 sh. 1602: λ_{max}^{EtOH} 235 nm (ε 29.100). 265 (4600). 278 (4500). 287 sh (4200). 317 (3300). 329 (3400) gradually reverting on standing to the spectrum of the isoquinolone ($t_{\frac{1}{2}}$ *ca.* 4 hr): NMR ($CDCl_3$): 7·66 (3H s. —O·CO·CH_3). 3·96 (2H s. —O·CH_2·O—) three 1H s at 3·01. 2·87. 2·78 (H-4. H-5. H-8). 1·26 (1H s. H-1). (Found: C. 62·6: H. 3·9: N. 6·1. Highest fragment ion at *m/e* 189. MW by isothermal distillation 249 ± 15. $C_{12}H_9NO_4$ requires: C. 62·3: H. 3·9: N. 6·1% MW 231). The acetate was hydrolysed only slowly on shaking with water or 4N NaOH aq but was rapidly converted by 6N HCl aq to the isoquinolone hydrochloride.

2-*Hydroxymethyl*-N-*methyl*-4.5-*methylenedioxyphenylacetamide* (XIII). The lactone IV (6·22 g) was refluxed with 33% ethanolic $MeNH_2$ (135 ml) for 6 hr. The *alcohol*. which separated on standing overnight. crystallized from EtOH in colourless needles (5·26 g. 73%). m.p. behaviour: subliming above 165 to needles. m.p. 172–173°: ν_{max}^{Nujol} cm^{-1}: 3280. 3100. 1635. 1590: λ_{max}^{EtOH} 241 nm (ε 4300). 290 (3500): NMR (CF_3CO_2H): Three 2H s at 5·94. 4·37 and 3·97 (Ar·CH_2·CO—. Ar·CH_2OH. —O·CH_2·O—). 3H d at 6·74 (J = 5. CH_3NH—). two 1H s at 3·15. 3·11 (H-3. H-6). (Found: C. 59·1: H. 5·7: N. 6·5. $C_{11}H_{13}NO_4$ requires: C. 59·2: H. 5·8: N. 6·3%).

N-*methyl*-4.5-*methylenedioxyphthalonimide* (XVIII. R = Me). A. The amido-alcohol XIII (180 mg) in acetone (5% aqueous. 20 ml) was shaken with MnO_2 (2 g) for 48 hr. Sublimation of product at 160–180°/0·03 mm gave the *phthalonimide* as bright yellow solid. m.p. behaviour: subliming above 190 to needles. m.p. 225–227°: ν_{max}^{KCl} cm^{-1}: 1726. 1692. 1675. 1627. 1614. 1593. 1502: $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (weak). 1701 (medium). 1681 (strong). 1616. 1605. 1596: λ_{max}^{EtOH} 227 nm inf (ε 6900). 267 (25.100). 337 inf (1600). 374 (2300). unchanged by addition of acid: NMR ($CDCl_3$): 6·55 (3H s. NMe). 3·76 (2H s. —O·CH_2·O—). two 1H s at 2·44. 2·30 (H-5 and H-8): NMR (CF_3CO_2H): 6·41 (3H s. NMe). 3·70 (2H s. —O·CH_2·O—). two 1H s at 2·30. 2·15 (H-5 and H-8). (Found: C. 56·9: H. 3·3: N. 6·1. M^+ at *m/e* 233. $C_{11}H_7NO_5$ requires: C. 56·7: H. 3·0: N. 6·0% MW 233). It was shown by TLC that the crude product contained traces of the isoquinolone XII (R = Me) and that this was a probable intermediate in the reaction.

B. The isoquinolone XII (R = Me) (50 mg) was shaken with MnO_2 (1 g) in $CHCl_3$ (10 ml) for 6 hr. (The characteristic fluorescence of the isoquinolone solution disappeared after 3 min but TLC showed only traces of phthalonimide at this stage). Separation of the least polar fraction by prep. TLC gave the phthalonimide as a bright yellow solid (20 mg 35%). m.p. behaviour: subliming above 180° to needles. m.p. 222–224°. identical (IR and TLC) with a sample prepared as in A.

Under these conditions. 2-pyridone and 2-methyl-1-isoquinolone were unchanged.

The importance of air, light and MnO_2 in this reaction was assessed in a series of experiments using 1–2 mg of XII (R = Me), carried out by standing in $CHCl_3$ at room temp for 72 hr. Almost all of the isoquinolone was found to be unchanged if air was excluded or by the action of air alone and at least half was unchanged by the action of air and MnO_2 in the absence of light. Almost complete conversion to the phthalonomide was effected by O_2 and light in the absence of MnO_2. use of MnO_2 gave cleaner product.

1,4-*Dihydro*-2-*methyl*-6,7-*methylenedioxy*-3(2H)-*isoquinolone*, XXIV, R = Me. A. Catalytic reduction of the isoquinolone XII (R = Me) in EtOH over PtO_2 for 4 hr and crystallization of the product from water gave the *dihydro derivative* as very pale yellow needles, m.p. behaviour: subliming over 115° to needles, m.p. 136–137°: ν_{max}^{KCl} cm^{-1}: 1650, 1500: $\nu_{max}^{CHCl_3}$ cm^{-1}: 1646·5: λ_{max}^{EtOH} 237·5 nm (ε 3400), 293 (4200): NMR ($CDCl_3$): 6·90 (3H s, NMe) two 2H t, J = 1·8 at 6·47 and 5·58 (H-4 and H-1 respectively), 4·03 (2H s, —O·CH_2·O—), 3·35 (2H s, H-5 and H-8). (Found: C, 64·7; H, 5·4; N, 6·9. $C_{11}H_{11}NO_3$ requires: C, 64·4; H, 5·4; N, 6·8%).

B. The isoquinolone (100 mg), suspended in 6N HCl aq (20 ml) was heated at 100° with Zn powder (1 g) during 1 hr. After basification of the filtered solution with NH_4OH, $CHCl_3$ extraction gave crude dihydro compound which was obtained after prep. TLC as a cream coloured solid (67 mg, 66%), m.p. behaviour: subliming over 110° to needles, m.p. 134–136°, identical (IR, UV, TLC) to a sample prepared as above.

C. The isoquinolone (100 mg) in MeOH (30 ml) was refluxed with $NaBH_4$ for 1 hr. After pouring into water, $CHCl_3$ extraction and prep. TLC gave the dihydro compound (60 mg, 59%), m.p. 133–137°, identical (IR and NMR) with a sample prepared as in A.

2-*Amino*-1,4-*dihydro*-6,7-*methylenedioxy*-3(2H)-*isoquinolone*, (XXIV, R = NH_2). Catalytic reduction of the isoquinolone XII (R = NH_2) in EtOH aq over PtO_2 for 3 hr and sublimation of the product at 160–175°/0·02 mm gave pale yellow needles, m.p. behaviour: subliming over 165° to needles, m.p. 182–186° decomp: ν_{max}^{KCl} cm^{-1}: 3326, 3208, 1644, 1623, 1616 sh, 1506: $\nu_{max}^{CHCl_3}$ cm^{-1}: 1644·5, 1615: λ_{max}^{EtOH} 242 nm (ε 4100), 292·5 (4000). (Found: C, 58·4; H, 4·7; N, 13·4. $C_{10}H_{10}N_2O_3$ requires: C, 58·3; H, 4·9; N, 13·6%).

1,4-*Dihydro*-6,7-*dimethoxy*-2-*hydroxy*-3(2H)-*isoquinolone*, (XXIII, R = OH). Catalytic reduction of the isoquinolone XI (R = OH) in EtOH aq over PtO_2 for 2½ hr and sublimation of the product at 140–170°/0·05 mm and crystallization from EtOH gave very pale yellow needles, m.p. 185–197° decomp: ν_{max}^{KCl} cm^{-1}: 3125 br, 1650 sh, 1635, 1615: $\nu_{max}^{CHCl_3}$ cm^{-1}: 3310 br, 1633: λ_{max}^{EtOH} 221·5 nm (ε 14.800), 284 (7400) (no shift on acidification). (Found: C, 59·1; H, 5·7; N, 6·3. $C_{11}H_{13}NO_4$ requires: C, 59·2; H, 5·8; N, 6·3%).

1,4-*Dihydro*-6,7-*dimethoxy*-3(2H)-*isoquinolone*, (XXIII, R = H). Catalytic reduction of the isoquinolone XI (R = H), in EtOH aq over PtO_2 for 5½ hr and prep. TLC on silica, followed by sublimation at 180–195°, 0·2 mm and crystallization from EtOH gave yellow leaflets, m.p. behaviour: subliming above 170° to prisms, m.p. 201–204° decomp: ν_{max}^{KCl} cm^{-1}: 3190, 1688, 1658, 1610: $\nu_{max}^{CHCl_3}$ cm^{-1}: 3402, 3205, 1673, 1658, 1613: λ_{max}^{EtOH} 230 nm (ε 2400), 285 (3600) (unchanged by addition of acid or base): NMR ($CDCl_3$): 6·45 (2H t, J = 1·8, Ar·CH_2·CO—), 6·11 (6H s, OMe), 5·50 (2H dd, $J_{1,4}$ = 1·8, $J_{1,2}$ = 5, H-1), 3·30 (2H s, H-5 and H-8), 2·33 (1H br m, NH). (Found: C, 63·7; H, 6·0; N, 6·8. M^+ at *m/e* 207: MW by isothermal distillation 220 ± 15. $C_{11}H_{13}NO_3$ requires: C, 63·8; H, 6·3; N, 6·8% MW 207).

The *N-Ac derivative* XXIII (R = CO·CH_3) (prepared by heating XXIII (R = H) at 100° with excess Ac_2O for 2 hr, decomposition of excess reagent with MeOH and evaporation) crystallized from EtOH (charcoal) in colourless prisms, m.p. behaviour: subliming above 125° to needles, m.p. 137–139°: ν_{max}^{KCl} cm^{-1}: 1697 br, 1613, 1522, $\nu_{max}^{CHCl_3}$ cm^{-1}: 1712, 1703, 1614: λ_{max}^{EtOH} 236 nm (ε 3900), 286 (3700): NMR ($CDCl_3$): 7·41 (3H s, —CO·CH_3), 6·30 (2H s, H-4), 6·11 (6H s, OMe), 5·10 (2H s, H-1), two 1H s at 3·23 and 3·14 (H-5 and H-8). (Found: C, 62·8; H, 6·1; N, 5·3. $C_{13}H_{15}NO_4$ requires: C, 62·7; H, 6·0; N, 5·6%). This derivative was rapidly hydrolysed back to the lactam by dil NaOH aq.

1,4-*Dihydro*-6,7-*methylenedioxy*-3(2H)-*isoquinolone*, (XXIV, R = H). Catalytic reduction of the isoquinolone XII (R = H) (100 mg) in HOAc (50 ml) over PtO_2 (50 mg) for 3 hr and crystallization of the product from EtOH gave the dihydroisoquinolone as pale yellow–green needles (63 mg, 63%), m.p. 219–224°. ν_{max}^{KCl} cm^{-1}: 1682 sh, 1663, 1502: $\nu_{max}^{CHCl_3}$ cm^{-1}: 3424, 1685, 1673·5: λ_{max}^{EtOH} 210 nm (ε 8300), 235 inf (3100), 291 (4100). (Found: C, 62·6; H, 4·8; N, 7·5. M^+ at *m/e* 191. $C_{10}H_9NO_3$ requires: C, 62·8; H, 4·7; N, 7·3% MW 191).

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