744. *Synthetic Work in the Aporphine Field*

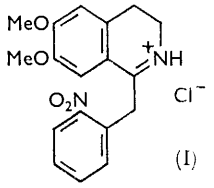
By I. Baxter and G. A. Swan

6-Acetyl-1,2-dimethoxynoraporphine has been synthesised. The acetylation of 3,4-dihydro-6,7-dimethoxy-1-(2-nitrobenzyl)isoquinoline has been examined and a number of products isolated.

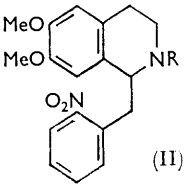
The synthesis of noraporphine derivatives from 1-(2-aminobenzyl)-1,2,3,4-tetrahydroisoquinolines has been investigated by a number of workers.[1] In all the examples investigated the nitrogen atom of the isoquinoline nucleus had basic properties. We have now examined this synthesis in the case where the isoquinoline nitrogen atom is non-basic.

[1] L. Marion, L. Lemay, and R. Ayotte, *Canad. J. Res.*, 1950, **288**, 21; D. H. Hey and L. C. Lobo, *J.*, 1954, 2246; J. A. Weisbach and B. Douglas, *J. Org. Chem.*, 1962, **27**, 3738.

3,4-Dihydro-6,7-dimethoxy-1-(2-nitrobenzyl)isoquinoline hydrochloride (I) was reduced by sodium borohydride to the corresponding tetrahydro-base (IIa) which on acetylation gave the amide (IIb). Catalytic reduction of the latter over platinum gave the primary amine (IIIa). The infrared spectrum of this base showed a low *N*-acetyl frequency (1613 cm.$^{-1}$) presumably owing to interaction between the carbonyl group of the amide and the primary amino-group. Acetylation of the base (IIIa) removed the possi-

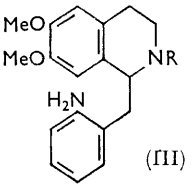


(I)



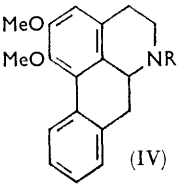
(II)

(IIa : R = H)
(IIb : R = COMe)



(III)

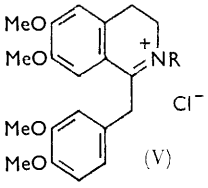
(IIIa : R = COMe)
(IIIb : R = Et)



(IV)

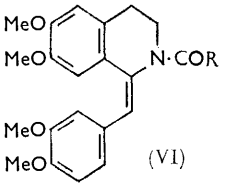
(IVa : R = COMe)
(IVb : R = Et)

bility of this interaction's occurring, and the tertiary *N*-acetyl frequency rose to a more normal value (1629 cm.$^{-1}$). 2-Acetyl-1-(4-aminobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline also showed a normal *N*-acetyl absorption (1634 cm.$^{-1}$). Diazotisation of the base (IIIa) followed by treatment with copper powder gave a neutral substance which was not identical with 2-acetyl-1-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline and must be 6-acetyl-1,2-dimethoxynoraporphine (IVa) (*dl*-*N*-acetylnornuciferine). The yield was 18%. Reduction of the latter with lithium aluminium hydride gave the corresponding 6-ethyl compound (IVb) which was isolated as its hydrochloride. The same hydrochloride was obtained by an alternative route. The dihydroisoquinoline hydrochloride (I) was converted into the corresponding ethiodide and then reduced with zinc and hydrochloric acid to the diamine (IIIb). Application of the Pschorr reaction to this diamine gave a gummy base whose hydrochloride was identical with that of the base (IVb).



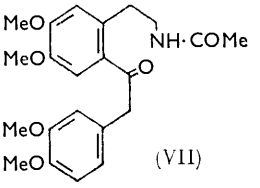
(V)

(Va : R = H)
(Vb : R = Me)



(VI)

(VIa : R = Me)
(VIb : R = H)



(VII)

When 3,4-dihydro-6,7-dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline hydrochloride (Va) was treated with either acetic anhydride in the presence of sodium acetate or acetic anhydride alone the *N*-acetyl compound (VIa) was obtained. A similar reaction was observed with 1-benzyl-3,4-dihydro-6,7-dimethoxyisoquinoline hydrochloride. Dilute hydrochloric acid converted the amide (VIa) into the deoxybenzoin (VII). A similar reaction has been reported by Brossi *et al.*[2] When the salt (Va) was treated with a mixture of formic acid and acetic anhydride in the presence of sodium acetate the *N*-formyl compound (VIb) was obtained which on reduction with lithium aluminium hydride followed by treatment with hydrogen chloride gave the methochloride (Vb).

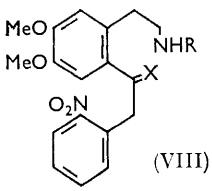
Acetylation of the salt (I) with acetic anhydride and sodium acetate gave rise to three compounds designated A, B, and C. When the acetylation was performed with either acetic anhydride and pyridine or acetic anhydride alone a compound D was isolated (see Table). Mild acid hydrolysis of A, B, and D gave compound C which, on the basis of analytical results, spectral evidence, and similarity to compound (VII), must be the ketone

[2] A. Brossi, H. Besendorf, B. Pellmont, M. Walter, and O. Schnider, *Helv. Chim. Acta*, 1960, **43**, 1459.

(VIIIa). Phosphorus oxychloride in benzene, or concentrated hydrochloric acid alone, converted the ketone (VIIIa) into the dihydroisoquinoline hydrochloride (I).

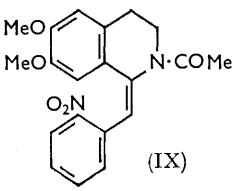
Compound	M. p.	Colour	Formula	$\lambda_{max.}$ (mμ)
A	136°	Yellow	$C_{20}H_{20}N_2O_5$	270
B	152	Yellow	$C_{20}H_{20}N_2O_5$	270
C	142	White	$C_{20}H_{22}N_2O_6$	230, 274
D	201	Yellow	$C_{20}H_{20}N_2O_5$	290

The infrared spectra of compounds A, B, and D showed differences for all three compounds but there appeared to be some similarities between those of A and B and A and D. The spectra of A and D showed a peak at 1639 cm.$^{-1}$ attributable to a tertiary *N*-acetyl group while the principal peak in the spectrum of B was at 1653 cm.$^{-1}$. Moreover, the peaks assigned to the nitro-group were in similar positions in the spectra of A and B but in different positions in the spectrum of D. It is proposed that compounds A and D are geometrical isomers arising from the presence of a stilbene nucleus in the molecule. Comparison of the ultraviolet spectra of compounds A and D with those of *cis*- and *trans*-2-nitrostilbene [3] suggests that A is the *cis*-compound (IX) and D the *trans*-compound (X).

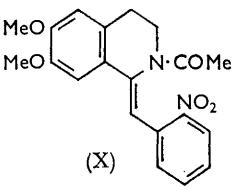


(VIII)

(VIIIa: R = COMe, X = O)
(VIIIb: R = H, X = N·OH)



(IX)



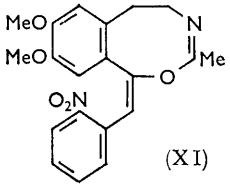
(X)

The spectral data for compound B indicated that it possessed the *cis*-configuration. When it was treated with hydroxylamine hydrochloride in pyridine a small quantity of a compound was obtained which was identical with the compound obtained from the ketone (VIIIa) under similar conditions. On the basis of the elemental analysis and spectral data this compound has been formulated as the deacetylated oxime (VIIIb). A similar reaction was not observed with compounds A and D. When compound B was treated in dry benzene solution with hydrogen chloride a solid was precipitated which on exposure to air rapidly reverted to a gum. Compound D did not react with hydrogen chloride in dry benzene. The proton magnetic resonance spectrum of compound B indicated the presence of a vinyl proton (τ 3·75), two adjacent methylene groups (triplets at τ 7·05 and 5·9), and a methyl group (τ 7·58). It is believed that both the reactions and the spectral data of compound B can be explained on the basis of structure (XI), *i.e.*, *cis*-5,6-dihydro-8,9-dimethoxy-3-methyl-1-(2-nitrobenzylidene)-1*H*-2,4-benzoxazocine. Attempted reduction of the latter with sodium borohydride in methanol gave the isomeric compound (X). This interconversion was also brought about by sodium methoxide.

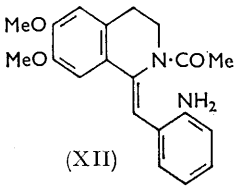
Attempts to prepare the primary amine (IIIa) from either compound (IX) or (X) by catalytic hydrogenation were unsuccessful. The conjugated olefinic bond was resistant to catalytic reduction. Reduction of the nitro-compound (X) over platinum gave the corresponding amino-compound (XII), which yielded a crystalline picrate but no hydrochloride. On treatment with aqueous or ethanolic hydrogen chloride, the base (XII) gave the 2-phenylindole (XIVa) which was further characterised by reduction to the *N*-ethyl compound (XIVb). Catalytic reduction of the *cis*-nitro-compound (IX) failed to yield any of the corresponding amine (XIII) but after treatment with dilute hydrochloric acid the 2-phenylindole (XIVa) and an unidentified base were isolated. Catalytic reduction of the oxazocine (XI) gave the amine (XII). The nitro-compounds (X) and (XI) were reduced

[3] D. F. DeTar and L. A. Carpino, *J. Amer. Chem. Soc.*, 1956, **78**, 475.

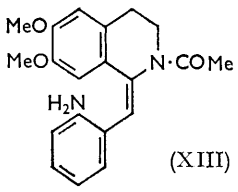
by hydrazine hydrate and Raney nickel to the amine (XII). Reduction of the nitro-compound (IX) gave a non-crystalline base which yielded a picrate which was not identical with the picrate of (XII), although it was isomeric with it. It is suggested that the non-crystalline base was the *cis*-2-aminostilbene (XIII).



(XI)

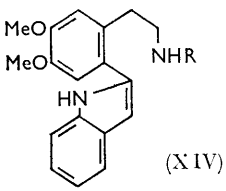


(XII)



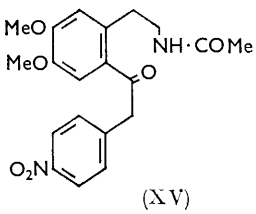
(XIII)

The acetylation of 3,4-dihydro-6,7-dimethoxy-1-(4-nitrobenzyl)isoquinoline under different conditions gave two isomeric compounds. Reduction of one of the isomers with hydrazine hydrate gave *trans*-2-acetyl-1-(4-aminobenzylidene)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline. Attempts to synthesise this base or its acetyl derivative from the corresponding 3,4-dihydroisoquinoline failed. On acid hydrolysis the two nitro-compounds were converted into the ketone (XV).

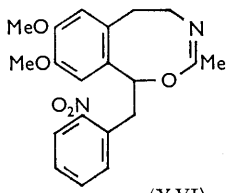


(XIV)

(XIVa : R = COMe)
(XIVb : R = Et)



(XV)



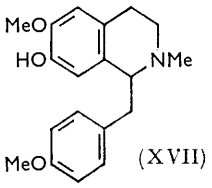
(XVI)

The action of a mixture of formic acid and formamide on a number of 1-benzylisoquinoline derivatives has been reported.[4] We have now examined the action of this reagent on a number of other isoquinoline derivatives. Formic acid and formamide converted 3,4-dihydro-6,7-dimethoxy-1-(2-nitrobenzyl)isoquinoline, 3,4-dihydro-6,7-dimethoxy-1-(4-nitrobenzyl)isoquinoline, and 3,4-dihydro-6,7-dimethoxy-1-(2-nitro-4,5-dimethoxybenzyl)-isoquinoline into the corresponding 2-formyl-1,2,3,4-tetrahydroisoquinolines in low yield. When 2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4-dimethoxybenzylidene)isoquinoline (VIa) was refluxed with formic acid and formamide, 2-formyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline was obtained. When the product from the acetylation of 3,4-dihydro-6,7-dimethoxy-1-(4-nitrobenzyl)isoquinoline with acetic anhydride alone was treated with formic acid and formamide, 2-formyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-nitrobenzyl)isoquinoline was obtained. No crystalline material could be isolated from the reaction between formic acid, formamide, and the nitro-compound (X). However, the nitro-compound (XI) was converted into a neutral substance, $C_{20}H_{22}N_2O_5$. The ultraviolet spectrum of the latter ($\lambda_{max.}$ 285 mμ) indicated the presence of isolated benzene rings, *i.e.*, reduction of the exocyclic double bond had occurred, while the infrared spectrum ($\nu_{max.}$ 1653 cm.$^{-1}$) suggested the presence of a C=N group. The structure (XVI) is proposed for this compound. On warming with dilute hydrochloric acid the compound (XVI) was converted into a non-crystalline material ($\lambda_{max.}$ 286 mμ) whose infrared spectrum indicated the absence of any carbonyl or imino-groups. Formic acid and formamide reacted with the ketone (XV) to give 2-formyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-nitrobenzyl)isoquinoline in good yield.

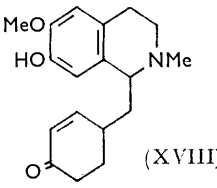
An attempt has been made to synthesise the isoquinoline (XVIII) in the hope that it might undergo cyclisation to give a hydrogenated aporphine derivative. Sodium and

[4] I. Baxter, L. T. Allan, and G. A. Swan, *J.*, 1965, 3645.

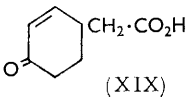
liquid ammonia in the presence of either ethanol or t-butyl alcohol failed to reduce the base (XVII). When sodium and liquid ammonia was used alone, demethylation occurred to a small extent. For the preparation of the base (XVIII) *via* the Bischler–Napieralski reaction the keto-acid (XIX) or some related compound was required. 4-Hydroxycyclohexene-1-acetic acid (XX) has been prepared but it failed to condense satisfactorily with a suitable phenethylamine.



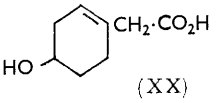
(XVII)



(XVIII)



(XIX)



(XX)

We had prepared 1,2,9-trimethoxyaporphine before a Paper [5] describing the synthesis of this compound by essentially the same method came to our notice. In general there was good agreement between our melting points and those obtained by the Japanese workers although a discrepancy of 17° existed in the melting point of 1-(2-amino-5-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline.

Experimental

The ultraviolet spectra were measured in ethanolic solution.

1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-(2-*nitrobenzyl*)*isoquinoline* (IIa). Sodium borohydride (0·85 g.) was added during 4 hr. to a refluxing solution of 3,4-dihydro-6,7-dimethoxy-1-(2-nitrobenzyl)isoquinoline hydrochloride [6] (3·1 g.) in methanol (60 ml.). The mixture was evaporated to dryness and the residue shaken with a mixture of chloroform and water. The chloroform was collected, dried (K_2CO_3), and evaporated to dryness under reduced pressure to give the title compound as an oil. The *hydrochloride* crystallised from dilute hydrochloric acid and had m. p. 240° (Found: C, 59·45; H, 5·95; N, 7·55. $C_{18}H_{21}ClN_2O_4$ requires C, 59·25; H, 5·8; N, 7·7%).

2-*Acetyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-(2-*nitrobenzyl*)*isoquinoline* (IIb). The foregoing base (2·8 g.) was refluxed with acetic anhydride (30 ml.) for 2 hr. and the reaction mixture poured into water. The solid which was deposited was collected, dried, and recrystallised from methanol. The *amide* (2·4 g.) had m. p. 172°, $\lambda_{max.}$ 285 mμ (log ε 3·92) (Found: C, 64·9; H, 6·1. $C_{20}H_{22}N_2O_5$ requires C, 64·85; H, 6·0%).

2-*Acetyl*-1-(2-*aminobenzyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (IIIa).—The foregong nitro-compound (1 g.) in ethanol (140 ml.) was shaken in an atmosphere of hydrogen with Adams catalyst (0·2 g.). When the hydrogen uptake was complete (3 mol.), the catalyst was filtered off and the filtrate concentrated. On cooling, the *base* formed needles, m. p. 195° $\lambda_{max.}$ 286 mμ (log ε 3·78), $\nu_{max.}$ 1613 cm.$^{-1}$ (*N*-acetyl) (Found: C, 70·55; H, 7·1; N, 8·4. $C_{20}H_{24}N_2O_3$ requires C, 70·55; H, 7·1; N, 8·25%). The *picrate* separated from acetone–ethanol and had m. p. 205° (Found: C, 54·75; H, 4·85; N, 12·4. $C_{26}H_{27}N_5O_{10}$ requires C, 54·85; H, 4·8; N, 12·3%). The *acetyl derivative* separated from methanol and had m. p. 170° (Found: C, 68·9; H, 6·85. $C_{22}H_{26}N_2O_4$ requires C, 69·05; H, 6·85%).

1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-(4-*nitrobenzyl*)*isoquinoline*.—Prepared from 3,4-dihydro-6,7-dimethoxy-1-(4-nitrobenzyl)isoquinoline hydrochloride [7] (4·66 g.) and sodium borohydride (0·78 g.) as described for its isomer (IIa). The *hydrochloride* crystallised from dilute hydrochloric acid and had m. p. 209° (Found: C, 59·6; H, 5·7. $C_{18}H_{21}ClN_2O_4$ requires C, 59·25; H, 5·8%).

2-*Acetyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-(4-*nitrobenzyl*)*isoquinoline*.—The foregoing base (2·9 g.) was acetylated as described for its isomer. The *amide* (2·9 g.) formed needles, m. p. 175° (Found: C, 64·65; H, 6·15; N, 7·95. $C_{20}H_{22}N_2O_5$ requires C, 64·85; H, 6·0; N, 7·55%).

2-*Acetyl*-1-(4-*aminobenzyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline*.—The foregoing amide (1 g.) was reduced with hydrogen in the presence of Adams catalyst (0·2 g.) as described

[5] M. Tomita and T. Kitamura, *J. Pharm. Soc. Japan*, 1959, **79**, 997.
[6] J. M. Gulland and R. D. Haworth, *J.*, 1928, 581.
[7] T. R. Govindachari and K. Nagarajan, *Proc. Indian Acad. Sci.*, 1955, **42**, *A*, 136.

for its isomer. The *base* formed needles from ethanol and had m. p. 183°, $\nu_{max.}$ 1634 cm.$^{-1}$ (Found: C, 69·95; H, 7·1; N, 8·45. $C_{20}H_{24}N_2O_3$ requires C, 70·55; H, 7·1; N, 8·25%).

6-*Acetyl*-1,2-*dimethoxynoraporphine* (IVa).—The base (IIIa) (0·435 g.) was dissolved in 2N-sulphuric acid (35 ml.) and diazotised at 2° with a solution of sodium nitrite (0·087 g.) in water (5 ml.). The solution was kept at 2° for 20 min. and then warmed at 60° for 4 hr. after the addition of copper powder (0·2 g.). The sticky solid which was deposited was collected by extraction with chloroform (A). The aqueous solution was filtered and warmed for 3 hr. after the addition of zinc dust (0·8 g.) and concentrated hydrochloric acid (3 ml.). The acid solution was filtered and extracted with chloroform (B), basified with ammonium hydroxide, and extracted with chloroform (C). Evaporation of the dried extract (A) gave a neutral oil which was chromatographed on alumina. Elution with benzene–chloroform gave a semi-solid which was dissolved in the minimum of hot methanol. On cooling, the *noraporphine* (0·064 g.) separated in white needles, m. p. 233°, $\lambda_{max.}$ 274 mμ (log ε 4·53), $\nu_{max.}$ 1629 cm.$^{-1}$ (*N*-acetyl) (Found: C, 74·8; H, 6·55; N, 4·3. $C_{20}H_{21}NO_3$ requires C, 74·3; H, 6·55; N, 4·35%). Evaporation of extract (B) gave a small quantity of an oil which was not investigated further, whilst extract (C) gave a solid which on recrystallisation from methanol gave the starting base (0·058 g.).

2-*Acetyl*-1-*benzyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline*.—1-Benzyl-3,4-dihydro-6,7-dimethoxyisoquinoline hydrochloride [8] (1·98 g.) was reduced with sodium borohydride (0·44 g.) in hot methanol (90 ml.) as described for the preparation of the base (IIa). The crude product was refluxed with acetic anhydride (10 ml.) for 1·5 hr. The *amide*, isolated in the usual way, formed needles from methanol and had m. p. 114°, $\lambda_{max.}$ 285 mμ (log ε 4·18) (Found: C, 73·85; H, 7·05. $C_{20}H_{23}NO_3$ requires C, 73·8; H, 7·15%).

6-*Ethyl*-1,2-*dimethoxynoraporphine* (IVb).—A suspension of the amide (IVa) (42 mg.) and lithium aluminium hydride (40 mg.) in dry tetrahydrofuran (6 ml.) was refluxed for 5 hr. The excess of hydride was decomposed by the addition of water and the resulting solution extracted with ether. The extract was evaporated to dryness, concentrated hydrochloric acid added to the residue, and the solution evaporated to dryness under reduced pressure. Recrystallisation of the residue from hydrochloric acid gave the *hydrochloride* as a cream coloured solid, m. p. 256°, $\lambda_{max.}$ 274 mμ (log ε 4·27) (Found: C, 69·25; H, 7·05. $C_{20}H_{24}ClNO_2$ requires C, 69·45; H, 7·0%).

3,4-*Dihydro*-6,7-*dimethoxy*-1-(2-*nitrobenzyl*)*isoquinoline Ethiodide*.—A mixture of the base liberated from the hydrochloride (I) (3·3 g.) and ethyl iodide (50 ml.) was refluxed for 3 hr. The mixture was evaporated to dryness and the residue crystallised from ethanol. The *ethiodide* (2·3 g.) formed needles, m. p. 204° (Found: C, 49·35; H, 4·8. $C_{20}H_{23}IN_2O_4$ requires C, 49·8; H, 4·8%).

1-(2-*Aminobenzyl*)-2-*ethyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (IIIb).—Zinc dust (3 g.) was added to a stirred suspension of the foregoing ethiodide (1·05 g.) in water (10 ml.) and concentrated hydrochloric acid (20 ml.) and the mixture heated on a water-bath for 3 hr. The mixture was filtered, cooled, basified with ammonium hydroxide, and extracted with ether. The dried (K_2CO_3) extract was evaporated to dryness and the residue chromatographed on alumina to give the title compound as an oil. The *dipicrolonate* separated from acetone–ethanol and had m. p. 204° (Found: C, 55·8; H, 5·1. $C_{40}H_{42}N_{10}O_{12}$ requires C, 56·2; H, 4·95%). Diazotisation of the diamine (0·5 g.) followed by treatment with copper powder, by method (*a*) described by Gulland and Haworth [6] for the preparation of 1,2-dimethoxyaporphine, gave 6-ethyl-1,2-dimethoxynoraporphine hydrochloride (26 mg.) identical with material obtained by lithium aluminium hydride reduction of 6-acetyl-1,2-dimethoxynoraporphine.

2-*Acetyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-(3,4-*dimethoxybenzylidene*)*isoquinoline* (VIa).—3,4-Dihydro-6,7-dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline hydrochloride [9] (Va) (1·14 g.) was warmed on a water-bath for 1 hr. with acetic anhydride (3·6 ml.) and fused sodium acetate (0·56 g.), and kept overnight at room temperature. Water (10 ml.) was added and the solid which was deposited was collected, dried, and recrystallised from ethanol. The *amide* (0·76 g.) formed white needles, m. p. 193°, $\lambda_{max.}$ 220, 332 mμ (log ε 4·45, 4·44), $\nu_{max.}$ 1631 cm.$^{-1}$ (*N*-acetyl) (Found: C, 68·85; H, 6·5; N, 3·8. $C_{22}H_{23}NO_5$ requires C, 68·9; H, 6·6; N, 3·65%).

2-*Acetyl*-1-*benzylidene*-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline*.—A mixture of 1-benzyl-3,4-dihydro-6,7-dimethoxyisoquinoline hydrochloride (0·80 g.) and acetic anhydride (5 ml.) was refluxed for 0·5 hr. and poured into water. The solid which was deposited was collected,

[8] R. A. Robinson, *J. Org. Chem.*, 1951, **16**, 1911.
[9] M. Onda, *J. Pharm. Soc. Japan*, 1954, **74**, 915.

dried, and recrystallised from ethanol. The *amide* (0·43 g.) formed needles, m. p. 164° (Found: C, 74·2; H, 6·7. $C_{20}H_{21}NO_3$ requires C, 74·3; H, 6·55%).

2-(2-*Acetamidoethyl*)-3′,4,4′,5-*tetramethoxydeoxybenzoin* (VII).—A mixture of the amide (VIa) (0·5 g.), 10% hydrochloric acid (5 ml.), and methanol (2·5 ml.) was heated on a water-bath for 1·5 hr. The methanol was distilled off and the aqueous solution neutralised with potassium carbonate and extracted with chloroform. Evaporation of the dried extract gave a residue which crystallised from benzene–light petroleum (b. p. 60—80°). The *ketone* (0·4 g.) formed needles, m. p. 133°, $\lambda_{max.}$ 230, 278 mμ (log ε 4·51, 4·15), $\nu_{max.}$ 1675 (ketone), 1637 cm.$^{-1}$ (*N*-acetyl) (Found: C, 66·15; H, 6·8. $C_{22}H_{27}NO_6$ requires C, 65·8; H, 6·8%).

2-*Formyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-(3,4-*dimethoxybenzylidene*)*isoquinoline* (VIb).—Prepared from the dihydroisoquinoline hydrochloride (Va) (0·98 g.), fused sodium acetate (0·73 g.), acetic anhydride (3·2 ml.), and 98—100% formic acid (1·2 ml.) as described for the amide (VIa). The *amide* (0·3 g.) crystallised from ethanol in needles, m. p. 168°, $\lambda_{max.}$ 220, 335 mμ (log ε 4·44, 4·34), $\nu_{max.}$ 1653 cm.$^{-1}$ (*N*-formyl) (Found: C, 68·25; H, 6·25; N, 3·9. $C_{21}H_{23}NO_6$ requires C, 68·25; H, 6·3; N, 3·8%).

A suspension of the foregoing amide (0·098 g.) and lithium aluminium hydride (0·02 g.) in dry ether (50 ml.) was stirred and refluxed for 6 hr. Water was added and the ethereal layer collected, dried, and concentrated to approximately one fifth of the original volume. The ethereal solution was saturated with dry hydrogen chloride and the solid which was deposited was collected. Recrystallisation from ethanol–ether gave 3,4-dihydro-6,7-dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline methochloride, m. p. 121° (lit.,[10] 120—121°).

Acetylation of 3,4-*Dihydro*-6,7-*dimethoxy*-1-(2-*nitrobenzyl*)*isoquinoline*.—(*a*) A mixture of the dihydroisoquinoline hydrochloride (I) (5·04 g.), fused sodium acetate (3 g.), and acetic anhydride (30 ml.) was warmed at 80° for 30 min. and kept overnight at room temperature. The mixture was diluted with water and the solid which was deposited was filtered off and recrystallised from ethanol. cis-5,6-*Dihydro*-8,9-*dimethoxy*-3-*methyl*-1-(2-*nitrobenzylidene*)-1H-2,4-*benzoxazocine* (B) (3·02 g.) formed yellow needles, m. p. 152°, $\lambda_{max.}$ 270 mμ (log ε 4·20) (Found: C, 65·25; H, 5·3; N, 7·6; O, 21·85. $C_{20}H_{20}N_2O_5$ requires C, 65·2; H, 5·5; N, 7·6; O, 21·7%). Concentration of the mother-liquor gave cis-2-*acetyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-(2-nitrobenzylidene)isoquinoline (A) (0·2 g.) which crystallised from ethanol in yellow needles, m. p. 136°, $\lambda_{max.}$ 270 mμ (log ε 4·18) (Found: C, 65·05; H, 5·6; N, 8·05. $C_{20}H_{20}N_2O_5$ requires C, 65·2; H, 5·5; N, 7·6%). Further concentration of the mother-liquor gave 2-(2-*acetamidoethyl*)-2′-*nitro*-4,5-*dimethoxydeoxybenzoin* (0·25 g.). Recrystallisation from a mixture of methanol and ether gave white needles, m. p. 142°, $\lambda_{max.}$ 230, 274 mμ (log ε 4·33, 4·04), $\nu_{max.}$ 1681 (aryl ketone), 1637 (*N*-acetyl), 3279 cm.$^{-1}$ (NH) (Found: C, 61·65; H, 5·9. $C_{20}H_{22}N_2O_6$ requires C, 62·15; H, 5·75%).

(*b*) A mixture of the dihydroisoquinoline hydrochloride (I) (1·16 g.) and acetic anhydride (6 ml.) was refluxed for 30 min. and poured into water. The solid which was deposited was filtered off and recrystallised from ethanol affording trans-2-*acetyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-(2-*nitrobenzylidene*)*isoquinoline* (D) (0·67 g.) as yellow needles, m. p. 201°, $\lambda_{max.}$ 290 mμ (log ε 4·09) (Found: C, 65·3; H, 5·4. $C_{20}H_{20}N_2O_5$ requires C, 65·2; H, 5·5%). Repetition of this reaction using pyridine as solvent also gave the *trans*-compound.

Acid Hydrolysis of trans-2-*Acetyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-(2-*nitrobenzylidene*)-*isoquinoline*.—The 1-benzylidene derivative (0·5 g.) was warmed on a water-bath with ethanol (2·5 ml.) and 10% hydrochloric acid (5 ml.) until the solution was colourless, and the reaction mixture worked up as described in the preparation of the ketone (VII). 2-(2-Acetamidoethyl)-2′-nitro-4,5-dimethoxydeoxybenzoin (0·45 g.) crystallised from a mixture of ethanol and ether in needles, m. p. 142°, and was identical with the white solid isolated in part (*a*) of the foregoing reaction. On refluxing with concentrated hydrochloric acid for 6 hr. it was converted into 3,4-dihydro-6,7-dimethoxy-1-(2-nitrobenzyl)isoquinoline hydrochloride, m. p. 227° (lit.,[6] 229°).

2-(2-*Aminoethyl*)-2′-*nitro*-4,5-*dimethoxydeoxybenzoin Oxime* (VIIIb).—A mixture of the benzoxazocine (XI) (0·198 g.), hydroxylamine hydrochloride (0·15 g.), and pyridine (5 ml.) was warmed on a water-bath for 3 hr. The mixture was diluted with water, and the solid which was deposited was collected. Several recrystallisations from ethanol gave the *oxime* (0·01 g.) as an off-white solid, m. p. 218°, $\lambda_{max.}$ 270 mμ (log ε 4·25), $\nu_{max.}$ 1626 cm.$^{-1}$ (C=N, oxime) (Found: C, 61·1; H, 6·0; N, 11·8. $C_{18}H_{21}N_3O_5$ requires C, 60·2; H, 5·9; N, 11·7%). The oxime was

[10] J. Knabe, *Arch. Pharm.*, 1959, **292**, 416.

also obtained from 2-(2-acetamidoethyl)-2′-nitro-4,5-dimethoxy benzoinon treatment with hydroxylamine hydrochloride in pyridine.

The Action of Sodium Borohydride on the Benzoxazocine (*B*) (XI).—Sodium borohydride (0·047 g.) was added to a solution of the benzoxazocine (0·135 g.) in a mixture of methanol (10 ml.) and water (0·5 ml.) and the mixture kept at room temperature overnight. The crystalline material which was deposited (0·052 g.) was filtered off and shown to be unchanged benzoxazocine, m. p. 152°. The filtrate was evaporated to dryness under reduced pressure and the residue shaken with a mixture of chloroform and water. Evaporation of the dried chloroform extract (Na_2SO_4) gave *trans*-2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-nitrobenzylidene)-isoquinoline, m. p. 199°. A similar result was obtained when the benzoxazocine was treated with sodium methoxide in methanol.

trans-2-*Acetyl*-1-(2-*aminobenzylidene*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (XII).—A mixture of the nitro-compound (X) (0·81 g.), Adams catalyst (0·16 g.), and ethanol (50 ml.) was stirred under hydrogen at 3·6 atm. for 4 hr. A white solid was deposited during the reduction and this was redissolved by warming. The solution was filtered and on cooling the *amine* (0·4 g.) was deposited. Recrystallisation from ethanol gave white needles, m. p. 192°, $\lambda_{max.}$ 224, 290, 341 mμ (log ε 4·66, 4·28, 4·28). On the addition of 10% hydrochloric acid the spectrum changed, $\lambda_{max.}$ 227, 330 mμ (log ε 4·47, 4·37) (Found: C, 70·95; H, 6·5; N, 8·4. $C_{20}H_{22}N_2O_3$ requires C, 71·15; H, 6·55; N, 8·3%). The *picrate* crystallised from acetone–ethanol in needles, m. p. 182° (Found: C, 55·05; H, 4·35; N, 12·45. $C_{26}H_{25}N_5O_{10}$ requires C, 55·0; H, 4·45; N, 12·35%). When a solution of the base in dry benzene was saturated with dry hydrogen chloride no precipitate was formed. Evaporation of the solution to dryness gave a residue which crystallised from ethanol, affording 2-(2-2′-*acetamidoethyl*-4,5-*dimethoxyphenyl*)*indole* as white needles, m. p. 203°, $\lambda_{max.}$ 295 mμ (log ε 4·29) (Found: C, 70·85; H, 6·9; N, 8·0. $C_{20}H_{22}N_2O_3$ requires C, 71·0; H, 6·55; N, 8·3%). The *acetyl derivative* separated from ethanol and had m. p. 154° (Found: C, 68·9; H, 6·5. $C_{22}H_{24}N_2O_4$ requires C, 69·4; H, 6·35%).

2-(2-2′-*Ethylaminoethyl*-4,5-*dimethoxyphenyl*)*indole* (XIVb).—A mixture of 2-(2-2′-acetamidoethyl-4,5-dimethoxyphenyl)indole (0·104 g.), lithium aluminium hydride (0·042 g.), dry ether (50 ml.), and tetrahydrofuran (5 ml.) was refluxed for 8 hr. The excess of hydride was decomposed with water and the reaction mixture basified by the addition of 40% sodium hydroxide solution and then extracted with chloroform. Evaporation of the dried extract gave a solid residue which crystallised from ethanol. The *base* formed cream coloured needles, m. p. 132°, $\lambda_{max.}$ 296 mμ (log ε 4·25) (Found: C, 73·55; H, 7·75. $C_{20}H_{24}N_2O_2$ requires C, 74·0; H, 7·45%). The base was also prepared as follows. To a hot solution of 3,4-dihydro-6,7-dimethoxy-1-(2-nitrobenzyl)isoquinoline ethiodide (0·138 g.) in ethanol (4 ml.) was added, during 1 hr., zinc dust (0·4 g.) and 10% sulphuric acid (10 ml.). The mixture was heated for a further 3 hr. and then the ethanol was distilled off. The reaction mixture was filtered, cooled, basified with ammonium hydroxide, and extracted with ether. The dried (Na_2SO_4) extract was evaporated to dryness and the residue recrystallised from methanol. The title base (0·09 g.) separated in needles, m. p. 132°.

Catalytic Hydrogenation of cis-2-*Acetyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-(2-*nitrobenzylidene*)-*isoquinoline*.—A mixture of the *cis*-nitro-compound (2·5 g.), Adams catalyst (0·5 g.), and ethanol (140 ml.) was stirred under hydrogen at 3·6 atmospheres for 4 hr. The catalyst was filtered off and the filtrate evaporated to dryness under reduced pressure. The residue was shaken with chloroform and 10% hydrochloric acid and the chloroform collected, dried (Na_2SO_4), and evaporated to dryness. Recrystallisation of the residue from ethanol gave 2-(2-2′-acetamidoethyl-4,5-dimethoxyphenyl)indole (1·2 g.), m. p. 203°. The original acid solution was basified and extracted with chloroform. Evaporation of the dried extract gave an oil which was dissolved in the minimum of hot ethanol. A *base* (0·1 g.) separated in white needles, m. p. 152°, $\lambda_{max.}$ 233, 284, 313 mμ (log ε 4·37, 4·02, 3·99) in acid solution, $\lambda_{max.}$ 245, 303, 364 mμ (log ε 4·21, 4·15, 3·80) (Found: C, 72·05; H, 6·8; N, 8·5. $C_{20}H_{22}N_2O_2,0{\cdot}5H_2O$ requires C, 72·45; H, 7·0; N, 8·45%).

Catalytic Hydrogenation of the Benzoxazocine (*B*) (XI).—A mixture of the benzoxazocine (0·18 g.), Adams catalyst (0·021 g.), and ethanol (50 ml.) was hydrogenated as described above. The product was *trans*-2-acetyl-1-(2-aminobenzylidene)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline, m. p. 192°.

Reduction of the Nitro-compounds (IX), (X), and (XI) *with Hydrazine Hydrate and Raney*

Nickel.—The *trans*-nitro-compound (X) (0·57 g.) was dissolved in hot ethanol (40 ml.) containing 100% hydrazine hydrate (1·6 ml.), Raney nickel was added, and the mixture refluxed for 45 min. The catalyst was filtered off and the filtrate concentrated. On cooling, *trans*-2-acetyl-1-(2-aminobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (0·42 g.) separated in needles, m. p. 192°.

The nitro-compound (XI) (0·6 g.) and 100% hydrazine hydrate (1·5 ml.) in a similar way gave *trans*-2-acetyl-1-(2-aminobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline, m. p. 189°. The picrate crystallised from acetone–ethanol in needles, m. p. 180°.

A mixture of the *cis*-nitro-compound (IX) (0·136 g.), 100% hydrazine hydrate (0·5 ml.), Raney nickel, and ethanol (10 ml.) was refluxed for 45 min. The catalyst was filtered off and the filtrate evaporated to dryness. The residue was dissolved in the minimum of hot ethanol and cooled. An amorphous base (0·082 g.), m. p. 122—123°, was deposited. The *picrate* crystallised from a mixture of acetone and ethanol and had m. p. 150° (Found: C, 54·8; H, 4·7; N, 12·5. $C_{26}H_{25}N_5O_{10}$ requires C, 55·0; H, 4·45; N, 12·35%).

Acetylation of 3,4-*Dihydro*-6,7-*dimethoxy*-1-(4-*nitrobenzyl*)*isoquinoline Hydrochloride.*—(*a*) The hydrochloride (0·98 g.) was refluxed with acetic anhydride (6 ml.) for 30 min. to give in the usual way an orange solid (0·6 g.). Recrystallisation from ethanol gave needles, m. p. 221°, $\lambda_{max.}$ 379 mμ (log ε 4·4), $\nu_{max.}$ 1661 cm.$^{-1}$ (Found: C, 65·5; H, 5·75. $C_{20}H_{20}N_2O_5$ requires C, 65·2; H, 5·5%). On reduction with hydrazine hydrate and Raney nickel as described earlier, the nitro-compound was converted into a primary amine. trans-2-*Acetyl*-1-(4-*aminobenzylidene*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* crystallised from ethanol and had m. p. 212°, $\lambda_{max.}$ 228, 345 mμ (log ε 4·42, 4·47), $\nu_{max.}$ 1629 cm.$^{-1}$ (*N*-acetyl) (Found: C, 70·75; H, 6·75; N, 8·3. $C_{20}H_{22}N_2O_3$ requires C, 71·15; H, 6·55; N, 8·3%). The *acetyl derivative* crystallised from benzene–light petroleum (b. p. 60—80°) and had m. p. 218°, $\lambda_{max.}$ 335 mμ (log ε 4·35) (Found: C, 69·05; H, 6·3. $C_{22}H_{24}N_2O_4$ requires C, 69·4; H, 6·35%).

(*b*) A mixture of the hydrochloride (0·6 g.), fused sodium acetate (0·3 g.), and acetic anhydride (3 ml.) was warmed on a water-bath for 30 min., kept overnight at room temperature, and worked up in the usual way to give a yellow solid. Recrystallisation from ethanol gave needles (0·36 g.), m. p. 174°, $\lambda_{max.}$ 358 mμ (log ε 4·16), $\nu_{max.}$ 1639 cm.$^{-1}$ (Found: C, 65·7; H, 5·45. $C_{20}H_{20}N_2O_5$ requires C, 65·2; H, 5·5%).

Attempted Preparation of 1-(4-*Acetamidobenzyl*)-3-4-*dihydro*-6,7-*dimethoxyisoquinoline.*—*N*-(3,4-Dimethoxyphenethyl)-4-nitrophenylacetamide [11] (3·0 g.) was reduced with hydrazine hydrate (6 ml.) and Raney nickel in ethanol (250 ml.) in the usual way, to give 4-*amino*-N-(3,4-*dimethoxyphenethyl*)*phenylacetamide* (1·9 g.), m. p. 155° (Found: C, 68·85; H, 6·95. $C_{18}H_{22}N_2O_3$ requires C, 68·75; H, 7·05%). The *hydrochloride* crystallised from ethanol–ether and had m. p. 202° (Found: C, 59·8; H, 6·4. $C_{18}H_{23}ClN_2O_3$ requires C, 60·25; H, 6·45%). The *acetyl derivative* crystallised from benzene in needles, m. p. 158° (Found: C, 67·3; H, 6·95. $C_{20}H_{24}N_2O_4$ requires C, 67·4; H, 6·8%). Attempts to perform the Bischler–Napieralski reaction with this amide or its acetyl derivative using phosphorus pentachloride in chloroform failed. The product was the amide hydrochloride.

2-(2-*Acetamidoethyl*)-4,5-*dimethoxy*-4′-*nitrodeoxybenzoin* (XV).—This was prepared from either of the products from the acetylation of 3,4-dihydro-6,7-dimethoxy-1-(4-nitrobenzyl)isoquinoline hydrochloride by treatment with dilute hydrochloric acid as described for the preparation of its isomer (VIIIa). The *ketone* crystallised from ethanol and had m. p. 177° (Found: C, 62 5; H, 5·75. $C_{20}H_{22}N_2O_6$ requires C, 62·15; H, 5·75%).

2-*Formyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-(2-*nitrobenzyl*)*isoquinoline.*—Prepared from the dihydroisoquinoline hydrochloride (I) (2·1 g.), 98—100% formic acid (12 ml.), and formamide (60 ml.) as described previously.[4] The crude product was collected with chloroform and chromatographed on alumina. Elution with benzene–chloroform (1 : 5) gave a solid which, when recrystallised from ethanol, gave the *amide* (0·7 g.), m. p. 162—163° (Found: C, 64·35; H, 5·85. $C_{19}H_{20}N_2O_5$ requires C, 64·05; H, 5·65%).

2-*Formyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-(4-*nitrobenzyl*)*isoquinoline.*—Prepared from 3,4-dihydro-6,7-dimethoxy-1-(4-nitrobenzyl)isoquinoline hydrochloride (0·52 g.), formic acid (5 ml.), and formamide (50 ml.) as described above. The *amide* (0·19 g.) separated from benzene and had m. p. 186° (Found: C, 64·05; H, 5·55. $C_{19}H_{20}N_2O_5$ requires C, 64·05; H, 5·65%).

This compound was also obtained by two other methods. The product from method (*a*) for the acetylation of 3,4-dihydro-6,7-dimethoxy-1-(4-nitrobenzyl)isoquinoline hydrochloride

[11] L. Marion, L. Lemay, and V. Portelance, *J. Org. Chem.*, 1950, **15**, 216.

0·25 g.) was refluxed for 2·5 hr. with formic acid (2·5 ml.) and formamide (12·5 ml.) and poured into water. The solution was extracted with chloroform and, after drying, the extract was evaporated. Crystallisation of the residue from methanol gave the amide (0·1 g.), m. p. 186°. In a similar way the ketone (XV) (0·08 g.), formic acid (1 ml.), and formamide (5 ml.) gave the amide (0·025 g.), m. p. 186°.

N-(3,4-*Dimethoxyphenethyl*)-4,5-*dimethoxy*-2-*nitrophenylacetamide*.—This was prepared from 3,4-dimethoxyphenethylamine (5·85 g.) and 4,5-dimethoxy-2-nitrophenylacetic acid [12] (5 g.) by a method analogous to that used [13] for the preparation of *N*-(3-methoxyphenethyl)-4,5-dimethoxy-2-nitrophenylacetamide. The *amide* (3·4 g.) crystallised from methanol and had m. p. 172° (Found: C, 59·2; H, 6·05. $C_{20}H_{24}N_2O_7$ requires C, 59·4; H, 6·0%).

3,4-*Dihydro*-6,7-*dimethoxy*-1-(2-*nitro*-4,5-*dimethoxybenzyl*)*isoquinoline Hydrochloride*.—The foregoing amide (1·08 g.) was treated with phosphorus pentachloride (1·2 g.) in dry chloroform in the usual way. The *hydrochloride* (0·64 g.) crystallised from ethanol–ether and had m. p. 234—235° (decomp.), $\lambda_{max.}$ 245, 306, 353 mμ (log ε 4·41, 4·21, 4·21) (Found: C, 55·6; H, 5·9. $C_{20}H_{23}ClN_2O_6,0·5H_2O$ requires C, 55·6; H, 5·6%).

2-*Formyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-(4,5-*dimethoxy*-2-*nitrobenzyl*)*isoquinoline*.—Prepared from the foregoing hydrochloride (0·3 g.), formic acid (1 ml.), and formamide (5 ml.) in the usual way. The *amide* (0·1 g.) crystallised from ethanol and had m. p. 193° (Found: C, 60·2; H, 5·75; N, 7·15. $C_{21}H_{24}N_2O_7$ requires C, 60·55; H, 5·8; N, 6·75%).

The Action of Formic Acid and Formamide on 2-*Acetyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-(3,4-*dimethoxybenzylidene*)*isoquinoline*.—A mixture of the benzylidene compound (0·875 g.), 98—100% formic acid (5 ml.), and formamide (25 ml.) was refluxed for 2 hr. and poured into water, and the aqueous solution extracted with chloroform. Evaporation of the dried extract gave an oil which soldified on trituration with ether. Recrystallisation from methanol gave 2-formyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline (0·477 g.), m. p. 135°.[4]

The Action of Formic Acid and Formamide on the Benzoxazocine (XI).—A mixture of the benzoxazocine (0·725 g.), 98—100% formic acid (6 ml.), and formamide (30 ml.) was refluxed for 2 hr. and poured into water. The solution was extracted with chloroform and, after drying (Na_2SO_4), the extract was evaporated to dryness. The residue was dissolved in hot benzene containing a little chloroform. On cooling, a solid was deposited which was collected and recrystallised from methanol, giving the *compound* (XVI) (0·077 g.) as white needles, m. p. 223°, $\lambda_{max.}$ 285 mμ (log ε 3·84), $\nu_{max.}$ 1653 cm.$^{-1}$ (Found: C, 64·75, 64·8; H, 6·2, 6·15; N, 7·65. $C_{20}H_{22}N_2O_5$ requires C, 64·85; H, 6·0; N, 7·55%).

4-*Acetoxy*-1-*cyanomethylcyclohexene*.—A mixture of 4-acetoxycyclohexanone [14] (7·82 g.), cyanoacetic acid (4·07 g.), ammonium acetate (0·23 g.), and dry benzene (100 ml.) was refluxed for 8 hr. in a flask equipped with a water-separator. The reaction mixture was evaporated to dryness and the residue heated at 170—180° for 2 hr. The residue was distilled to give the *nitrile* (5·8 g.), b. p. 120°/2 mm., $\nu_{max.}$ 1724 (ester), 2247 cm.$^{-1}$ (nitrile) (Found: C, 65·0; H, 7·05; N, 7·15. $C_{10}H_{13}N_2$ requires C, 67·0; H, 7·3; N, 7·75%).

4-*Hydroxycyclohexylideneacetonitrile*.—The foregoing ester (5·0 g.) was refluxed for 0·5 hr. on a water-bath with a mixture of 10% sodium hydroxide solution (50 ml.) and ethanol (50 ml.). The ethanol was distilled off and the remaining solution, after dilution with water, was extracted continuously with hot chloroform. Evaporation of the dried (Na_2SO_4) extract gave a residue which was distilled. The *nitrile* (2·36 g.) formed a viscous liquid, b. p. 150°/2 mm., $\nu_{max.}$ 3413 (OH), 2212 cm.$^{-1}$ (αβ-unsaturated nitrile) (Found: C, 70·1; H, 7·95. $C_8H_{11}NO$ requires C, 70·05; H, 8·1%). The 3,5-*dinitrobenzoate* crystallised from benzene in needles, m. p. 114° (Found: C, 54·85; H, 3·9. $C_{15}H_{13}N_3O_6$ requires C, 54·4; H, 3·95%).

4-*Hydroxycyclohexene*-1-*acetic acid* (XX).—A mixture of the foregoing nitrile (1·5 g.), 60% aqueous potassium hydroxide solution (10 ml.), and ethanol (15 ml.) was refluxed for 8 hr. The ethanol was distilled off and the remaining solution diluted with water. The alkaline solution was extracted with chloroform, acidified, and extracted continuously with hot chloroform. The latter extract, after drying (Na_2SO_4), was evaporated to dryness under reduced pressure, and the residue crystallised from ethyl acetate. The *acid* (0·3 g.) formed cream coloured

[12] R. K. Callow, J. M. Gulland, and R. D. Haworth, *J.*, 1929, 658.
[13] K. W. Bentley and E. T. Blues, *J.*, 1956, 1732.
[14] J. B. Aldersley, G. N. Burkhardt, A. E. Gillam, and N. C. Hindley, *J.*, 1940, 10.

plates, m. p. 144°, $\nu_{max.}$ 3344 (OH), 1712 cm.$^{-1}$ (saturated acid) (Found: C, 61·6; H, 7·8. $C_8H_{12}O_3$ requires C, 61·5; H, 7·75%).

The Reaction between 4-Acetoxycyclohexanone and Ethyl Bromoacetate.—A mixture of ethyl bromoacetate (2·5 g.), 4-acetoxycyclohexanone (2·3 g.), dry toluene (5 ml.), and benzene (7 ml.) was prepared. Approximately one fifth of this solution was added to clean zinc wool (0·97 g.) and the mixture stirred on a boiling water-bath, after the addition of a crystal of iodine. After 10 min. the remainder of the prepared solution was added slowly. The mixture was heated for 2·5 hr., cooled, and treated with 6N-sulphuric acid. The organic layer (A) was collected and dried. Phosphorus pentoxide (3 g.) was added to the extract and the mixture refluxed for 3 hr. Water was added and organic layer collected, dried, and evaporated to dryness. The residue was refluxed with 10% sodium hydroxide solution for 2·5 hr. and the mixture worked up as described in the preceding experiment to give 4-hydroxycyclohexene-1-acetic acid (0·15 g.), m. p. 144°.

When the organic layer (A) was evaporated to dryness and refluxed for 45 min. with acetic anhydride (10 ml.), an ester, $\nu_{max.}$ 1732 cm.$^{-1}$, was isolated, b. p. 130—140°/20 mm. Hydrolysis of this ester with 10% sodium hydroxide solution in the normal way gave *4-hydroxycyclohexylideneacetic acid* (0·45 g.) which crystallised from ethyl acetate and had m. p. 154°, $\nu_{max.}$ 3401 (OH) 1689 cm.$^{-1}$ (αβ-unsaturated acid) (Found: C, 61·6; H, 7·65. $C_8H_{12}O_3$ requires C, 61·5; H, 7·75%).

1-(2-Amino-5-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline.—Concentrated hydrochloric acid (50 ml.) and zinc dust (30 g.) were added gradually during 1 hr. to a solution of 3,4-dihydro-6,7-dimethoxy-1-(5-methoxy-2-nitrobenzyl)isoquinoline methiodide (4 g.) in acetic acid (200 ml.) and water (50 ml.) and the mixture kept overnight in a refrigerator. Further hydrochloric acid (50 ml.) and zinc dust (5 g.) were added and the mixture again kept overnight in a refrigerator, then filtered. The filtrate was basified with ammonium hydroxide and extracted with ether. Evaporation of the extract gave a gum (2·4 g.) which was chromatographed on alumina. Elution with benzene–light petroleum (1 : 1) gave the base which crystallised from benzene–light petroleum in colourless needles, m. p. 94—95° (lit.,[5] 76·5—78°) (Found: C, 69·95; H, 8·0; N, 8·3. Calc for $C_{20}H_{26}N_2O_3$: C, 70·2; H, 7·6; N, 8·2%). The dipicrolonate crystallised from ethanol and had m. p. 195° (lit.,[5] 194°) (Found: C, 53·0; H, 5·0. Calc. for $C_{40}H_{42}N_{10}O_{13},2H_2O$: C, 53·0; H, 5·1%).

1,2,9-Trimethoxyaporphone.—This was prepared from the foregoing base. The hydrochloride crystallised from ethanol and had m. p. 241° (decomp.) (lit.,[5] 206—208°) (Found: C, 60·2; H, 6·6. Calc for $C_{20}H_{24}ClNO_3,2H_2O$: C, 60·35; H, 7·1%).

The *picrate* crystallised from acetone–ethanol and had m. p. 204° (with softening and decomp.) (Found: C, 56·3; H, 4·4. $C_{26}H_{26}N_4O_{10}$ requires C, 56·3; H, 4·7%).

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