Tetrahedron, 1965, Vol. 21, pp. 1907 to 1915. Pergamon Press Ltd. Printed in Northern Ireland

1,2-DIHYDROISOQUINOLINES—I

REARRANGEMENT[1]

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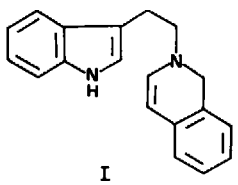
Abstract—1-(3,4-Methylenedioxy)benzyl-2-methyl-6,7-dimethoxy-1,2-dihydroisoquinoline has been shown to rearrange to 3-(3,4-methylenedioxy)benzyl-2-methyl-6,7-dimethoxy-3,4-dihydroisoquinolinium chloride when treated with 2% hydrochloric acid.

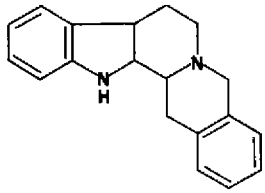
1,2-DIHYDROISOQUINOLINES have been obtained from isoquinolinium salts by reduction with sodium dithionite,[2] LAH[3] or dialkyl aluminium hydrides,[4] or by the reaction with Grignard reagents[5] (to yield 1-substituted derivatives). Various other methods have also been described.[6] There are several reports describing the instability of 1,2-dihydroisoquinolines, especially in the presence of air,[3,7] but compounds such as 1-hydroxy-2-cyano-1,2-dihydroisoquinoline are quite stable,[8] as are the dihydroberberines; a phenyl group in the 3-position seems to confer stability upon a 1,2-dihydroisoquinoline, and 1-phenyl-1,2-dihydroisoquinoline is quite stable to acids (in the absence of air).[9–11]

Interest in 1,2-dihydroisoquinolines has been revived recently firstly, by the observation[12] that derivatives such as (I) are readily cyclized to (II) and secondly, that pavine (VI), a product isolated[13] from the reduction of papaverine (III), with tin and

[1] A Preliminary account has been published: S. F. Dyke and M. Sainsbury, *Tetrahedron Letters* 1545 (1964).
[2] P. Karrer, *Helv. Chim. Acta* **21**, 223 (1938).
[3] For example [a] H. Schmid and P. Karrer, *Helv. Chim. Acta* **32**, 960 (1949);
[b] T. Kametani and K. Fukumoto, Yakugaku Zasshi, **80**, 1288 (1960); *Chem. Abstr.* **55**, 3589f (1961).
[4] W. P. Newmann, *Angew. Chem.* **70**, 401 (1958).
[5] W. Bradley and S. Jeffrey, *J. Chem. Soc.* 2770 (1954).
[6] J. Gademer, M. Oberlin and A. Schoeler, *Arch. Pharm.* **263**, 81 (1925).
[7] T. Kametani, K. Kukumoto and T. Katagi, *Chem. Pharm. Bull.* **7**, 567 (1959); J. Hagimiwa, I Murakoshi and Y. Ohe, *Yakugaku Zasshi* **79**, 1578 (1959).
[8] M. D. Johnson, *J. Chem. Soc.* 200 (1964).
[9] M. Freund and C. Bode, *Ber. Dtsch. Chem. Ges.* **42**, 1746 (1909).
[10] P. R. Brook and P. Karrer, *Helv. Chim. Acta* **40**, 260 (1957).
[11] S. F. Dyke and M. Sainsbury, unpublished work.
[12a] P. L. Julian and A. Magnani, *J. Amer. Chem. Soc.* **71**, 3207 (1949);
[b] J. W. Huffman, *Ibid.* **80**, 5193 (1958);
[c] E. Wenkert, R. A. Massy-Westropp and R. G. Lewis, *Ibid.* **84**, 3732 (1962);
[d] K. T. Potts and R. Robinson, *J. Chem. Soc.* 2675 (1955);
[e] D. R. Liljegren and K. T. Potts, *J. Org. Chem.* **27**, 377 (1962);
[f] K. T. Potts and D. R. Liljegren, *Ibid.* **28**, 3066, 3202 (1963);
[g] B. Belleau, *Chem. & Ind.* 229 (1955);
[h] R. C. Elderfield and B. A. Fisher, *J. Org. Chem.* **23**, 332 (1958).
[13a] F. L. Pyman, *J. Chem. Soc.* **95**, 1610 (1909);
[b] F. L. Pyman and W. C. Reynolds, *J. Chem. Soc.* **97**, 1320 (1910).

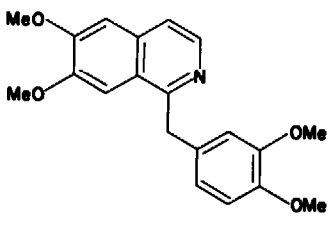


I

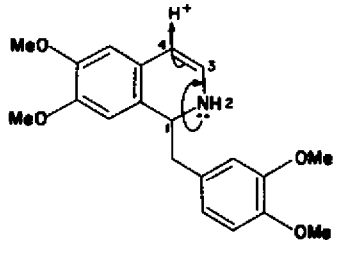


II

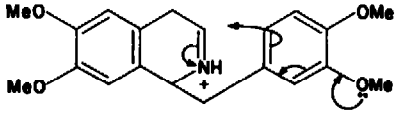
hydrochloric acid, can be regarded[14] as being formed by protonation and ring-closure of the intermediate reduction product, 1,2-dihydropapaverine (IV), as shown in IV → VI. The parent ring system was later obtained[15] by the cyclization of 1-benzyl-2-methyl-1,2-dihydroisoquinoline with phosphoric acid. As pointed out by Battersby,[14] 1,2-dihydroisoquinolines should be susceptible to electrophilic attack at C_4 and to nucleophilic attack at C_3. The former type of reaction is closely related to the known[16] alkylation of enamines by alkyl halides, and is illustrated by the synthesis[17] of corydaline (X) from palmatine (VII) via (VIII) and (IX), and by the reductive condensation of isoquinoline methiodide and benzaldehyde[18] to 2-methyl-4-benzyl-1,2,3,4-tetrahydroisoquinoline. Nucleophilic attack at C_3 of a 1,2-dihydroisoquinoline,



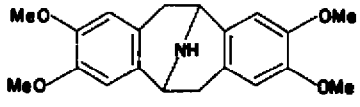
III



IV

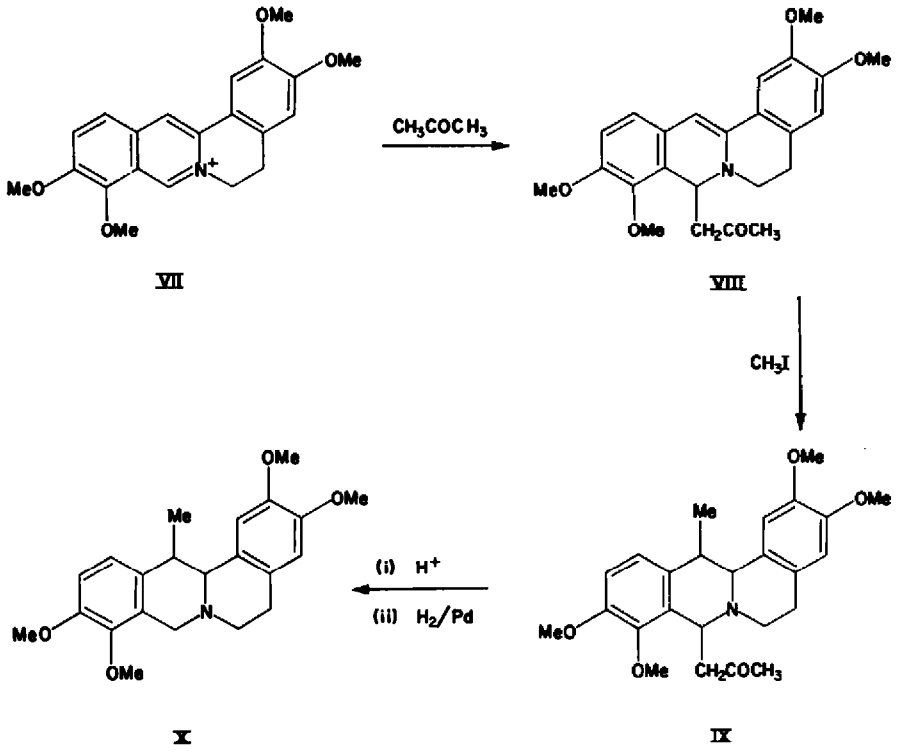


V

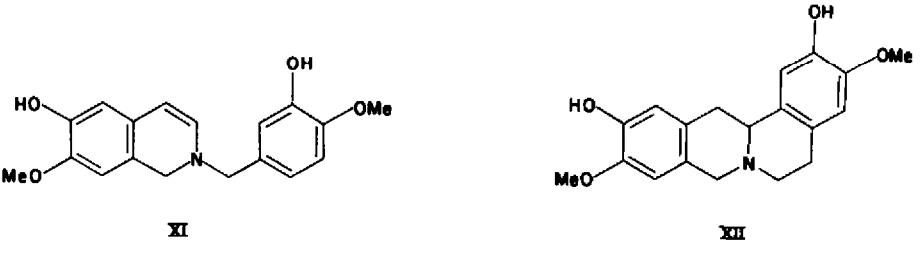


VI

[14] A. R. Battersby and R. Binks, *J. Chem. Soc.* 2888 (1955).
[15] C. Wittig, H. Tenhaeff, W. Schoch and C. Koenig, *Liebigs Ann.* **1**, 572 (1951).
[16a] E. E. P. Hamilton and R. Robinson, *J. Chem. Soc.* **109**, 1029 (1916);
[b] R. Robinson, *Ibid.* **109**, 1038 (1916);
[c] R. Robinson and J. E. Saxton, *Ibid.* 976 (1962);
[d] C. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *J. Amer. Chem. Soc.* **85**, 207 (1963);
[e] J. Szmuszkovicz, *Advances in Organic Chemistry, Methods and results* Vol. 4; p. 1. Interscience, New York (1963).
[17] F. Bruckhausen, *Arch. Pharm.* **261**, 28 (1922).
[18] R. Grewe, W. Kruger and E. Vandernidin, *Chem. Ber.* **97**, 120 (1964).



illustrated by the formation of pavine, has been extended[19] to the synthesis of (±)-coreximine (XII) by treating the corresponding 1,2-dihydroisoquinoline (XI) with concentrated acids, and other examples of the synthesis of the protoberberine ring system have been described.[20] A closely related ring-closure of an N-phenylethyl-

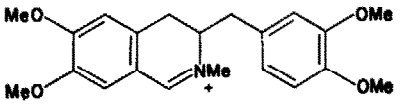


isocarbostyril has also been observed.[20] More recently a new reaction of 1,2-dihydroisoquinolines was uncovered,[21] when it was found that treatment of 2-methyl-1,2-dihydropapaverine with acids under very mild conditions caused rearrangement to

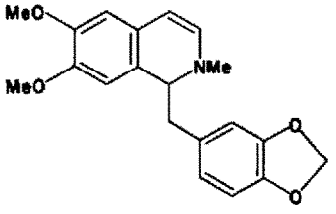
[19] A. R. Battersby, D. J. Le Count, S. Garratt and R. I. Thrift, *Tetrahedron* **14**, 46 (1961).
[20a] J. W. Huffman and E. C. Miller, *J. Org. Chem.* **25**, 90 (1960);
[b] D. W. Brown and S. F. Dyke *Tetrahedron Letters* 3587 (1964).
[21a] J. Knabe and J. Kubitz, *Angew. Chem.* (Int. Ed.) **2**, 689 (1963); German Version **75**, 981 (1963);
[b] *Arch. Pharm.* **297**, 129 (1964);
[c] J. Knabe and N. Ruppenthal, *Ibid.* **297**, 141, 268 (1964).

the 2-methyl-3-(3,4-dimethoxy)benzyl-6,7-dimethoxy-3,4-dihydroisoquinolinium salt (XIII).

It was of interest to us to study the action of dilute acids upon a 1-benzyl-1,2-dihydroisoquinoline whose aromatic rings are unsymmetrically substituted, and we selected the derivative (XIV). 1-(3,4-Methylenedioxy)benzyl-6,7-dimethoxyisoquinoline has been prepared[23] by the action of phosphorus oxychloride upon the trimethoxy compound (XV); yields of the order of 40% were claimed, but in our hands the yield never exceeded 8%. A more satisfactory method involved the standard[24] Bischler-Napieralski ring-closure to the 3,4-dihydroisoquinoline (XVI, R = H), followed by catalytic dehydrogenation. Reduction of the isoquinoline methiodide with LAH in boiling ether, or in tetrahydrofuran at room temperature, yielded (XIV) as in oil, whose UV spectrum (qualitative) exhibited maxima at 215, 255, 290 and 335 mμ, in close agreement with the reports of previous workers[19] for 1,2-dihydroisoquinolines. This substance was, without purification, and without delay, warmed with 2% aqueous hydrochloric acid as described by Knabe and Kubitz[21,22]; the initially deep wine-coloured solution rapidly changed to bright yellow. Neutralization of the solution and extraction with ether gave a tertiary base which proved to be identical with 1-(3,4-methylenedioxy)benzyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XVII), obtained by the reduction of XVI, (R = Me) with sodium borohydride. No



XIII



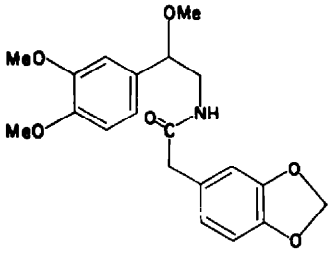
XIV

trace of the N-methylpavine type of structure could be found. It has always been assumed that reduction of isoquinolinium salts by LAH does not proceed beyond the 1,2-dihydroisoquinoline stage, but we have been able to show, by the use of thin film chromatography, that the crude reduction product (XIV) is contaminated with a small amount of XVII, the amount increasing with increasing reaction time. The quaternary salt (XVIII), whose UV spectrum was typical of that of a 3,4-dihydroisoquinolinium salt, was isolated from the neutral aqueous layer either as the pseudobase by extraction with chloroform, or as the pseudocyanide (m.p. 129°) by precipitation with potassium cyanide. Reduction of XVIII with $NaBH_4$ yielded the tetrahydroisoquinoline (XIX), the structure of which rests upon the following evidence. The pseudocyanide m.p. 129° was shown by mixed m.p. determination to be different from the pseudocyanide (m.p. 134°) of the authentic 3,4-dihydroisoquinolinium salt (XVI,

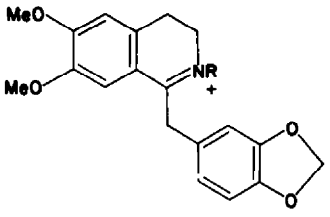
[22] We are indebted to Prof. Knabe for disclosing the experimental details before publication of his work.

[23] C. Mannich and O. Walter, *Arch. Pharm.* **265**, 1 (1927).

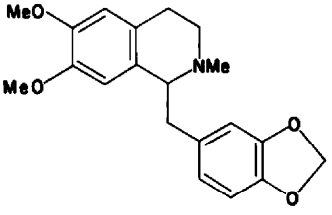
[24] W. M. Whaley and T. R. Govindachari, *Org. Reactions* Vol. VI, p. 74. J. Wiley, New York (1957).



XV

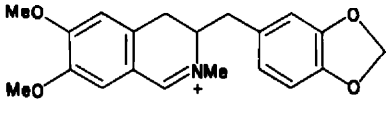


XVI

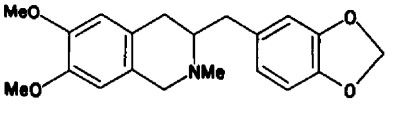


XVII

$R = CH_3$) (the IR spectra of these two pseudocyanides are similar, and the spectra of XVII and XIX are almost identical). Hofmann degradation of XIX yielded a styrenoid methine base formulated as XX, with the double bond in conjugation with the methylenedioxybenzene nucleus, since ozonolysis gave piperonal (80% yield) as the only neutral aldehyde fragment. The expected amino-aldehyde (XXI) was very



XVIII

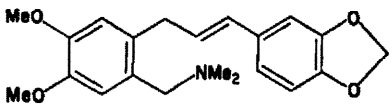


XIX

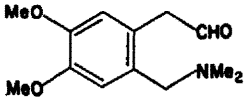
unstable, presumably due to cyclization to, and decomposition of the 1,2-dihydroisoquinoline (XXII).

Gensler *et al.*[25] have shown that 3,4-dihydroisoquinolines, for example XXIII, can be degraded to styrenoid aldehydes such as XXIV by treatment with alkaline dimethyl sulphate; 1-substituted 3,4-dihydroisoquinolines yield styrenoid ketones. When this method was applied to XVIII, a nitrogen-free oil was obtained, which was shown by thin-layer chromatography to be a mixture (presumably of double bond isomers) of two very similar substances. Crystallization of the major component from methanol afforded a pale yellow solid, m.p. 115°. The NMR spectrum (Fig. 1) is entirely in accord with structure XXV. The aldehyde stretching frequency appears at 1675 cm^{-1}

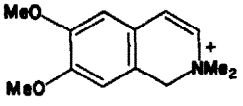
[25] W. J. Gensler, E. M. Healy, I. Unshuus and A. L. Bluhm., *J. Amer. Chem. Soc.* **78**, 1713 (1956).



XX

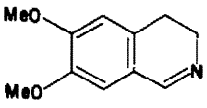


XXI

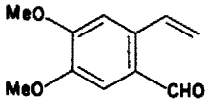


XXII

in the IR spectrum; the aldehyde (XXIV) also exhibits a band at 1675 cm^{-1}, and this shift to lower frequencies is presumably due to the influence of the styrenoid double bond in the *ortho* position. Oxidation of XXV with potassium permanganate caused extensive degradation but the presence of small amounts of piperonylic acid and

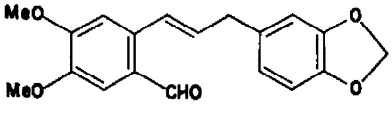


XXIII

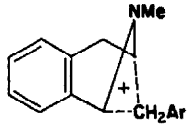


XXIV

m-hemipinic acid was demonstrated chromatographically. Ozonolysis of XXV, followed by oxidation with silver oxide gave, ultimately, *m*-hemipinic acid, and the presence of some homopiperonylic acid was indicated by thin layer chromatography.



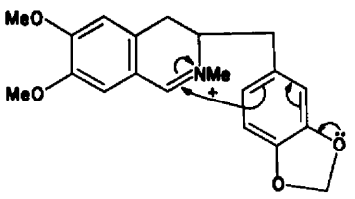
XXV



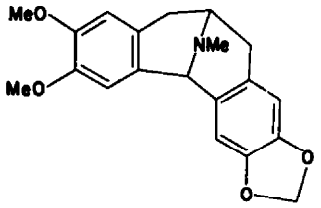
XXVI

Our evidence agrees completely with the conclusions of Knabe and Kubitz,[21] and the reaction clearly involves the migration of the benzyl group from C_1 to C_3 of the isoquinoline ring, most probably through an intermediate such as XXVI. Knabe[26] independently suggested the same mechanism, also suggesting that it is of the type[27] "allyl rearrangement with internal return." It might be anticipated that the reaction should be reversible, but treatment of XVIII with dilute mineral acids led only to recovered starting material. The possibility also exists that a pavine-type structure

[26] J. Knabe, private communication; J. Knabe and N. Ruppenthal, *Naturwiss.* **51**, 482 (1964).
[27] W. C. Young, S. Winstein and H. L. Goering, *J. Amer. Chem. Soc.* **73**, 1958 (1951).



XXVII



XXVIII

XXVIII may arise as shown in XXVII → XXVIII, but once again starting material was recovered when XVIII ≡ XXVII was heated with a mixture of formic acid and phosphoric acid under the conditions[14] whereby 2-methyl-1,2-dihydropapaverine was converted into N. methyl pavine.

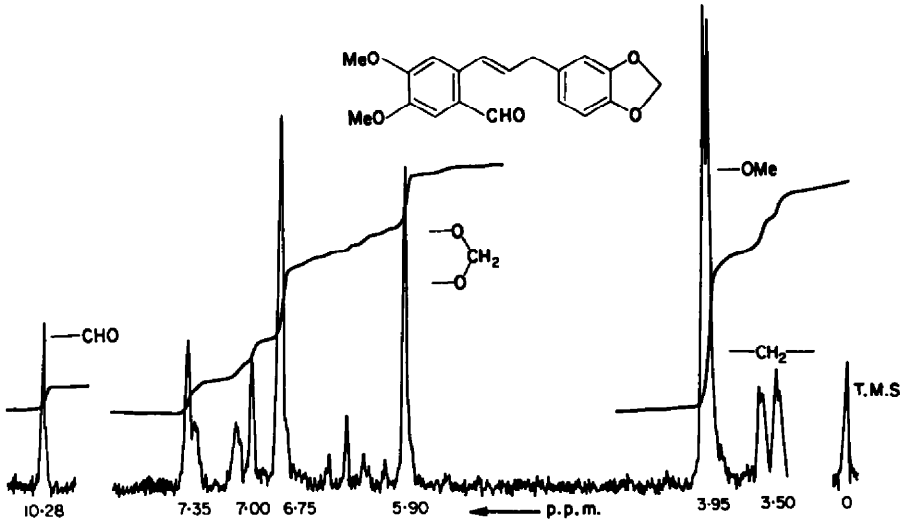


FIG. 1

EXPERIMENTAL

1-(3,4-*Methylenedioxy*)*benzyl*-6,7-*dimethoxyisoquinoline*. A solution of 1-(3,4-methylenedioxy) benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline[28] (14 g) in diphenyl ether (12 ml) was heated with Pd-black (1·5 g) at 170° for 4 hr, in a stream of CO_2. After cooling, the mixture was diluted with xylene (50 ml), filtered to remove the catalyst, and the filtrate extracted with 50% HCl (5 × 20 ml). The combined acid extracts were neutralized with 5% NaOH aq and extracted with benzene (3 × 20 ml). The benzene solution was washed with 2 N Na_2CO_3 aq, and then with water, dried and evaporated. The residue was crystallized from benzene–petrol (b.p. 60–80°) to yield the required isoquinoline (8·3 g) m.p. 123° (lit.,[28] m.p. 123°).

The methoidide was obtained as pale yellow prisms from EtOH m.p. 230–234°.

2-*Methyl*-3-(3,4-*methylenedioxy*) *benzyl*-6,7-*dimethoxy*-3,4-*dihydroisoquinolinium salts* XVIII. The above methiodide (2·0 g) was added to a slurry of LAH (1·0 g) in tetrahydrofuran (150 ml) and the mixture was shaken at room temp. for 18 hr. The excess of LAH was decomposed by the cautious addition of 30% aqueous sodium potassium tartrate. The tetrahydrofuran was decanted, diluted with water and evaporated under N_2. The residual aqueous suspension was extracted with ether (3 × 50 ml) and the combined extracts dried and evaporated to leave XIV as a brown oil (1·0 g). UV absorption (qualitative in EtOH) λ_{max} 216, 294, 335 mμ; λ_{min} 275, 307 mμ. The crude base was spotted

[28] Z. Kitasato and H. Shishido, *Liebigs Ann.* **527**, 176 (1937).

onto a 0·2 mm film of silica gel and developed with a mixture of methanol:acetone:diethylamine (10:10:1) when two spots were observed R_f 0·87 and 0·69. Authentic XVII has, under the same conditions, R_f 0·69.

The crude 1,2-dihydroisoquinoline (1·0 g) was dissolved in 2% HCl (30 ml) and the solution was warmed on the water-bath for 30 min; the initial intense violet-red colour quickly faded to yellow. The solution was neutralized with $NaHCO_3$ aq or 2 N. NaOH, and extracted with $CHCl_3$ (3 × 10 ml). The combined extracts were dried and evaporated under N_2 to leave a brown oil (0·8 g), which exhibited a green fluorescence (qualitative UV absorption in EtOH, λ_{max} 214, 245, 290 and 335 mμ; λ_{min} 228, 272 and 302 mμ). ν_{max} (liquid film) 1650 cm^{-1}.

The pseudocyanide was obtained as colourless prisms from ether m.p. 129° λ_{max}(log ε) 214(4·08), 245(3·88), 290(3·74) 315(3·56) and 350(3·72) mμ. (Found: C, 69·1; H, 6·4. $C_{21}H_{22}N_2O_4$ requires: C, 68·8; H, 6·05%.)

2-*Methyl*-3-(3,4-*methylenedioxy*)*benzyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* XIX. The 3,4-dihydroisoquinolinium hydroxide obtained above (100 mg) was dissolved in EtOH (25 ml) and water (10 ml); $NaBH_4$ (200 mg) was then added portionwise and the green fluorescence of the solution was immediately discharged. The mixture was left overnight at room temp and then evaporated to small bulk. Water (10 ml) was added and the solution extracted with ether (3 × 10 ml). The ethereal extracts were washed with water, dried and evaporated to leave a brown glass, which crystallized from EtOH to give colourless prisms (60 mg) m.p. 170–171. (Found: C, 70·4; H, 6·6; $C_{20}H_{23}NO_4$ requires: C, 70·4; H, 6·8%.)

The methiodide monohydrate was obtained from aqueous ethanol as pale brown plates m.p. 160–163° dec. (Found: C, 50·4; H, 5·8. $C_{21}H_{26}INO_4.H_2O$ requires: C, 50·3; H, 5·6%.)

1-(3,4-*Methylenedioxy*)*benzyl*-2-*methyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* XVII. This was obtained from XVI, (R = Me) by reduction with $NaBH_4$ as detailed above. Crystallization from EtOH gave colourless prisms, m.p. 116° (lit.,[28] m.p. 116°). (Found: C, 70·3; H, 6·6. Calc. for $C_{20}H_{23}NO_4$: C, 70·4; H, 6·8%.)

The methiodide monohydrate crystallized from aqueous EtOH as almost colourless small prisms, m.p. 220–223°. (Found: C, 50·4; H, 5·5. $C_{21}H_{26}INO_4H_2O$ requires: C, 50·3; H, 5·6%.)

Hofmann degradation of XIX. The methiodide of XIX (2·0 g) was heated under reflux with 35% NaOH aq (250 ml) for 36 hr. After cooling, the emulsion formed was extracted with ether (4 × 20 ml) the combined ethereal solutions were washed with water, dried and evaporated to leave the methine base (XX) as a pale yellow oil (1·1 g). The perchlorate crystallized from EtOH–ether as colourless needles m.p. 155–158° dec, λ_{max}(log ε) 271 (4·20), 292 (3·85) mμ. (Found: C, 55·4; H, 6·05. $C_{21}H_{25}NO_4.HClO_4$ requires: C, 55·3; H, 5·75%.)

A solution of the methine base (0·5 g) in $CHCl_3$ (25 ml) was treated with a stream of ozonized O_2, at room temp until the theoretical amount of O_2 had been absorbed. The solvent was removed under red. press. and the ozonide decomposed with Zn dust (0·1 g) in water (50 ml) containing one drop of 2 N $AgNO_3$. The filtered solution was extracted with ether, the ethereal solution washed with dil. HCl, then with water, dried and evaporated to leave piperonal (0·17 g) identified by mixed m.p. determination of it and its *p*-nitrophenylhydrazone with authentic specimens.

1-*Cyano*-1-(3,4-*methylenedioxy*)*benzyl*-2-*methyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline*. Compound XVI (R = Me; 0·2 g) was dissolved in water (6 ml) and a conc. KCN aq added. The precipitated pseudocyanide was collected and crystallized from ether, m.p. 134–135°, λ_{max}(log ε) 213 (4·29), 237 (4·14), 287 (3·97) mμ. (Found: C, 68·6; H, 6·0; $C_{21}H_{22}N_2O_4$ requires: C, 68·8; H, 6·05%.)

A mixed m.p. of this material and the pseudocyanide of the rearrangement product (XVIII) showed a clear depression. Thin film chromatograms were run on silica gel using methanol:acetone: diethylamine 10:10:1; the spots were viewed in UV light. The pseudocyanide of XVI (R = Me) had R_f 0·55 and the pseudocyanide of (XVIII) had R_f 0·78.

Degradation of (XVIII) *to the o-formylstyrene* (XXV). The pseudocyanide of (XVIII) (0·2 g) was decomposed with 5% HCl aq (5·0 ml) and the yellow solution obtained was made alkaline with 2 N NaOH in an atmosphere of N_2. Dimethyl sulphate (2·0 ml) was then added, followed by an excess of 2 N NaOH (10 ml). The mixture was heated on a water-bath for 2 hr, then cooled and extracted with ether. The combined ether extracts were washed with dil. HCl aq, dried and evaporated under N_2 to yield a pale yellow oil (0·15 g). Thin film chromatograms were conducted on silica gel using benzene:acetic acid:methanol 45:4:8 as developing solvent. Two spots at R_f 0·75 (dark green) and 0·95 (violet) were apparent on spraying with conc. H_2SO_4. Repeated recrystallization of the crude

product from MeOH eventually afforded the styrene (XXV) as yellow needles m.p. 115°, λ_{max}(log ε) 212 (4·12), 254 (4·14), 292 (3·95) mμ ν_{max} 1675 cm^{-1}. (Found: C, 70·0; H, 5·5. $C_{19}H_{18}O_5$ requires: C, 69·9; H, 5·6%.)

The oxime was crystallized from MeOH, m.p. 170°. (Found: C, 66·7; H, 5·6 $C_{19}H_{19}NO_5$ requires: C, 66·85; H, 5·6%.)

Ozonolysis of the styrene (XXV). The above styrene (XXV; 100 mg) in $CHCl_3$ (25 ml) was treated with ozonized-O_2 until no more O_2 was absorbed. The $CHCl_3$ was evaporated under red. press. and the residual gum dissolved in EtOH (2·0 ml). KOH (150 mg), water (2·0 ml), and a solution of $AgNO_3$ (200 mg) in water (2·0 ml) were added. The black suspension was swirled and warmed at 75° for 3 min, then cooled and kept overnight. The filtrate, after removal of the suspended solids, was clarified with charcoal, acidified with 50% HNO_3 aq, and extracted with ether. The extracts were worked up in the usual way to give a brown acidic gum (25 mg). This material was streaked onto a film of silica gel (1 mm thick) and the plate was developed with a 25% solution of petrol (b.p. 60–80°) in ethyl acetate. The band at R_f 0·68–0·72 was removed and extracted with boiling $CHCl_3$. The solvent was evaporated and the residue was crystallized from water to yield *m*-hemipinic acid m.p. and mixed m.p. 179–179·5°.