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1,2-DIHYDROISOQUINOLINES—XI[1]

FURTHER BERBINE SYNTHESES[2]

M. SAINSBURY, D. W. BROWN, S. F. DYKE and G. HARDY

School of Chemistry and Chemical Engineering, Bath University of Technology, Bath, Somerset, England

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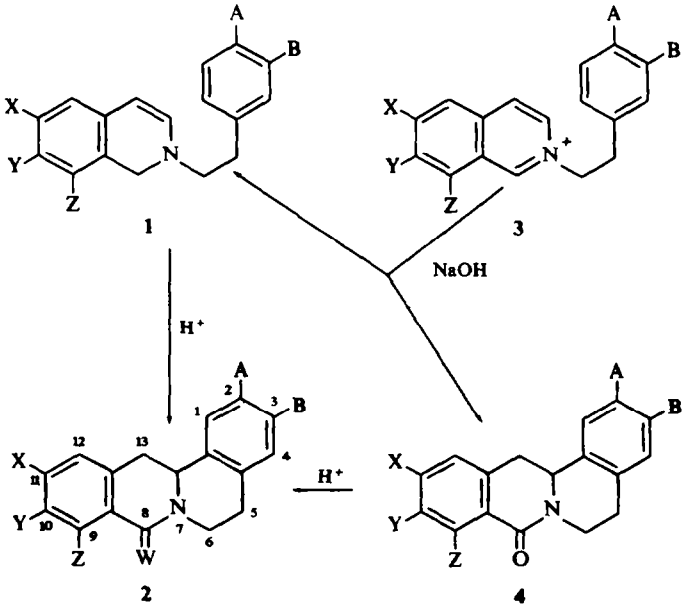
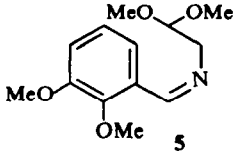
Abstract—New syntheses of tetrahydroberberine and tetrahydropalmatine are described and some other potential routes to the berbine skeleton are explored.

IN PART II of this series[3] we showed how the route to the berbine skeleton (**2**, W = H_2) involving[4,5] the cyclization of an N-β-arylethyl-1,2-dihydroisoquinoline (**1**) with acids could be simplified by generating the 1,2-dihydroisoquinoline by disproportionation of the parent isoquinolinium salt (**3**) with alkali. The isocarbostyril (**4**) also formed was found, unexpectedly, to cyclize to the 8-oxoberbine derivative (**2**, W = O). The majority of berberine and tetrahydroberberine alkaloids possess[6] a 2,3,9,10-tetra-oxygenation pattern whereas the above method of synthesis, which requires a pre-formed isoquinoline nucleus, gives rise most easily to a 2,3,10,11-tetraoxysubstitution pattern. 7,8-Dioxyisoquinolines were, until recently, very difficult to prepare, but by employing the modification of the Pomeranz–Fritsch[7] synthesis described by Bobbitt *et al.*,[8,9] 7,8-dioxy-1,2,3,4-tetrahydroisoquinolines (**8b**, R = H) are readily available. In this method a benzalaminoacetaldehyde dialkyl



acetal (**5**) is hydrogenated to **6**, dissolved in 6N HCl and the acid solution is hydrogenated again at room temperature. It was originally postulated that the reaction involves an acid-catalysed cyclization of **6** to the 1,2-dihydroisoquinoline **7**, which is then reduced to (**8b**, R = H), but it has now been shown[10] that the intermediate



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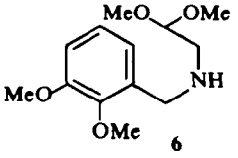

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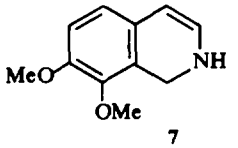

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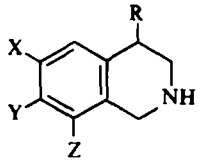
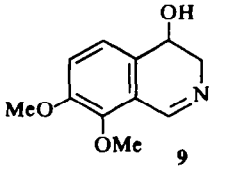


8a: X = Y = OMe; Z = H
8b: Y = Z = OMe; X = H



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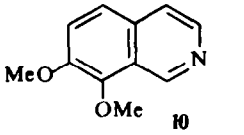

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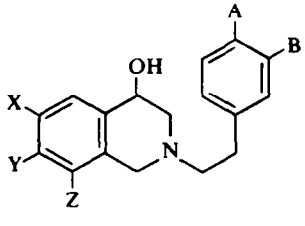
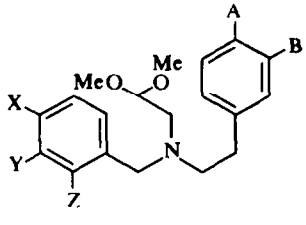
8b (R = OH) and not **7** is involved. Although in principle the tetrahydroisoquinoline **8b** (R = H) can be dehydrogenated to the fully aromatic structure **10** by standard methods, yields are very erratic, and a far superior method involves the treatment of **8b** (R = OH) with one mole of N-bromosuccinimide when an almost quantitative yield of the 3,4-dihydro-4-hydroxyisoquinoline **9** can be obtained; dehydration of this to the fully aromatic structure **10** is easily achieved in high yield by warming it with aqueous ethanolic HCl.

2-β-(3,4-Dimethoxyphenyl)ethyl-7,8-dimethoxyisoquinolinium bromide (**3**, A = B = Z = Y = OMe; X = H) was prepared either from **10** and β-3,4-dimethoxyphenylethyl bromide, or by reacting the 4-hydroxytetrahydroisoquinoline **11b** with N-bromosuccinimide; compound **11b** itself was prepared in high yield by



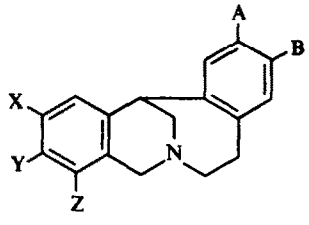
11a: X = Y = A = B = OMe; Z = H
11b: Y = Z = A = B = OMe; X = H

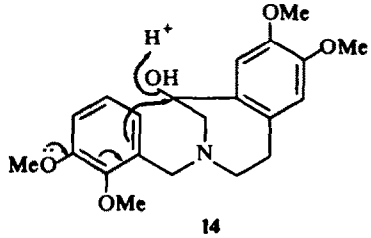


12a: X = Y = A = B = OMe; Z = H
12b: Y = Z = A = B = OMe; X = H

alkylation of **8b** (R = OH). Successive application of LAH and mineral acid as previously described[3–5] to the quaternary salt **3** gave tetrahydropalmatine (**2**, A = B = Y = Z = OMe; X = H; W = H_2) in 66% yield. Repetition of the sequence of reactions with **3** (X = H; Y = Z = OMe; A,B = —OCH_2O—) gave tetrahydroberberine in 58% yield, so that in principle a large number of the naturally occurring 2,3,9,10-tetraoxyberbines are accessible in a relatively simple manner. The full scope of this synthetic approach is now being studied.

Since the cyclization of benzylaminoacetals of type **6** involves the use of acid conditions, and since the cyclization of 2-β-arylethyl-1,2-dihydroisoquinolines of type **1** requires essentially similar conditions, it occurred to us[2] that the double cyclization of a suitably constituted benzylamino acetal, for example **12**, may be possible leading directly to a berbine derivative. When compound **12b** prepared from **6** and β-(3,4-dimethoxyphenyl)ethyl bromide was dissolved in conc HCl and the solution allowed to stand at room temperature for five days, a base hydrochloride $C_{21}H_{25}NO_4$ HCl could be isolated in 83% yield. The NMR spectrum of this material clearly indicates the presence of only FOUR aromatic protons, suggesting that a double cyclization had indeed occurred. The UV spectrum is benzenoid and there was no observable absorption in the IR in the 1600–1750 cm^{-1} region, but the product differs from an authentic sample of tetrahydropalmatine. It seemed possible that the first cyclization of **12b** had occurred to yield **11b** and that the second cyclization had occurred at C_4 of **11b** to yield **13b** and not at C_3 of a 1,2-dihydroisoquinoline to yield **2** (Y = Z = A = B = OMe; X = H; W = H_2). When the alcohol **11b**





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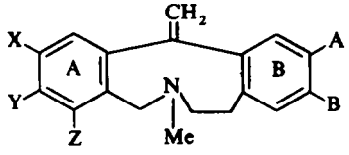
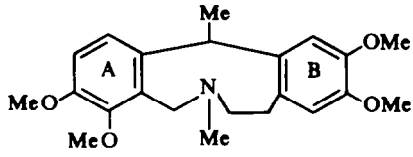
13a: X = Y = A = B = OMe; Z = H
13b: Y = Z = A = B = OMe; X = H
13c: X = H; Y = Z = OMe; A,B = OCH_2O
13d: X = A = B = OMe; Y = OH; Z = H

was treated with HCl under the conditions employed in the double cyclization of **12b** the product again was **13b** suggesting that the alternative initial cyclization of **12b** to **14**, followed by nucleophilic displacement of the OH group to yield **13b** is a less likely route for the reaction.

The structure **13b** is supported by the fact that Hofmann degradation yielded a methine base **15b** whose NMR spectrum (in $CDCl_3$) clearly supports the presence of the $\rangle C = CH_2$ group (a two proton quartet centred at 5·0 ppm). Further, when subjected to catalytic hydrogenation, one mole of gas was absorbed to yield a base whose NMR spectrum is devoid of absorption at 5·0 ppm but which exhibits instead

a three proton doublet (J = 7·5 Hz) at 1·7 ppm and a one proton quartet (J = 7·5 Hz) centred at 4·54, in agreement with the requirements for structure **16**. When compound **15b** was warmed with acetic acid a high yield of a quaternary salt was isolated (as the perchlorate) which is formulated as **17b**, the product of a transannular addition





15a: X = Y = A = B = OMe; Z = H
15b: Y = Z = A = B = OMe; X = H
15c: X = H, Y = Z = OMe; A,B = OCH_2O

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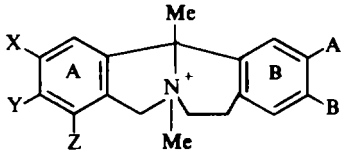
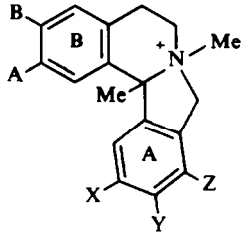




17a: X = Y = A = B = OMe; Z = H
17b: Y = Z = A = B = OMe; X = H

of the methylamino group to the exocyclic methylene group. The NMR spectrum of this material exhibits three proton singlets at 2·05 ppm (CH_3—C<) and at 3·25 ppm (CH_3—$\overset{+}{N}$<), a two proton singlet at 4·9 ppm and clearly defined signals associated with four aromatic protons, four OMe groups and the A_2X_2 system of the >$\overset{+}{N}$—CH_2—CH_2—Ar fragment.

The cyclization of several differently substituted amino acetals of type **12** were studied under the standard conditions of conc HCl at room temperature for five days, but in each case cyclization occurred, not to the berbine skeleton, but to structures analogous to **13b**. The results are collected into Table 1. In all cases except No. 4 (which was methylated) Hofmann degradation yielded a methine analogous to **15b** and the conversion of No. 1 and No. 2 to **17b** and **17a** respectively was effected. The free amino aldehyde **20**, prepared as indicated in **18** → **20** was treated with conc HCl but again cyclization to **21** occurred, and not to the berbine.

With the readily available dimethyl acetal **12a** a variety of conditions of acid treatment and temperature was studied in an effort to cause cyclization to occur to the berbine, but without success. In fact when a solution of the amino acetal in phosphoric acid was allowed to stand at room temperature for two days, the yield of **21** was raised to 90%. All attempts to synthesize the cyclized product **22** have so far failed.

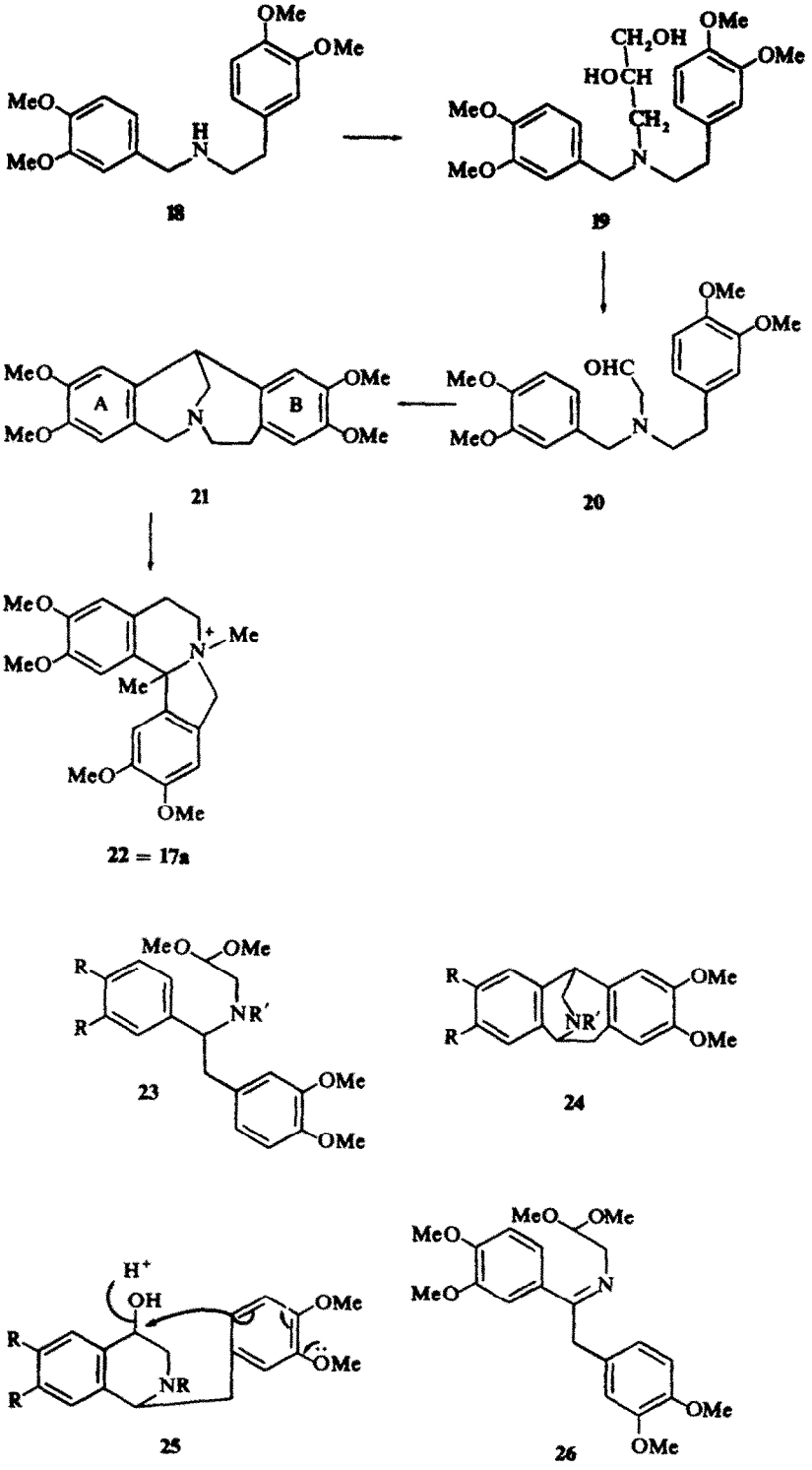
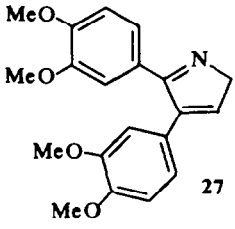

OMe
OMe
MeO
MeO
H
N
18
CH2OH
HOCH
CH2
19
OHC
20
A
B
21
Me
22 = 17a
R
R'
23
24
H+
OH
NR
25
26

TABLE 1. CYCLIZATION OF THE BENZYLAMINOACETALDEHYDE DIMETHYLACETALS

Expt. No.	X	Y	Z	A	B	Yield %	m.p. HCl—	Molecular formula	Analysis Required C	H	N	Cl	Found C	H	N	Cl
1	H	OMe	OMe	OMe	OMe	83	225–6°	$C_{21}H_{26}NO_4Cl$	64·37	6·64	3·58	9·06	64·20	6·58	3·39	—
2	OMe	OMe	H	OMe	OMe	76	248–9°	$C_{21}H_{26}NO_4Cl$	64·37	6·64	3·58	9·06	64·09	6·82	3·54	8·80
3	H	OMe	OMe	O—CH_2—O		76	244–6°	$C_{20}H_{22}NO_4Cl$	63·92	5·86	3·73	9·45	63·73	6·12	3·95	9·20
4	OMe	OH	H	OMe	OMe	50	252–4°	$C_{20}H_{24}NO_4Cl$	63·57	6·36	3·69	4·39	63·62	6·62	3·46	8·99

An analogy for the observed double cyclization of the benzylamino acetals of type **12** is provided by the ring-closure of **23** (R = OMe; R′ = H) to give **24**(R = OMe; R′ = H) termed[13] isopavine. It is possible that this reaction proceeds by cyclization first to the 4-hydroxytetrahydroisoquinoline **25**, which then undergoes internal nucleophilic displacement of the OH group by the 3,4-dimethoxyphenyl ring. By treating **23** (R,R = OCH_2O; R′ = Me) with conc HCl we have been able to prepare a compound which has identical physical properties[14] to amurensinine **24** (R,R = OCH_2O; R′ = Me). Similarly the methiodide of **23** (R,R = OCH_2O; R′ = Me) gave a quaternary iodide which is identical with the methiodide of amurensinine. (We are indebted to Professor Santavy for the IR and NMR spectra of the alkaloid).

In 1903 Fritsch[15] reported that when the benzalamino-acetal **26** was treated with conc H_2SO_4 a base was obtained in 15% yield for which Guthrie *et al.*[12] proposed structure **27**. Although this was questioned by Battersby and Yeowell,[13] they did



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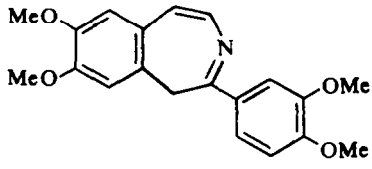

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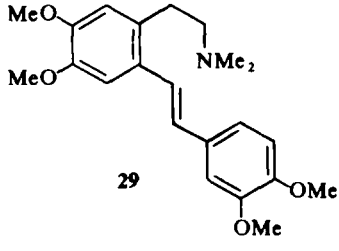
not make any alternative proposals. We have now found that the product described by Fritsch and by Guthrie *et al.* can be obtained in 37% yield merely by using conc HCl instead of conc H_2SO_4. The NMR spectrum of the base (Fig. 1) can be interpreted completely in terms of structure **28** and this deduction was confirmed by showing that the methine base **29** obtained from the tetrahydro derivative of **28** is identical with that produced from tetrahydropapaverine. Other unusual products have been



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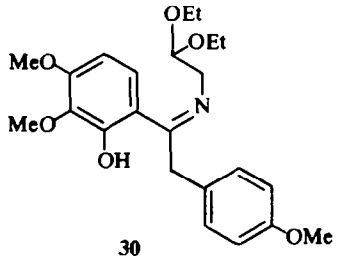
reported from time to time when benzalamino acetals were treated with acids. Thus, treatment of **30** with acids is reported[16] to yield a mixture of the expected isoquinoline and the novel structure **31**.

Another approach to the berbine skeleton was based upon the observation[17] that the isoquinoline Reissert[18] compound **32** when treated with perchloric acid yields a cyclic perchlorate **33**, which can be reduced by $NaBH_4$ or by catalytic



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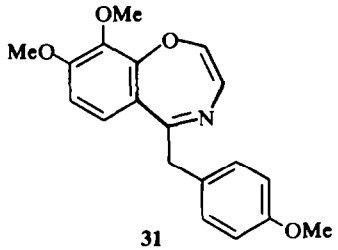

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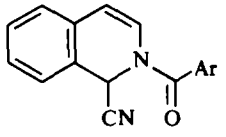

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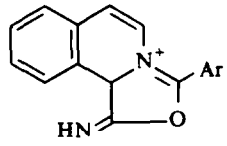

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hydrogenation, to the 2-benzylisoquinaldamide **34** (A = B = C = W = X = Y = H), thus offering an improvement on the original[19] method. The amide **34** (A = B = C = W = H; X = Y = OMe) was easily prepared by this method and hydrolysed with 30% methanolic KOH to the carboxylic acid, which, with polyphosphoric acid

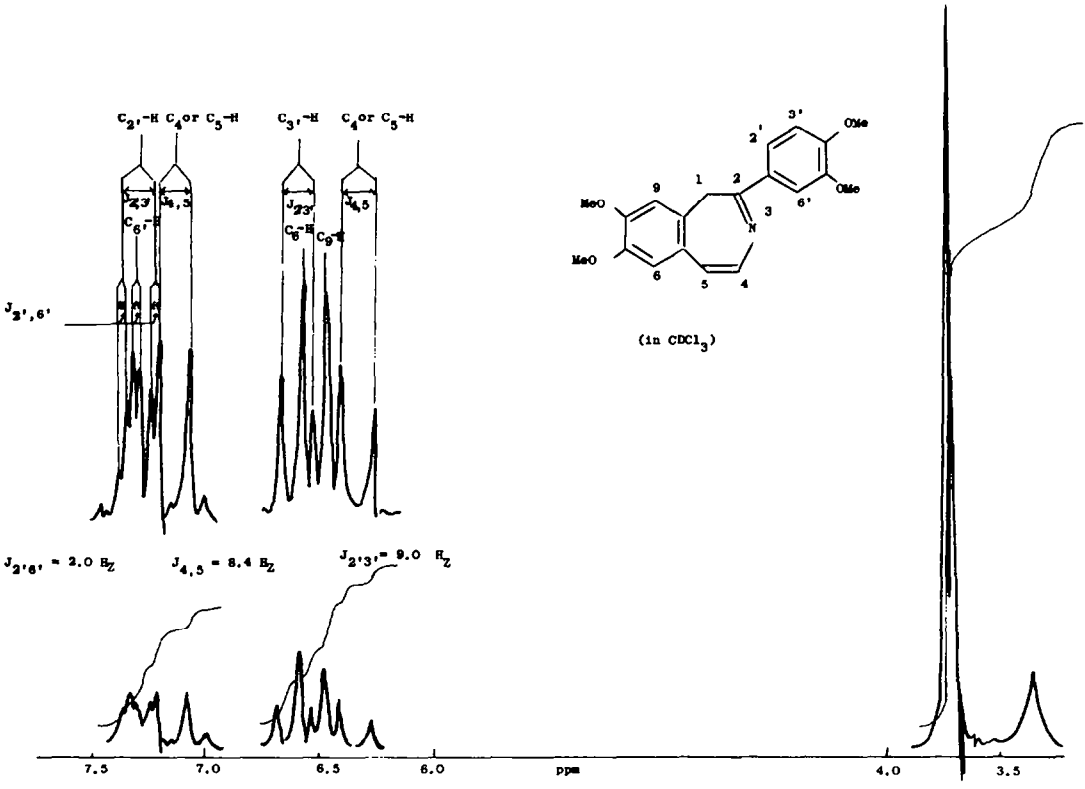
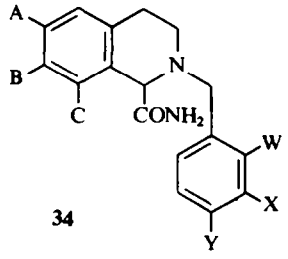


FIG. 1.

was converted into a weak base, isolated as the perchlorate. This substance, $C_{19}H_{18}NO_3$ $HClO_4$ exhibited a UV absorption spectrum more complicated than that expected for a 13-oxoberbine, and one which is radically altered by the addition of base. The NMR spectrum contains signals associated with *seven* protons in the aromatic region; a band at 1690 cm^{-1} in the IR spectrum is consistent with the



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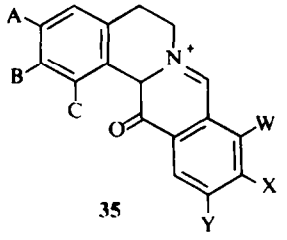

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absorption expected for an aromatic ketone and structure **35** (A = B = C = W = H; X = Y = OMe) was allotted to the substance.

With this route to the berbine skeleton established, an attempt was made to cyclize **34** (A = B = C = Y = H; W = X = OMe) but without success. Another attempt was made with the known[19] amide **34** (A = B = W = X = OMe; C = Y = H) which was reported[19] to be stable to boiling alkali and to acids. We were able, however, to hydrolyse this compound to the corresponding acid easily with 30% methanolic KOH, but all attempts to cyclize the acid have so far failed; decarboxylation has been observed instead with the formation of 2-(2,3-dimethoxybenzyl)6,7-dimethoxy-3,4-dihydroisoquinolinium salts.

EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined in EtOH soln; IR spectra were measured as nujol mulls and chemical shifts are expressed in ppm downfield from TMS as an internal standard.

6,7-*Dimethoxy*-4-*hydroxy*-1,2,3,4-*tetrahydroisoquinoline* (**8a**, R = OH). N-3,4-Dimethoxylbenzyldimethylaminoacetal (5·0 g) was dissolved in 6N HCl (100 ml) and allowed to stand at room temp overnight. The soln was then cooled to 0° and basified with 30% NaOH aq; extraction with $CHCl_3$ and evaporation of the dried $CHCl_3$ extracts then afforded a pale yellow oil, which crystallized on exposure to acetone (2·9 g, 69%). Recrystallization from this solvent gave colourless solid m.p. 137–139° ν_{max} cm^{-1} 3340, 3170, 1610. (Found: C, 63·4; H, 7·6; N, 6·6. $C_{11}H_{15}NO_3$ requires: C, 63·1; H, 7·2; N, 6·7%).

7,8-*Dimethoxy*-4-*hydroxy*-1,2,3,4-*tetrahydroisoquinoline* (**8b**, R = OH), m.p. 140–141° (64%) was prepared in an analogous manner from N-2,3-dimethoxybenzyldimethylaminoacetal. (Found: C, 63·0; H, 7·2; N, 7·2. $C_{11}H_{15}NO_3$ requires: C, 63·1; H, 7·2; N, 6·7%).

2-β-(3,4-*Dimethoxyphenyl*)*ethyl*-4-*hydroxy*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (**11a**). 6,7-Dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinoline (2·1 g) was treated with 3,4-dimethoxyphenethyl bromide (2·45 g) and Na_2CO_3 (1·0 g) in EtOH (15 ml) containing water (10 ml). The mixture was heated under reflux for 12 hr and the solvent then evaporated to yield semi solid which crystallized when triturated with acetone, yield 86%, m.p. 119–120° (from acetone) ν_{max} cm^{-1}, 3450, 1610, 1590. λ_{max} (ε) nm., 230 sh (9,060), 284 (3,100); NMR ($CDCl_3$) ppm, 6·75 singlet [3] (aromatic protons of phenethyl group); 6·9 singlet [1] (C_8—H); 6·5 singlet [1] (C_5—H); 4·5 triplet [1], J = 4Hz (—CH_2—CH—OH); 3·8 singlet [12] (4 × OCH_3); 3·6 singlet [2] (Ar—CH—N<); 3·4 singlet [1] (OH, lost on deuteration); 2·8 multiplet [6] ($ArCH_2CH_2N$<, + —CH_2CHOH). (Found: C, 67·7; H, 7·2; N, 3·9; $C_{20}H_{27}NO_5$ requires: C, 67·5; H, 7·3; N, 3·8%). When treated with conc HCl at room temp in the course of 4 days this compound yielded 72% of a product shown to be **13a**.

2-β-(3,4-*Dimethoxyphenyl*)*ethyl*-4-*hydroxy*-7,8-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (**11b**) was prepared similarly as a colourless oil. Characterized as hydrochloride salt m.p. 206–207° (from aqueous EtOH),

ν_{max} cm^{-1}, 3320, 2620, 1610, 1590. (Found: C, 61·6; H, 6·8; N, 3·2; Cl, 8·6. $C_{20}H_{28}NO_5Cl$ requires: C, 61·6; H, 6·8; N, 3·4; Cl, 8·7%).

2-β-(3,4-*Dimethoxyphenyl*)*ethyl*-6,7-*dimethoxyisoquinoline iodide* (3, X = Y = A = B = OMe, Z = H). The above 4-hydroxy-2-phenethyltetrahydroisoquinoline (1·0 g) in $CHCl_3$ (20 ml) was treated with small portions of NBS (total 0·48 g) during 15 min and the mixture then stirred for a further 3 hr. The brown soln was poured into a large volume of ether, and the solid which separated was then collected, dissolved in 6N HCl in EtOH (25 ml) and heated on a water-bath for 30 min. Evaporation yielded a dark residue which was taken up in hot-water and treated with KI, which caused a yellow crystalline solid to separate, yield 67%, m.p. 210–211° (lit.,[4] 209–210°) from aqueous MeOH. A mixed m.p. with an authentic specimen of 2-β-(3,4-dimethoxyphenyl)ethyl-6,7-dimethoxyisoquinoline iodide caused no depression.

2-β-(3,4-*Dimethoxyphenyl*)*ethyl*-7,8-*dimethoxyisoquinolinium iodide*, was prepared in an analogous manner from 2-β-(3,4-dimethoxyphenyl)ethyl-(4-hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline, yield 72%, m.p. 162–163, identical with a sample prepared by the quaternization of 7,8-dimethoxyisoquinoline with 3,4-dimethoxyphenylbromide followed by anion exchange (see below).

7,8-*Dimethoxyisoquinoline* (10). 7,8-Dimethoxy-4-hydroxytetrahydroisoquinoline (6·0 g) was treated with an equimolar quantity of NBS in a manner similar to that described in the preceding experiment. The residue, however, was not treated with aqueous KI soln but merely basified with NH_4OH to yield the free isoquinoline (3·85 g) in 71% yield as an oil, ν_{max} cm^{-1}, 1630, 1590, 1565; NMR (CF_3CO_2H) ppm, 9·8 doublet [1], J = 7Hz (C_1—H); 8·4 broad singlet [2] (C_3—H, C_4—H); 8·1 broad singlet [2] (C_5—H, C_6—H); 4·3, 4·2 two singlets [6] (2 × OCH_3). The free base was characterized as the perchlorate, bright yellow needles, m.p. 166–167° (from EtOH), ν_{max} cm^{-1}, 3260, 1640, 1605, 1590; λ_{max} (ε) nm., 236 (21,500), 252 (22,420), 290 sh (3,070), 360 (1,900). (Found: C, 45·5; H, 4·2; N, 4·8. $C_{11}H_{12}NO_6Cl$ requires: C, 45·6; H, 4·2; N, 4·8%).

2-β-(3,4-*Dimethoxyphenyl*)*ethyl*-7,8-*dimethoxyisoquinolinium iodide* (3, Y = Z = A = B = OMe; X = H). 7,8-Dimethoxyisoquinoline (0·9 g) and 3,4-dimethoxyphenethylbromide (1·25 g) in acetone (10 ml) were heated together for 20 hr, the solvent then removed and the residue triturated with ether. The crystalline bromide thus obtained was dissolved in water and KI added. The product a yellow solid recrystallized from EtOH/ether as needles, m.p. 162–163° (85%); ν_{max} cm^{-1}, 1635, 1610, 1570; λ_{max} (ε) nm., 258 (30,800), 287 sh (5530). The perchlorate salt was also prepared m.p. 164–165°. (Found: C, 55·5; H, 5·3; N, 3·15; Cl, 7·8. $C_{21}H_{24}NO_4Cl$ requires: C, 55·5; H, 5·3; N, 3·10; Cl, 7·8%).

±*Tetrahydropalmatine* (2, Y = Z = A = B = OMe; X = H, W = 2H). The above quaternary iodide (0·95 g) was suspended in THF (100 ml) and LAH (1·0 g) added in small portions. Stirring was continued for a total of 5 hr and the excess LAH then destroyed with 30% sodium potassium tartarate soln. The product 1,2-dihydroisoquinoline was extracted into CH_2Cl_2:ether (1:1) and the combined extracts evaporated to yield an oil (0·57 g); λ_{max} nm., 325. Without purification this oil was dissolved in conc HCl (10 ml) and allowed to stand at room temp for 5 days. After removal of the solvent the semi-solid residue was triturated with acetone affording a colourless solid which recrystallized from MeOH as needles, m.p. 210–212 (65·7%). The free base was liberated from this hydrochloride with ammonia, crystallizing as colourless prisms from EtOH m.p. 146–148° (lit.,[20] 147°); λ_{max} (ε) nm., 232 sh (16,800), 287 (4880), identical with an authentic specimen of ±tetrahydropalmatine. (Found: C, 71·7; H, 7·3; N, 4·1. Calc. for $C_{21}H_{25}NO_4$: C, 71·0; H, 7·1; N, 3·9%).

2-(3,4-*Methylenedioxyphenethyl*)7,8-*dimethoxyisoquinolinium iodide* (3, X = H; Y = Z = OMe; A,B = OCH_2O). This compound, golden needles m.p. 181–182° (from EtOH/ether), was prepared from the interaction of 3,4-methylenedioxyphenethyl bromide and 7,8-dimethoxyisoquinoline, followed by anion exchange, in 79·2% yield; ν_{max} cm^{-1}, 1630, 1600, 1560; λ_{max} (ε) nm., 258 (36,700), 293 (6690); NMR (CF_3CO_2H) ppm 9·25 singlet [1] (C_1—H); 8·25 singlet [2] (C_3—H, C_4—H); 8·05 singlet [2] (C_5—H, C_6—H); 6·8–6·5 multiplet [3] (aromatic protons of phenethyl substituent); 5·95 singlet [2] (OCH_2O); 5·0 triplet [2], J = 7·5 Hz ($ArCH_2CH_2\overset{+}{N}\langle$); 4·20 singlet [6] (2 × OCH_3); 3·35 triplet [2] ($ArCH_2$—$CH_2\overset{+}{N}\langle$). (Found: C, 51·8; H, 4·1; N, 3·2; I, 26·8. $C_{20}H_{20}NO_4I$ requires: C, 51·6; H, 4·3; N, 3·0; I, 27·3%).

±*Canadine* (2, X = H; Y = Z = OMe; A,B = OCH_2O; W = 2H). The above iodide (0·61 g) was reduced to the corresponding 1,2-dihydroisoquinoline in the manner previously described, and the crude product treated with conc HCl (10 ml). After 5 days at room temp the soln was diluted, washed with benzene and evaporated. The residue crystallized upon trituration with EtOH, and the yellow product was then recrystallized from aqueous EtOH as prisms (58%) m.p. 160–162° (lit.,[24] 230–232°, this compound was not characterized however). (Found: C, 61·5; H, 6·4. $C_{20}H_{22}NO_4Cl$, H_2O requires: C, 61·0; H, 6·1%). The free base was liberated from the hydrochloride with NH_4OH and recrystallized from MeOH, giving white

prisms; λ_{max} (ε) nm., 230 sh (10,500), 292 (7520); m.p. 169–170° (lit.,[21] 170–171°). (Found: C, 71·0; H, 6·4; N, 4·3. Calc. for $C_{20}H_{21}NO_4$: C, 70·8; H, 6·2; N, 4·1%).

Preparation of N,N-*benzylphenylethylaminoacetals.* The benzylaminoacetal (0·1 m) in EtOH containing the appropriate β-arylethylbromide (0·01 m) was treated with Na_2CO_3 (1·0 g) and water (10 ml). After heating for 20 hr, under reflux, the EtOH was removed under reduced press and the oily base which had separated was extracted into ether. Removal of the ether gave the required dialkylated aminoacetals, in yields ranging from 92–95%, as pale yellow oils.

General cyclization procedure. The N,N-diakylaminoacetals (0·005 m) in conc HCl (10 ml) were allowed to stand at room temp for 5 days. The resultant red coloured solns were then washed with ether to remove non-basic material and evaporated to dryness. Trituration of the residues with acetone eventually afforded solid hydrochlorides which were recrystallized from EtOH. Yields, m.p. and analytical data for these salts are collected into Table 1. Compound **13b** was converted into the corresponding methiodide, m.p. 195–197°, which crystallized as colourless cubes from EtOH; ν_{max} cm^{-1}, 1610; λ_{max} (ε) nm., 240 sh (9650), 288 (5940); NMR (CF_3CO_2H) ppm, 6·8 singlet [2] (aryl protons ring A); 6·9 singlet [1] and 6·5 singlet [1] (aryl protons ring B); 4·8 triplet [1], J = 6 Hz (>C<u>H</u>—<u>CH</u>$_2$—N<); 4·0–2·8 multiplet [8] (aliphatic protons); 3·9 and 3·8 two singlets [12] (4 × —OC<u>H</u>$_3$); 3·4 singlet [3] (>N—C<u>H</u>$_3$). The methoperchlorate was also prepared, m.p. 240–242°, as colourlesss microcrystalline prisms from EtOH. (Found: C, 56·15; H, 6·0; N, 3·1. $C_{22}H_{28}NO_8Cl$ requires: C, 56·2; H, 6·0; N, 3·0%).

Compound **13a**, [NMR ($CDCl_3$) 6·7, 6·5, 6·35, 6·3 singlets [4] (four aromatic protons); 3·8, 3·6 singlets [12] (4 × —OC<u>H</u>$_3$); 4·8–2·5 multiplets [10] (aliphatic protons)] was converted into the corresponding base, colourless prisms m.p. 154–155° (from EtOH) and thence to the methoperchlorate, deep yellow needles, m.p. 270–272° (EtOH). (Found: C, 56·2; H, 6·0; N, 3·2; Cl, 7·45. $C_{22}H_{28}NO_8Cl$ requires: C, 56·2; H, 6·0; N, 3·0; Cl, 7·7%).

Compound **13c** was converted into the methiodide m.p. 274–275° and treated with perchloric acid to form the methoperchlorate, buff coloured prisms, m.p. 294–296°, from EtOH. (Found: C, 55·4; H, 5·4; H, 3·4; Cl, 7·5. $C_{21}H_{24}NO_8Cl$ requires: C, 55·6; H, 5·3; H, 3·1; Cl, 7·8%).

Compound **13d** when treated with MeI and Na_2CO_3 in acetone gave the same methiodide, m.p. 259–260° as obtained from **13a**, and addition of perchloric acid to this methiodide gave the identical methoperchlorate m.p. 270–272° (mixed m.p. and comparison of IR spectra) to that obtained in the above experiment.

General Hofmann degradative procedure. A suspension of the methiodide (or methoperchlorate) of the tetracyclic base (0·001 m) in 30% NaOH aq (25 ml) was heated under reflux for 3 hr, with constant stirring. On cooling the soln was extracted with ether (3 × 50 ml) and the dried combined extracts evaporated to yield the corresponding methine base.

Methine **15b** was obtained as an almost colourless resinous solid (75%) NMR ($CDCl_3$) ppm, 6·8 doublet [1], J = 8 Hz and 6·6 doublet [1], J = 8 Hz (aromatic protons ring A); 6·4 singlet [1] and 6·35 singlet [1] (aromatic protons ring B); 5·05 quartet [2], J = 2 Hz (>C=C<u>H</u>$_2$); ~3·7 two singlets [12] (4 × OC<u>H</u>$_3$); 3·4 singlet [2] (Ar C<u>H</u>$_2$—N<); 2·65 broad doublet [4] (>N—C<u>H</u>$_2$C<u>H</u>$_2$Ar); 2·15 singlet [3] (>N—C<u>H</u>$_3$). This compound was characterized as the methiodide, m.p. 213–215°, white prisms (acetone); ν_{max} cm^{-1}, 1600, 895; λ_{max} (ε) nm., 245 sh (10, 850), 294 (6650). (Found: C, 53·8; H, 6·1; N, 2·7; I, 24·8. $C_{23}H_{26}NO_4I$ requires: C, 54·0; H, 5·9; N, 2·7; I, 24·8%).

Methine **15a** recrystallized from EtOH as colourless prisms, m.p. 154–156°, 68%; ν_{max} cm^{-1}, 1605, 865 (>C=CH$_2$); λ_{max} (ε) nm., 245 sh (13,650), 290 (6820), NMR ($CDCl_3$) ppm 6·65 and 6·45 singlets [2] (protons ring A); 6·4 singlet [2] (protons ring B); 5·1 quartet [2], J = 2 Hz (>C=C<u>H</u>$_2$); ~3·7 three singlets [12H] (4 × OC<u>H</u>$_3$); 3·25 singlet [2] (Ar—C<u>H</u>$_2$—N<); 2·65 broad singlet [4H] (—C<u>H</u>$_2$—C<u>H</u>$_2$—); 2·15 singlet [3] (>N—C<u>H</u>$_3$). (Found: C, 71·6; H, 7·3; N, 3·8. $C_{22}H_{23}NO_4$. C, 71·5; H, 7·4; N, 3·8%).

Methine **15c** was obtained as a semi solid (52%); ν_{max} cm^{-1}, 1605, 1025, 860; λ_{max} nm., 245, 290 sh; NMR ($CDCl_3$) ppm, 6·8 doublet [1], J = 8 Hz and 6·5 doublet [1], J = 8 Hz (aromatic protons ring A); 6·4 singlet [2] aromatic protons ring B); 5·65 singlet [2] (—O—CH$_2$O—), 5·05 quartet [2], J = 2 Hz

(>C=C$\underline{H}_2$); 3·7, 3·6 singlets [6] (2 × OC$\underline{H}_3$); 3·4 singlet [2H] (ArC$\underline{H}_2$—); ~2·7 multiplet [4H] (Ar—C$\underline{H}_2$C$\underline{H}_2$—N<); 2·15 singlets [3] (>N—C$\underline{H}_3$). The methiodide of this methine crystallized from EtOH as cream coloured prisms, m.p. 224–226°; ν_{max} cm^{-1}, 1600, 1025, 880; λ_{max} (ε) nm., 247 sh (17,600), 302 (7730). (Found: C, 53·1; H, 5·5; N, 2·5; I, 25·9. $C_{22}H_{24}NO_4I$ requires: C, 53·3; H, 5·25; N, 2·8; I, 25·65%).

Reduction of methine base (**15b**). The base (0·4 g) was dissolved in 3N HCl (25 ml) and the soln hydrogenated over PtO_2 (50 mg) at room temp and atm press for 16 hr. The catalyst was then removed, and the soln made basic with NH_4OH and extracted with ether. Removal of the solvent from the combined extracts afforded the reduced **16** as a yellow oil (0·34 g), λ_{max} n.m., 285, which was characterized as the perchlorate salt. This latter compound, flesh coloured needles, m.p. 245–247°, crystallized from EtOH; λ_{max} (ε) 240 sh (4710), 285 (2190); NMR (CF_3COOH) ppm, 7·35 d [1], J = 9 Hz and 7·0 doublet [1], J = 9 Hz (aromatic protons ring A); 6·8, 6·6 two singlets [1] (aromatic protons ring B); 4·8–4·4 multiplet [3] (ArC$\underline{H}_2\overset{+}{N}$< and >C$\underline{H}$—CH$_3$); 3·8 broad based singlet [14] (4 × OC$\underline{H}_3$ and Ar—C$\underline{H}_2$—CH$_2$—$\overset{+}{N}$<); 3·1 multiplet [5] (>$\overset{+}{N}$—C$\underline{H}_3$ and >$\overset{+}{N}$C$\underline{H}_2$—CH$_2$—); 1·7 doublet [3], J = 7 Hz (>CH—C$\underline{H}_3$). (Found: C, 56·2; H, 6·5; N, 3·5; Cl, 7·6. $C_{22}H_{39}NO_8Cl$ requires: C, 56·0; H, 6·4; N, 3·0; Cl, 7·5%).

Transannular cyclization of the methine bases. A soln of the methine base (0·001 m) in glacial AcOH (25 ml) was allowed to stand overnight at room temp. Evaporation of the solvent gave a gummy residue which dissolved in 2N HCl (10 ml) and the soln washed with ether (2 × 10 ml), basified with NH_4OH and extracted with CH_2Cl_2 (3 × 10 ml). Removal of the solvent from the dry combined extracts yielded a resinous solid, which when dissolved in EtOH (10 ml) and a few drops of perchloric acid added crystallized as the corresponding perchlorate salt.

The perchlorate salt **17b** obtained in 39·6% yield, recrystallized from a large volume of EtOH as colourless needles, m.p. 254–255°; ν_{max} cm^{-1}, 1610; λ_{max} (ε) nm., 240 sh (10,200), 290 (5480); NMR (CF_3CO_2H) ppm, 6·95 singlet [3] and 6·7 singlet [1] (aromatic protons); 4·8 singlet [2] (Ar C$\underline{H}_2$—$\overset{+}{N}$<); ~3·9 broad based singlet [14] (4 × OC$\underline{H}_3$ and —CH$_2$C$\underline{H}_2$Ar); ~3·3 broad singlet [5] (>$\overset{+}{N}$—CH$_3$ and >$\overset{+}{N}$—C$\underline{H}_2$CH$_2$—); 2·15 singlet [3] (>C—C$\underline{H}_3$). (Found: C, 56·0; H, 6·4; Cl, 7·3. $C_{22}H_{28}NO_8Cl$ requires: C, 56·2; H, 6·0; Cl, 7·7%).

N-3,4-*Dimethoxybenzyl*-N-3,4-*dimethoxyphenylethylaminoacetaldehyde* (**20**). The amine **18** and an equimolar amount of glycidol were heated on a water-bath for 2 hr, the mixture was then diluted with $CHCl_3$ and water and cooled to 0°. Sodium metaperiodate (0·01M) in water was then added dropwise with vigorous agitation during 15 min. The two phase soln was then made basic (pH 8) with N NaOH and further stirred for 3 hr. The $CHCl_3$ layer was then removed and evaporated to give an orange-yellow oil (80%), ν_{max} cm^{-1}, 1730, which was not purified but used directly in cyclization experiments under conditions previously described for the corresponding dimethylacetal, the product **21** was identical in all respects with that obtained from the aminoacetal (No. 2 in Table 1).

Benzylaminoacetal (**23**, R = R = OCH_2O; R′ = Me). 3,4-Dimethoxylbenzyl-3,4-methylenedioxyphenyl ketone (1·5 g) and aminoacetal (2·0 g) were heated together at reflux temp for 3 hr during which time excess aminoacetal was slowly allowed to distill. The residual oil was dissolved in EtOH (50 ml) and hydrogenated at 2 atm press over PtO_2 (0·5 g) during 5 hr. The benzylaminoacetal was then converted directly into its N-Me derivative by the addition to the above soln of glacial AcOH (0·5 ml), 37% aqueous formalin (0·5 ml) and continuation of the hydrogenation for a further 4 hr. Removal of the catalyst and solvent gave an oil which was dissolved in ice cold 2N H_2SO_4 and washed with ether. The purified product was liberated from the acid phase with NH_2OH and extracted into CH_2Cl_2. After evaporation of the solvent from these latter extracts the product (1·8 g) was obtained as a yellow oil; ν_{max} cm^{-1}, 1610, 1590.

Amurensinine (**24**, R,R = OCH_2O, R′ = Me). Without further purification the oil was cyclized in the usual manner, basification of the acid soln produced a brown oil which was purified by chromatography upon an alumina column. Elution with benzene:pet ether (1:1) yielded amurensine (0·36 g), 24%. m.p. 158–160° (lit.[14], 160–164°); λ_{max} nm, 233 sh, 253, 296, ν_{max} cm^{-1}, 1606. The methiodide was obtained as

colourless prisms, m.p. 266–268° (lit,[14] 273–275°), from MeOH/ether; ν_{max} cm^{-1}, 1610; λ_{max} (ε) nm, 233 sh (12,700), 253 sh (4020), 296 (6680); NMR (CF_3CO_2H) ppm 7·05, 6·95, 6·90, 6·80 four singlets [4] (aromatic protons); 6·05 quartet [2], J = 2 Hz (OCH_2O); 4·8 triplet [1], J = 6 Hz, (CH—CH_2), 3·9–4·1 multiplet [3] (aliphatic protons); 4·0, 3·9 two singlets (2 × OMe); 3·58, 3·20, two singlets [6] (2 × $\overset{+}{N}CH_3$). (Found: C, 52·0; H, 5·2; N, 2·7; I, 26·6. Calc. for $C_{21}H_{24}NO_4I$, C, 52·4; H, 5·2; N, 2·9; I, 26·4%).

The Fritsch product (**28**). The compound was obtained as previously described by Guthrie *et al.*,[12] and recrystallized from EtOH as yellow needles, m.p. 161–162° (lit.,[12] 164–165°); ν_{max} cm^{-1}, 1590 (>C=N—), 1565 (>C=C<); λ_{max} (ε) nm, 228 (22,100), 261 (13,100), 318 sh (7360), 346 (8470), NMR, see Fig. 1. By using conc HCl at RT during 24 hr the yield of **28**, as the hydrochloride, was increased to 37%.

Reduction of the Fritsch product. Hydrogenation of the above base (0·4 g) in EtOH (100 ml) over Adams catalyst (0·05 g) at 2 atm press afforded a colourless oil (0·4 g) which was characterized as the hydrochloride; colourless solid m.p. 230–232° (from EtOH/ether) ν_{max} cm^{-1}, 2750, 2650, 2440, 1610. The methiodide was isolated as colourless nodules m.p. 179–180°, from MeOH–ether, containing 1 mol MeOH of crystallization; ν_{max} cm^{-1}, 3350–3450, 1610; λ_{max} (ε) nm, 236 sh (18,100), 283 (7960). (Found: C, 51·4; H, 6·35; N, 2·4; I, 24·5. $C_{22}H_{30}NO_4I$ requires: C, 51·9; H, 6·40; N, 2·6; I, 24·0%).

Formation of the methine (**29**). The above methiodide (0·3 g) was heated under reflux with 30% NaOH aq (20 ml) for 3 hr. After cooling the soln was extracted with ether and the combined extracts evaporated to yield a colourless oil. This was dissolved in ether and the soln saturated with gaseous HCl, causing the corresponding hydrochloride to separate as a colourless solid, which recrystallized from aqueous EtOH, m.p. 218–220 (lit.,[23] 220–221°), yield 90%. This product was converted into the perchlorate salt, m.p. 206–208° (from EtOH), λ_{max} (ε) nm, 296 sh (15,700), 331 (22,300). This UV spectrum is identical with that reported by Knabe.[22] (Found: C, 55·95; H, 6·3; N, 3·2; Cl, 7·4. $C_{22}H_{30}NO_8Cl$ requires: C, 56·0; H, 6·4; N, 3·0; Cl, 7·5%).

2-(3,4-*Dimethoxylbenzoyl*)1,2-*dihydroisoquinaldonitrile.* Isoquinoline (12 g) in CH_2Cl_2 (70 ml), KCN (30 g) in water (300 ml) and veratroyl chloride [from veratric acid (22 g)] were shaken vigorously together for 5 min. The solid product (11·5 g) was filtered off washed with water and EtOH; addition of EtOH to the filtrate afforded a further crop of crystalline product (4·5 g). The combined crops were recrystallized from EtOH to yield 2-(3,4-dimethoxybenzoyl)-1,2-dihydroisoquinaldonitrile as very small colourless prisms (16 g), m.p. 213–215°. λ_{max} (ε) nm, 228 (25,800), 296 (15,100). ν_{max} cm^{-1}, 1660, 1640. (Found: C, 71·5; H, 5·15; N, 8·85. $C_{19}H_{16}N_2O_3$ requires: C, 71·25; H, 5·05; N, 8·75%).

2-(2,3-*Dimethoxybenzoyl*)1,2-*dihydroisoquinaldonitrile.* This compound was prepared in an identical procedure to that described above from 2,3-dimethoxybenzoyl chloride. Recrystallization from EtOH gave colourless prisms (12 g), m.p. 132–134°; λ_{max} (ε) nm, 228 (26,700), 290 (15,500); ν_{max} cm^{-1}, 1680, 1640. (Found: C, 71·1; H, 5·15; N, 8·9. $C_{19}H_{16}N_2O_3$ requires: C, 71·25; H, 5·05; N, 8·75%).

2-(2,3-*Dimethoxybenzoyl*)6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinaldonitrile.* As above, using 6,7-dimethoxy-3,4-dihydroisoquinoline (12·0 g) and 2,3-dimethoxybenzoylchloride (15 g). The product was recrystallized from EtOH; yield (6 g), m.p. 163–165°; ν_{max} cm^{-1}, 1650. (Found: C, 65·5; H, 5·65; N, 7·2. $C_{21}H_{22}N_2O_5$ requires: C, 65·9; H, 5·8; N, 7·35%).

Preparation of perchlorate salts. 2-(3,4-Dimethoxybenzoyl)1,2-dihydroisoquinaldonitrile was treated with glacial AcOH, a little 60% perchloric acid added and the yellow soln thus obtained was warmed for 20 min upon a water-bath. On cooling an almost quantitative yield of the perchlorate salt was obtained, which recrystallized from a large volume of EtOH as yellow needles, m.p. 205–206°, ν_{max} cm^{-1}, 3400–3180, 1670, 1640. (Found: C, 54·2; H, 4·9; N, 6·35; Cl, 8·4. $C_{19}H_{16}N_2O_3$, $HClO_4$ requires: C, 53·9; H, 4·95; N, 6·60; Cl, 8·35%).

The perchlorates of 2-(2,3-dimethoxybenzyl)1,2-dihydroisoquinaldonitrile and 2-(2,3-dimethoxylbenzyl)6,7-dimethoxy-1,2,3,4-tetrahydroisoquinaldonitrile were similarly prepared as yellow needles, m.p. 186–189°. (Found: C, 53·85; H, 4·95; N, 6·65; Cl, 8·45. $C_{19}H_{16}N_2O_3$, $HClO_4$ requires: C, 53·7; H, 4·95; N, 6·6; Cl, 8·35%), and m.p. 236°. (Found: C, 51·8; H, 5·05; N, 5·8; Cl, 7·65. $C_{21}H_{22}N_2O_5$, $HClO_4$ requires: C, 52·2; H, 4·8; N, 5·8; Cl, 7·35%) respectively.

2-(3,4-*Dimethoxybenzyl*)1,2,3,4-*tetrahydroisoquinaldamide* (**34**, A = B = C = W = H; X = Y = OMe). 2-(3,4-Dimethoxylbenzoyl)1,2-dihydroisoquinaldonitrile perchlorate (14 g) in 50% aqueous EtOH (240 ml) was heated on a water-bath and $NaBH_4$ (4 g) added in small portions over 20 min. After a further 30 min the volume of the soln was decreased to about 140 ml and allowed to cool. The colourless crystalline product was recrystallized from EtOH as long needles (4·6 g) m.p. 179°. ν_{max} cm^{-1}, 3450, 3320, 1670, 1630. (Found:

C, 69·55; H, 6·75; N, 8·55. $C_{19}H_{22}N_2O_3$ requires: C, 69·9; H, 6·8; N, 8·6%). This compound was characterized as the perchlorate salt, colourless prisms from EtOH, m.p. 209–210°. (Found: C, 53·45; H, 5·2; N, 6·6; Cl, 8·55. $C_{19}H_{22}N_2O_5$, $HClO_4$ requires: C, 53·45; H, 5·45; N, 6·55; Cl, 8·3%).

2-(2,3-*Dimethoxybenzyl*)1,2,3,4-*tetrahydroisoquinaldamide* (**34**, A = B = C = Y = H; W = X = OMe). This was obtained in an identical manner to that described above as a yellow oil (14 g), characterized as the perchlorate, colourless prisms m.p. 204·5–205° from EtOH. (Found: C, 53·65; H, 5·15; N, 6·7; Cl, 8·6. $C_{19}H_{22}N_2O_3$, $HClO_4$ requires: C, 53·45; H, 5·45; N, 6·55; Cl, 8·5%).

2-(3,4-*Dimethoxybenzyl*)6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinaldamide* (**34**, A = B = X = Y = OMe; C = W = H). In a similar experiment 2-(3,4-dimethoxybenzoyl)6,7-dimethoxy-1,2,3,4-tetrahydroisoquinaldonitrile perchlorate (2·7 g) was reduced to give the corresponding aldamide (0·3 g) as long colourless needles m.p. 189–192° (lit., 191°) from aqueous EtOH. Attempts to prepare the perchlorate salt failed.

2-(3,4-*Dimethoxybenzyl*)1,2,3,4-*tetrahydroisoquinoline*-1-*carboxylic acid.* 2-(3,4-Dimethoxylbenzyl)1,2,-3,4-tetrahydroisoquinaldamide (7 g) in conc HCl (80 ml) was heated at reflux for 1 hr and then cooled. Some resinous material was removed and the soln made alkaline with 30% NaOH aq and made just acid with AcOH; after filtration through Kieselguhr the soln was extracted with CH_2Cl_2 (4 × 60 ml) and the combined extracts were then dried and evaporated to give the corresponding acid; which recrystallized as long, colourless needles (2·0 g), m.p. 164–165°, from EtOH. (Found: C, 67·3; H, 6·8; N, 4·65. $C_{19}H_{21}NO_4\frac{1}{2}H_2O$ requires: C, 67·87; H, 6·6; N, 4·15%). This acid was also prepared from the amide (9·0 g) by heating at reflux with 30% ethanolic KOH (100 ml) for 24 hr, yield 5·6 g.

2-(2,3-*Dimethoxybenzyl*)1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline*-1-*carboxylic acid.* 2-(2,3-Dimethoxybenzyl)1,2,3,4-tetrahydro 6,7-dimethoxyisoquinaldamide (0·4 g) was heated under reflux with 30% ethanolic KOH (10 ml) for 24 hr, some EtOH was then distilled and water (10 ml) added. After filtration the soln was extracted with CH_2Cl_2 (4 × 20 ml) and the combined extracts evaporated to yield the acid as an oil, which crystallized, on trituration with EtOH, as small prisms m.p. 183–185°, ν_{max} cm^{-1} 3100–3200, 1620. This material was not further purified, but used directly in subsequent experiments.

2-(2,3-*Dimethoxylbenzyl*)1,2,3,4-*tetrahydroisoquinoline*-1-*carboxylic acid.* This compound was obtained from the corresponding amide (16 g) by hydrolysis with conc HCl (100 ml) as described above. Addition of EtOH to the oily product (3·5 g) did not effect crystallization; the compound was, however, characterized as the perchlorate, colourless prisms, m.p. 190°, from EtOH, ν_{max} cm^{-1} 3200–2300, 1740. (Found: C, 53·2; H, 5·45; N, 3·2; Cl, 8·45. $C_{19}H_{21}NO_4$, $HClO_4$ requires: C, 53·35; H, 5·2; N, 3·35; Cl, 8·3%). Basification of this salt yielded only resinous material.

2,3-*Dimethoxy*-7,8-*dihydro*-13-*oxo*-*berberinium perchlorate.* **35** (A = B = C = W = H; X = Y = OMe). 2-(3,4-Dimethoxybenzyl)1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (4·5 g) in polyphosphoric ester, prepared from P_2O_5 (30 g), $CHCl_3$ (30 ml) and ether (60 ml), was heated at 130° for 2·5 hr. The dark purple coloured soln was poured into water (300 ml) containing HCl (10 ml) and then made alkaline with NaOH aq. The yellow product which separated was collected and dissolved in EtOH (20 ml); addition of 60% perchloric acid (1 ml) to this soln caused the separation of colourless needles (3·0 g), m.p. 291–293°; λ_{max} (ε) nm, 228 (8400), 289 (36,000), 320 (7100) inflexion, 365 (2900); ν_{max} cm^{-1}, 1690; NMR ($CDCl_3$) ppm 9·15 singlet [1] (C_7-H), 8·5 singlet [1] (C_{12}-H) 7·9 complex [1] (C_1-H), ~7·5 complex [5] (aromatic protons), 4·7 triplet [2] J = 7·5 Hz ($\equiv\overset{+}{N}-CH_2-CH_2-$), 4·2, 4·1 two singlets [6] (2 × $-OCH_3$), 3·3 triplet [2] J = 7·5 Hz ($\equiv -CH_2-CH_2-$). (Found: C, 56·0; H, 4·7; N, 3·3; Cl, 8·4. $C_{19}H_{18}NO_3$, $HClO_4$ requires: C, 55·7; H, 4·6; N, 3·2; Cl, 8·4%). This compound was also obtained from the acid by a cyclization reaction using polyphosphoric acid, at 125° for 3 hr the yield of product being somewhat lower.

All attempts to effect the cyclization of 2-(2,3-dimethoxy)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid, using polyphosphoric ester or polyphosphoric acid, failed.

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