Tetrahedron. Vol. 29, pp. 1265 to 1272. Pergamon Press 1973. Printed in Great Britain

THE PROTOBERBERINE → SPIROBENZYLISOQUINOLINE → DIBENZOCYCLOPENT[*b*]AZEPINE REARRANGEMENT[1]

M. SHAMMA* and J. F. NUGENT

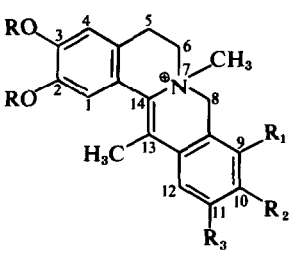
Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

(*Received in the USA* 30 *October* 1972; *Received in the UK* 8 *January* 1973)

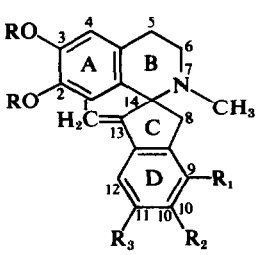
Abstract—Dihydroprotoberberine salts **5**, **10**, and **14**, rearrange in base to the spirobenzylisoquinolines **8**, **12**, and **16**, respectively. But the dihydroprotoberberine salt **18**, which does not possess a phenolic function in ring D, rearranges to the dibenzocyclopent[*b*]azepine **21** through the intermediacy of the aziridinium ion **20**.

Although the actual biogenesis of the spirobenzylisoquinoline alkaloids still remains to be established by *in vivo* experiments using labeled precursors, one possible biogenetic route appeared to be through the intermediacy of a diphenolic dihydroprotoberberine salt such as **1** which could rearrange in base to the spirobenzylisoquinoline **2**.[2] To test this hypothesis, the related diphenolic salt **3** was prepared and was indeed found to rearrange under basic conditions to the spiro compound **4** in good yield.[3]

It was now relevant to determine if the two phenolic functions of the dihydroprotoberberine salt precursor had to be present in the same ring, as in **3**, or if they could alternatively be placed in different rings such as in salt **5**. For this purpose, the dihydroprotoberberine salt **5** was prepared by a route parallel to that used in the synthesis of **3**, and described in detail in the Experimental. Refluxing of this material in ethanol solution with excess sodium hydroxide under a nitrogen atmosphere for 4 days gave a 50% yield of the desired spirobenzylisoquinoline **8** via the intermediacy of the quinone methides **6** and **7** (Scheme 1). The NMR spectrum of **8** in $CDCl_3$ closely resembled that of the diphenol **4**.[3] The N-Me protons were present as a singlet at δ 2·23, and the two vinylic protons appeared as singlets at δ 4·96 and 5·62. Additionally, the rearranged product **8** was hydrogenated and then O-acetylated to afford the dihydrodiacetate derivative **9** whose NMR spectrum showed a doublet for the C-13 Me group at δ 1·01 ($J = 7$ Hz).

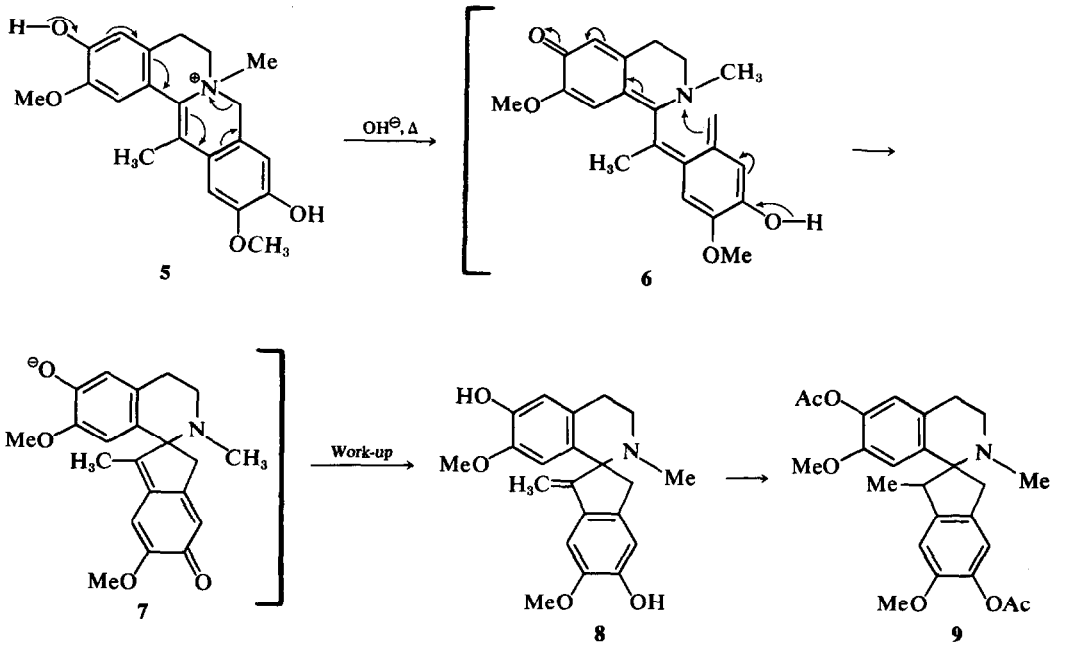


1: $R_1 = R_2 = OH$; $R_3 = H$
3: $R_1 = H$; $R_2 = R_3 = OH$

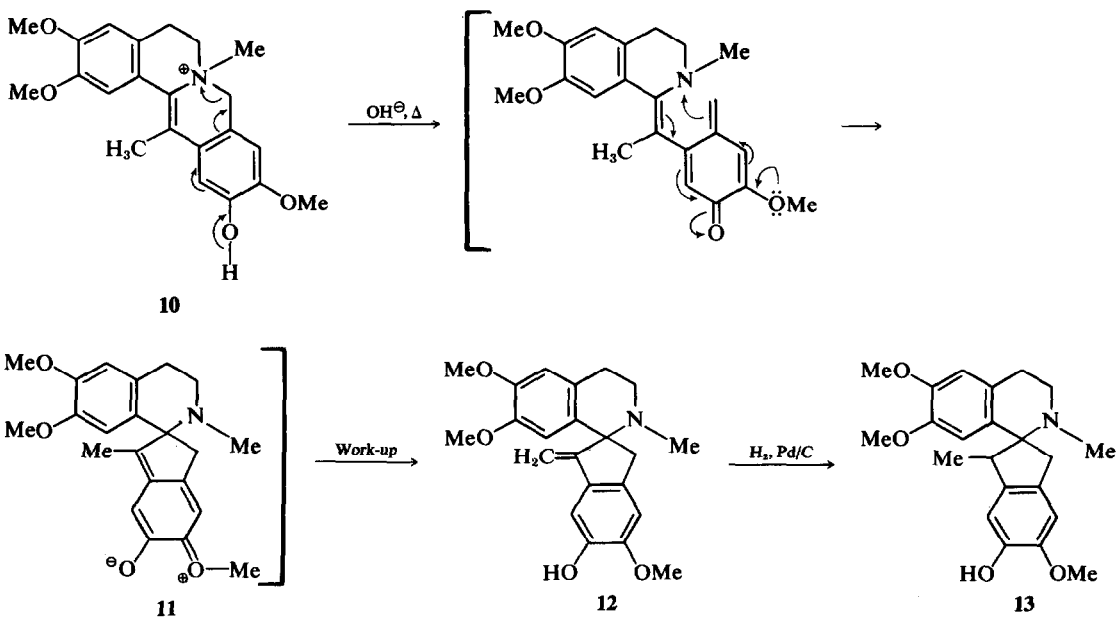


2: $R_1 = R_2 = OH$; $R_3 = H$
4: $R_1 = H$; $R_2 = R_3 = OH$

To find out next if the rearrangement would proceed with only one phenolic group present in the dihydroprotoberberine salt precursor, compounds **10** and **14** were prepared, again by routes similar to those followed in the construction of salts **3** and **5**. When salt **10** was subjected to the rearrangement conditions, it became apparent that the reaction was essentially complete after only 16 hours. The NMR spectrum of the product **12** resembled those of spirobenzylisoquinolines **4** and **8**. The N-Me singlet was at δ 2·14, and the one proton singlets at δ 4·86 and 5·49 were assigned to the two vinylic protons of the exocyclic methylene. Catalytic hydrogenation of **12** furnished the dihydro derivative **13** with a C-13 Me doublet at δ 0·90 ($J = 7$ Hz). It is worth noting in this instance the relatively short reaction time needed for the rearrangement of salt **10** to occur, induced by the *para* relationship of the phenolic function and the C-8 C atom which allows for the facile cleavage of the N-7 to C-8 bond (Scheme 2).



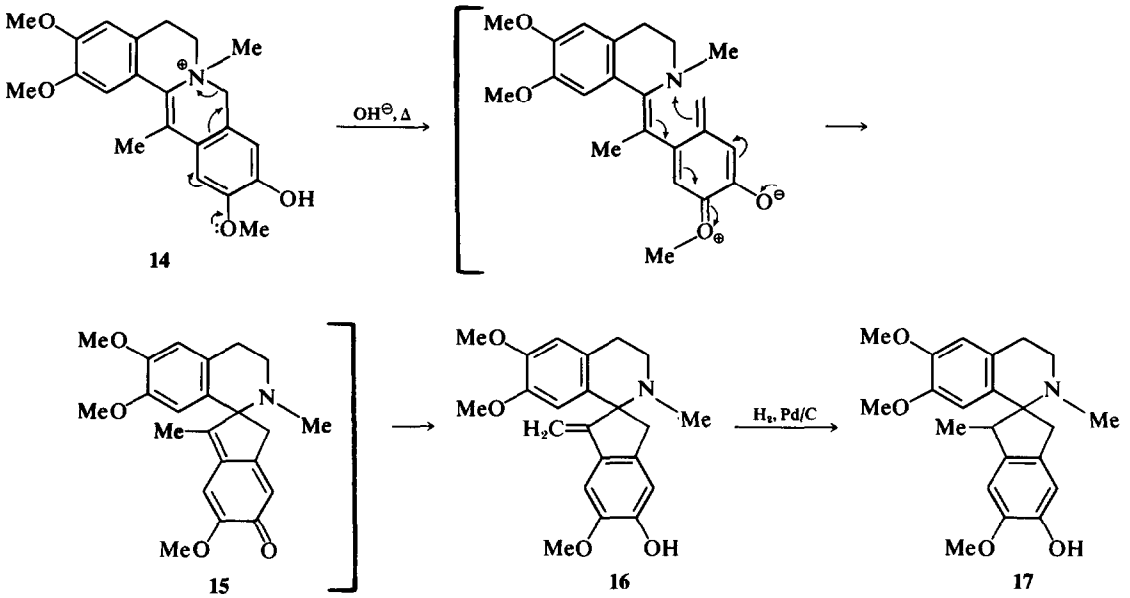
SCHEME 1



SCHEME 2

In like fashion, the monophenolic dihydroprotoberberine salt precursor **14** was found to arrange to the spirobenzylisoquinoline **16**, although the required reflux time was 4 days. The dihydro derivative **17** obtained by hydrogenation of **16** showed an NMR spectrum which contained the expected C-13 Me doublet at δ 0·94 ($J = 7$ Hz), Scheme 3.

At this stage, an important dihydroprotoberberine salt left to study was **18**. This material was prepared by a route exactly analogous to that used previously for the precursors **3**, **5**, **10** and **14**. The



SCHEME 3

attempted rearrangement of **18** was carried out again under basic conditions over a period of 4 days, and the product was obtained as a crystalline solid. Since amorphous materials had been obtained from all the previous rearrangements, the isolation of a crystalline product in the present case was the first indication that the reaction might have taken a different course. Indeed, spectral data revealed that the product **21** was skeletally different from that of a spirobenzylisoquinoline.

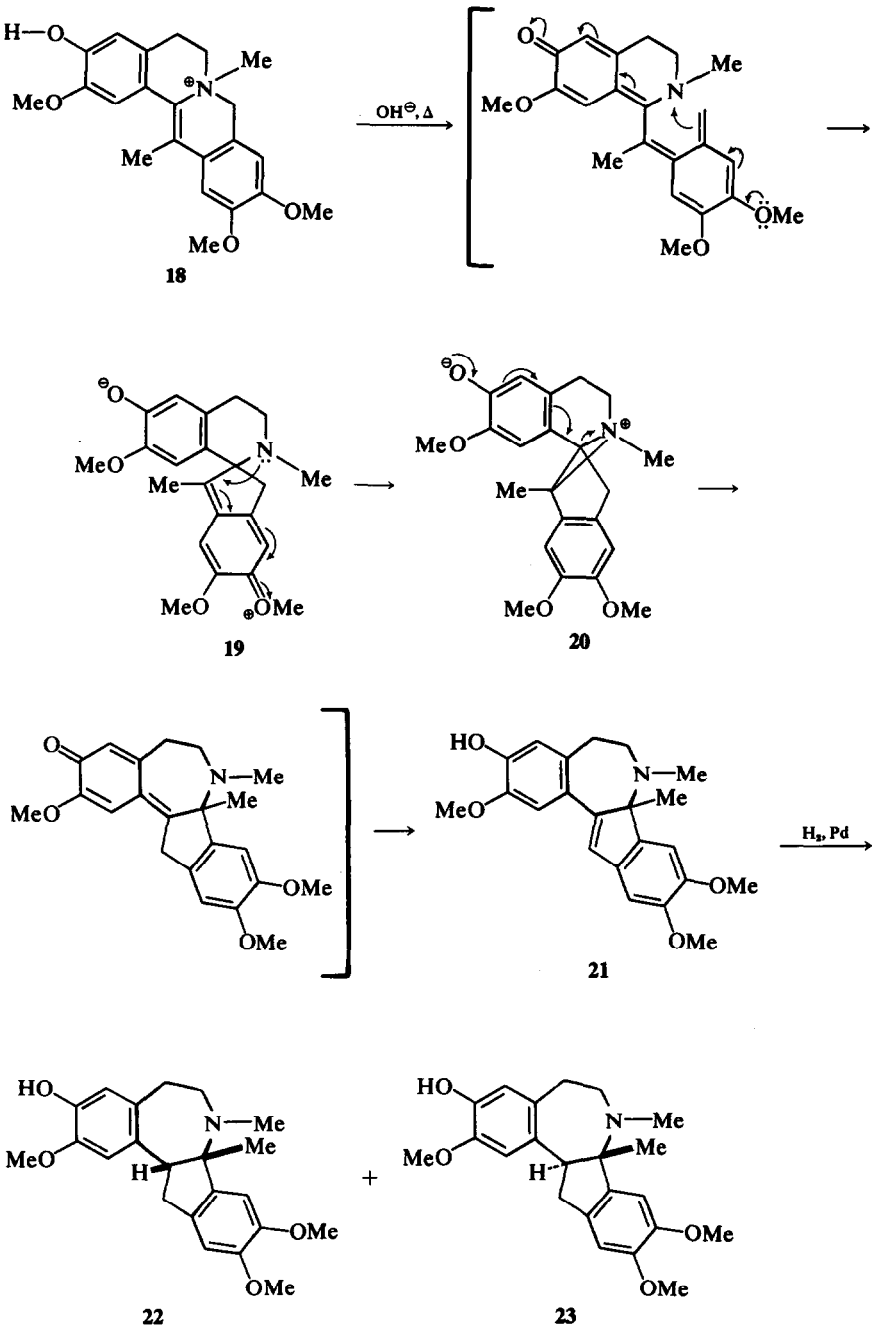
The NMR spectrum of **21** contained a three proton singlet at δ 2·82 assigned to the N-Me group, and another three proton singlet at δ 1·72 due to a deshielded aliphatic Me group. Significantly, only one vinylic proton singlet (δ 5·46) was present, a fact which ruled out the possibility of an exocyclic double bond. Elemental analysis and high resolution mass spectroscopy established the formula $C_{22}H_{25}O_4N$. The parent peak at *m/e* 367 was also the base peak in the low resolution mass spectrum of **21**, and the only other significant fragment was at *m/e* 352 corresponding to the loss of a Me group. The UV spectrum was suggestive of a stilbenoid system with λ_{max}^{EtOH} 232sh, 291 and 312 nm (log ε 4·37, 4·07 and 4·17), and was substantially different from the spectra for products **4**, **8**, **12** and **16**.

Catalytic hydrogenation of the rearrangement product **21** led to a separable mixture of the dihydro derivatives **22** and **23** in approximately equal amounts. The NMR spectra of **22** and **23** were quite close and contained signals for the C-Me group at δ 1·5–1·6 and for the N-Me at about δ 2·40.

The apparent delinquency in the rearrangement of the dihydroprotoberberine salt **18** to the dibenzocyclopent[*b*]azepine system instead of to a spirobenzylisoquinoline can be rationalized as shown in Scheme 4. The key difference is that the intermediate quinone methide **19** bears a full positive charge distributed between rings C and D, which was not the case in any of the other quinone methides. There is now, therefore, a definite impetus for the lone pair of electrons on the N atom to attack intramolecularly at C-13 and form the aziridinium ion **20** which in turn breaks down to generate the dibenzocyclopent[*b*]azepine system. It follows that those dihydroprotoberberine salts which do not possess a phenolic function in ring D will rearrange in base to dibenzocyclopent[*b*]azepines rather than to spirobenzylisoquinolines.

In some recent reports in the literature, several spirobenzylisoquinolines have been rearranged to dibenzocyclopent[*b*]azepines, and although no mechanisms were offered for these transformations, it is logical to assume that they too proceed through the intermediacy of aziridinium ions. In one instance, the spirobenzylisoquinoline **24** was treated with methanesulfonyl chloride in triethylamine and dry THF to yield dibenzocyclopent[*b*]azepines **25** and **26**,[4] most probably by the route shown in Scheme 5.

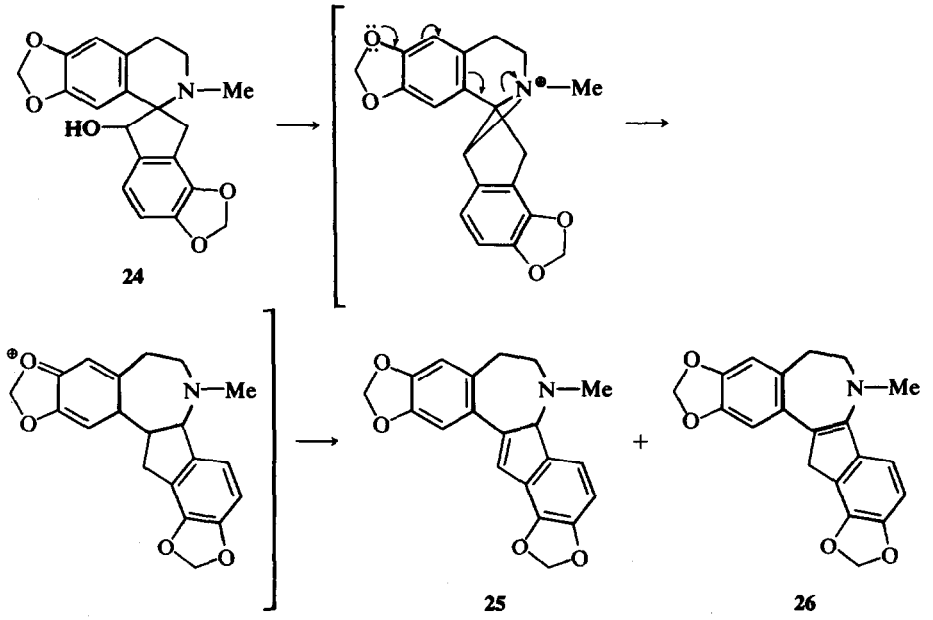
In another instance, pyrolysis of the new spirobenzylisoquinoline alkaloids fumaritrine (**27**) and fumaritridine (**28**) was reported to furnish the dibenzocyclopent[*b*]azepines **31** and **32** respectively which were characterized mainly through IR and NMR spectroscopy.[5a] There is no facile



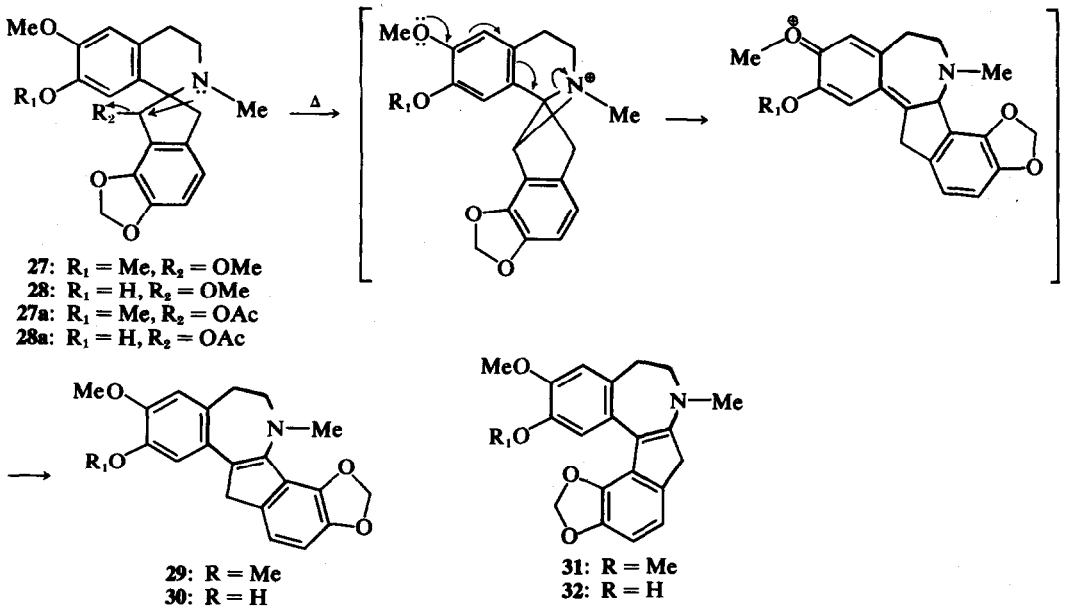
SCHEME 4

mechanism by which structures **31** and **32** can be generated from the two alkaloids. Instead, the pyrolysis products should be represented by structures **29** and **30** formed as indicated in Scheme 6, and which fully conform to the spectral requirements. In a third instance, pyrolysis of O-methylfumarophycine (**27a**) and fumarophycine (**28a**) has been assumed to give rise also to **31** and **32**,[5] instead structures **29** and **30** should be representative of the products formed.

Finally, it should be emphasized again that conclusive proof for a biogenetic process can come



SCHEME 5



SCHEME 6

only through feeding experiments using labeled precursors.

EXPERIMENTAL

Standard experimental procedures. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis. M.ps are uncorrected. The NMR data were recorded at 60 MHz in $CDCl_3$ unless indicated otherwise; TMS was the internal reference. Mass spectra were obtained on an AEI MS-902 spectrometer. All TLC was on Merck Silica Gel-254 plates.

I. *Preparation of diphenolic salt* **5**

A. *2-(3′-Methoxy-4′-benzyloxyphenyl)propionic acid.* Sodium amide (0·0552 mol) in liquid NH_3 (250 ml) was prepared and ethyl 3-methoxy-4-benzyloxyphenylacetate[6] (16·42 g, 0·0545 mol) in ether was added dropwise. After 10 min, MeI (45 g, 0·317 mol) in ether was also added dropwise, and the mixture was stirred at −33° for 2 hr. Ammonium chloride was added, the ammonia evaporated, and the organic material extracted in $CHCl_3$. The crude ester was refluxed with KOH in EtOH-water for 4 hr. Work-up gave 10·9 g of

the required acid, m.p. 119–120° (EtOH). NMR (DMSO-d_6) δ 1·39 (3H, d, $J = 7$ Hz, $CHCH_3$), δ 3·77 (3H, s, $ArOCH_3$), and δ 5·06 (2H, s, $PhCH_2O$). (Found: C, 71·26; H, 6·45. Calcd. for $C_{17}H_{18}O_4$: C, 71·31; H, 6·34%).

B. *N-(3-Benzyloxy-4-methoxyphenylethyl)-2-(3'-methoxy-4'-benzyloxyphenyl)propionamide.* A mixture of the above acid (15 g, 0·0524 mol) and 3-benzyloxy-4-methoxy-β-phenethylamine[7] (15·7 g, 0·0612 mol) was heated at 195° for 2 hr under N_2. Work-up yielded 9·66 g of amide, m.p. 107–108° (EtOH); NMR δ 1·44 (3H, d, $J = 7$ Hz, $CHCH_3$), δ 3·82 (6H, s, $ArOCH_3$), and δ 5·07 and 5·10 (4H, s, $PhCH_2O$). (Found: C, 75·31; H, 6·87. Calcd. for $C_{33}H_{35}NO_5$: C, 75·40; H, 6·71%).

C. *1-(α-Methyl-3'-methoxy-4'-benzyloxybenzyl)-3,4-dihydro-6-benzyloxy-7-methoxyisoquinoline.* A mixture of the above amide (19·3 g, 0·0368 mol), $POCl_3$ (20 ml, 0·213 mol), and toluene (500 ml) was refluxed for 90 min. The solvent was evaporated and $CHCl_3$ added. Work-up gave the imine as a thick oil which was used without further purification.

D. *1-(α-Methyl-3'-methoxy-4'-benzyloxybenzyl)-1,2,3,4-tetrahydro-6-benzyloxy-7-methoxyisoquinoline.* A soln of the above imine in EtOH was cooled to 0°, and after slow addition of $NaBH_4$ (7 g, 0·202 mol) was stirred 3 hr at 0°. *The mixture was acidified with* HCl *aq. neutralized* with dil NaOH, and the soln concentrated. Extraction with chloroform yielded the title amine as an amorphous solid.

E. *2,11-Dimethoxy-3,10-dibenzyloxy-13α-methyl-14α-H-tetrahydroprotoberberine.* The amine prepared above, formic acid (100 ml), and formalin (100 ml) were refluxed for 5 hr, cooled, and the mixture evaporated to dryness. The residue was partitioned between NaOH aq and $CHCl_3$. Work-up gave 13·8 g of the tetrahydroprotoberberine (72% from the amide). Recrystallization from EtOH *afforded colorless crystals, m.p.* 153–154°; NMR δ 1·48 (3H, d, $J = 7$ Hz, $CHCH_3$), δ 3·83 and 3·86 (6H, s, $ArOCH_3$), and δ 5·10 (4H, s, $PhCH_2O$). (Found: C, 78·18; H, 6·82. Calcd. for $C_{34}H_{35}NO_4$: C, 78·28; H, 6·76%).

F. *2,11-Dimethoxy-3,10-dibenzyloxy-13-methylprotoberberine iodide.* A mixture of the above tetrahydroprotoberberine (8·8 g, 0·0169 mol), 20% AcOH (250 ml), and mercuric acetate (24 g, 0·0755 mol) was heated on a steam bath for 6 hr, filtered while hot, and the filtrate saturated with H_2S. The mixture was heated to 100° for 3 min, filtered, and the ppt washed with water. The combined filtrates were treated with KI aq. and filtered. The yellow iodide salt was crystallized from chloroform, 8·6 g (79%), m.p. 229–230° (dec); λ_{max}^{MeOH} 264, 287, 305sh nm (log ε 4·50, 4·66, 4·56); NMR (DMSO-d_6) δ 3·01 (3H, s, C=C—CH_3). (Found: C, 62·97; H, 5·60. Calcd. for $C_{34}H_{32}NO_4I$: C, 63·25; H, 5·40%).

G. *2,11-Dimethoxy-3,10-dibenzyloxy-13-methyl-7,8-dihydroprotoberberine methiodide.* The above protoberberine iodide (4·46 g, 6·28 mmol) was slowly added to a stirred slurry of LAH (2 g, 52·8 mmol) in dry THF (200 ml) at 0°; the stirring was continued for 30 min under a steady stream of N_2. The excess reagent was decomposed by cautious addition of a cold salt soln Na_2SO_4, and the ether slurry was dried over Na_2SO_4. The flask was immediately filled with N_2, sealed and transferred to a nitrogen dry box. The slurry was filtered, dried over K_2CO_3, and evaporated to yield the yellow enamine. The enamine was immediately dissolved in acetonitrile (75 ml), and MeI (50 ml, 804 mmol) was added. The mixture was refluxed under N_2 for 30 min. Evaporation and crystallization from MeOH yielded 2·068 g (51%) of the yellow iodide salt, m.p. 205–208° (dec); λ_{max}^{EtOH} 264sh, 270sh, 293sh *and* 327 *nm* (log ε 4·14, 4·11, 4·04, *and* 4·36); NMR δ 2·47 (3H, s, C=C—CH_3), δ 3·15 (3H, s, $N^{\oplus}$—CH_3), δ 3·93 (6H, s, $ArOCH_3$), and δ 5·22 (4H, s, $PhCH_2O$). (Found: I, 19·19. Calcd. for $C_{35}H_{36}NO_4I$: I, 19·18%).

H. *2,11-Dimethoxy-3,10-dihydroxy-13-methyl-7,8-dihydroprotoberberine methobromide* (5). The methiodide salt produced in sequence G (1·926 g, 2·92 mmol) was refluxed under N_2 for 6 hr in the dark with a deoxygenated mixture of EtOH (10 ml) and 48% HBr (10 ml). The yellow foam resulting from evaporation to dryness and trituration with ether was crystallized from MeOH, 0·885 g (60%), m.p. 234–236° (dec); λ_{max}^{EtOH} 230 and 231 nm (log ε 4·45 and 4·55); NMR (DMSO-d_6) δ 2·33 (3H, s, C=C—CH_3), δ 2·94 (3H, s, $N^{\oplus}$—CH_3), δ 3·83 and 3·88 (3H × 2, s, $ArOCH_3$). (Found: C, 55·82; H, 5·80. Calcd. for $C_{21}H_{24}NO_4Br.H_2O$: C, 55·76; H, 5·79%).

Rearrangement of diphenolic salt 5 to *2,11-dimethoxy-3,10-dihydroxy-13-methyleneochotensane* (8). Salt 5 (0·2 g, 0·446 mmol) in 50% EtOH containing 0·2 ml of 10% NaOH aq was refluxed under N_2 for 4 days. The mixture was acidified with conc HCl, neutralized with $NaHCO_3$, *and concentrated in vacuo. Extraction with* chloroform and evaporation yielded 92 mg (56%) of 8 as an amorphous solid; λ_{max}^{EtOH} 266sh, 272sh, 294, 316 and 328sh nm (log ε 3·94, 3·94, 3·75, 3·95 and 3·92); NMR δ 2·23 (3H, s, NCH_3), δ 3·65 and 3·96 (3H × 2, s, $ArOCH_3$), δ 4·96 and 5·62 (1H × 2, s, C=CH_2), δ 6·29, 6·60, 6·82 and 7·03 (1H × 4, s, ArH); low resolution mass spec *m/e* 353 (M^+, 100), 352 (30), and 338 (60).

High resolution mass measurement, $M^{\oplus}$: Found: *m/e* 353·1627. Calcd. for $C_{21}H_{23}NO_4$: *m/e* 353·1627.

2,11-Dimethoxy-3,10-diacetoxy-13-methylochotensane (9). *Spirobenzylisoquinoline* 8 *was hydrogenated with* 5% Pd/C in MeOH over a period of 18 hr. The crude product was acetylated with acetyl chloride and triethylamine at 0° for 2 hr. The amorphous 9 exhibited λ_{max}^{EtOH} 282 and 286sh nm (3·78 and 3·77); NMR δ 1·01 (3H, d, $J = 7$ Hz, $CHCH_3$), δ 2·27 and 2·30 (3H × 2, s, CH_3COO), δ 2·59 (3H, s, NCH_3), δ 3·45 and 3·83 (3H × 2, s, $ArOCH_3$), δ 6·40, 6·74, 6·81 and 6·94 (1H × 4, s, ArH).

High resolution mass measurement, $M^{\oplus}$: Found: *m/e* 439·1955. Calcd. for $C_{25}H_{29}NO_6$: *m/e* 439·1993.

11. Preparation of monophenolic salts 16

2-(3'-Benzyloxy-4'-methoxyphenyl)propionic acid. 3-Benzyloxy-4-methoxyphenylacetic acid has been prepared.[7] The title acid was prepared as described in procedure A above, crystals, m.p. 130–131° (EtOH). (Found: C, 71·10; H, 6·52. Calcd. for $C_{17}H_{18}O_4$: C, 71·31; H, 6·34%).

N-(3,4-*Dimethoxyphenylethyl*)-2-(3'-*benzyloxy*-4'-*methoxyphenyl*)-*propionamide.* A mixture of the above acid (18·55 g, 0·0642 mol) and homoveratrylamine (15 g, 0·0829 mol) was treated as in B above to yield, after recrystallization from EtOH, 26·56 g (92%) of colorless amide m.p. 111°. (Found: C, 72·38; H, 7·29. Calcd. for $C_{27}H_{31}NO_5$: C, 72·14; H, 6·95%).

1-(α-*Methyl*-3'-*benzyloxy*-4'-*methoxybenzyl*)-3,4-*dihydro*-6,7-*dimethoxyisoquinoline.* A mixture of the above amide (24·3 g, 0·0542 mol), $POCl_3$ (25 ml, 0·265 mol), and toluene (500 ml) was treated as in procedure C to yield the title imine as a viscous oil which was used in the next step.

1-(*α-Methyl-3'-benzyloxy-4'-methoxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline*. Procedure D was followed for the $NaBH_4$ reduction. The product was an oil which was used without further purification.

2,3,10-*Trimethoxy*-11-*benzyloxy*-13*α-methyl*-14*α*-H-*tetrahydroprotoberberine*. A mixture of the above amine was treated with formic acid and formalin as in E, to yield 8·50 g (35% from the amide) of colorless crystals, m.p. 141–142° (EtOH); NMR δ 1·40 (3H, d, $J = 7$ Hz, $CHC\underline{H}_3$). (Found: C, 75·25; H, 7·10. Calcd. for $C_{28}H_{31}NO_4$: C, 75·48; H, 7·01%).

2,3,10-*Trimethoxy*-11-*benzyloxy*-13-*methylprotoberberine iodide*. A mixture of the above tetrahydroprotoberberine (8·24 g, 0·0185 mol), 20% AcOH (180 ml) and mercuric acetate (20 g, 0·0625 mol) was treated as in sequence F to yield, after recrystallization from chloroform 7·62 g of yellow iodide (73%), m.p. 195–197° (dec); λ_{max}^{MeOH} 263, 287 and 305sh nm (log ε 4·48, 4·60 and 4·49); NMR (DMSO-d_6) δ 2·98 (3H, s, C=C—CH_3). (Found: C, 58·97; H, 5·31. Calcd. for $C_{28}H_{28}NO_4I$: C, 59·06; H, 4·96%).

2,3,10-*Trimethoxy*-11-*benzyloxy*-13-*methyl*-7,8-*dihydroprotoberberine methiodide*. A mixture of the above iodide salt (4·00 g, 7·03 mmol) and LAH (2 g, 52·8 mmol) in dry THF (200 ml) was treated as in procedure G to yield an enamine which was immediately quaternized with MeI to yield yellow crystals, m.p. 153–156° (dec); λ_{max}^{EtOH} 264, 293sh and 326 nm (log ε 4·07, 4·12 and 4·34); NMR δ 2·30 (3H, s, C=C—$C\underline{H}_3$). (Found: I, 22·05. Calcd. for $C_{29}H_{32}NO_4I$: I, 21·68%).

2,3,10-*Trimethoxy*-11-*hydroxy*-13-*methyl*-7,8-*dihydroprotoberberine methobromide* (**10**). A mixture of the above methiodide salt (1·506 g, 2·57 mmol), EtOH (10 ml) and 48% HBr was treated as in sequence H to yield 0·687 g (60%) of yellow salt **10**, m.p. 216–218° (dec; EtOH); λ_{max}^{EtOH} 233, 290 and 327 nm (log ε 4·23, 4·00 and 4·24); NMR (DMSO-d_6) δ 2·28 (3H, s, C=C—$C\underline{H}_3$), δ 2·98 (3H, s, N^+—CH_3), δ 3·85, 3·88 and 3·88 (3H × 3, s, $ArOC\underline{H}_3$). (Found: C, 56·56; H, 5·66. Calcd. for $C_{22}H_{26}NO_4Br.H_2O$: C, 56·66; H, 6·05%).

Rearrangement of monophenolic salt **10** *to* 2,3,10-*trimethoxy*-11-*hydroxy*-13-*methyleneochotensane* (**12**). A mixture of **10** (0·208 g, 0·464 mmol) and 9 ml of 1·06 N NaOH in 500 ml EtOH was refluxed under N_2 for 16 hr. The work-up was the same as in the preparation of analog **8**. The amorphous product weighed 0·122 g (71%); λ_{max}^{EtOH} 262, 270, 287sh, 293, 316 and 327sh nm (log ε 4·11, 4·09, 3·75, 3·78, 4·00 and 3·96); NMR δ 2·14 (3H, s, $NC\underline{H}_3$), δ 3·62, 3·83 and 3·86 (3H × 3, s, $ArOC\underline{H}_3$), δ 4·86 and 5·49 (1H × 2, s, C=$C\underline{H}_2$), δ 6·32, 6·53, 6·72 and 7·07 (1H × 4, s, $Ar\underline{H}$); low resolution mass spec *m/e* 367 ($M^{\oplus}$, 69), 352 (100).

High resolution mass measurement, $M^{\oplus}$: Found: *m/e* 367·1745. Calcd. for $C_{22}H_{25}NO_4$: *m/e* 367·1783.

2,3,10-*Trimethoxy*-11-*hydroxy*-13-*methylochotensane* (**13**). Reduction of **12** with 5% Pd/C in MeOH afforded the amorphous **13**, λ_{max}^{EtOH} 230sh and 290 nm (log ε 4·06 and 3·82); NMR δ 0·90 (3H, d, $J = 7$ Hz, $CHC\underline{H}_3$), δ 2·44 (3H, s, $NC\underline{H}_3$), δ 3·51, 3·83 and 3·85 (3H × 3, s, $ArOC\underline{H}_3$), δ 6·36, 6·56, 6·66 and 6·74 (1H × 4, s, $Ar\underline{H}$).

High resolution mass measurement, $M^{\oplus}$: Found: *m/e* 369·1917. Calcd. for $C_{22}H_{27}NO_4$: *m/e* 369·1939.

III. *Preparation of monophenolic salt* **14**

N-(3,4-*Dimethoxyphenylethyl*)-2-(3'-*methoxy*-4'-*benzyloxyphenyl*)*propionamide*. A mixture of 2-(3'-methoxy-4'-benzyloxyphenyl)propionic acid (15·21 g, 0·0531 mol) and homoveratrylamine (13 g, 0·0718 mol) was treated as in B above to yield, after recrystallization from EtOH, 18·95 g (80%) of colorless amide m.p. 106°. (Found: C, 71·72; H, 6·60. Calcd. for $C_{27}H_{31}NO_5$: C, 72·14; H, 6·95%).

1-(*α-Methyl-3'-methoxy-4'-benzyloxybenzyl*)-3,4-*dihydro*-6,7-*dimethoxyisoquinoline*. A mixture of the above amide was treated with $POCl_3$ as in procedure C to yield a viscous imine.

1-(*α Methyl-3'-methoxy-4'-benzyloxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline*. Procedure D was followed. The product was an oil which was used without further purification.

2,3,11-*Trimethoxy*-10-*benzyloxy*-13*α-methyl*-14*α*-H-*tetrahydroprotoberberine*. A mixture of the above amine was treated as in section E to yield 6·50 g (36% from the amide) of colorless crystals, m.p. 169–171° (EtOH); NMR δ 1·48 (3H, d, $J = 7$ Hz, $CHC\underline{H}_3$). (Found: C, 75·54; H, 7·10. Calcd. for $C_{28}H_{31}NO_4$: C, 75·48; H, 7·01%).

2,3,11-*Trimethoxy*-10-*benzyloxy*-13-*methylprotoberberine iodide*. The above tetrahydroprotoberberine was treated as in sequence F to yield, after recrystallization from chloroform, 5·25 g (71%) of yellow iodide, m.p. 210–214° (dec); λ_{max}^{EtOH} 263, 287 and 305sh nm (4·24, 4·40 and 4·30); NMR (DMSO-d_6) δ 3·00 (3H, s, C=C—$C\underline{H}_3$). (Found: C, 58·71; H, 5·10. Calcd. for $C_{28}H_{28}NO_4I$: C, 59·06; H, 4·96%).

2,3,11-*Trimethoxy*-10-*benzyloxy*-13-*methyl*-7,8-*dihydroprotoberberine methiodide*. The above iodide salt (4 g) yielded 2·466 g (60%) of the required yellow salt via procedure G, m.p. 129–131° (dec; EtOH); λ_{max}^{EtOH} 264, 292sh, 327 nm (log ε 4·04, 4·09 and 4·35); NMR δ 2·40 (3H, s, C=C—CH_3). (Found: C, 58·86; H, 6·12. Calcd. for $C_{29}H_{32}NO_4I$: C, 59·49; H, 5·51%).

High resolution mass measurement, $M^+ - I^-$: Found: *m/e* 458·2319. Calcd. for $C_{29}H_{32}NO_4$: *m/e* 458·2330.

2,3,11-*Trimethoxy*-10-*hydroxy*-13-*methyl*-7,8-*dihydroprotoberberine methobromide* (**14**). Hydrolysis of the above methiodide salt (1·2 g, 2·09 mmol) by procedure H yielded 0·6 g (64%) of yellow crystals of **14**, m.p. 183–186° (dec; EtOH); λ_{max}^{EtOH} 235 and 330 nm (log ε 4·33 and 4·42); NMR (DMSO-d_6) δ 2·37 (3H, s, C=C—$C\underline{H}_3$), δ 2·98 (3H, s, N^+—CH_3), δ 3·85, 3·88 and 3·92 (3H × 3, s, $ArOC\underline{H}_3$). (Found: C, 58·37; H, 5·88. Calcd. for $C_{22}H_{26}NO_4Br.1/4H_2O$: C, 58·35; H, 5·90%).

High resolution mass measurement, $M^+ - Br^-$: Found: *m/e* 368·1844. Calcd. for $C_{22}H_{26}NO_4$: *m/e* 368·1861.

Rearrangement of monophenolic salt **14** *to* 2,3,11-*trimethoxy*-10-*hydroxy*-13-*methyleneochotensane* (**16**). A mixture of **14** (0·204 g, 0·456 mmol), and 10 ml of 1·06 N NaOH in 1·51 EtOH was refluxed for 4 days under N_2. The work-up was the same as in the preparation of analogs **8** and **12**. The amorphous product weighed 0·059 g (32·3%); λ_{max}^{EtOH} 263sh, 272sh, 292sh, 315 and 328sh nm (log ε 4·04, 4·04, 3·83, 4·02 and 3·99); NMR δ 2·19 (3H, s, NCH_3), δ 3·64, 3·86 and 3·95 (3H × 3, s, $ArOC\underline{H}_3$), δ 4·92 and 5·58 (1H × 2, s, C=CH_2), δ 6·31, 6·55, 6·82 and 7·03 (1H × 4, s, ArH); low resolution mass spec *m/e* 367 ($M^{\oplus}$, 100), 352 (43).

High resolution mass measurement, $M^{\oplus}$. Found: *m/e* 367·1779. Calcd. for $C_{22}H_{25}NO_4$: *m/e* 367·1783.

2,3,11-*Trimethoxy*-10-*hydroxy*-13-*methylochotensane* (**17**). The hydrochloride salt of base **16** was reduced with 5% Pd/C in MeOH. The amorphous product **17** exhibited λ_{max}^{EtOH} 231sh and 291 nm (log ε 4·07 and 3·89); NMR

δ 0·94 (3H, d, $J = 7$ Hz, $CHC\underline{H}_3$), δ 2·44 (3H, s, $NC\underline{H}_3$), δ 3·51, 3·83 and 3·85 (3H × 3, s, $ArOC\underline{H}_3$), δ 6·35, 6·56, 6·62 and 6·78 (1H × 4, s, Ar$\underline{H}$).

High resolution mass measurement, $M^{\oplus}$: Found: *m/e* 369·1929. Calcd. for $C_{22}H_{27}NO_4$: *m/e* 369·1939.

IV. *Preparation of monophenolic salt* **18**

2-(3′,4′-Dimethoxyphenyl)propionic acid. The ethyl ester of 3,4-dimethoxyphenylacetic acid was C-alkylated as in procedure A above, and then saponified to yield crystals, m.p. 45–47° (EtOH). (Found: C, 62·45; H, 6·88. Calcd. for $C_{11}H_{14}O_4$: C, 62·85; H, 6·71%).

N-(3-Benzyloxy-4-methoxyphenylethyl)-2-(3′,4′-dimethoxyphenyl)propionamide. A mixture of the above acid (17·5 g, 0·0833 mol) and 3-benzyloxy-4-methoxy-β-phenethylamine[7] (21·4 g, 0·0831 mol) was treated as in B above to yield 21·5 g (57%) of colorless amide, m.p. 114·115° (EtOH). (Found: C, 72·19; H, 7·11. Calcd. for $C_{27}H_{35}NO_5$: C, 72·14; H, 6·95%).

1-(α-Methyl-3′,4′-dimethoxybenzyl)-3,4-dihydro-6-benzyloxy-7-methoxyisoquinoline. A mixture of the above amide was treated as in procedure C to yield a viscous imine.

1-(α-Methyl-3′,4′-dimethoxybenzyl)-1,2,3,4-tetrahydro-6-benzyloxy-7-methoxyisoquinoline. Procedure D was followed. The product was an oil which was used without further purification.

2,10,11-Trimethoxy-3-benzyloxy-13α-methyl-14α-H-tetrahydroprotoberberine. The above amine was treated as in reaction E to yield colorless crystals, m.p. 122–123° (EtOH), in 64% yield; NMR δ 1·48 (3H, d, $J = 7$ Hz, $CHC\underline{H}_3$). (Found: C, 75·60; H, 7·16. Calcd. for $C_{28}H_{31}NO_4$: C, 75·48; H, 7·01%).

2,10,11-Trimethoxy-3-benzyloxy-13-methylprotoberberine iodide. The above tetrahydroprotoberberine was treated as in sequence F to yield, after recrystallization from chloroform, a yellow iodide, m.p. 232–233° (dec) in 95% yield; λ_{max}^{EtOH} 264, 287 and 305sh nm (4·45, 4·65 and 4·54); NMR (DMSO-d_6) δ 2·99 (3H, s, C=C—$C\underline{H}_3$). (Found: C, 58·76; H, 5·32. Calcd. for $C_{28}H_{28}NO_4I$: C, 59·06; H, 4·96%).

2,10,11-Trimethoxy-3-benzyloxy-13-methyl-7,8-dihydroprotoberberine methiodide. The above iodide salt (4 g) yielded 2·25 g (53%) of the required yellow methiodide salt via procedure G, m.p. 212–214° (dec; EtOH); λ_{max}^{EtOH} 293sh, 327 nm (log ε 4·13 and 4·39); NMR δ 2·42 (3H, s, C=C—$C\underline{H}_3$). (Found: C, 59·10; H, 5·50. Calcd. for $C_{29}H_{32}NO_4I$: C, 59·49; H, 5·51%).

2,10,11-Trimethoxy-3-hydroxy-13-methyl-7,8-dihydroprotoberberine methobromide (**18**). Hydrolysis of the above methiodide salt (2·00 g, 3·42 mmol) by procedure H yielded 1·10 g (55%) of yellow crystals of **18**, m.p. 177–180° (dec; EtOH); λ_{max}^{EtOH} 233 and 329 nm (log ε 4·39 and 4·39); NMR (DMSO-d_6) δ 2·38 (3H, s, C=C—$C\underline{H}_3$), δ 2·99 (3H, s, $N^{\oplus}$—CH_3), δ 3·87 3·91 and 3·91 (3H × 3, s, $ArOC\underline{H}_3$). (Found: Br, 17·56. Calcd. for $C_{22}H_{26}NO_4Br$: Br, 17·82%).

Rearrangement of monophenolic salt **18** *to 5,6,7,7a-tetrahydro-2,9,10-trimethoxy-7,7a-dimethylbenz[d]indeno[1,2-b]azepin-3-ol* (**21**). A mixture of salt **18** (0·72 g, 1·61 mmol), and 9 ml of 0·188 N NaOH in 3 l EtOH was refluxed for 4 days under N_2. The work-up was the same as in the preparations of analogs **8**, **12**, and **16**. The colorless crystals weighed 0·243 g (41%; EtO$\underline{H}$); NMR δ 1·72 (3H, s, C—$C\underline{H}_3$), δ 2·82 (3H, s, $NC\underline{H}_3$), δ 3·70, 3·92 and 3·92 (3H × 3, s, $ArOC\underline{H}_3$), δ 5·46 (1H, s, C=C$\underline{H}$), δ 6·69, 6·77, 7·02 and 7·06 (1H × 4, s, Ar$\underline{H}$); low resolution mass spec *m/e* 367 (M^+, 100), 352 (80), 337 (25). (Found: C, 71·53; H, 6·76. Calcd. for $C_{22}H_{25}NO_4$: C, 71·91; H, 6·86%).

High resolution mass measurement, $M^{\oplus}$: Found: *m/e* 367·1749. Calcd. for $C_{22}H_{25}NO_4$: *m/e* 367·1783.

Cis- and trans-5,6,7,7a,12,12a-Hexahydro-2,9,10-trimethoxy-7,7a-dimethylbenz[d]indeno[1,2-b]azepin-3-ol (**22** and **23**). The hydrochloride of **21** (0·235 g, 0·641 mmol) was hydrogenated over Pd-C in MeOH to yield 0·135 g (57%) of **22** and **23**. Prep TLC using $CHCl_3$-MeOH (8:2) and precoated Brinkmann Silica Gel F-254 plates afforded a band with R_f 0·72 which crystallized from EtOH, 0·056 g of isomer A, m.p. 192–194°; λ_{max}^{EtOH} 232 and 285 nm (4·12 and 3·88); NMR δ 1·53 (3H, s, C—$C\underline{H}_3$), δ 2·40 (3H, s, $NC\underline{H}_3$), δ 3·79, 3·91 and 3·91 (3H × 3, s, $ArOC\underline{H}_3$), δ 6·72, 6·79, 7·04 and 7·33 (1H × 4, s, Ar$\underline{H}$); low resolution mass spec *m/e* 369 (M^+, 4), 368 (4), 354 (14), 218 (7), 204 (7), 190 (11), 179 (100), 164 (7), 151 (4). (Found: C, 70·55; H, 7·34. Calcd. for $C_{22}H_{27}NO_4.1/4H_2O$: C, 70·66; H, 7·41%).

High resolution mass measurement, $M^{\oplus}$: Found: *m/e* 369·1929. Calcd. for $C_{22}H_{27}NO_4$: *m/e* 369·1939.

The band with R_f 0·34 crystallized from EtOH to yield 0·60 g of isomer B, m.p. 197–198°; λ_{max}^{EtOH} 230sh and 286 nm (4·20 and 3·99); NMR δ 1·64 (3H, s, CC$\underline{H}_3$), δ 2·37 (3H, s, $NC\underline{H}_3$), δ 3·69, 3·87 and 3·91 (3H × 3, s, $ArOC\underline{H}_3$), δ 6·21, 6·57, 6·77 and 6·99 (1H × 4, s, Ar$\underline{H}$); low resolution mass spec *m/e* 369 (M^+, 18), 354 (33), 218 (15), 204 (15), 190 (26), 179 (100), 164 (15), and 151 (7). (Found: C, 70·70; H, 7·38. Calcd. for $C_{22}H_{27}NO_4.1/4H_2O$: C, 70·66; H, 7·41%).

High resolution mass measurement, $M^{\oplus}$: Found: *m/e* 369·1960. Calcd. for $C_{22}H_{27}NO_4$: *m/e* 369·1939.

Acknowledgements—The authors are grateful to the National Institutes of Health for research grant CA-11450 and to the Hoffmann-La Roche Foundation for an unrestricted grant.

REFERENCES

[1]Some of the results described in this paper have appeared in communication form, see M. Shamma and J. F. Nugent, *Tetrahedron Letters* 2625 (1970); and *Chem. Commun.* 1642 (1971)

[2]For a recent review on the spirobenzylisoquinoline alkaloids see M. Shamma, *The Alkaloids* (Edited by R. H. F. Manske), Vol. 13, p. 165. Academic Press, New York (1971)

[3]M. Shamma and C. D. Jones, *J. Am. Chem. Soc.* **92**, 4943 (1970)

[4]H. Irie, S. Tani and H. Yamane, *Chem. Commun.* 1713 (1970)

[5a]N. M. Mollov, H. G. Kirjakov and G. I. Yakimov, *Phytochemistry* **11**, 2331 (1972); [b]N. M. Mollov and G. I. Yakimov, *C.R. Acad. Bulg. Sci.* **24**, 1325 (1971)

[6]T. Kametani and J. Serizawa, *J. Pharm. Soc. Japan* **72**, 1084 (1952)

[7]R. Robinson and S. Sugasawa, *J. Chem. Soc.* 3167 (1931)