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SYNTHESIS IN THE EMETINE SERIES—XIV[1]

A NEW SYNTHESIS OF 2,3,11-TRISUBSTITUTED BERBINES

A. BROSSI, H. BRUDERER,[2] A. I. RACHLIN and S. TEITEL
Chemical Research Departments, Hoffmann-La Roche Inc., Nutley, New Jersey
and F. Hoffmann-La Roche & Co., AG, Basel

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Abstract—A new synthesis of 2,3,11-trisubstituted berbines is described. By this method the dimethoxy-substituted benzoquinolizidine keto ester I is annelated with a four carbon unit, cyclized and aromatized in the presence of an alcohol to give the 2,3-dimethoxy-11-alkoxy-substituted berbines VIII, IX and X. The stereochemistry of the intermediate compounds has been elucidated by physical–chemical methods.

A NEW approach to the synthesis of various 2,3,11-trisubstituted berbines which is based on the formation of ring D is described. In this scheme (Charts I and II)* the benzoquinolizidine keto-ester I substituted with two OMe groups at the 9,10-positions and containing rings A, B and C of the berbine molecule is annelated with a four carbon unit and then transformed into any of the three tetracyclic intermediates—IV, V and VI. Each of the latter can be converted in high yield to the key compound, the α,β-unsaturated ketone VII, which is then aromatized by reaction with cupric bromide in the presence of alcohols to afford the 2,3-dimethoxy-11-alkoxyberbines VIII, IX and X. Except for V, all compounds are *trans* B/C fused due to the presence of a Bohlmann band in the IR and the absence of a single proton signal below δ 3·8 in the NMR.[3]

Michael reaction of the enolized [$NMR_{HA\text{-}100}(CDCl_3)$: δ 11·8 (OH)] keto-ester I[4] with methyl vinyl ketone afforded the di-keto-ester II which on treatment with sodium ethoxide yielded the hydroxy-keto-ester IV. The latter was dehydrated with aqueous acid to form the *cis* B/C fused† unsaturated keto-ester V.

The di-keto-ester II was isomerized with hydrochloric acid to give a mixture of II and its epimer III, the latter predominating in a ratio of 3 to 2. Pure III, on treatment with acid yielded this same ratio of isomers, which suggests an equilibration via a

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* All compounds are racemates. The indicated structures therefore represent one of the two optical isomers.

† Such an isomerization can be explained if an equilibrium exists with a tautomer which is formed by rupture of the bond between the C_{13a} carbon and the nitrogen. One such possibility can be postulated as follows:

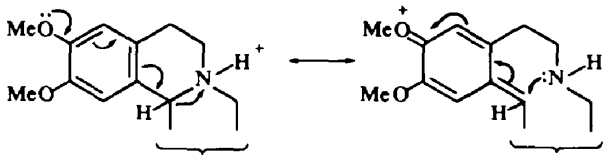
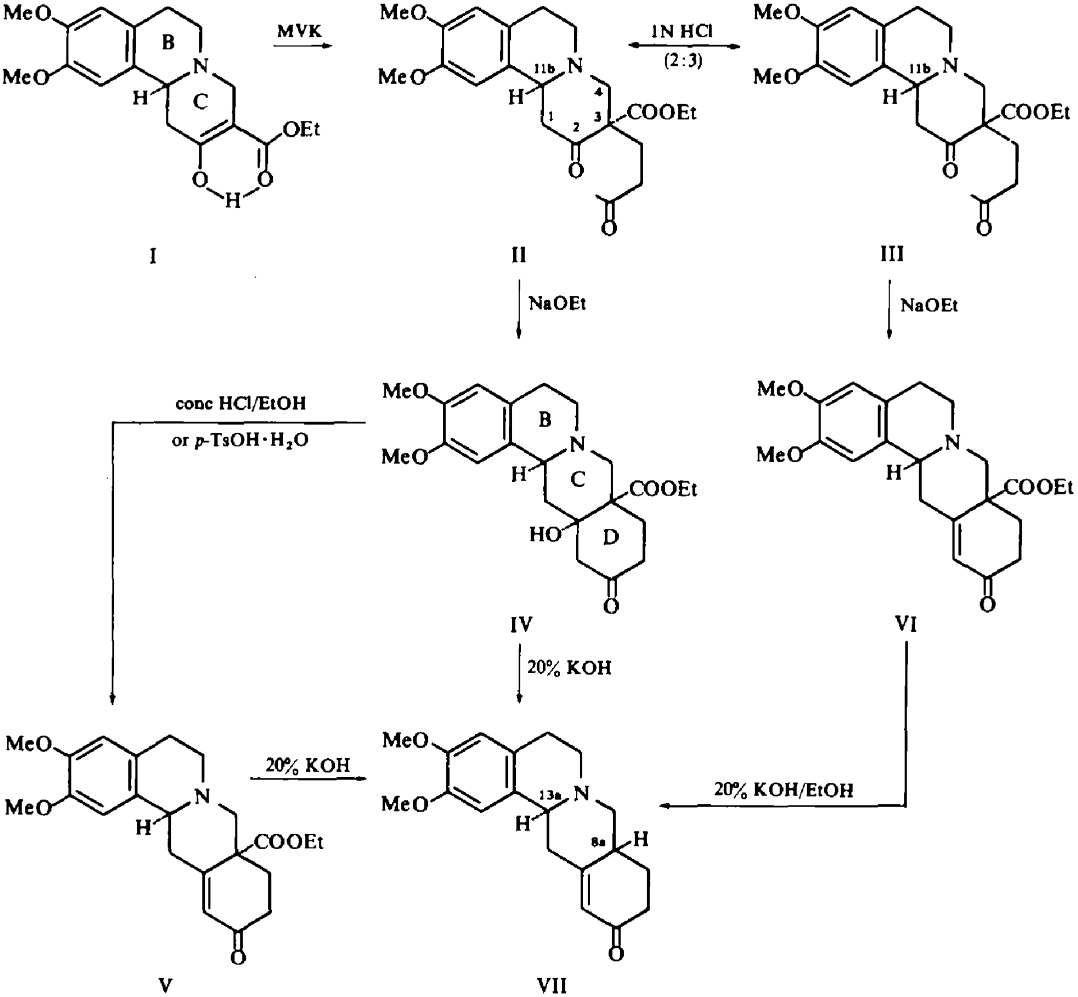
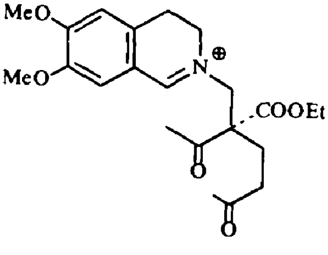


Chart I



common dihydroisoquinolinium intermediate* or, as one of the many other possibilities, an isomerization of the type previously mentioned.† It appears that III is the thermodynamically more stable epimer where the larger 3-keto-butyl group is



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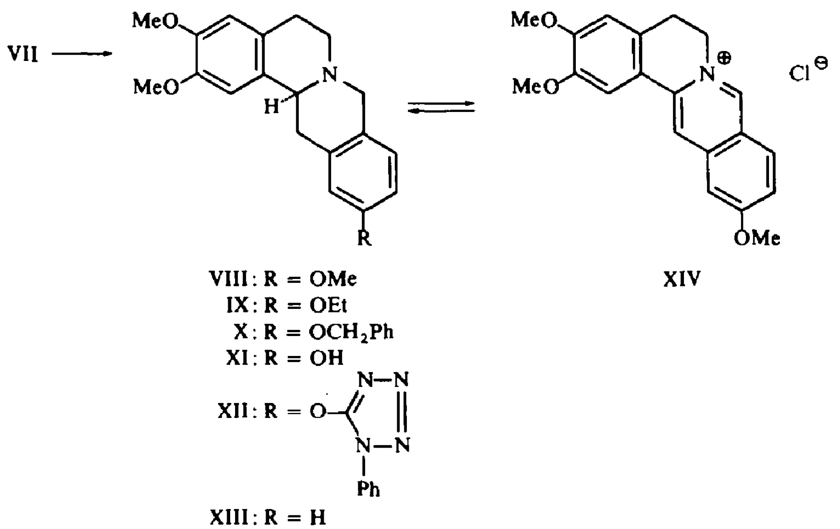
† See footnote on p. 4277

oriented equatorially. This is in agreement with the stereochemistry assigned to II since the di-keto-ester III behaved differently from II with sodium ethoxide and gave directly the unsaturated keto-ester VI, an epimer of the unsaturated keto-ester V. Both V and VI were recovered unchanged on treatment with 1N hydrochloric acid at 100°.

Each of the above three intermediates—the two epimeric α,β-unsaturated keto-esters V and VI as well as the hydroxy-ester IV—was converted by refluxing with 20% potassium hydroxide to give the α,β-unsaturated ketone VII which has the thermodynamically favored *trans* C_{8a}/C_{13a} stereochemistry. Treatment of the latter (as its hydrobromide) with cupric bromide and methanol according to the procedure of Fort[5] effected aromatization to the known[6] 2,3,11-trimethoxyberbine (VIII; Chart II). As an extension of this aromatization reaction, the α,β-unsaturated ketone VII (as its hydrobromide) was treated with cupric bromide in the presence of ethanol and benzyl alcohol to give the corresponding 11-ethoxy berbine IX and the 11-benzyloxy berbine X, respectively. However, attempts to substitute water or water and dioxane for alcohols in this aromatization reaction failed to form the corresponding known[7] 11-hydroxy berbine XI. The latter was therefore prepared by ether cleavage of the 11-benzyloxy intermediate X with a mixture of conc hydrochloric acid and benzene. Finally, XI was converted to the known[8] 2,3-dimethoxyberbine (XIII) by the procedure of Musliner and Gates[9] for the removal of a phenolic OH group. Reaction of XI with 5-chloro-1-phenyl-1H-tetrazole afforded the tetrazolyl ether XII which was hydrogenated in the presence of Pd–C to effect ether cleavage and the formation of XIII.

CHART II



VIII: R = OMe
IX: R = OEt
X: R = OCH_2Ph
XI: R = OH
XII: R =
XIII: R = H

XIV

Oxidation of the trimethoxyberbine VIII with excess mercuric acetate effected aromatization of ring C to give the dehydroberbinium chloride XIV which, on treatment with sodium borohydride, was reconverted to VIII.

EXPERIMENTAL[*]

(±)-9,10-*Dimethoxy*-1,3,4,6,7,11b-*hexahydro*-2-*oxo*-3-(3-*oxobutyl*)2H-*benzo*[*a*]*quinolizine*-3-*carboxylic acid ethyl ester* (II; *isomer of* III)

(a) ***Preparation from*** **I**. To a soln of 40 g (0·12 mole) of I[4] in 400 ml abs EtOH, stirred at 55° under N_2, was added 25 g (0·357 mole) methyl vinyl ketone over 0·5 hr. The mixture was stirred at 55° for 36 hr, the volatiles evaporated, the residue triturated with ice-cold abs EtOH (50 ml) and the resulting solid crystallized from 100 ml EtOH to give 38·3 g (79%) of II, m.p. 104–106°. An analytical specimen prepared from ether exhibited: m.p. 105–107°; TLC (system A): single spot at R_f 0·15; UV (isopropanol): λ_{max} infl 229 ($\varepsilon = 8000$), 282 ($\varepsilon = 3950$), 286 ($\varepsilon = 3970$) and infl 292 mμ ($\varepsilon = 3200$); IR ($CHCl_3$): 2770 (Bohlmann band), 1715 cm^{-1} (carbonyls); $NMR_{A\text{-}60}$ ($CDCl_3$): δ 1·29 (CH_3 triplet, $J = 7$ c/s), 4·25 (CH_2O quartet, $J = 7$ c/s), 2·12 (CH_3CO singlet), 3·67 (C_{11b} doublet of doublets, $J = 4$ and 10 c/s), 3·83, 3·87 ($2CH_3O$ singlets), 6·57, 6·63 (aromatic singlets). (Found: C, 65·51; H, 7·22; N, 3·68. $C_{22}H_{29}NO_6$ requires: C, 65·49; H, 7·25; N, 3·47%).

(b) ***Preparation from*** **III**. A soln of 1·5 g (3·7 mmole) of III dissolved in 7·5 ml 1N HCl was stirred at 100° for 1 hr and then evaporated at 60°. The residue was dissolved in 7·5 ml water, neutralized by the addition of solid $CaCO_3$ and the mixture extracted with two 20 ml portions of CH_2Cl_2. The extracts were combined, evaporated, the residual oil dissolved in 5 ml toluene and stored at 25° for 18 hr. The resulting crystals were filtered off and dried to give 0·72 g (64% of the material recovered) of III, m.p. 150–152° (identical with starting material by m.m.p., TLC and NMR). The toluene filtrate was evaporated and the residual oil crystallized from 5 ml ether to give 0·40 g (36% of the material recovered) of II, m.p. 103–105° (identical in m.m.p., TLC and NMR to II obtained by method (a)).

(±)-9,10-*Dimethoxy*-1,3,4,6,7,11b-*hexahydro*-2-*oxo*-3-(3-*oxobutyl*)2H-*benzo*[*a*]*quinolizine*-3-*carboxylic acid ethyl ester* (III; *isomer of* II)

A soln of 15 g (37·2 mmole) of II dissolved in 75 ml 1N HCl was stirred at 100° for 1 hr and then evaporated at 60°. The residue was dissolved in 75 ml water, neutralized by the addition of solid $CaCO_3$ and the mixture extracted with three 150 ml portions of CH_2Cl_2. The extracts were combined, evaporated and the residual oil triturated with 50 ml ice-cold toluene. The resulting solid was filtered and crystallized from 40 ml toluene to give 6·4 g (61% of the material recovered) of III, m.p. 152–153°. An analytical specimen prepared from toluene exhibited: m.p. 154–155°; TLC (system A): single spot at R_f 0·34; IR ($CHCl_3$): 2770 (Bohlmann band), 1717 cm^{-1} (broad, carbonyls); $NMR_{HA\text{-}100}$ ($CDCl_3$): δ 1·22 (CH_3 triplet, $J = 7$ c/s), 4·13 (CH_2O quartet, $J = 7$ c/s), 2·11 (CH_3CO singlet), 3·44 (C_{11b} doublet of doublets, $J = 4$ and 10 c/s), 3·78, 3·79 ($2CH_3O$ singlets), 6·51, 6·56 (aromatic singlets). (Found: C, 65·69; H, 7·46; N, 3·60. $C_{22}H_{29}NO_6$ requires: C, 65·49; H, 7·25; N, 3·47%).

The original toluene filtrate obtained from the triturated reaction product was evaporated and the residue crystallized from ether to give 4·1 g (31% of the total recoverable material) of II, m.p. 103–105° (identical in m.m.p. and TLC to starting material II).

(±)-5,6,8,8a,9,10,12,12a,13,13a-*Decahydro*-12a-*hydroxy*-2,3-*dimethoxy*-11-*oxo*-11H-*dibenzo*[*a.g*]*quinolizine*-8a-*carboxylic acid ethyl ester* (IV)

A mixture of 70 g (0·165 mole) of II dissolved in a freshly prepared soln of 2·02 g (0·087 mole) Na in 2 l. abs EtOH was stirred at room temp under N_2 for 18 hr, cooled to 4°, and adjusted to pH 2 with a 9N soln of HCl in isopropanol. The resulting solids were filtered off, suspended in a mixture of 125 ml water and 250 ml benzene and neutralized with $NaHCO_3$. The benzene extract was separated, evaporated and the residue crystallized from a mixture of EtOAc and petroleum ether to give 47 g (66 %) of IV, m.p. 138–140°.

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[*] All m.ps (corrected) were taken in open capillary tubes with a Thomas–Hoover melting apparatus unless otherwise noted. All TLC employed silica gel G plates which were developed for 15 cm with either solvent system A: 40 chloroform–5 acetone–20 toluene–10 acetic acid or solvent system B: 99 ethyl acetate–1 conc ammonium hydroxide and were detected with Dragendorff's reagent. UV spectra were measured with a Cary Model 14M spectrophotometer and the IR spectra were determined with a Beckman Model IR-9 recording spectrophotometer. The NMR spectra were obtained with either a Varian A-60 or a Varian HA-100 instrument using TMS as internal standard and the mass spectra were run on a CEC 21-110 spectrometer with a direct inlet system. All petroleum ether used in crystallizations had b.p. 30–60°. Extracts of products in organic solvents were washed with water and dried over Na_2SO_4.

A recrystallized sample exhibited: m.p. 141–143°; TLC (system B): single spot at R_f 0·58; UV (isopropanol): λ_{max} infl 227 (ε = 9050), infl 276 (ε = 3000), 282 (ε = 3780), 286 (ε = 3800), and infl 292 mμ (ε = 3000); IR ($CHCl_3$): 3500 (broad, OH), 2790 and 2760 (Bohlmann bands), 1710 cm^{-1} (broad, carbonyls); $NMR_{A\text{-}60}$ ($CDCl_3$): δ 1·33 (CH_3 triplet, J = 7 c/s), 4·28 (CH_2O quartet, J = 7 c/s), 3·63 (C_{13a}, J_{aa} = 10 c/s), 3·83 ($2CH_2O$ singlet), 4·35 (OH singlet), 6·57, 6·63 (aromatic singlets); mass spectrum: m/e 403 (molecular ion), 402, 374, 312, 304, 248, 205 and 191. (Found: C, 65·35; H, 7·27; N, 3·47. $C_{22}H_{29}NO_6$ requires: C, 65·49; H, 7·25; N, 3·47%).

(±)-2,3-*Dimethoxy*-5,6,8,8a,9,10,13,13a-*octahydro*-11-*oxo*-11H-*dibenzo*[*a.g*]*quinolizine*-8a-*carboxlyic acid ethyl ester* (V; *isomer of* VI)

(a) *Preparation from* IV *via hydrochloric acid.* A mixture of 500 mg (1·25 mmole) of IV in 0·8 ml conc HCl and 8 ml EtOH was stirred at 75° for 3 hr, stored at 4° for 18 hr and filtered to give 420 mg (81%) of V ·HCl, m.p. 219–220° (dec). An analytical sample prepared from a mixture of MeOH and ether exhibited m.p. 220–221° (dec). (Found: C, 62·89; H, 6·69; N, 3·20. $C_{22}H_{27}NO_5 \cdot HCl$ requires: C, 62·63; H, 6·69; N, 3·32%).

An aliquot of V ·HCl was dissolved in water, rendered alkaline with NH_4OH and extracted with ether. The ether extracts were evaporated and the residue crystallized from a mixture of EtOAc and petroleum ether to give V which exhibited: m.p. 141–143°, mixture m.p. with IV 122–125°; TLC (system B): single spot at R_f 0·36; UV (isopropanol): λ_{max} 230 (ε = 21,400), 281 (ε = 4500), infl 286 (ε = 4400) and infl 291 mμ (ε = 3600); IR ($CHCl_3$): no bands in Bohlmann region, 1727 (ester), 1673 cm^{-1} (α,β-unsaturated ketone); $NMR_{A\text{-}60}$ ($CDCl_3$): δ 1·30 (CH_3 triplet, J = 7 c/s), 4·30 (CH_2O quartet, J = 7 c/s), 3·85 ($2CH_3O$ singlet), 4·23 (C_{13a} band partly concealed by CH_2O), 6·03 (C_{12} singlet), 6·60, 6·70 (aromatic singlets); mass spectrum: m/e 385 (molecular ion), 384, 356, 329, 312, 205, 203 and 191. (Found: C, 68·66; H, 7·03; N, 3·55. $C_{22}H_{27}NO_5$ requires: C, 68·55; H, 7·06; N, 3·63%).

(b) *Preparation from* IV *via* p-*toluene sulfonic acid.* A mixture of 2 g (5 mmole) of IV and 10 g *p*-toluene sulfonic acid monohydrate in 200 ml benzene was stirred and refluxed for 18 hr, cooled, diluted with water and rendered alkaline with Na_2CO_3. The benzene extract was evaporated, the residue dissolved in alcoholic HCl, evaporated and then crystallized from a mixture of MeOH and ether to give 1·05 g (50%) of V ·HCl, m.p. 219–220° (identical in m.m.p. and TLC to V ·HCl obtained via (a)).

(±)-2,3-*Dimethoxy*-5,6,8,8a,9,10,13,13a-*octahydro*-11-*oxo*-11H-*dibenzo*[*a.g*]*quinolizine*-8a-*carboxylic acid ethyl ester* (VI; *isomer of* V)

A mixture of 4·29 g (10·6 mmole) of III dissolved in a freshly prepared soln of 0·25 g (10·6 mmole) Na in 130 ml abs EtOH was stirred at room temp under N_2 for 18 hr, cooled to 4° and rendered acidic with ethanolic HCl. The resulting soln was evaporated and the residue crystallized from a mixture of EtOH and ether and then recrystallized from a mixture of EtOAc and ether to give 3·65 g (78%) of VI ·HCl·H_2O, m.p. 163–165°. (Found: C, 60·07; H, 6·80; N, 3·26. $C_{22}H_{27}NO_5 \cdot HCl \cdot H_2O$ requires: C, 60·05; H, 6·87; N, 3·18%).

An aliquot of VI ·HCl·H_2O was dissolved in water, rendered alkaline with NaOH and extracted with benzene. The benzene extracts were evaporated and the residue crystallized from a mixture of ether and petroleum ether to give VI which exhibited: m.p. 109–111°; TLC (system B): single spot at R_f 0·63; UV (isopropanol): λ_{max} 232 (ε = 25,600), infl 276 (ε = 4400), 282 (ε = 5200), 286 (ε = 5150) and infl 292 mμ (ε = 4300); IR ($CHCl_3$): 2770 (Bohlmann band), 1728 (ester) and 1675 cm^{-1} (α,β-unsaturated ketone); $NMR_{A\text{-}60}$ ($CDCl_3$): δ 1·23 (CH_3 triplet, J = 7 c/s), 4·23 (CH_2O quartets, J = 7 c/s), 3·35 (C_{13a} doublet of doublets, J = 4 and 10 c/s), 3·85, 3·88 ($2CH_3O$ singlets), 6·12 (C_{12} singlet), 6.62, 6.68 (aromatic singlets). (Found: C, 68·69; H, 7·29; N, 3·42. $C_{22}H_{27}NO_5$ requires: C, 68·55; H, 7·06; N, 3·63%).

(±)-2,3-*Dimethoxy*-5,6,8,8a,9,10,13,13a-*octahydro*-11H-*dibenzo*[*a.g*]*quinolizin*-11-*one* (VII)

(a) *Preparation from* IV. A mixture of 6·5 g (16·1 mmole) of IV and 65 ml 20% KOH aq was stirred and refluxed under N_2 for 2 hr, cooled and the crystals filtered off, washed with water and dried to give 4·9 g (97%) of VII, m.p. 185–187°. An analytical specimen prepared from a mixture of CH_2Cl_2 and petroleum ether exhibited: m.p. 189–191°; TLC (system B): single spot at R_f 0·22; UV (isopropanol): λ_{max} 231 (ε = 25,900), infl 275 (ε = 4200), 281 (ε = 4980), 285 (ε = 4920) and infl 291 mμ (ε = 4000); IR ($CHCl_3$): 2770 (Bohlmann band) and 1670 cm^{-1} (α,β-unsaturated ketone); $NMR_{HA\text{-}100}$ ($CDCl_3$): δ 3·81, 3·84 ($2CH_3O$ singlets), 5·98 (C_{12} narrow band), 6·59, 6·63 (aromatic); mass spectrum: m/e 313 (molecular ion), 312, 298, 282, 257, 256, 203, 191 and 190. (Found: C, 72·47; H, 7·40; N, 4·39. $C_{19}H_{23}NO_3$ requires: C, 72·82; H, 7·40; N, 4·47%).

An aliquot of VII was acidified with ethanolic HCl, evaporated and crystallized from water to give VII ·HCl, m.p. 238–239°. (Found: C, 65·10; H, 6·99; N, 3·80. $C_{19}H_{23}NO_3 \cdot HCl$ requires: C, 65·24; H, 6·92; N, 4·00%).

An aliquot of VII was acidified with ethanolic HBr, evaporated and crystallized from water to give VII ·HBr, m.p. 254–255°. (Found: C, 58·14; H, 6·28; N, 3·53. $C_{19}H_{23}NO_3 \cdot HBr$ requires: C, 57·88; H, 6·13; N, 3·55%).

(b) *Preparation from* V. A mixture of 2·1 g (5 mmole) of V ·HCl and 21 ml 20% KOHaq was stirred and refluxed under N_2 for 3 hr, cooled and the crystals filtered off, washed with water and dried to give 1·42 g (91%) of VII, m.p. 189–191° (identical in m.m.p., TLC and NMR to VII obtained via (a)).

(c) *Preparation from* VI. A soln of 550 mg (1·25 mmole) of VI ·HCl·H_2O in a mixture of 5 ml 20% KOHaq and 5 ml EtOH was refluxed under N_2 for 1 hr, concentrated to ca. 5 ml, cooled and the resulting crystals filtered off, washed with water, dried and recrystallized from a mixture of CH_2Cl_2 and petroleum ether to give 360 mg (92%) of VII, m.p. 188–190° (identical in m.m.p., TLC and NMR to VII obtained via (a)).

(±)-2,3,11-*Trimethoxyberbine hydrobromide* VIII

A mixture of 6 g (15·2 mmole) of VII ·HBr and 6·9 g (30·4 mmole) $CuBr_2$ in 400 ml MeOH was stirred and refluxed under N_2 for 2 hr, cooled and evaporated. The residue, partitioned between a mixture of benzene and water, was rendered alkaline with NH_4OH, the benzene extract was acidified with ethanolic HBr, the volatiles evaporated and the residue crystallized from water (200 ml) to give 3·9 g (63%) of VIII, m.p. 250–252°. An analytical specimen prepared from water exhibited: m.p. 252–254°, TLC (system B): single spot at R_f 0·60; UV (MeOH): λ_{max} 224 (ε = 18,550), 279 (ε = 7400) and 284 mμ (ε = 7600); $NMR_{A\text{-}60}$ (DMSO-d_6): δ 3·80, 3·82 ($3CH_3O$ singlets), 4·67 (C_{13a} broad). (Found: C, 58·96; H, 6·06; N, 3·44. $C_{20}H_{23}NO_3 \cdot HBr$ requires: C, 59·13; H, 5·95; N, 3·45%).

An aliquot of VIII in water was rendered alkaline with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated and the residue crystallized from a mixture of benzene and petroleum ether to give VIII as the free base which exhibited: m.p. 103–104°; IR ($CHCl_3$): 2740 cm^{-1} (Bohlmann band); mass spectrum: *m/e* 325 (molecular ion), 324, 190, 135 and 134. By m.m.p., IR, TLC and NMR, VIII base was identical with an authentic sample.[6] (Found: C, 73·98; H, 7·41; N, 4·33. $C_{20}H_{23}NO_3$ requires: C, 73·82; H, 7·12; N, 4·30%).

An aliquot of VIII base was dissolved in benzene, acidified with ethanolic HCl, evaporated and crystallized from water to give VIII hydrochloride hemihydrate, m.p. 204–206°, no depression in m.p. on admixture with an authentic sample,[6] m.p. 195–198°. (Found: C, 64·59, 64·68; H, 6·55, 6·75; N, 4·00, 4·18. $C_{20}H_{23}NO_3 \cdot HCl \cdot \frac{1}{2}H_2O$ requires: C, 64·77; H, 6·79; N, 3·78%).

(±)-2,3-*Dimethoxy*-11-*ethoxyberbine hydrobromide hemihydrate* (IX)

A mixture of 6·26 g (15·9 mmole) of VII ·HBr and 7·2 g (31·8 mmole) $CuBr_2$ in 400 ml abs EtOH was stirred and refluxed under N_2 for 3 hr and then evaporated. The residue was rendered alkaline with dil NaOHaq and extracted with benzene. The benzene extract was acidified with ethanolic HBr, evaporated and the residue crystallized from MeOH to give 4·4 g (64%) of IX, m.p. 217–220°. An aliquot prepared from MeOH exhibited: m.p. 220–222°; TLC (system B): single spot at R_f 0·64. (Found: C, 58·80; H, 6·26; N, 3·26. $C_{21}H_{25}NO_3 \cdot HBr \cdot \frac{1}{2}H_2O$ requires: C, 58·74; H, 6·34; N, 3·26%).

An aliquot of IX in water was rendered alkaline with NaOH and extracted with benzene. The benzene extract was evaporated and the residue crystallized from a mixture of EtOH and water to give IX as the free base which exhibited: m.p. 82–84°; UV (isopropanol): λ_{max} 228(ε = 16,000), infl 276 (ε = 5400), 281 (ε = 6550) and 286 mμ (ε = 6520); IR ($CHCl_3$): 2740 cm^{-1} (Bohlmann band); $NMR_{HA\text{-}100}$ ($CDCl_3$): δ 1·37 (CH_3 triplet, J = 7 c/s), 3·96 (CH_2O quartet, J = 7 c/s), 3·81, 3·84 ($2CH_3O$ singlets); mass spectrum: *m/e* 339 (molecular ion), 338, 190, 149, 148 and 120. (Found: C, 74·51; H, 7·47; N, 4·20. $C_{21}H_{25}NO_3$ requires: C, 74·31; H, 7·42; N, 4·13%).

(±)-11-*Benzyloxy*-2,3-*dimethoxyberbine hydrobromide* (X)

A mixture of 7·2 g (18·2 mmole) of VII ·HBr and 8·25 g (36·4 mmole) $CuBr_2$ in 140 ml benzyl alcohol was stirred under N_2 at 75° for 2 hr, cooled, diluted with 800 ml ether and filtered. The solids were suspended in dil NH_4OH and extracted with benzene. The benzene extract was acidified with ethanolic HBr, evaporated and the residue crystallized from MeOH to give 3·4 g (39%) of X, m.p. 255–257°. A specimen prepared from a mixture of 95% EtOH and acetonitrile exhibited: m.p. 256–258°; TLC (system B): single spot at R_f 0·68. (Found: C, 64·43; H, 6·10. $C_{26}H_{27}NO_3 \cdot HBr$ requires: C, 64·73; H, 5·85%).

An aliquot of X in water was rendered alkaline with NH_4OH and extracted with benzene. The benzene extract was evaporated and the residue crystallized from a mixture of EtOH and water to give X as the free base which exhibited: m.p. 83–85°; UV (isopropanol): λ_{max} 226 (ε = 19,700), infl 275 (ε = 5600), 279 (ε = 6350), 284 (ε = 6600) and infl 290 mμ (ε = 4000); IR ($CHCl_3$): 2750 cm^{-1} (Bohlmann band); $NMR_{HA\text{-}100}$ ($CDCl_3$): δ 3·80, 3·82 ($2CH_3O$ singlets), 5·00 (CH_2O singlet), 7·32 (aromatic broad; mass spectrum: *m/e* 401 (molecular ion), 400, 310, 211, 190 and 91. (Found: C, 78·19; H, 6·62; N, 3·57. $C_{26}H_{27}NO$ requires: C, 77·78; H, 6·78; N, 3·49%).

(±)-2,3-*Dimethoxy*-11-*hydroxyberbine* (XI)

A mixture of 2·56 g (6·4 mmole) of X as the free base in 45 ml of conc HCl and 45 ml benzene was stirred vigorously under N_2 at 25° for 48 hr, filtered and the solids crystallized from a mixture of EtOH and ether to give 1·92 g of XI $\cdot HCl \cdot H_2O$, m.p. 270–272°. (Found: C, 62·40, 62·53; H, 6·30, 6·30; N, 3·73, 3·73. $C_{19}H_{21}NO_3 \cdot HCl \cdot H_2O$ requires: C, 62·37; H, 6·61; N, 3·83%).

An aliquot of XI $\cdot HCl \cdot H_2O$ in water was rendered alkaline with NH_4OH and extracted with EtOAc. The EtOAc extract was evaporated and the residue crystallized from EtOH to give XI which exhibited: m.p. 253–255°;[10] TLC (system B): single spot at R_f 0·44; IR ($CHCl_3$): 3410–3340 (OH) and 2770 cm^{-1} (Bohlmann band); $NMR_{HA\text{-}100}$ ($DMSO\text{-}d_6$): δ 3·68, 3·71 ($2CH_3O$ singlets), 8·97 (OH singlet). (Found: C, 73·57; H, 6·78; N, 4·47. $C_{19}H_{21}NO_3$ requires: C, 73·29; H, 6·80; N, 4·50%).

(±)-2,3-*Dimethoxy*-11-(1-*phenyl*-1H-*tetrazol*-5-*yloxy*)*berbine hydrochloride* (XII)

A mixture of 622 mg (2 mmole) of XI, 360 mg (2 mmole) 5-chloro-1-phenyl-1H-tetrazole and 552 mg anhyd K_2CO_3 in 40 ml dimethylformamide was stirred at 80° for 7 hr, diluted with water and extracted with benzene. The benzene extract was acidified with ethanolic HCl. The resulting crystals were filtered off and recrystallized from a mixture of EtOH and ether to give 690 mg (70%) of XII which exhibited: m.p. 218–220°; TLC (system B): single spot at R_f 0·54; $NMR_{A\text{-}60}$ ($DMSO\text{-}d_6$): δ 3·78 ($2CH_3O$), 4·4–5·0 (C_8 and C_{13a}), 6·83, 7·05 (aromatic C_1 and C_4), 7·25–8·0 (ring D and phenyl). (Found: C, 63·42; H, 5·54. $C_{26}H_{25}N_5O_3 \cdot HCl$ requires: C, 63·48; H, 5·33%).

(±)-2,3-*Dimethoxyberbine hydrochloride* (XIII)

A soln of 500 mg (1·02 mmole) of XII in 210 ml EtOH was hydrogenated in the presence of 400 mg 10% Pd–C at 35° and 3 atmospheres. The catalyst was filtered off and the filtrate evaporated. The residue was rendered alkaline with dil NH_4OH and extracted with ether. The ether extract was acidified with ethanolic HCl, evaporated and crystallized from EtOH to give 170 mg (50%) of XIII which exhibited: m.p. 250–252°;* TLC (system B): single spot at R_f 0·63; UV (isopropanol): λ_{max} 231 (ε = 8400), infl 270 (ε = 2500), 281 (ε = 4050), 285 (ε = 4100) and infl 290 mμ (ε = 3500); IR ($CHCl_3$): 2750 cm^{-1} (Bohlmann band); $NMR_{HA\text{-}100}$ ($DMSO\text{-}d_6$): δ 3·81, 3·83 ($2CH_3O$), 4·75 (C_{13a} broad), 6·79, 7·01 (aromatic C_1 and C_4), 7·28 (ring D); mass spectrum: *m/e* 295 (molecular ion), 294, 280, 190, 105 and 104. (Found: C, 69·01; H, 6·87; N, 4·06. $C_{19}H_{21}NO_2 \cdot HCl$ requires: C, 68·77; H, 6·68; N, 4·22%).

5,6-*Dihydro*-2,3,11-*trimethoxydibenzo*[*a.g*]*quinolizinium chloride* (XIV)

A mixture of 651 mg (2 mmole) of VIII base and 2·55 g (8 mmole) mercuric acetate in 30 ml 10% AcOH was stirred at 70° for 18 hr, filtered and the filtrate was treated with excess H_2S. The mixture was filtered and the filtrate was adjusted at 4° to pH 1 with HCl. The resulting crystals were isolated and recrystallized from a mixture of MeOH and ether to give 600 mg (84%) of XIV, m.p. 238–240°. An analytical specimen prepared from water exhibited: m.p. 238–240°; UV (isopropanol): λ_{max} 239 (ε = 20,500), 253 (ε = 19,700), 289 (ε = 25,400), 314 (ε = 19,750), infl 345 (ε = 14,500) and infl 380 mμ (ε = 7000); IR (KBr): 1630 cm^{-1} ($C{=}N^+$); $NMR_{HA\text{-}100}$ ($DMSO\text{-}d_6$): δ 3·40, 5·05 (CH_2CH_2), 4·04, 4·11, 4·21 ($3CH_3O$ singlets), 7·28, 7·88, 9·17, 10·12 (aromatic singlets), 8·49 (C_9 doublet, J = 9 c/s), 7·69 (C_{10}), 7·81 (C_{12}); mass spectrum: *m/e* 322, 320, 306, 304, 279 and 277. (Found: C, 67·39; H, 5·42; N, 4·01. $C_{20}H_{20}ClNO_3$ requires: C, 67·13; H, 5·63; N, 4·10%).

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* A m.p. of 230·8° was obtained with the Mettler FPI melting apparatus. Ref. 8 gives m.p. 236–238°.

Treatment of 100 mg (0·29 mmole) of XIV with 50 mg of $NaBH_4$ in 10 ml MeOH gave 75 mg (83%) of VIII base, m.p. 102–103° (identical in m.m.p. and TLC to VIII obtained from VII).

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[10] Ref. 1 gives m.p. 260°.