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Heterocycles. III.[1] Syntheses of Berbans from 6,7-Dimethoxy-3,4-dihydroisoquinoline

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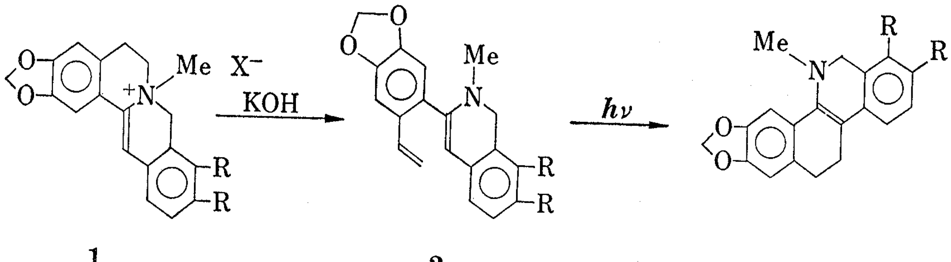
Twice annulations of 6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride (**7**) stereoselectively give the pseudoberbenone (**12**), the catalytic reduction of which preferentially affords the alloberbanone (**15**). On a series of reactions (oxidation, O-methylation, sodium borohydride reduction, ether cleavage and catalytic reduction) **12** is converted into the berbanone (**25**) *via* the berbadienone (**21**). Oxidations of **15** and **25** with mercuric acetate smoothly afford the 1,11-didehydro compounds (**17**) and (**26**), respectively. Two isomeric metho salts (**18**) and (**19**) obtained from **17**, and the one (**31**) from **21** are found to give the starting materials by demethylation under conditions of the Hofmann degradation. Stereostructures of the compounds obtained here are examined on the basis of the infrared and nuclear magnetic resonance spectra. Their formation pathways are also discussed.

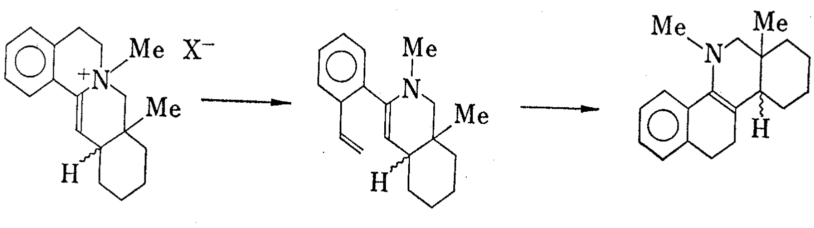
Keywords——berbans; annulation; Hofmann degradation; stereochemistry; IR; NMR

The objective of this study, in view of biological interests, is to synthesize aza-steroids. We previously reported the synthesis of the tetrahydrobenzo[*c*]phenanthridine alkaloid (**3**) from the dihydroprotoberberine methosulfate (**1**) *via* the methine base (**2**).[3] If 1,11-didehydroberban metho salt (**4**) can be converted into the methine base (**5**), a synthesis of 11-aza-D-homo-11-methyl-1,3,5(10),8-estratetraene (**6**) may be achieved by the same procedure (Chart 1).



1 **2** **3**

R : OMe, R,R : OCH_2O



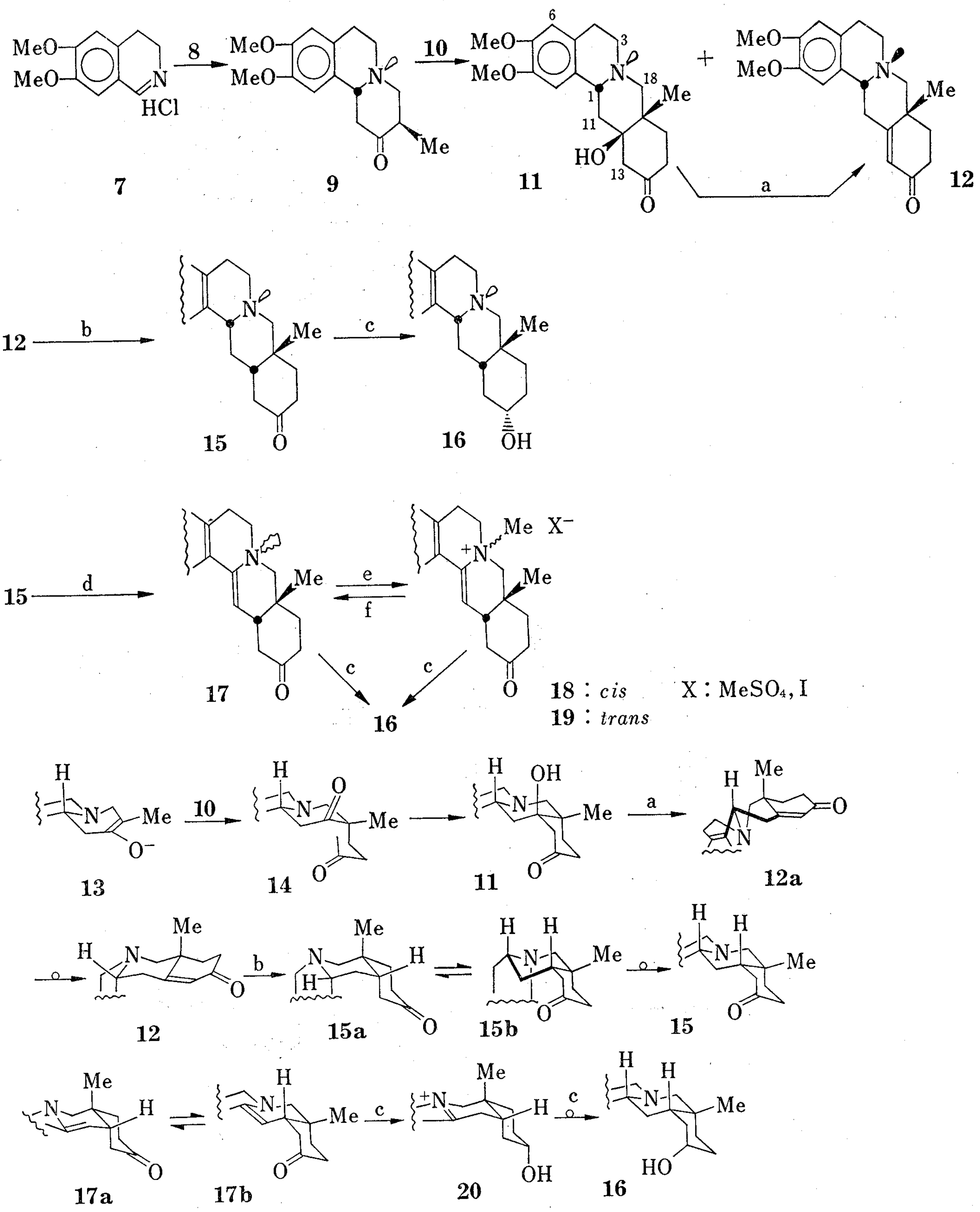
4 **5** **6**

Chart 1

1) Part II: M. Onda, Y. Harigaya, and T. Suzuki, *Heterocycles*, **4**, 1669 (1976). The nomenclature and numbering are referred to L. Szabó, K. Honty, L. Töke, and C. Szántay, *Chem. Ber.*, **105**, 3231 (1972).
2) Location: *Minato-ku, Tokyo 108, Japan.*
3) M. Onda, K. Yonezawa, and K. Abe, *Chem. Pharm. Bull.* (Tokyo), **19**, 31 (1971).

However, attempts to obtain the derivatives of **5** from those of **4** were found to be unsuccessful. This paper describes structural proofs and formation pathways of the intermediates obtained in a projected approach to the derivative of **6**.

Reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride (**7**) with 2-methyl-1-dimethylaminobutan-3-one (**8**) gave the hexahydrobenzo[*a*]quinolizinone (**9**)[4] which was subsequently annulated with 1-diethylaminobutan-3-one methiodide (**10**) in the presence



a : 10%H_2SO_4; b : H_2/PtO_2 or Pd-C; c : $NaBH_4$; d : $Hg(OAc)_2$; e : $Me_2SO_4/CHCl_3$ or MeOH; f : KOH/MeOH for methosulfate, Ag_2O for methiodide

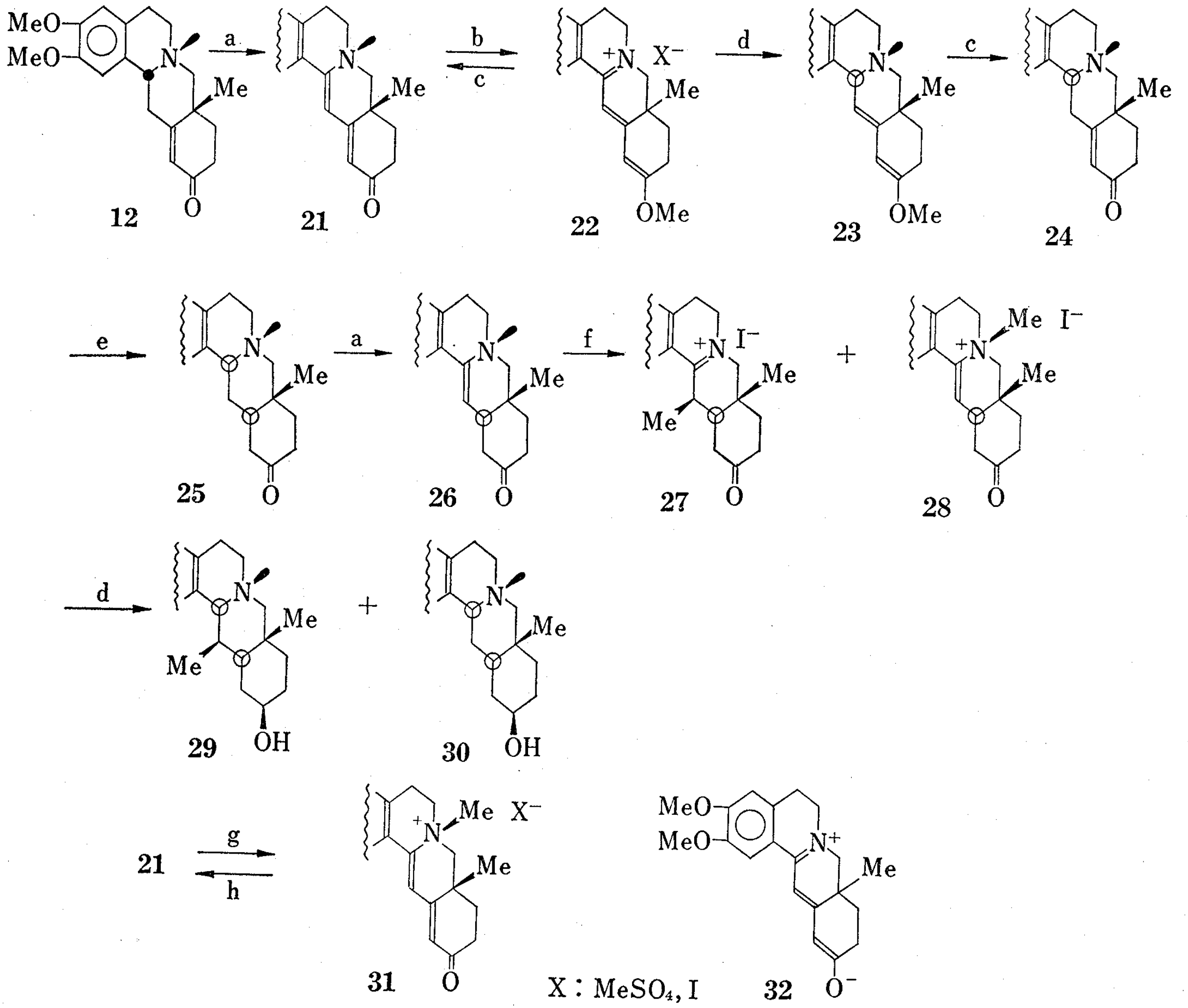
Chart 2

of sodium ethoxide[5] to give the hydroxy alloberbanone (**11**) and pseudoberbenone (**12**). On treatment with dilute sulfuric acid **11** easily afforded **12**. The infrared (IR) spectra show the Bohlmann bands at 2825, 2800 and 2750 cm^{-1} for **11** and no one for **12**. The proton magnetic resonance (PMR) spectra of **11** and **12** reveal the signals for the 1-H at δ 3.31 (q, J 8 and 4 Hz) and 4.28 (W_H 12 Hz), respectively. On the basis of the spectral criteria generally recognized in the quinolizidine field,[6] the B/C ring fusion can be assigned *trans* for **11** and *cis* for **12**. If the enolate ion (**13**) of **9** is normally axial-attacked at the C-3 by **10**, the diketone (**14**) resulted must inevitably afford **11** having the allo configuration. Dehydration of **11** must provide **12** possessing the pseudo configuration by the nitrogen inversion in the unstable conformer (**12a**) initially produced (Chart 2).

The pseudoberbenone (**12**) was hydrogenated in the presence of platinum oxide or palladium-carbon to give the alloberbanone (**15**) indicating the Bohlmann bands at 2825, 2800 and 2750 cm^{-1} in the IR spectrum and the PMR signal for the 1-H at δ 3.04 (d, J 10 Hz). Its structure is further established by comparison of the carbon-13 nuclear magnetic resonance (^{13}C NMR) spectrum with that of the berbanone (**25**) obtained by another route (*vide infra*). From the structure of **15**, it can be seen that **12** was preferentially hydrogenated from the *syn* side to the 17-Me group, less hindered side, to give initially the unstable conformers (**15a**) and (**15b**) accompanied with the nitrogen inversion to **15**. Reduction of **15** with sodium borohydride exclusively gave the alloberbanol (**16**) by the attack of borohydride ion from the less hindered side. The 14-axial OH group is assignable from the half-height width (10 Hz) of the 14-H (δ 4.00) in the PMR spectrum. Oxidation of **15** with mercuric acetate gave the epialloberbenone (**17**) in a fast equilibrium of the conformers (**17a**) and (**17b**). Methylation of **17**, interestingly, with dimethyl sulfate in chloroform and methanol preferentially gave the *cis* (**18**) and *trans* methosulfate (**19**),[7] respectively. Their structures are deduced on the basis of the PMR signals for the 17-Me group at δ 1.32 in **18** and 1.13 in **19**. The metho salts (**18**) and (**19**), on the contrary to anticipation, gave **17** and no compound corresponding to **5** under conditions of the Hofmann degradation. On reduction of **17**, **18** and **19** with sodium borohydride **16** was obtained as sole product. Its formation pathway would be as follows. The iminium salt (**20**), which is derived from **17a** under "product development control"[8] accompanied with the shift of double bond and from **17b** under "steric approach control" accompanied with the nitrogen inversion and shift of the double bond, is attacked by borohydride ion from the less hindered side accompanied with the nitrogen inversion to give **16**. Although demethylation of the N-Me group is emerged before or after reduction of the carbonyl group, **18** and **19** are considered to convert into **16** in a similar manner to the case of **17**.

Despite the B/C ring fusion in **12** is *cis*,[9] oxidation of **12** with mercuric acetate smoothly gave the berbadienone (**21**). Its structure is supported by the PMR spectrum showing two vinyl-H signals at δ 5.70 and 5.60 and disappearance of the signal for the 1-H existed in **12**. Methylation of **21** with dimethyl sulfate in chloroform exclusively afforded the O-methylated compound (**22**), from which **21** was recovered on treatment with dilute hydrochloric acid. Its structure is further confirmed on the basis of the subsequent reactions (Chart 3).

4) N. Whittaker, *J. Chem. Soc.*, **1969**, 85.
5) J.W. Conforth and R. Robinson, *J. Chem. Soc.*, **1949**, 1855; W.S. Johnson, J. Szmuskovicz, E.R. Rogier, H.I. Hadler, and H. Wynberg, *J. Am. Chem. Soc.*, **78**, 6285 (1956).
6) F. Bohlmann, *Chem. Ber.*, **91**, 2557 (1958); T.A. Crabb, R.F. Newton, and D. Jackson, *Chem. Rev.*, **71**, 109 (1971); M. Uskokovic, H. Bruderer, C. von Planta, T. William, and A. Brossi, *J. Am. Chem. Soc.*, **86**, 3364 (1964); H. Bruderer, M. Baumann, M. Uskokovic, and A. Brossi, *Helv. Chim. Acta*, **47**, 1852 (1964).
7) *cis* and *trans* are referred to the 17-Me group.
8) D.M. Kirk and M.P. Hartshorn, "Steroidal Reaction Mechanisms," Elsevier, London, 1968, p. 135.
9) S.K. Malhotra, "Enamines: Synthesis, Structure, and Reaction," ed. by A.G. Cook, Marcel Dekker, New York, 1969, p. 73. Since **12** was gradually converted into **21** on storage, this oxidation might be simple dehydrogenation with air at the C-1 and -11.



a : $Hg(OAc)_2$; b : $Me_2SO_4/CHCl_3$; c: 10%HCl; d : $NaBH_4$; e : H_2/PtO_2; f : $MeI/CHCl_3$; g : $Me_2SO_4/MeOH$; h:KOH/MeOH

Chart 3

TABLE I. The C-13 Chemical Shifts of **12** and **24** (δ)

	C-1	C-4	C-18
12	57.7	23.5	59.6
24	62.9	29.4	69.2

Reduction of **22** with sodium borohydride gave the berbadiene (**23**), the *trans* B/C conformation of which was identified by the IR spectrum showing the Bohlmann bands at 2825, 2800 and 2750 cm^{-1}. Treatment of **23** with dilute hydrochloric acid afforded the berbenone (**24**). The Bohlmann bands at 2825, 2800 and 2750 cm^{-1} in the IR spectrum and the PMR signal for the 1-H at δ 3.19 (q, J 10 and 4 Hz) indicate the B/C ring fusion in **24** to be *trans*. Accordingly, **12** and **24** are isomeric with respect to the B/C ring fusion. It is known that the ^{13}C NMR spectra of yohimbine and pseudoyohimbine characteristically show the deshielding of 6, 5 and 9.5 ppm for the C-3, -6 and -21, respectively, in the former compared to those in the latter.[10] For **12** and **24**, it is observed that the shielding differences of the C-1, -4 and

10) E. Wenkert, C.-J. Chang, H.P.S. Chawla, D.W. Cochran, E.W. Hagaman, J.C. King, and K. Orito, *J. Am. Chem. Soc.*, **98**, 3645 (1976).

-18 lie in the same trend as those in the above yohimboids (Table I). If the enone system similarly influences on the carbon shieldings in question in both compounds, this observation provides a further supporting evidence for the structures of **12** (pseudo) and **24** (normal). Treatment of **12** with dilute hydrochloric acid did not give **24**, indicating that **12** and **24** did not mutually isomerize under acidic conditions.

Hydrogenation of **24** in the presence of platinum oxide afforded the berbanone (**25**) which showed the Bohlmann bands at 2825, 2800 and 2750 cm^{-1} in the IR spectrum and the PMR signal for the 1-H at δ 3.06 (bd, J 10 Hz), the B/C ring fusion being *trans*.

Stereochemistry of **15** and **25**, at this stage, should be decided. The characteristic ^{13}C NMR data of both compounds and the related yohimboids are listed in Table II. The C-3, -16 and -21 in epialloyohimbane absorb at higher field by 5.5, 10.6—8.6 and 6.6—6.8 ppm, respectively, than those in yohimbane and alloyohimbane.[10] Since the C-1, -13 and -18 shieldings are apparently identical for **15** and **25**, the epiallo configuration for them can be straightly excluded. From the fact that the shielding differences of the C-11 and -16 in **25** and **15** are similar to those of the C-14 and -19 in yohimbane and alloyohimbane, the normal and allo configuration can be assigned for **25** and **15**, respectively, From the structure of **25**, it is understood that preferential hydrogenation of **24** occurs from the *anti* side to the 17-Me group.

Table II. The C-13 Chemical Shifts of **15**, **25** and the Yohimboids[a] (δ)

	C-3	C-14	C-16	C-19	C-21
Y	60.1	36.3	32.5	30.1	61.7
A	60.1	31.6	30.5	26.5	61.9
E	54.6	35.7	21.9	29.7	55.1

	C-1	C-11	C-13	C-16	C-18
25	63.1	34.8	44.0	37.7	69.1
15	63.2	31.2	43.7	35.3	68.1

a) Y: yohimbane, A: alloyohimbane, E: epialloyohimbane. lit.[10]

On oxidation with mercuric acetate **25** gave the berbenone (**26**) isomeric to **17** with respect to the C/D ring fusion. Its methylation with methyl iodide gave a mixture of the iminium iodide (**27**) and methiodide (**28**) which could not be isolated. Its PMR spectrum shows the signal for the 11-Me group at δ 1.39 (d, J 7 Hz) in **27** having the integral intensity of seven tenth for one methyl group. Reduction of the mixture of **27** and **28** with sodium borohydride gave the berbanols (**29**) and (**30**). The latter should be arised from the reduction of **28** in the same manner as those of **18** and **19**. The *trans* B/C conformation and 14-equatorial OH group in both compounds are easily assignable from the Bohlmann bands (2825, 2800 and 2750 cm^{-1}) in the IR spectra and the half-height width (24—30 Hz) of the 14-H in the PMR spectra. The 11-axial Me group is deduced from comparison of the PMR spectrum showing the Me signal at δ 1.11 (d, J 7 Hz)[11] with that of **30** (see Experimental).

On treatment with dimethyl sulfate in methanol **21** was exclusively methylated at the nitrogen atom to give the N-methylated compound (**31**). As mentioned above, methylation of **21** in chloroform exclusively occurs at the oxygen atom. This remarkable difference of the chemical behavior may depend on the extent of overlapping of the dienamino ketone system

11) C.K. Yu and D.B. MacLean, *Can. J. Chem.*, **48**, 3673 (1970); C. Tani, S. Takao, and K. Tagahara, *Yakugaku Zasshi*, **93**, 197 (1973); P.W. Jeffes, "The Alkaloids," Vol. 9, ed. by R.H.F. Manske, Academic Press, New York, 1967, p. 78.

induced by the solvent in question. The Hofmann degradation of **31** gave **21** as sole product and no methine-type compound.

Thus, attempts to obtain the methine base as intermediate for the 11-aza-D-homo-steroid were unsuccessful. An attempt, in turn, to transform **9** to the derivative of benzo[*h*]quinoline and then construct the D ring is in progress.

We refer, finally, to the characteristic NMR data of the berbans obtained here. Comparisons of the 17-Me group in **25** (δ 1.21), **24** (δ 1.41) and **12** (δ 1.46) with the 10-Me group in 5α-cholestan-3-one (δ 1.03) and cholest-4-en-3-one (δ 1.21) exhibit the deshielding (*ca.* 0.2 ppm) due to the axial electron pair on the nitrogen atom for the berbans.[12] The 17-Me group in **15**, however, which is *trans* to the nitrogen lone pair, also absorbs at a low field (δ 1.23). This seems probably to be ascribed to the C/D non-steroidal conformation.[13] As also seen from the above data, the Δ^{12}-bond deshields the 17-Me group (*ca.* 0.2 ppm). This is in accord with the fact that the Δ^{4}-bond in 5α-steroids deshields the 10-Me group in a similar manner.[13] The Δ^{6}-bond in steroids shields the 10-Me group (−0.02 ppm).[14] The $\Delta^{1(11)}$-bond strongly shields the 17-Me group: **26** (δ 1.13)−**25** (δ 1.21)=−0.08 ppm, **21** (δ 1.25)−**12** (δ 1.46)=−0.21 ppm, **21** (δ 1.25)−**24** (δ 1.41)=−0.16 ppm. The large differences of shielding observed for the berbans would be due to the modified interaction of the nitrogen lone pair to the 17-Me group by overlapping of the enamine system. In the latter two cases, the canonical form (**32**) arised from the effective overlapping of the dienamino ketone system would contribute to

Table III. The C-13 Chemical Shift Differences between **15**, **25** and the Steroids[a] (ppm)

	C-2	C-4	C-7	C-9	10-Me
$\delta_C^{5\beta}-\delta_C^{5\alpha}$	−1.1	−2.4	−5.1	−13.0	11.2

	C-15	C-13	C-1	C-18	17-Me
$\delta_C^{15}-\delta_C^{25}$	0.2	0.7	0.1	−1.0	7.6

a) 5α- and 5β-cholestan-3-one. lit.[15]

Table IV. The C-13 Chemical Shift Differences between **24**, **25** and the Steroids[a] (ppm)

	C-1	C-2	C-6	C-7	C-9	C-10	10-Me
$\delta_C^{5\alpha}-\delta_C^{\Delta^4}$	3.9	4.5	−3.1	1.0	0.2	−2.1	−6.0

	C-16	C-15	C-11	C-1	C-18	C-17	17-Me
$\delta_C^{25}-\delta_C^{24}$	3.2	3.6	−4.0	0.2	−0.1	−3.3	−6.6

a) 5α: 5α-cholestan-3-one, Δ^4: cholest-4-en-3-one. lit.[15]

12) M. Shamma and J.M. Richey, *J. Am. Chem. Soc.*, **85**, 2507 (1963); W.F. Trager, C.M. Lee, and A.B. Beckett, *Tetrahedron*, 23, 365 and 375 (1967); J. Gutzwiller, G. Pizzolato, and M. Uskokovic, *J. Am. Chem. Soc.*, 93, 3907 (1971); T.A. Crabb, "Annual Reports on NMR spectroscopy," Vol. 6A, ed. by E.F. Mooney, Academic Press, London, 1975, pp. 351, 354 and 355.
13) W.G. Dauben, R.M. Coates, N.D. Vietmeyer, L.J. Durham, and C. Djerassi, *Experientia*, **21**, 565 (1965).
14) N.S. Bhacca and D.H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, 1964, p. 19.

the upfield shift of the 17-Me group by cancelling to some extent the deshielding effect of the enone system in the D ring.

It is also instructive to compare the carbon shieldings of the C and D rings in the berbans with those of the A and B rings in steroids. As shown in Table III, the shielding differences of the C-15, -13, -1, -18 and 17-Me in **25** and **15** are quite dissimilar to those of the corresponding carbons in 5α- and 5β-cholestan-3-one.[15] This reflects the C/D non-steroidal conformation for **15** and accordingly the changes of surrounding for the carbons in question compared to the 5β-steroid. Comparison of the ^{13}C NMR spectra of **24** and **25** reveals that influences of the Δ^{11}-bond on the carbons in the C and D rings and the 17-Me group are in a similar trend to those of the Δ^4-bond on the corresponding carbons in 5α-steroids[15] (Table IV).

Experimental

Melting points were determined on a micro hot-stage and are uncorrected. IR spectra were taken on a JASCO IR-G in a chloroform solution. PMR and ^{13}C NMR spectra were recorded on a JEOL JNM PS-100 at 100 and 25.1 MHz, respectively, for a deuterochloroform solution unless otherwise stated. Mass spectra (MS) were measured with a JEOL JMS-01S.

1,3,4,6,7,11b-Hexahydro-*2H*-9,10-dimethoxy-3-methyl-2-oxobenzo[*a*]quinolizine (9)——A solution of **7** (4.0 g) and **8** (2.7 g) in H_2O (5 ml) was stirred overnight at room temperature. The precipitate was collected and recrystallized from methanol to give **9** (4.2 g) as colorless needles of mp 142—143°. IR ν_{max} cm^{-1}: 2825, 2800, 2750 (Bohlmann bands), 1705 (C=O). PMR δ: 6.60 (1H, s, 11-H), 6.54 (1H, s, 8-H), 3.83 (3H, s, OMe), 3.81 (3H, s, OMe), 3.52 (1H, q, *J* 10 and 4 Hz, 11b-H), 1.04 (3H, d, *J* 6 Hz, 3-Me). *Anal.* Calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.75; H, 7.78; N, 5.04.

12-Hydroxy-7,8-dimethoxy-17-methyl-14-oxoalloberban (11) and 7,8-Dimethoxy-17-methyl-14-oxo-12,13-didehydropseudoberban (12)——a) To a mixture of **9** (100 mg) and **10** (118 mg) in dry benzene (2 ml) was added 2.1% solution of NaOEt in dry ethanol (1.2 ml). The reaction mixture was stirred for 2 hr at 5—6° and then overnight at room temperature under N_2. After removal of solvent *in vacuo* and addition of H_2O, the reaction mixture was extracted with chloroform, giving an oil (108 mg) which was purified by pre. TLC[16] (alumina plates; benzene/ethyl acetate=3:1, v/v). The zone with *Rf* 0.33 gave **11** (56 mg) as oil. IR ν_{max} cm^{-1}: Bohlmann bands, 3500 (OH), 1713 (C=O). PMR δ: 6.58 (1H, s, 9-H), 6.54 (1H, s, 6-H), 3.84 (6H, s, 2×OMe), 3.31 (1H, q, *J* 8 and 4 Hz, 1-H), 2.05 (1H, s, OH),[17] 1.16 (3H, s, 17-Me). MS *m/e*: M$^+$, 345.191. Calcd. for $C_{20}H_{27}NO_4$: M, 345.194. The Hydrogen Oxalate: colorless needles, mp 190—192° (from methanol). *Anal.* Calcd. for $C_{22}H_{29}NO_8\cdot 1/2H_2O$: C, 59.45; H, 6.80; N, 3.15. Found: C, 59.58; H, 6.56; N, 3.30. The zone with *Rf* 0.56 afforded **12** (21 mg) as oil. IR ν_{max} cm^{-1}: 1680 (C=O), 1630 (C=C). PMR δ: 6.62 (1H, s, 9-H), 6.55 (1H, s, 6-H), 5.78 (1H, s, 13-H), 4.28 (1H, W_H 12 Hz, 1-H), 3.82 (6H, s, 2×OMe), 1.46 (3H, s, 17-Me). ^{13}C NMR δ: 57.7 (d, C-1), 51.4 (t, C-3), 23.5 (t, C-4), 126.4 (s, C-5), 112.0 (d, C-6), 147.4 (s, C-7), 147.6 (s, C-8), 109.1 (d, C-9), 126.9 (s, C-10), 35.0 (t, C-11), 165.6 (s, C-12), 126.0 (d, C-13), 198.6 (s, C-14), 33.6 (t, C-15), 34.6 (t, C-16), 36.2 (s, C-17), 59.6 (t, C-18), 22.8 (q, 17-Me), 56.0 (q, OMe), 55.8 (q, OMe). The Hydrogen Oxalate: colorless needles, mp 196—197° (from methanol). *Anal.* Calcd. for $C_{22}H_{27}NO_7\cdot 1/2H_2O$: C, 61.96; H, 6.62; N, 3.28. Found: C, 61.61; H, 6.54; N, 3.05. The zone with *Rf* 0.73 gave **9** (20 mg). Treatment of **11** with 10% H_2SO_4 quantitatively afforded **12**.

b) To a mixture of **9** (500 mg) and **10** (590 mg) in dry benzene (10 ml) was added 2.1% solution of NaOEt in dry ethanol (4 ml). After treatment as mentioned above, the oil obtained was heated with 10% H_2SO_4 (5 ml) for 1 hr at 80°. The reaction mixture was made alkaline with 10% aq. NaOH and extracted with chloroform. The chloroform residue (622 mg) was chromatographed on neutral alumina (grade III, 31 g) using benzene as solvent to give **12** (412 mg) and **9** (133 mg).

7,8-Dimethoxy-17-methyl-14-oxoalloberban (15)——a) A solution of the **12** hydrogen oxalate (100 mg) in methanol (10 ml) was shaken with H_2 over 10% Pd-C (20 mg) for 2.5 hr. After filtration and removal of solvent *in vacuo*, the resulting residue was made alkaline with 10% aq. NaOH and extracted with chloroform. The chloroform residue (75 mg) was purified by pre. TLC (silica gel plates, methanol). The zone with *Rf* 0.65 gave **15** (31 mg) as oil. IR ν_{max} cm^{-1}: Bohlmann bands, 1710 (C=O). PMR δ: 6.63 (1H, s, 9-H), 6.55 (1H, s, 6-H), 3.82 (6H, s, 2×OMe), 3.04 (1H, bd, *J* 10 Hz, 1-H), 1.23 (3H, s, 17-Me). ^{13}C NMR δ: 63.2 (d, C-1), 52.4 (t, C-3), 29.2 (t, C-4), 126.8 (s, C-5), 111.5 (d, C-6), 147.1 (s, C-7), 147.4 (s, C-8), 108.1

15) H.J. Reich, M. Jautelat, M.T. Messe, F.J. Weigert, and J.D. Robert, *J. Am. Chem. Soc.*, **91**, 7445 (1969); D. Leibfritz and J.D. Roberts, *ibid.*, **95**, 4996 (1973); J.L. Gough, J.P. Guthrie, and J.B. Stothers, *J. Chem. Soc., Chem. Commun.*, **1972**, 979.
16) Preparative thin-layer chromatography.
17) On addition of D_2O this signal was disappeared.

(d, C-9), 129.5 (s, C-10), 31.2 (t, C-11), 43.7 (d, C-12), 43.7 (t, C-13), 211.4 (s, C-14), 37.5 (t, C-15), 35.3 (t, C-16), 32.9 (s, C-17), 68.1 (t, C-18), 23.9 (q, 17-Me), 56.0 (q, OMe), 55.8 (q, OMe). MS *m/e*: M^+, 329.198. Calcd. for $C_{20}H_{27}NO_3$: M, 329.199. The Hydrogen Oxalate: colorless needles, mp 198—200° (from methanol). *Anal.* Calcd. for $C_{22}H_{29}NO_7 \cdot H_2O$: C, 60.40; H, 7.14; N, 3.20. Found: C, 60.58; H, 6.80; N, 3.33. From the zone with *Rf* 0.53 **12** (29 mg) was recovered.

b) A solution of the **12** hydrogen oxalate (100 mg) in methanol (10 ml) was shaken with H_2 over Pt black obtained from PtO_2 (50 mg) for 1 hr. The work-up gave **15** (44 mg).

7,8-Dimethoxy-17-methyl-14-oxo-1,11-didehydroepialloberban (17)——To a solution of the **15** hydrogen oxalate (50 mg) in 1% acetic acid (3 ml) was added a solution of $Hg(OAc)_2$ (73 mg) and EDTA-2Na·$2H_2O$[18] (128 mg) in 1% acetic acid (3 ml), and the reaction mixture was heated for 1 hr at 55° under N_2. After filtration and removal of solvent *in vacuo*, the resulting residue was made alkaline with 10% aq. NaOH and extracted with chloroform. The chloroform residue (35 mg) was purified by pre. TLC (alumina plates; chloroform/methanol=100/1, v/v) to give **17** (27 mg) as oil. IR ν_{max} cm^{-1}: 1705 (C=O), 1620 (C=C). PMR δ: 7.05 (1H, s, 9-H), 6.54 (1H, s, 6-H), 4.80 (1H, bs, 11-H), 3.86 (3H, s, OMe), 3.84 (3H, s, OMe), 1.21 (3H, s, 17-Me). MS *m/e*: M^+, 327.180. Calcd. for $C_{20}H_{25}NO_3$: M, 327.183. The Picrate: yellow needles, mp 174—176° (from ethanol). *Anal.* Calcd. for $C_{26}H_{28}N_4O_{10} \cdot H_2O$: C, 54.35; H, 5.26; N, 9.75. Found: C, 54.13; H, 5.36; N, 9.57.

Methylation of 17——a) A solution of **17** (81 mg) and dimethyl sulfate (120 mg) in chloroform (3 ml) was stirred overnight at room temperature. The reaction mixture was evaporated *in vacuo* and washed with ether to give **18** (X: $MeSO_4$) (100 mg), whose crystallization from chloroform gave colorless needles of mp 185—187°. PMR (CD_3OD) δ: 7.43 (1H, s, 9-H), 7.02 (1H, s, 6-H), 3.97 (6H, s, 2×Me), 3.95 (3H, s, Me), 3.63 (3H, s, $MeSO_4^-$), 1.32 (3H, s, 17-Me). *Anal.* Calcd. for $C_{22}H_{31}NO_7S \cdot 1/4CHCl_3$: C, 55.28; H, 6.52; N, 2.90. Found: C, 55.41; H, 6.34; N, 2.80. The methiodide (**18**) (X: I) was obtained as colorless needles of mp 235—237° from the methosulfate with NaI. *Anal.* Calcd. for $C_{21}H_{28}NO_3I \cdot 1/2H_2O$: C, 52.72; H, 6.11; N, 2.92. Found: C, 52.61; H, 5.89; N, 2.79.

b) A solution of **17** (78 mg) and dimethyl sulfate (121 mg) in methanol (3 ml) was stirred overnight at room temperature. The work-up gave **19** (X: $MeSO_4$) (108 mg), whose crystallization from chloroform afforded colorless needles of mp 236—240°. PMR (CD_3OD) δ: 7.42 (1H, s, 9-H), 7.03 (1H, s, 6-H), 3.94 (6H, s, 2×Me), 3.90 (3H, s, Me), 3.66 (3H, s, $MeSO_4^-$), 1.13 (3H, s, 17-Me). *Anal.* Calcd. for $C_{22}H_{31}NO_7S \cdot CHCl_3$: C, 48.46; H, 5.74; N, 2.44. Found: C, 48.22; H, 5.63; N, 2.44.

***trans*-14-Hydroxy-7,8-dimethoxy-17-methylalloberban (16)**——a) To a solution of **15** (55 mg) in methanol (2 ml) was added $NaBH_4$ (25 mg) and the reaction mixture was stirred for 30 min at room temperature. The work-up gave an oil, whose pre. TLC (silica gel plates; methanol) gave **16** (53 mg) as oil. IR ν_{max} cm^{-1}: Bohlmann bands, 3625 (OH). PMR δ: 6.70 (1H, s, 9-H), 6.55 (1H, s, 6-H), 4.00 (1H, W_H 10 Hz, 14-H), 3.83 (6H, s, 2×OMe), 3.14 (1H, bd, *J* 10 Hz, 1-H), 1.79 (1H, s, OH),[19] 0.91 (3H, s, 17-Me). MS *m/e*: M^+, 331.211. Calcd. for $C_{20}H_{29}NO_3$: M, 331.214. The Hydrogen Oxalate: colorless needles, mp 193—196° (from methanol). *Anal.* Calcd. for $C_{22}H_{31}NO_7 \cdot H_2O$: C, 60.12; H, 7.57; N, 3.19. Found: C, 59.93; H, 7.63; N, 3.10.

b) The alloberbanol (**16**) was obtained from **17** and **18** (X: I) in 72% and quantitative yield, respectively, by the same precedure as above. Identification of the product as **16** was carried out by comparisons of the IR, PMR spectra and mp of the hydrogen oxalate.

c) Formation of **16** from **19** (X: $MeSO_4$) was observed as sole product by TLC.

Hofmann Degradations of 18 and 19——a) A solution of **18** (X: $MeSO_4$) (43 mg) in 25% KOH/methanol (2 ml) was stirred for 30 min at room temperature. After removal of solvent *in vacuo*, the resulting residue was extracted with chloroform. The chloroform residue was purified by pre. TLC (alumina plates; chloroform/methanol=100; 1, v/v) to give **17** (25 mg) as oil which afforded the picrate as yellow needles of mp 174—176° (from ethanol). Its identification as **17** was achieved by comparisons of the IR, PMR spectra and mp of the picrate.

b) A mixture of **19** (X: I) (143 mg) obtained from the methosulfate with NaI and Ag_2O (151 mg) in methanol (10 ml) was refluxed for 4 hr. After filtration and removal of solvent *in vacuo*, the resulting residue was purified by pre. TLC as mentioned above. The zone with *Rf* 0.48 afforded **17** (19 mg) as oil, whose identification as **17** was achieved by comparisons of the IR, PMR spectra and mp of the picrate (mp 174—176°). The zone with *Rf* 0.60 gave **21** (16 mg) as yellow needles of mp 225—227° which was considered to arise secondarily from oxidation of **17** with air. Its identification as **21** was carried out by comparisons of the IR, PMR spectra and mp of the compound obtained later.

7,8-Dimethoxy-17-methyl-14-oxo-1,11,12,13-tetradehydroberban (21)——To a solution of the **12** hydrogen oxalate (100 mg) in 1% acetic acid (3 ml) was added a solution of $Hg(OAc)_2$ (146 mg) and EDTA-2Na·$2H_2O$ (255 mg) in 1% acetic acid (3 ml), and the reaction mixture was heated for 1 hr at 55° under N_2. After filtration and removal of solvent *in vacuo*, the resulting residue was made alkaline with 10% aq. NaOH and

18) Disodium dihydrogen ethylenediaminetetraacetate.
19) On addition of D_2O this signal was disappeared.

extracted with chloroform, giving a yellow solid (78 mg). Its pre. TLC (alumina plates; chloroform/methanol =100/1, v/v) afforded **21** (67 mg) as yellow needles of mp 225—227° (from benzene) from the zone with *Rf* 0.24. IR ν_{max} cm^{-1}: 1640 (C=O). PMR δ: 7.17 (1H, s, 9-H), 6.63 (1H, s, 6-H), 5.70 (1H, s, 11-H), 5.60 (1H, s, 13-H), 3.93 (3H, s, OMe), 3.90 (3H, s, OMe), 1.25 (3H, s, 17-Me). MS *m/e*: M$^+$, 325.168. Calcd. for $C_{20}H_{23}NO_3$: M, 325.168.

7,8,14-Trimethoxy-17-methyl-1,11,12,13,14-pentadehydroberbanium Salt (**22**)——A solution of **21** (45 mg) and dimethyl sulfate (68 mg) in chloroform (3 ml) was refluxed for 10 hr. On removal of solvent *in vacuo* and washing with ether, **22** (X: $MeSO_4$) (69 mg) was obtained as oil. To a solution of the methyl sulfate (69 mg) in methanol (0.4 ml) was added NaI (25 ml). The precipitate (49 mg) was collected and recrystallized from ethanol to give **22** (X: I) (38 mg) as yellow needles of mp 194—195°. PMR (CD_3OD) δ: 7.44 (1H, s, 9-H), 7.03 (1H, s, 6-H), 6.78 (1H, d, *J* 2 Hz, 11-H), 6.02 (1H, bs, 13-H), 3.93 (3H, s, OMe), 3.90 (3H, s, 2×OMe), 1.20 (3H, s, 17-Me). *Anal.* Calcd. for $C_{21}H_{26}NO_3I \cdot 1/2H_2O$: C, 52.94; H, 5.71; N, 2.94. Found: C, 53.12; H, 5.75; N, 2.81.

Conversion of 22 into 21——A solution of **22** (X: I) (99 mg) in 10% HCl (2 ml) was heated for 1.5 hr at 50°. The reaction mixture was made alkaline with 10% aq. NaOH and extracted with chloroform. The chloroform residue (70 mg) was recrystallized from benzene to give **21** (63 mg) as yellow needles of mp 225—227°. Its identification as **21** was carried out by comparisons of the IR, PMR spectra and mp.

7,8-Dimethoxy-17-methyl-14-oxo-12,13-didehydroberban (**24**)——To a solution of **22** (X: I) (300 mg) in methanol (12 ml) was added $NaBH_4$ (135 mg) and the reaction mixture was refluxed for 1 hr. The work-up gave 7,8,14-trimethoxy-17-methyl-11,12,13,14-tetradehydroberban (**23**) (251 mg) as oil. IR: Bohlmann bands. A solution of **23** (251 mg) in 10% HCl (15 ml) was stirred for 30 min at room temperature. The reaction mixture was made alkaline with 10% aq. NaOH and extracted with chloroform. The chloroform residue (211 mg) was purified by pre. TLC (alumina plates; benzene/ethyl acetate=3/1, v/v). From the zone with *Rf* 0.73 **24** (102 mg) was obtained as oil. IR ν_{max} cm^{-1}: Bohlmann bands, 1675 (C=O), 1623 (C=C). PMR δ: 6.64 (1H, s, 9-H), 6.60 (1H, s, 6-H), 5.85 (1H, d, *J* 1 Hz, 13-H), 3.85 (3H, s, OMe), 3.83 (3H, s, OMe), 3.19 (1H, q, *J* 10 and 4 Hz, 1-H), 1.41 (3H, s, 17-Me). ^{13}C NMR δ: 62.9 (d, C-1), 52.1 (t, C-3), 29.4 (t, C-4), 127.0 (s, C-5), 111.5 (d, C-6), 147.3 (s, C-7), 147.6 (s, C-8), 108.1 (d, C-9), 128.9 (s, C-10), 38.8 (t, C-11), 167.3 (s, C-12), 124.6 (d, C-13), 199.2 (s, C-14), 33.7 (t, C-15), 34.5 (t, C-16), 36.9 (s, C-17), 69.2 (t, C-18), 22.9 (q, 17-Me), 56.2 (q, OMe), 55.9 (q, OMe). MS *m/e*: M$^+$, 327.186. Calcd. for $C_{20}H_{25}NO_3$: M, 327.183. The Hydrogen Oxalate: colorless needles, mp 205—209° (from methanol). *Anal.* Calcd. for $C_{22}H_{27}NO_7 \cdot 1/2H_2O$: C, 61.96; H, 6.62; N, 3.28. Found: C, 62.08; H, 6.65; N, 3.10. The zone with *Rf* 0.28 afforded **21** (56 mg) which was considered to arise secondarily from oxidation of **24** with air.

7,8-Dimethoxy-17-methyl-14-oxoberban (**25**)——A solution of the **24** hydrogen oxalate (268 mg) in methanol (15 ml) was shaken with H_2 over Pt black obtained from PtO_2 (134 mg) for 10 min. After filtration and removal of solvent *in vacuo*, the resulting residue was made alkaline with 10% aq. NaOH and extracted with chloroform. The chloroform residue (202 mg) was purified by pre. TLC (alumina plates; benzene/ethyl acetate=5/1, v/v) to afford **25** (135 mg) as oil (*Rf* 0.62). IR ν_{max} cm^{-1}: Bohlmann bands, 1710 (C=O). PMR δ: 6.65 (1H, s, 9-H), 6.55 (1H, s, 6-H), 3.83 (6H, s, 2×OMe), 3.06 (1H, bd, *J* 10 Hz, 1-H), 1.21 (3H, s, 17-Me). ^{13}C NMR δ: 63.1 (d, C-1), 52.8 (t, C-3), 29.4 (t, C-4), 127.0 (s, C-5), 111.5 (d, C-6), 147.1 (s, C-7), 147.4 (s, C-8), 108.1 (d, C-9), 129.3 (s, C-10), 34.8 (t, C-11), 43.9 (d, C-12), 44.0 (t, C-13), 210.7 (s, C-14), 37.3 (t, C-15), 37.7 (t, C-16), 33.6 (s, C-17), 69.1 (t, C-18), 16.3 (q, 17-Me), 56.1 (q, OMe), 55.8 (q, OMe). The Hydrogen Oxalate: colorless needles, mp 217—220° (from methanol). *Anal.* Calcd. for $C_{22}H_{29}NO_7 \cdot 1/2H_2O$: C, 61.67; H, 7.05; N, 3.27. Found: C, 61.93; H, 7.07; N, 3.16.

7,8-Dimethoxy-17-methyl-14-oxo-1,11-didehydroberban (**26**)——To a solution of the **25** hydrogen oxalate (129 mg) in 1% acetic acid (5 ml) was added a solution of $Hg(OAc)_2$ (188 mg) and EDTA-2Na·$2H_2O$ (330 mg) in 1% acetic acid (5 ml), and the reaction mixture was heated for 1 hr at 55° under N_2. After filtration and removal of solvent *in vacuo*, the resulting residue was made alkaline with 10% aq. NaOH and extracted with chloroform, giving an oil (74 mg). Its pre. TLC (alumina plates; chloroform/methanol=20/1, v/v) afforded **26** (51 mg) as oil (*Rf* 0.30). IR ν_{max} cm^{-1}: 1710 (C=O), 1615 (C=C). PMR δ: 7.07 (1H, s, 9-H), 6.56 (1H, s, 6-H), 3.87 (3H, s, OMe), 3.85 (3H, s, OMe), 4.58 (1H, bs, 11-H), 1.13 (3H, s, 17-H). The Picrate: yellow needles, mp 147—149° (from ethanol). *Anal.* Calcd. for $C_{26}H_{28}N_4O_{10} \cdot 3/4H_2O$: C, 54.77; H, 5.22; N, 9.83. Found: C, 54.72; H, 4.90; N, 9.79.

Methylation of 26 and Successive Reduction——A solution of **26** (51 mg) and methyl iodide (116 mg) in chloroform (3 ml) was stirred overnight at room temperature. After removal of solvent *in vacuo*, the resulting residue was washed with ether, giving a mixture (72 mg) of 7,8-dimethoxy-*cis*-11,17-dimethyl-14-oxo-1-dehydroberbanium iodide (**27**) and the methiodide (**28**) as oil in an approximate ratio of 7: 3.[20] PMR δ: 7.41 (1H, s, 9-H), 6.86 (1H, s, 6-H), 4.01 (3H, s, OMe), 3.98 (3H, s, OMe), 1.39 (3H, d, *J* 7 Hz, 11-Me),[20] 1.22 (3H, s, 17-Me). To a solution of the above mixture (72 mg) in methanol (5 ml) was added $NaBH_4$ (25 mg) and the reaction mixture was stirred for 10 min at room temperature. The work-up gave an oil (48 mg) which was purified by pre. TLC (alumina plates; benzene/ethyl acetate=3/1, v/v). The zone with

20) The ratio was deduced from the integral intensity of the 17-Me signal in the PMR spectrum.

Rf 0.38 afforded *cis*-14-hydroxy-7,8-dimethoxy-*cis*-11,17-dimethylberban (**29**) (20 mg) as oil. IR ν_{max} cm^{-1}: Bohlmann bands, 3500 (OH). PMR δ: 6.71 (1H, s, 9-H), 6.56 (1H, s, 6-H), 3.83 (6H, s, 2×OMe), 3.59 (1H, W_H 30 Hz, 14-H), 1.97 (1H, s, OH),[21] 1.10 (3H, d, *J* 7 Hz, 11-Me), 1.02 (3H, s, 17-Me). The Hydrogen Oxalate: colorless needles, mp 134—137° (from ethanol). *Anal.* Calcd. for $C_{23}H_{33}NO_7 \cdot H_2O$: C, 60.91; H, 7.78; N, 3.09. Found: C, 61.05; H, 7.63; N, 2.99. The zone with *Rf* 0.52 gave *cis*-14-hydroxy-7,8-dimethoxy-17-methylberban (**30**) (10 mg) as oil. IR ν_{max} cm^{-1}: Bohlmann bands, 3500 (OH). PMR δ: 6.70 (1H, s, 9-H), 6.55 (1H, s, 6-H), 3.82 (6H, s, 2×OMe), 3.60 (1H, W_H 24 Hz, 14-H), 1.01 (3H, s, 17-Me). The Hydrogen Oxalate: colorless needles, mp 149—154° (from ethanol). *Anal.* Calcd. for $C_{22}H_{31}NO_7 \cdot 3/4H_2O$: C, 60.74; H, 7.53; N, 3.19. Found: C, 60.63; H, 7.47; N, 3.02.

7,8-Dimethoxy-17-methyl-14-oxo-1,11,12,13-tetradehydroberban Metho Salt (31)——A solution of **21** (70 mg) and dimethyl sulfate (108 mg) in methanol (5 ml) was allowed to stand for 50 hr at 5—10°. On removal of solvent *in vacuo* and washing with ether, **31** (X: $MeSO_4$) (89 mg) was obtained as yellow crystals of mp 192—195°. PMR (CD_3OD) δ: 7.43 (1H, s, 9-H), 7.01 (1H, s, 6-H), 6.54 (1H, s, 11-H), 5.86 (1H, s, 13-H), 3.92 (6H, s, 2×Me), 3.90 (3H, s, Me), 3.66 (3H, s, $MeSO_4^-$), 1.22 (3H, s, 17-Me). The methiodide (**31**) (X: I) was obtained as yellow needles of mp 237—242° (from ethanol) from the methosulfate with NaI. *Anal.* Calcd. for $C_{21}H_{26}INO_3 \cdot 3/4H_2O$: C, 52.44; H, 5.76; N, 2.91. Found: C, 52.30; H, 5.68; N, 2.83.

Hofmann Degradation of 31——A solution of **31** (X: $MeSO_4$) (89 mg) in 25% KOH/methanol (3 ml) was refluxed for 1 hr. After removal of solvent *in vacuo*, the resulting residue was extracted with benzene. The benzene residue (63 mg) was recrystallized from benzene to afford **21** (60 mg) as yellow needles of mp 225—227°. Its identification as **21** was achieved by comparisons of the IR and PMR spectra and mp.

21) On addition of D_2O this signal was disappeared.