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NUCLEOPHILIC DEQUATERNIZATION OF CONDENSED AZETIDINIUM SALTS—II[1]

8-*METHYL*-8-*AZONIUM* TRICYCLO [2.2.1.1.^{2,8}] NONANE SALTS—AN NMR STUDY

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Abstract—8-Methyl-8-*azonium* tricyclo [2.2.1.1.^{2,8}] nonane chloride (IIa) was obtained in quantitative yield from 2β-chloromethyl-3β-hydroxytropane (Ib). Its structure was proven by NMR in particular double irradiation, mass spectroscopic and IR data. The products of nucleophilic dequaternization of IIa were also investigated.

IN A previous paper nucleophilic dequaternization[1] of a lupinine derivative, 1,5-methano-2H-quinolizinium tosylate, i.e., 5-*azonium* tricyclo [0.^{5,10}4.3.1.1.^{1,5}] nonane tosylate on the action of neutral salts was described, leading to 1-halomethyl-2H-quinolizines.

In order to study the scope and limitations of this new reaction, we extended our investigations now to the field of two natural products, viz., ε-coniceines[2] and the *aza*tricyclo [2.2.1.1.^{2,8}] nonane system.[3] We had two reasons to undertake this project. First, the mechanistic aspects, including the relative stabilities of these systems were deemed of great interest. Secondly, similar ring-opening reactions might be expected to occur with nucleophilic prosthetic groups in the tissue with the hope to find out new potential biological alkylating agents. Aziridines[4] are known to act in this way, while monocyclic azetidines usually do not respond.[5] The stereoelectronic effects indicated by the facile ring-opening of the 2H-quinolizine derivatives seemed to forecast such an effect.

In order to synthesize an *aza*tricyclo [2.2.1.1.^{2,8}] nonane, 2β-chloromethyl-3β-hydroxytropane (Ib) an intermediate in the earlier cocaine work,[6] seemed to serve this purpose adequately. Actually the compound undergoes very easy intramolecular alkylation under conditions[1,7] comparable to those found in the case of lupinine tosylate and brosylate. By heating to its m.p., 2β-chloromethyl-3β-hydroxytropane (Ib) gave a salt-like compound[6,8] in quantitative yield.

There are six possible structures II, IV, V, VI and two dimeric ones for the thermally isomerized product. Dimeric structures of an ammonium salt or the ether were ruled out previously on the basis of ebullioscopic molecular weight determination[8] (apparent mol wt was found to be 95 corresponding to the monomeric structure). Furthermore, recent mass spectrometric work[9] of 2β-chloromethyl-3β-hydroxytropane (Ib) proved the presence of a molecular ion, *m/e* 154 which corresponds precisely to the cation formed on intramolecular quaternization. Structure V was eliminated[3]

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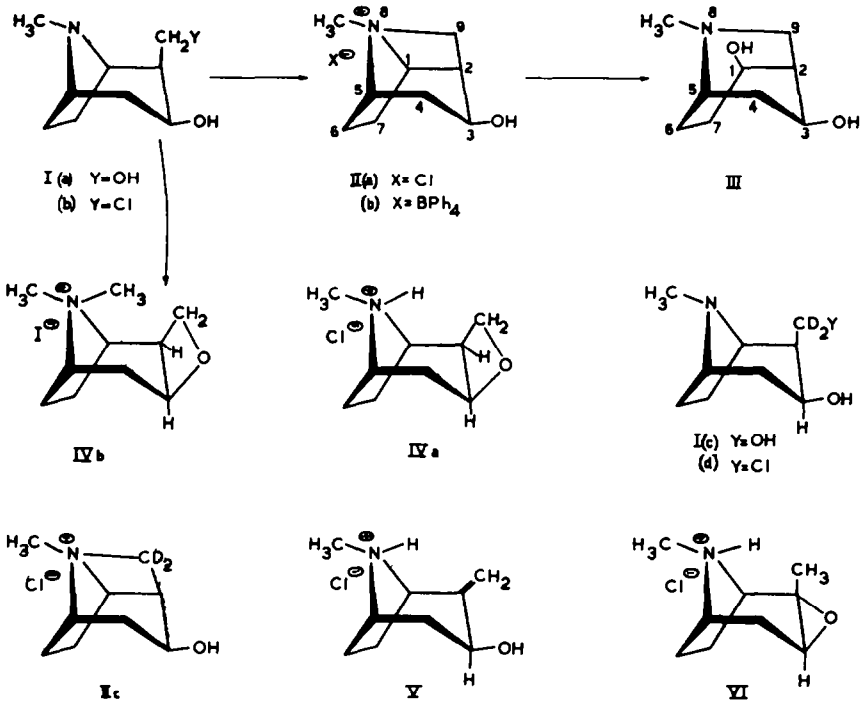

because NMR data failed to provide evidence for the exomethylene protons. The PMR spectrum of the salt showed no evidence for the absorption in the Me region therefore structure VI was also discarded.[3] Finally, the choice is left between structures IIa and IVa. Elimination of hydrogen chloride from structure IVa should lead to one unit less than the observed *m/e* 154. Attempts to liberate the base from this salt by alkali in the usual way failed. Furthermore it does not remove from the starting line in the TLC on alumina, unlike all hydrochlorides of tertiary bases of the same series. This fact is equally inconsistent with IVa, V and VI. Nevertheless a systematic NMR study was needed to achieve positive evidence for either structure.

The IR spectrum of the salt (Fig. 1a) shows characteristic absorption at 3230 cm^{-1} for strongly hydrogen bonded OH group. When the chloride is replaced by the hydrophobic tetraphenylborate anion the OH absorption appears at 3600 cm^{-1} (Fig. 1b). The characteristic ring skeletal vibrations appear in the finger-print region.

The NMR spectrum (Fig. 2) of the chloride salt (IIa) shows a rather complex, nevertheless interesting pattern. Interpretation of the spectrum has been made by systematic analysis.

(1) Addition of *p*-toluenesulfonic acid shifts the HOD peak downwards, thus showing three doublets centered at δ 4·4 instead of a pair of doublets in the original spectrum.

(2) Measurement of the integrated areas of the signals at δ 5·15, 4·90, 4·4, 4·25, 3·15, 3·0 and 2·8–2·0 ppm correspond to protons in the ratio 1:1:1:3:3:1:6, respectively.

(3) In order to locate the methylene protons on C-9, we have prepared the corresponding dideuterated sample (IIc) from cocaine by reduction with LAD to 2β-hydroxymethyl-d_2-3β-hydroxytropane (Ic) followed by treatment with thionyl

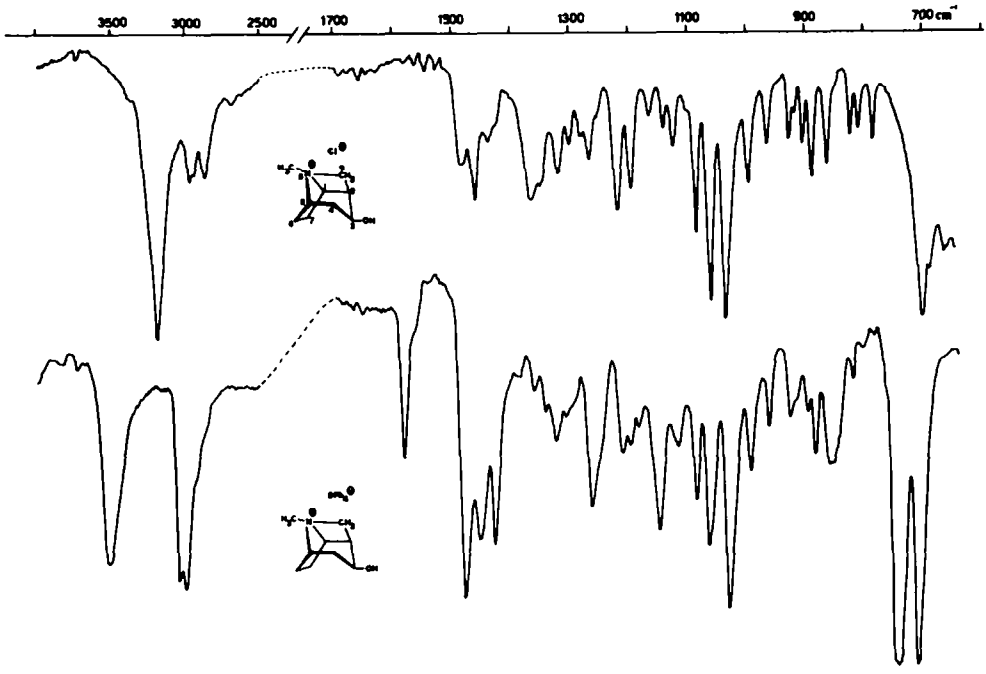

FIG. 1 IR spectra of: (a) the chloride salt (IIa), (b) the tetraphenylborate salt (IIb).

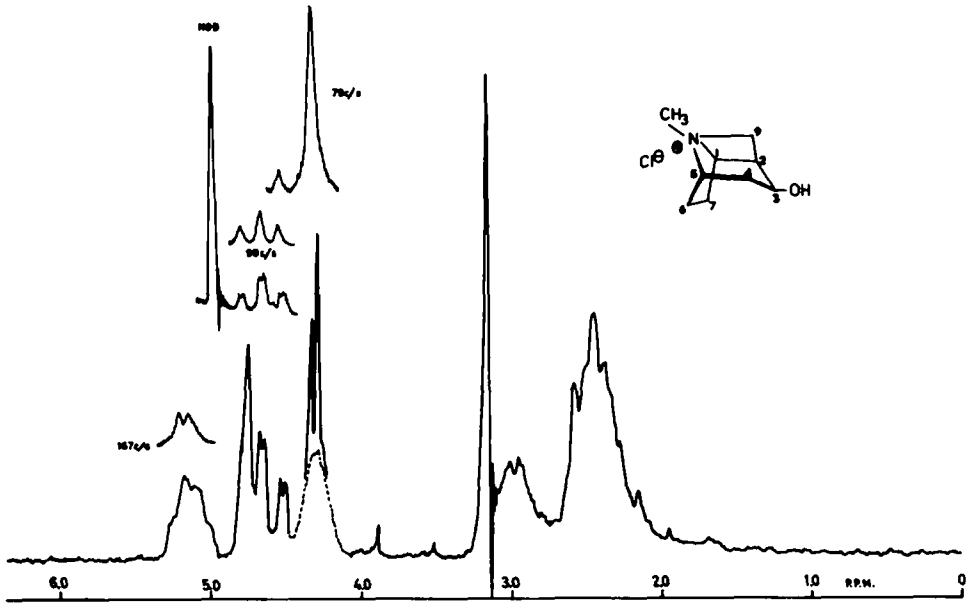

FIG. 2 NMR spectrum of the chloride salt (IIa) in D_2O.

chloride to Id and cyclization to IIc. The NMR spectrum of IIc showed the absence of a doublet at δ 4·25 (J = 3 c/s). Hence this doublet was assigned to C-9 methylene protons. Interestingly, a broad multiplet (base width 22 c/s: half-line width 11 c/s) corresponding to one proton was detected and this was covered under the C-9 methylene doublet in the nondeuterated salt (IIa). The broad multiplet centered at δ 3·0 in the chloride (IIa) was simplified to a broad doublet (J = 4 c/s) by deuteration at C-9 in IIc thereby indicating the location of C-2 proton. The doublet with J = 3·0 c/s at δ 4·2 ppm collapsed into a sharp singlet by double irradiation at 79 c/s (corresponding to the signal at δ 3·0); The position of the H-2 was thus further ascertained.

(4) As a further step the C-3 and C-1 protons had to be identified. In the case of the azetidinium salt (IIa) C-1 proton was expected to be very strongly deshielded and close to this, that of C-3 proton should be found. The broad multiplet (base width 23 c/s and half-line width 12 c/s) centered at δ 5·15, corresponding to one proton, proved indeed coupled with the C-2 proton, since double irradiation at 125 c/s gave a broad doublet (more like a triplet). On the other hand, irradiation of the H-2 at 90 c/s simplified the original triplet of doublets (to 1 : 2 : 1 triplet, J = 7·5 c/s) centered at δ 4·4 indicating the position of C-3 proton. Further decoupling of the same with C-4 protons at 130 c/s produced a broad doublet confirming this assignment completely.

(5) The N-Me protons appeared at δ 3·15 as a singlet while all the ring methylene protons (C-4, C-6 and C-7) are found in the region δ 2·8–2·0 ppm. Assignment of the latter is based on the earlier work of partially deuterated tropanes.[10]

(6) The C-5 proton should appear downfield due to neighbouring positive nitrogen and hence, the broad multiplet at δ 4·25 (covered under C-9 methylene doublet in the salt IIa), was assigned to this proton. The large difference in chemical shifts between H-1 and H-5 shows their non-equivalent chemical environment as expected for IIa. In the case of alternative structure IVa ring strain on C-2, C-9 and C-3 would hardly exert much more influence on H-1 than on H-5. So these two protons had to resonate much closer than they do in fact. All these data prove consistently the presence of the tricyclic azetidinium salt structure IIa.

Although the evidence presented above was in complete agreement with *aza*tricyclononane structure IIa, we went further to investigate the physical characteristics of the related condensed oxetanes. For this purpose 2β-chloromethyl-3β-hydroxytropane has been converted into the methiodide[8] by treatment with methyl iodide followed by ring closure with alkali.

The IR and NMR (Fig. 3) data for that product are in agreement with structure IVb. There is no OH absorption around 3,200–3,400 cm^{-1} while at 910, 930 and 965 cm^{-1} the bands characteristic for the oxetane and at 1,460 cm^{-1} for typical tropane skeletal vibration are present. The NMR spectrum showed a downfield chemical shift for the methylene protons of the oxetane ring to δ 5·5 ppm giving a six line pattern. Protons H-1 and H-5 appear at δ 4·6 very closely, as expected. The Me's on N resonate at different field. This is attributed to the fact that the equatorial Me signal δ 3·55 should be more deshielded[11, 12] than the axial one. H-3 appears at δ 4·12 and H-2 at δ 3·55. One broad multiplet at δ 1·8–2·6 contains H-4, H-6 and H-7.

Table 1 presents characteristic proton signals in the tropane derivatives based on an earlier work[10] and our present measurements. The protons on C-4, C-6 and

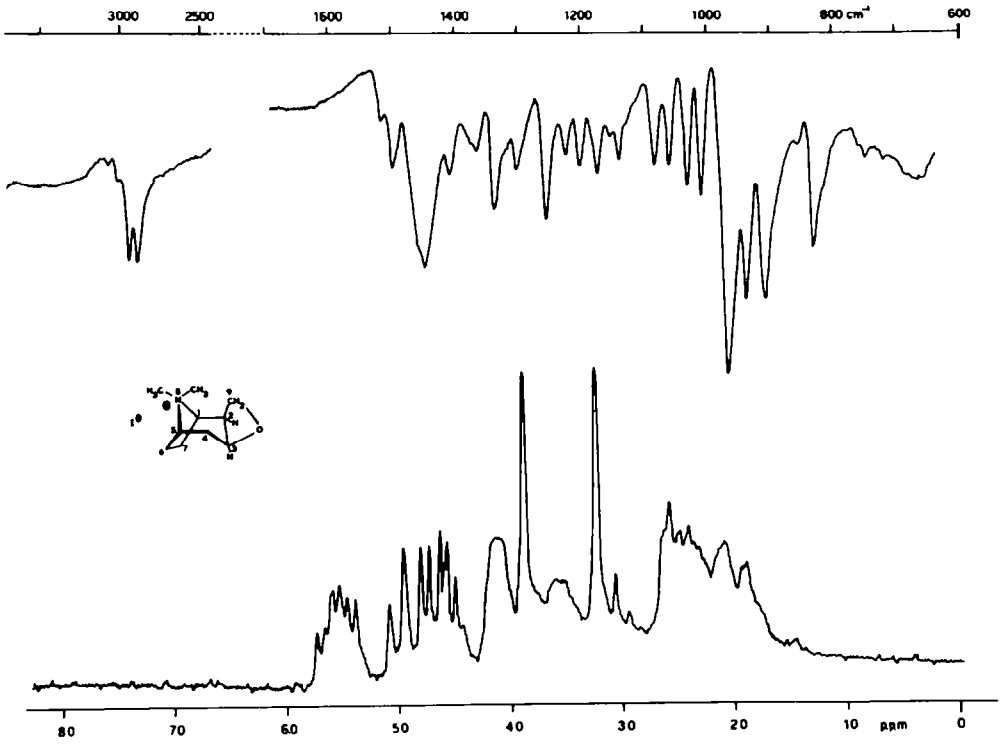

FIG. 3 IR and NMR spectra of 2',3-anhydro-2β-hydroxymethyl-3β-hydroxytropane methiodide (IVb).

C-7 appear in the δ 1·4–2·0 region. The characteristic IR frequencies for the same series are also being presented (Table 2). The chemical behaviour of the new tricyclic azetidinium system is very similar to the methano-2H-quinolizinium series. Treatment of the salt with aqueous alkali gave a mixture of two compounds which are identified as ecgoninol (Ia)[6,8] and 8-methyl-8-*aza*bicyclo [3.2.2.^{2,5}]-nonane-1,3-diol (III) in 1:2 proportion. The NMR spectrum (D_2O and also pyridine-d_5) of the latter (Fig. 4) was analyzed in detail. There are eight regions which should be considered. The assignments of the protons appear at δ 4·75 due to HOD (δ 5·65 for the OH in pyridine-d_5 as a solvent) and at δ 2·2 due to Me on N are relatively easy. Integrated areas (with respect to N-Me) are in the ratio of 1:1:2:1:3:1:6 (for signals appearing at δ 4·2, 3·8, 3·3, 2·8, 2·2, 2·1 and 2·0–1·1 ppm, respectively). The NMR spectrum of the C-9 dideuterated compound showed the absence of pair of doublets (or quartet) at δ 3·3. Hence, undoubtedly the quartet was due to methylenes on C-9. The coupling of 5·5 c/s is explained by geminal coupling (giving rise to doublet with 11 c/s) followed by vicinal coupling with C-2 proton, thereby splitting into a quartet.[13] In pyridine one would notice the difference in chemical shifts for C-9 and C-5, whereas in D_2O they have the same chemical shift or are superimposed one over the other. Decoupling experiments indicate the C-4 protons to appear at δ 2·1. The protons that appear at δ 4·2 and δ 3·8 are on C-3 and C-1, respectively, decoupled with C-2 and they appear as broad doublets (137 c/s for δ 4·2 and 127 c/s for δ 3·8). The proton appearing at δ 3·8 is assigned to C-1 based on the assumption that it should be strongly shielded

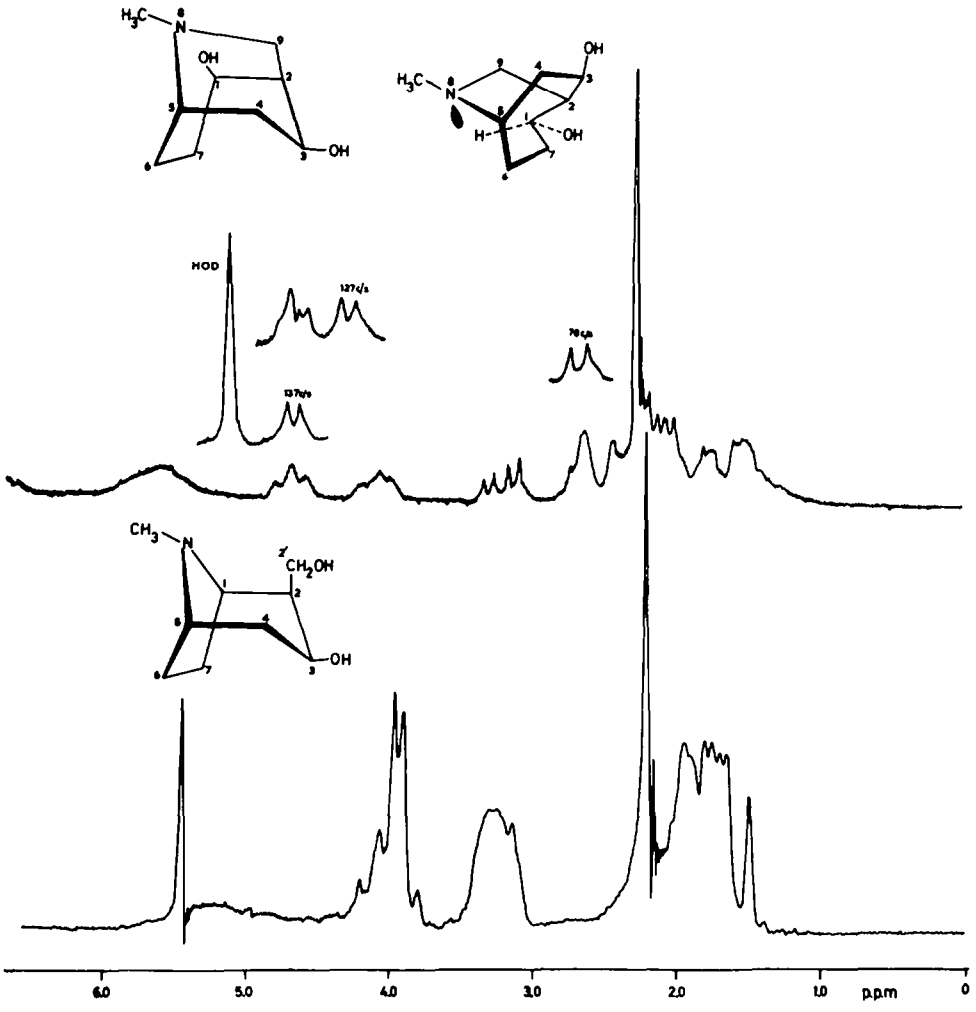

FIG. 4 NMR spectra of 8-methyl-8-*aza*bicyclo [3.2.2.^{2,5}] nonane-1.3-diol (III) and ecgoninol (Ia).

due to lone pair of electrons on nitrogen. Similar instances have been noticed, in particular, the recent example in lupinine series[7] where the bridge hydrogen is strongly shielded by the lone pair of electrons, thus showing up at higher field.

Then the other proton at δ 4·2 must be due to C-3. When decoupled (70 c/s) the C-1 proton appears as doublet (i.e. one pair of the adjacent methylene protons which appear at δ 2·0–1·1 has been decoupled). All the protons on C-2, C-6 and C-7 appear between δ 2·0–1·0 ppm.

The IR spectrum of the bicyclic dihydroxy compound (Fig. 5) contains characteristic frequencies for the OH (3390 cm^{-1}) and other vibrations all in complete agreement with the structure III.

Our further interest lies in the chemical correlation of the diol III with a monocyclic compound of known constitution, and this is now in progress.

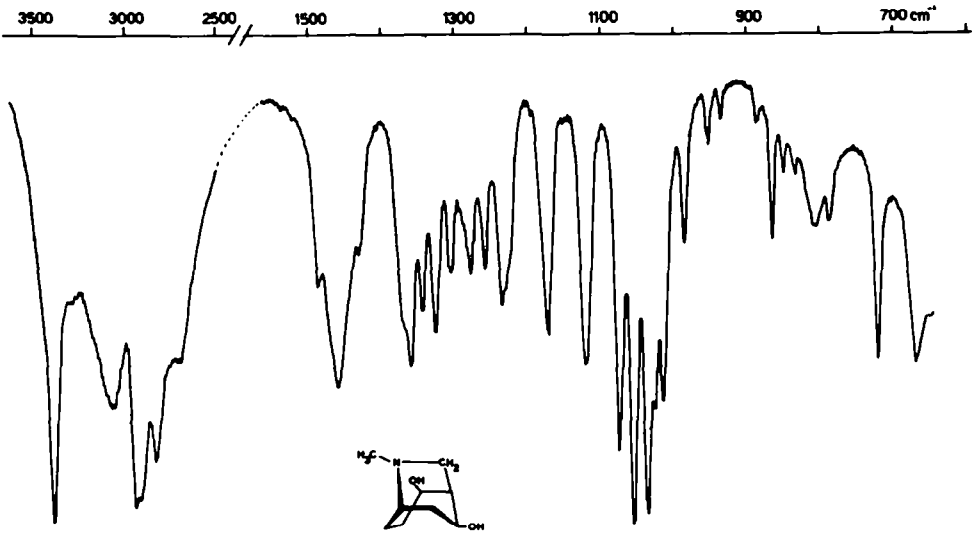

FIG. 5 IR spectrum of 8-methyl-8-*aza*bicyclo [3.2.2.^{2,5}] nonane-1,3-diol (III).

EXPERIMENTAL

All m.ps were taken in open capillary tubes using Electrothermal m.p. apparatus and are uncorrected. A few measurements have been checked on a Metlar F P-1 apparatus giving corrected values. The IR spectra were run on a Beckman-IR 4 spectrophotometer as films on NaCl cells or as KBr pellets. The NMR spectra were recorded by Varian A-60 and A-60-A instruments. The decoupling experiments were carried out on A-60-A using Varian Model V-6058 A spin decoupler. TMS was used as an internal standard when the samples were run in either chloroform-d or acetone-d_6 and when the spectra were recorded in D_2O, the previously calibrated Me resonance of sodium *p*-toluenesulfonate was taken as standard. Specific rotations were obtained with a Schmidt–Haensch polarimeter with model No. 16479 and the values given are for the sodium D line. Mass spectrum was obtained on C.E.C. Model 21-103C mass spectrometer equipped with an all glass inlet system.

2β-*Hydroxymethyl*-3β-*hydroxytropane* (*'ecgoninol'*) *hydrochloride* (Ia–HCl). This compound has been prepared employing essentially the same conditions except in work-up as those of the previous experiment.[17] Thus after treatment of cocaine (60·6 g, 0·2 mole) with LAH (38 g, 1 mole) in anhydrous ether (1800 ml) water (50 ml) was added and the white solid was extracted continuously with $CHCl_3$. Evaporation of combined ether and $CHCl_3$ extracts gave an oil which was treated with ethanolic HCl to give 32 g (77%) of ecgoninol hydrochloride as white crystalline material, m.p. 285–286° (reported m.p. 270–272°), $[\alpha]_D^{25}$ −37·5° (*c*, 3·2 water).

The free base Ia was liberated in 80% yield from ecgoninol hydrochloride by treatment with Ag_2O in water giving an oil. $[\alpha]_D^{25}$ −42·49° (*c*, 8·55 EtOH).

Compound Ic–HCl was prepared in 87% yield from cocaine by treatment with LAD following the afore-mentioned procedure.

2β-*Chloromethyl*-3β-*hydroxytropane hydrochloride* (Ib–HCl). This was prepared in a similar fashion as described earlier.[6] Thus from 33·2 g (0·16 mole) of ecgoninol hydrochloride and 115 ml $SOCl_2$, there was obtained 34·6 g (95%) of Ib–HCl, m.p. 222–223° after recrystallization from MeOH (reported m.p. 207–209°), $[\alpha]_D^{25}$ −59·22° (*c*, 4 water)

2β-*Chloromethyl*-3β-*hydroxytropane* (Ib). The experiment was performed in cold room (0–4°) for the liberation of free base following the earlier procedure.[6] To a soln of Ib–HCl (56·5 g, 0·25 mole) in 250 ml water, 21 g (0·25 mole) $NaHCO_3$ and 25·5 g (0·25 mole) Na_2CO_3 was added and extracted 10 times with 220 ml portions of ether followed by 4 times with 150 ml portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent evaporated at 0° under 25 mm to give white crystalline material (m.p. 82–84°) which was recrystallized in cold from benzene–pet. ether (b.p. 40–60°); yield: 40·7 g (86%), m.p. 84–85° (83·8° on Metlar FP 1) [reported m.p. 76–78°], $[\alpha]_D^{25}$ −67·3° (*c*, 4·11 EtOH). This was stored in a deep freezer

TABLE 1. PROTONS CHEMICAL SHIFTS (ppm on δ scale)

-Tropane	H-1 & H-5	H-6 & H-7	H-2 & H-4	N-Me	H-3	H-O	H-2′ or H-9
3-Oxo-	3·35	1·4–2·0	2·2	2·41	—	—	—
3-Oxo-2,4-d_4-	3·38	1·4–2·0	—	2·42	—	—	—
3α-Hydroxy (ax.)-	3·0	2·05*	1·6–1·9	2·16	3·90	4·3	—
3α-Hydroxy-2,4-d_4-	2·97	2·00†	—	2·18	3·88	3·36	—
3α-Hydroxy-6.7-d_2-	2·98	2·05	1·6–2·0	2·18	3·89	3·4	—
3β-Hydroxy (eq.)-	3·07	1·5–1·8	1·5–1·8	2·22	3·70	3·51	—
3β-Hydroxy-2,4-d_4-	3·09	1·8	—	2·20	3·73	4·79	—
3β-Hydroxy-2β-hydroxymethyl-	3·28	1·48–2·15	1·48–2·15	2·2	4·0	5·45	4·1 (J = 3·5 c/s)
3β-Hydroxy-2β-chromethyl-	3·1 & 3·4	1·42–2·15	1·42–2·15	2·2	4·20	3·82	4·08 (J = 2·5 c/s)
3β-Hydroxy-2β-chloromethyl (HCl)	3·95–4·7	1·9–2·9	1·9- 2·9	2·92	4·0–4·7	4·72	3·95–4·78
8-Methyl-8-azoniumtricyclo-[2.2.1.1.^{2,8}]-nonane chloride	5·15 & 4·28	2·0–2·8	3·0 and between 2·0–2·8	3·15	4·4	4·75	4·2 (J = 3 c/s)
8-Methyl-8-*aza*bicyclo-[3.2.2.^{2,5}] nonane-1,3-diol	2·8 & 3·8	1·1–2·0	1·1–2·0 for H-2 and 2·1	2·2	4·2	4·75	3·3 (J = 5·5 c/s)
2′,3-Anhydro-2β-hydroxymethyl-3β-hydroxy-tropane methiodide	4·6	1·8–2·6	3·55 for H-2 & between 1·8–2·6	3·2 & 3·85	4·12	—	5·5

* 4 protons
† 2 protons

TABLE 2. CHARACTERISTIC INFRARED FREQUENCIES (cm^{-1})

Compound	—OH	C—H Vibrations		Ring Vibrations	Deuterium Absorption
		Stretching	Deformation		
2β-Hydroxymethyl-3β-hydroxytropane Ecgoninol	3380	2950	1480 1450	1070 1050 1030	2210 2090
Ecgoninol hydrochloride	3250	3000 2850	1495 1485 1455	1082 1045 1030 1010	2210 2100
2β-Chloromethyl-3β-hydroxytropane	3200	2975 2800	1478 1450	1075 1050 1040 1010	2230 2100
2β-Chloromethyl-3β-hydroxytropane-hydrochloride	3320	2995 2820 2730 2590	1485 1460 1430	1100 1082 1050 1022	2250 2100
8-Methyl-8-*azonium*tricyclo-[2.2.1.1.^{1,5}] nonane chloride	3200	2975 2870	1482 1460 1438	1082 1060 1038	2200 2030
8-Methyl-8-*azonium*tricyclo[2.2.1.1.^{1,5}] tetraphenylborate	3520	3040 3000	1480 1455 1430	1085 1065 1030	—
8-Methyl-8-*aza*bicyclo[3.2.2.^{2,5}]-nonane-1,3-diol	3390	3090 2950 2830	1460	1078 1058 1038 1018	2180 2060
2',3-Anhydro-2β-hydroxymethyl-3β-hydroxytropane methiodide	—	2950 2890	1450	965 935 910	—

8-*Methyl*-8-azonium *tricyclo* [2.2.1.1.^{2,8}] *nonane chloride* (IIa). Compound Ib (18·95 g, 0·1 mole) was gently heated to 90° in oil-bath and kept at 95–100° for 30 min. During this period a clear melt initially obtained gradually solidified, yield: 18·9 g, m.p. 231–232° (232·2° on Metlar FP 1) (reported[8] m.p. 222–223°), $[\alpha]_D^{25}$ −88·1° (*c*, 4·08 water).

8-*Methyl*-8-azonium *tricyclo* [2.2.1.1.^{2,8}] *nonane tetraphenylborate* (IIb). To a suspension of the salt IIa (1·4 g, 7·36 mmoles) in 100 ml acetone, 2·6 g (7·6 mmoles) sodium tetraphenylborate was added and the mixture heated under reflux for 5 hr. After evaporation of the acetone, the residue was put in 50 ml water, filtered, and the ppt washed with water. Finally, the salt was recrystallized from MeOH, yield 3·3 g (90%), m.p. 256–257° (255·4° on Metlar FP 1).

Dequaternization experiments

8-*Methyl*-8-azabicyclo [3.2.2.^{2,5}] *nonane*-1,3-*diol* (III). The chloride IIa (18 g, 0·095 moles) in 1N NaOH (1000 ml) was heated under reflux for 6 hr. The cooled soln was saturated with K_2CO_3. Evaporation of water gave a solid which was extracted continuously with CH_2Cl_2 for 20 hr. Removal of most of the solvent separated the diol III as colourless crystals. These were recrystallized from CH_2Cl_2, yield: 9·42 g (58%), m.p. 145–146° (reported[8] m.p. 139–141°), $[\alpha]_D^{25}$ +34·6° (*c*, 2·61 EtOH).

Evaporation of mother liquors gave an oil (4·7 g, 29%) which was characterized as Ia by conversion to its hydrochloride, yield: 5·7 g, m.p. 284–286°. (Total yield after dequaternization: 87%).

2β-*Chloromethyl*-3β-*hydroxytropane methiodide* (Ib–MeI). To a soln of 2β-chloromethyl-3β-hydroxytropane (1·0 g, 5·27 mmoles) in 4 ml abs EtOH 5 ml MeI was added and the mixture was kept at 0° with stirring for 7 days. The white ppt was separated by filtration and recrystallized from water–acetone, yield: 1·6 g (91%), m.p. 261–262° (reported[8] m.p. 262–263°), $[\alpha]_D^{25}$ −1·88 (*c*, 2·4 water).

2',3-*Anhydro*-2β-*hydroxymethyl*-3β-*hydroxytropane methiodide* (IVb). A mixture of 0·85 g (2·56 mmoles) of Ib–MeI, 24 ml water and 5 ml 1N NaOH was heated on steam-bath for 1 hr and the soln was acidified with 0·1N HCl (P_H 5). Evaporation of water gave a white solid which was recrystallized from EtOH, yield: 0·55 g (72%), m.p. 283–284° (reported[8] m.p. 266–268°), $[\alpha]_D^{25}$ +12·85 (*c*, 2·32 water).

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