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SYNTHESIS OF A cis-PERHYDROAZULENE DERIVATIVE RELATED TO GRAYANOTOXIN

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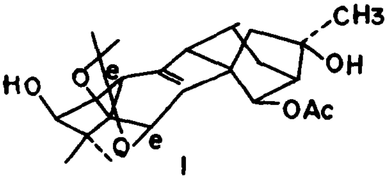
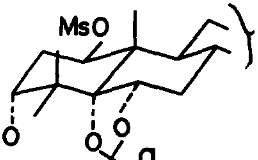
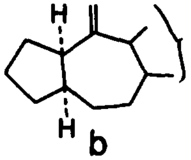
The stereochemistry 1 has been suggested for anhydrograyanotoxin I acetonide1). The cis-perhydroazulene moiety of 1 is expected to be formed by solvolysis of 1β-mesyloxy-5α,6α-dihydroxy-trans-decalin derivative of type a (the mirror image is shown) and in fact a simpler perhydroazulene system b has been obtained from a 5α-cholestan-1β-ol derivative2). On the other hand, solvolysis of 1α-mesyloxy-5β,6β-dihydroxy-cis-decalin derivative of steroid type such as c is supposed to yield, as shown in the Figure, a cis-perhydroazulene with conformation d as one of the possible products3). In this paper we should like to report formation of the latter type cis-perhydroazulene from 13.



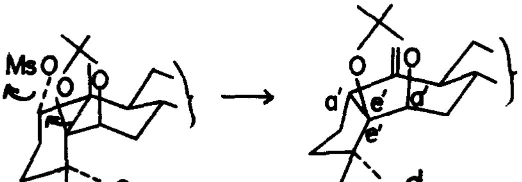
1



a

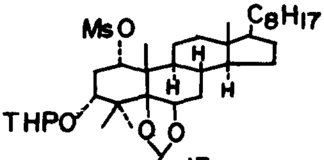


b



c

d



13

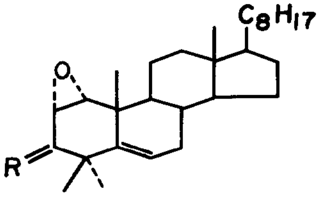
The 1α,2α-epoxyketone 2 4), m.p. 140-141°, $(\alpha)_D$+22°(c=0.82, $CHCl_3$) was obtained from 4,4-dimethylcholest-1,5-dien-3-one by treatment with alkaline hydrogen peroxide. Sodium borohydride reduction of the ketone 2 gave a mixture of two epimers, which was separated by chromatography on silica gel to give 3 and 4 in the ratio of 3 to 2; 3, m.p. 109-110°, $(\alpha)_D$ -38.6°(c=1.49, $CHCl_3$), 4, m.p. 158-159°, $(\alpha)_D$+6°(c=0.86, $CHCl_3$). The epoxyalcohol 3 was then converted into the corresponding tetrahydropyranyl ether 5, m.p. 144-145°, $(\alpha)_D$-4°(c=0.95, $CHCl_3$), and $LiAlH_4$ reduction of this compound gave 1α-hydroxyl compound 6, m.p. 148-149°,

$(\alpha)_D$+4°(c=1.02, $CHCl_3$). The α-configuration of the substituents at C-1 and C-3 of 6 was confirmed by the strong hydrogen bonding ($\Delta\nu$108cm^{-1})[5] observed in the i.r. spectrum of hydrolyzed compound 6a, m.p. 181-182°. For the conversion of the axial hydroxyl group at C-1 into an equatorial one, the alcohol 6 was oxidized at this stage with CrO_3-pyridine to a ketone, 7, m.p. 131-132°, $(\alpha)_D$-25.9°(c=1.08, $CHCl_3$), ν_{max} 1709cm^{-1}. Subsequent OsO_4 hydroxylation of the ketone afforded a diol 8, m.p. 214-216°, $(\alpha)_D$-29.7°(c=1.28, $CHCl_3$), δ 0.70(3H, s), 0.91(6H, d, J=6Hz), 0.96(3H, d, J=5Hz), 1.17(3H, s), 1.30(3H, s), 1.33(3H, s), 3.5-4.2 (4H, m), 4.6(1H, m). An A/B trans configuration for the hydroxylation product was suggested by the result of preliminary experiment of hydroxylation of 4,4-dimethylcholest-5-en-3-one with the same reagent[6]. However, the stereochemistry of 8 was disclosed to have an A/B cis juncture by study of n.m.r. spectra. The spectra of the compounds 8, 9, 10 and 11 showed respectively multiplet(W_H~6Hz in all spectra) at δ 4.16, 4.35, 4.32 and 5.38 attributable to the C-6 proton and pointed thereby to the C-6α hydrogen[7]. The diol 8 reacted with acetaldehyde and anhydrous $ZnCl_2$ to yield two ethylidene derivatives. One was a THP ether 9, amorph, $(\alpha)_D$-29°(c=1.0, $CHCl_3$), no absorption band for hydroxyl group, δ 1.43(3H, d, J=5Hz), 5.12(1H, q, J=5Hz), and the other was an alcohol 10, m.p. 190-191°, $(\alpha)_D$-33°(c=1.0, $CHCl_3$), which could be converted into 9. Lithium aluminium hydride reduction of the ketone 9 afforded, expectedly, only a single alcohol 12, amorph, $(\alpha)_D$-12°(c=1.0, $CHCl_3$). The alcohol 12 was then transformed by treatment with MsCl-pyridine into a mesylate 13, m.p. 94-96°, $(\alpha)_D$-18.8°(c=0.93, $CHCl_3$), δ 1.42(3H, d, J=5Hz), 3.05(3H, s), 3.5-4.25(4H, m), 4.5-4.9(2H, m), 5.03(1H, q, J=5Hz). Solvolysis of the mesylate 13 with t-BuOH-t-BuOK gave an approximately 1:1 mixture of olefins (14 and 15) which could not be separated at this stage. However, acid hydrolysis of the mixture gave two alcohols which were separated by chromatography on alumina. The structure of one alcohol, amorph, $(\alpha)_D$+26.7°(c=1.57, $CHCl_3$), was deduced to be 16 on the basis of spectral evidences as follows. The n.m.r. spectrum exhibited a singlet at δ 5.0(2H) attributable to exocyclic methylene protons and signals for seven methyl groups at δ 0.81 (3H, s), 0.85(3H, s), 0.99(9H, bs), 1.12(3H, s), 1.40(3H, d, J=5Hz). The i.r. spectrum also demonstrated a charactaristic bands for an exocyclic methylene group at ν_{max} 3080, 1630 and 895cm^{-1}. The other alcohol, m.p. 136-137°, $(\alpha)_D$+2°(c=1.45, $CHCl_3$), had a structure 17 produced by 1,2-elimination from 13. The n.m.r. spectrum of 17 showed a singlet at δ 5.52 (2H) attributable to C-1 and C-2 olefinic protons. This singlet signal may be caused by the accidental same chemical shifts of the two olefinic protons and by the dihedral angle of approximately 90° between C-2 and C-3 protons.

These structures were ascertained by oxidation of the alcohols. Chromium trioxide-pyridine oxidation of the alcohols 16 and 17 gave ketones 18 and 19 respectively. The i.r. spectrum of 18 indicated absorption bands at ν_{max} 3080, 1630, 900 and 1745cm^{-1} due to an exocyclic methylene group and a five membered ketone. The n.m.r. spectrum also showed the signal for an exocyclic methylene group as a singlet at δ 5.00(2H). Formation of 5,6 cis hydroxylated cis-perhydroazulene is thus accomplished. It is of interest to note the rotatory dispersion curve(a=-122 in dioxane) of 18 is quite similar to that of grayanotoxin[1,8]. On the other hand, the i.r. spectrum of 19 indicated an absorption band at ν_{max} 1680cm^{-1}, and the n.m.r. spectrum showed an AB quartet at δ 5.86 and 6.53(J=11Hz) attributable to protons on a six membered α,β-unsaturated carbonyl group. Moreover, the u.v. spectrum which showed an absorption band at λ_{max}^{EtOH} 228 mμ(ε=10700) satisfies the above mentioned structure. Detailed study of the conformation of 18 is under progress.

REFERENCES

1. T.Matsumoto and M.Watanabe, *Tetrahedron Letters*, 6019 (1968) and other references cited therein.
2. C.W.Shoppee, R.E.Lack, S.C.Sharma and L.R.Smith, *J. Chem. Soc.*, 1155 (1967).
3. In this conformation both five membered cyclopentane and dioxolane rings are fused to the cycloheptane through quasi-equatorial and quasi-axial bonds, while in the product from a each fusion is formed through two quasi-equatorial bonds(for conformational analysis of cis-perhydroazulene see J.B.Hendrickson, *J. Am. Chem. Soc.*, 83, 4537 (1961)). Since steric interaction is appreciable in d, this conformation could be distorted.
4. All numbered compounds except 14 and 15 in this communication gave correct elementary analyses. All n.m.r. spectra were measured in $CDCl_3$ at 60 Mc.
5. H.Mühle and Ch.Tamm, *Helv. Chim. Acta.*, 46, 268 (1963).
6. In this reaction the 5α,6α-configuration of hydroxyl groups was shown on the basis of the n.m.r. spectrum which indicated a multiplet at δ 4.10 with a large half-band width(18Hz) attributable to the 6β axial proton[7].
7. N.S.Bhacca and D.H.Williams, Application of NMR spectroscopy in organic chemistry. Holden-Day, San Francisco (1964).
8. H.Kakisawa, T.Kozima, M.Yanai and K.Nakanishi, *Tetrahedron*, 21, 3091 (1965).

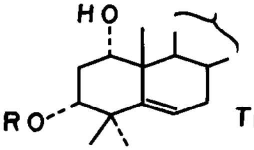


2, R = O

3, $R = {<}^{\cdots OH}_{H}$

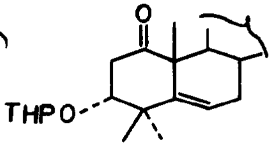
4, $R = {<}^{\cdots H}_{OH}$

5, $R = {<}^{\cdots OTHP}_{H}$

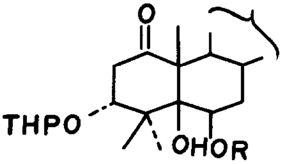


6, R = THP

6a, R = H

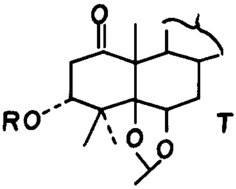


7



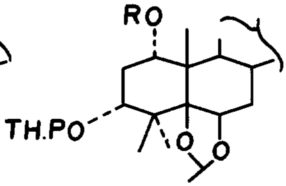
8, R = H

11, R = Ac



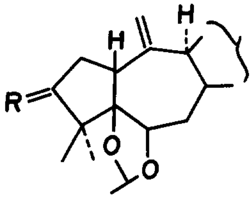
9, R = THP

10, R = H



12, R = H

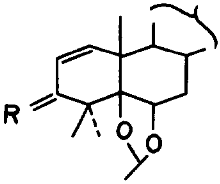
13, R = Ms



14, $R = {<}^{\cdots OTHP}_{H}$

16, $R = {<}^{\cdots OH}_{H}$

18, R = O



15, $R = {<}^{\cdots OTHP}_{H}$

17, $R = {<}^{\cdots OH}_{H}$

19, R = O