AN ENTRY INTO AN OXATWISTANE SYSTEM: INVESTIGATIONS OF CROSSWISE RING CLOSURES IN BICYCLO[2.2.2]OCTENE OR BICYCLO[2.2.2]OCTANE SYSTEMS[1)]

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Abstract--- Crosswise ring closures in bicyclo[2.2.2]octene or bicyclo-[2.2.2]octane systems were studied in order to construct an oxatwistane frame. An entry into the oxatwistane system could be achieved by either crosswise etherization of a methylbicyclooctene-methanol(20) with 12N-HCl/EtOH or intramolecular dehydration of a hydroxy-methylbicyclo-octane-methanol(25).

Among cage carbotricyclic systems, twistane(1) has received particular attention because of its characteristic structural features and remarkable geometry and thus several syntheses of this molecule have been accomplished.[2)]
In contrast, synthesis of the corresponding oxatwistane system(2) has not been recorded[3)] although those of azatwistane(3) have recently been reported.[4)]


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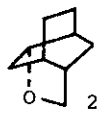

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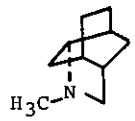

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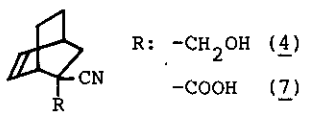
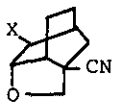
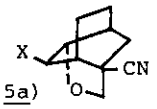
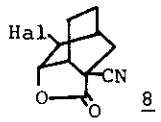
Here we wish to describe the first entry into such oxatwistane system and also some investigations of crosswise intramolecular cyclizations in bicyclo[2.2.2]octene or bicyclo[2.2.2]octanes.
Our previous attempts in the synthesis of oxacage tricyclic systems[1a)] failed in the case of oxatwistane. Thus, cyclization of a bicyclooctene-methanol(4) with N-bromosuccinimide(NBS) or $Hg(OAc)_2/NaBH_4$ gave only a frontwise cyclized product with an oxaisotwistane skeleton(5a or 5b, respectively). Photocyclization of 4 did not yield the twisted product(6b) either. Moreover, iodolactonization of a bicyclooctene-carboxylic acid(7) was also found to give only a γ-lactone(8), and no appreciable crosswise cyclized product, a δ-lactone(9a), which was expected to be an equivalent synthon for the target system.





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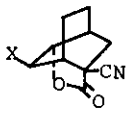

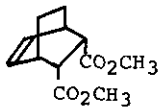
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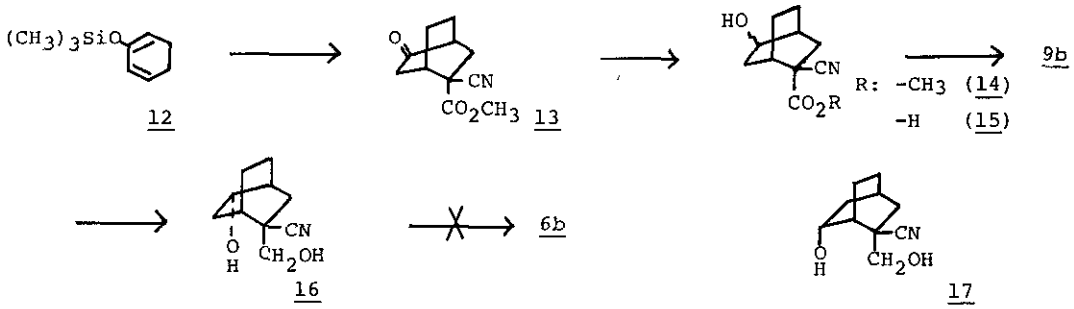
In addition to the unsuccessful results described above, we have also investigated the reaction of methyl bicyclooctene-carboxylate(10) with halogens according to a procedure reported[5] to yield both γ- and δ-lactones in the case of dimethyl bicyclooctene-dicarboxylate(11). The lactone obtained by this procedure, however, was principally the γ-lactone(8).[6]

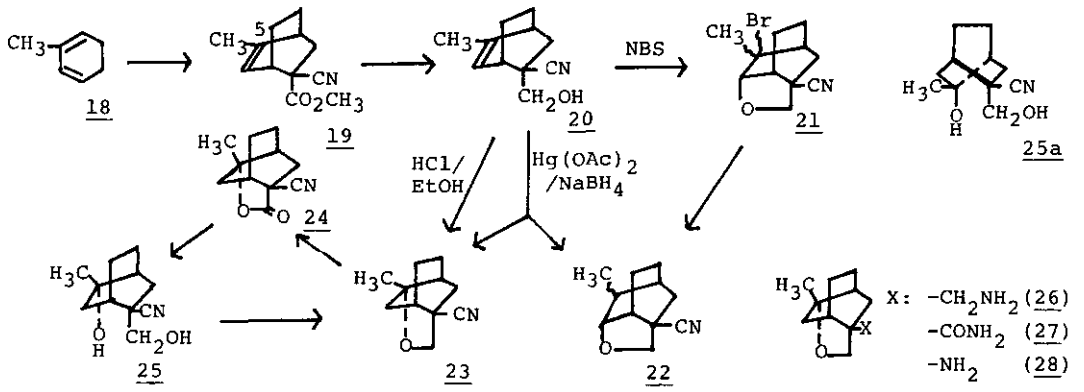
The δ-lactone(9b) was finally synthesized by an alternative route as outlined below[7] and an attempt to construct the target system(6b) from 9b was made.



Reaction of trimethylsilyloxy-cyclohexadiene(12)[8] with methyl α-cyanoacrylate was carried out by refluxing in benzene, followed by treatment with methanol to give the bicyclo[2.2.2]octanone[13, 63% from 12, mp 101-102°C, ir(KBr): 1740, 1720, nmr ($CDCl_3$): 3.8(s,3H), 2.7(m,2H), 2.5(t,H)]. Reduction of 13 with $NaBH_4$ in methanol at 0°C gave an isomeric mixture of alcohols(14, the main *endo*-isomer, mp 90-91°C), which was hydrolyzed with aq. NaOH to give the hydroxy acid(15). Treatment of 15 with triphenylphosphine-2,2'-dipyridyl disulfide[9] in toluene yielded the target δ-lactone[9b, 70% from 14, mp 198-199.5°C, ir($CHCl_3$): 1765, nmr($CDCl_3$): 4.8(t,H), 2.5(t,2H)], which was reduced with $Ca(BH_4)_2$ to give the hydroxy-bicyclooctane-methanol(16, oil, FD-Mass, m/e=181). The diol(16) was subjected to intramolecular dehydration by heating with p-toluenesulfonyl chloride(TsCl) and pyridine, but no cyclized product(6b) could be obtained although the isomeric diol(17) was

successfully cyclized under the same conditions to give the oxaisotwistane system (5b, 60% yield).[10]

Next, the same type of reactions were applied to a bicyclooctene bearing a methyl group at the 5-position(19) since it was expected that a carbonium cation would be induced favorably at the 5-position due to the methyl group.



Thus, the Diels-Alder reaction of methyl cyclohexadiene(18)[11] with methyl cyanoacrylate yielded the bicyclooctene as a main product[19, nmr($CDCl_3$): 5.7(d,H), 3.8 (s,3H), 3.0(m,H)]. Reduction of 19 with $Ca(BH_4)_2$ gave the methanol(20), which was subjected to cyclization induced by electrophiles such as NBS or $Hg(OAc)_2$. The reaction of 20 with NBS, however, yielded the frontwise cyclized bromoether(21) the structure of which was assigned after debromination of 21 to 22 with Bu_3SnH.[12] When 20 was allowed to react with $Hg(OAc)_2$ and then treated with $NaBH_4$ in dil. NaOH, an isomeric mixture of the ethers were obtained in 51% yield(the ratio, about 3:2).

The minor isomer was identical with 22,[13] and the major one was assigned to be the target ether(23) with an oxatwistane skeleton although attempts to separate 23 from the mixture failed.

The target ether(23) could be obtained in a pure form as follows: treatment of 20 with 12N-HCl/EtOH(1:1) at 80°C was found to give 23 in 24% yield[23, mp 81-83°C, nmr($CDCl_3$): 4.1(dd,H), 3.7(d,H), 1.1(s,3H)].[14] On the other hand, oxidation of 23 with $CrO_2(t\text{-}BuO)_2$ in CCl_4-AcOH-Ac_2O under reflux for 2 hr gave the δ-lactone[24 , 70%, mp 163-166°C, ir($CHCl_3$): 1765, nmr($CDCl_3$): 2.47(m,H), 1.46(s,3H)], which was reduced with $Ca(BH_4)_2$ to give the diol[25, 72%, mp 103-105°C, nmr($CDCl_3$): 1.3 (s,3H)].

Unlike the case of 16, crosswise intramolecular dehydration was found to occur by refluxing of 25 with TsCl/pyridine to give the target ether (23, 35%).

Examination of Dreiding models indicates that there would be some significant difference in conformation between 16 and 25: the most favorable conformer for 25 would be the one(25a) owing to repulsions of the methyl group to the nieghboring methylene groups, and thus the two hydroxyl groups of 25a would face closely due to their *axial*-conformations. The two hydroxyl groups of 16, on the other hand, would be comparatively far apart due to their *quasi-equatorial*-conformations in the most favorable conformer for 16. In the course of crosswise etherization of 20 to 23, there would also be a similar steric effect of the methyl group on conformations[15] in addition to its electronic effect. Thus, the results obtained here, suggest that the crosswise ring closures in bicyclo[2.2.2]octene or octane systems are disfavored mainly due to the poor proximity between the two reaction sites.[16]

Modification of the cyano group of 23 in a similar manner as reported before[1] provided a series of oxatwistane derivatives such as 26[HCl salt, mp 224-226°C (decomp.)], 27(mp 110-112°C) and 28[HCl salt, mp 235-236°C(decomp.)].[17]

REFERENCES AND NOTES

1) Heterocage Compound[III]. Part I of this series, a) Heterocycles, 1982, 19, 1419. Part II, b) ibid., 1982, 19, 1901.

2) a) H.W. Whitelock Jr., J. Am. Chem. Soc., 1962, 84, 3412; b) K. Adachi, K. Naemura and M. Nakazaki, Tetrahedron Lett., 1968, 5467; c) M. Tichy and J. Sicher, ibid., 1969, 4609; d) M. Tichy, ibid., 1972, 2001.

3) The formation of an isomeric oxatwistane system has been recorded in the following literature: N.V. Averina, G. Gleizniene, N.S. Zefirov, P. Kadziauskas and N.K. sadovaya, Zh. Org. Chem., 1974, 10, 1125. Chem. Abstr., 1974, 81, 63469c.

4) a) R. Tadayoni, T. Lacrampe, A. Heumann, R. Furstos and B. Waegell, Tetrahedron Lett., 1975, 735; b) R.W. Lockhart, K. Hanaya, F.W.B. Einstein and Y. L. Chow, Chem. Commun., 1975, 344; c) R. Furstos and B. Waegell, Tetrahedron Lett., 1976, 365; d) R. Furstos, R. Tadayoni and B. Waegell, J. Org. Chem., 1977, 42, 2844.

5) D.G. Garatt, M.D. Ryan and P.L. Beaulien, J. Org. Chem., 1980, 45, 839: Garatt et al., reported that the δ-lactone was produced more predominantly, and they assigned the δ-lactone structure to the thermodynamically more stable lactone in each case. However, conflicting results against those of D.G. Garatt have

quite recently been reported by V. Alberts et al.,; V. Alberts, D.L. Breknell, R.M. Carman and S.S. Smith, Aust. J. Chem., 1981, 34, 1719.

6) The γ-lactone was obtained in 5.4% yield with I_2, 45% with Br_2 and 43% with Cl_2; an appreciable amount of the δ-lactone could not be detected.

7) Synthesis of the δ-lactones without a cyano group from bicyclooctanones was also described by D. Davalian, P.J. Garatt and R. Riguera, J. Org. Chem., 1977, 42, 368.

8) G.M. Rubottom and J.M. Gruber, J. Org. Chem., 1977, 42, 1051.

9) E.J. Corey, D.J. Brunell and P.J. Stork, Tetrahedron Lett., 1976, 3405.

10) The diol(16) could not be cyclized under more drastic conditions(treatment of the tosylate of 16 with NaH/DMSO).

11) M. Mousseron and F. Winternits, Bull. Soc. Chim. Fr., 1964, [V] I, 13, 232.

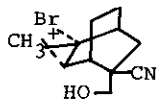
12) The product was found to be an epimeric mixture(67:33): the major epimer was assumed to be an *endo*-methyl- and the minor one an *exo*-methyl-oxaisotwistane. The methyl signals in their nmr(C_6D_6) appeared at δ 0.75 and 0.65 as a doublet, respectively.

13) Mainly the *endo*-methyl epimer.

14) The methanol(4) could not be cyclized under the same conditions.

15) A similar steric effect was exemplified in reference 7.

16) Strictly speaking, the proximity between the two reaction sites in the transition state is thought to be important. Thus, the difference between the cases of NBS and $Hg(OAc)_2/NaBH_4$ in the cyclization of 20 might be explained by assumption of the difference in the type of the intermediate in the transition state. Thus, in the course of the cyclization with NBS, a fairly stable bridged(triangled) bromonium ion would be accepted as its probable intermediate(29), rigid feature of which would not allow the crosswise cyclization due to the poor proximity. On the other hand, in the case of $Hg(OAc)_2$, the intermediate would be a more loose bridged ion(or a classical carbonium ion), loose feature of which would allow both cyclizations leading to both frontwise and crosswise cyclized products.



(29)

17) The amines(26 and 28) were found to have a significant antiviral(influenza A) activity similar to amantadine, but negligible CNS effects.[1a)]

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