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Oxidation of Cyclododecane-1,5,9-triol

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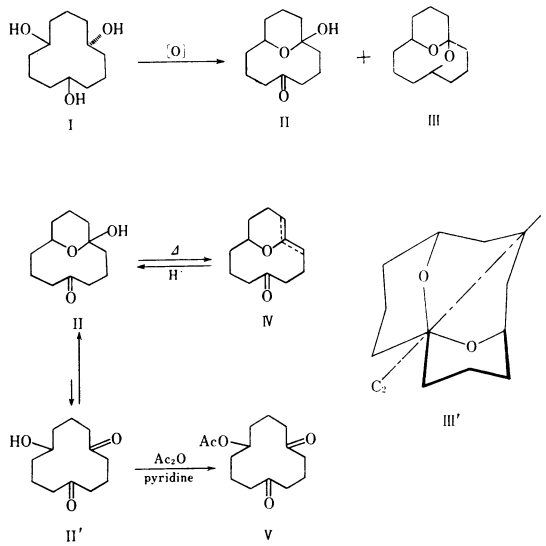
Although transannular reactions of 8-10-membered cyclic compounds have been well investigated,[1] few examples have been reported on cyclododecane derivatives.[2] The present paper deals with a new transannular interaction in the oxidation of *cis,cis,trans*-cyclododecane-1,5,9-triol (I).[3]

Oxidation of I by the Brown procedure (sodium dichromate-sulfuric acid-ether) gave a hemiacetal (II) and an acetal (III) (II : III=43 : 57). The product ratio was considerably changed (II : III= 74 : 26) in the Cornforth oxidation (chromium-(VI) oxide-pyridine-water) of I. No detectable amount of cyclododecane-1,5,9-trione was obtained in each case. Facile formation of six-membered cyclic acetals seems to prevent the oxidation from proceeding to the stage of trione.

Compound II exhibited IR absorptions at 3490 (ν_{O-H}) and 1697 cm^{-1} ($\nu_{C=O}$) and was dehydrated quite easily on distillation and/or gas chromatography to give the corresponding enol ether (IV) (1710 and 1677 cm^{-1}). The reverse hydration of IV afforded the starting compound II. Acetylation of II with acetic anhydride yielded 9-acetoxycyclododecane-1,5-dione (V). The structure of V was shown to be monocyclic, since its NMR spectrum exhibited the signal of a methine proton adjacent to acetoxyl group at δ 4.47 ppm. Consequently, compound II must be the intramolecular hemiacetal of 9-hydroxycyclododecane-1,5-dione (1-hydroxy-13-oxabicyclo[7.3.1]tridecan-5-one), which is in equilibrium with monocyclic hydroxydione II′ affording V on acetylation.

Another oxidation product (III) exhibited IR absorptions between 1250—900 cm^{-1} attributable to ethereal function. The absence of carbonyl group was proved by the IR spectrum. The parent peak at *m/e* 196 in the mass spectrum and the elementary analysis established the molecular formula of $C_{12}H_{20}O_2$. The NMR spectrum in carbon tetrachloride showed the signal of the methylene protons as a complex multiplet. Hence, III was concluded to be the intramolecular acetal of 5,9-dihydroxycyclododecanone (13,14-dioxatricyclo[7.3.1.$1^{1,5}$]tetradecane). Although the stereochemistry of III is not certain at present, the strainless configuration of C_2 symmetry (III′) may be preferred on the basis of the Dreiding model.



Experimental

Oxidation of *cis,cis,trans*-cyclododecane-1,5,9-triol (I). *(a) Brown's Oxidation.*[4] To a mixture of I (5.41 g, 25 mmol), water (25 m*l*) and ether (100 m*l*)

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2) a) B. Camerino and B. Patelli, *Experientia*, **20**, 260 (1964). b) L. A. Paquette and M. L. Wise, *Tetrahedron*, **24**, 2937 (1968). c) T. Mori, K. Matsui and H. Nozaki, This Bulletin, **43**, 231 (1970).

3) a) G. W. Rotermund and R. Köster, *Ann. Chem.*, **686**, 153 (1965). b) H. C. Brown and W. C. Dickason, *J. Amer. Chem. Soc.*, **91**, 1226 (1969).

4) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).

a mixture of sodium dichromate dihydrate (5.00 g, 17 mmol), 95% sulfuric acid (3.80 m*l*) and water (23 m*l*) was added dropwise for 20 min at 0°C. Stirring was continued for an additional 2 hr. The ether layer was separated and the aqueous layer was extracted twice with ether. The combined extracts were washed with aqueous sodium hydrogen carbonate and then with water, dried over sodium sulfate and concentrated *in vacuo* to give a crude mixture (4.50 g) of II and III. The ratio (II : III=43 : 57) was determined by gas chromatography (High Vacuum Silicone Grease 30% on Celite 545, 190°C). The two components were separated through a silica gel column using benzene as a solvent. The first elute was the acetal (III) (1.39 g, 28%), bp 137°C/21 mmHg. IR (neat): 1220, 1209, 1160, 1124, 1096, 1040, 1006, 962, 934, 899 and 870 cm^{-1}. NMR (CCl_4): δ 4.5—3.6 (2H, multiplet, O–CH) and 2.8—1.1 (18H, fine-structured multiplet). MS *m/e* 196 (M^+).

Found: C, 73.2; H, 10.2%. Calcd for $C_{12}H_{20}O_2$: C, 73.4; H, 10.3%.

The second elute was the hemiacetal(II) (1.21 g, 23%) as large plates, mp 54—56°C. IR (Nujol): 3490, 1697, 1320, 1237, 1206, 1180, 1158, 1141, 1118, 1086, 1046, 1017, 970, 958, 936 and 902 cm^{-1}. NMR (CCl_4): δ 4.1—3.4 (1H, multiplet, O–CH), 3.4—3.1 (1H, broad, OH) and 3.0—1.1 (18H, multiplet).

Found: C, 67.4; H, 9.5%. Calcd for $C_{12}H_{20}O_3$: C, 67.9; H, 9.5%.

Gas chromatographic separation (High Vacuum Silicone Grease, 30% on Celite 545, 198—225°C) of II resulted in dehydration to give IV as an oil, bp 115°C (bath temperature)/1 mmHg. IR (neat): 1710, 1678, 1302, 1225, 1183, 1155, 1082, 1050, 956 and 906 cm^{-1}. NMR (CCl_4): δ 4.5—4.3 (1H, multiplet, OC=CH) and 4.0—1.1 (17H. multiplet). MS *m/e* 194 (M^+).

Found: C, 74.2; H, 9.4%. Calcd for $C_{12}H_{18}O_2$: C, 74.2; H, 9.3%.

(b) Cornforth's Oxidation.[5] To cooled pyridine (300 m*l*) was added an aqueous solution (25 m*l*) of chromium(VI) oxide (33.0 g, 0.33 mol) and then a solution of I (10.8 g, 0.050 mol) in pyridine (50 m*l*) during 10 min. Stirring was continued for an additional 30 min at 0°C and the mixture was allowed to stand at room temperature for 2 days. The mixture was poured into water and extracted with ether. The ether extracts were combined, washed successively with water, 5% hydrochloric acid and aqueous sodium hydrogen carbonate, and dried over sodium sulfate. After concentration, the residue (5.18 g) was subjected to gas chromatography (II : III=74 : 26).

Hydration of IV. A solution of IV (0.1 g) in ether (15 m*l*) and 5% hydrochloric acid (10 m*l*) were stirred overnight at room temperature. The aqueous layer was extracted with ether and dried over sodium sulfate. Evaporation of the solvent gave hemiacetal II which was identical with the authentic sample.

9-Acetoxycyclododecane-1,5-dione (V). A mixture of II (4.77 g, 22 mmol), acetic anhydride (15 m*l*) and pyridine (20 m*l*) was stirred at 100°C for 3 days. The reaction mixture was diluted with water (200 m*l*) and extracted with ether. The combined ether extracts were washed successively with water, 5% hydrochloric acid, aqueous sodium hydrogen carbonate and water. Drying over sodium sulfate and subsequent concentration gave the crude product (4.14 g) which was subjected to chromatographic separation on a silica gel column with benzene as a solvent. After the recovered hemiacetal (0.52 g, 11%) was eluted, the product (V) (2.03 g, 36%) was obtained as needles (*n*-hexane), mp 81—82°C. IR (CCl_4): 1737, 1711 and 1244 cm^{-1}. NMR (CCl_4): δ 4.6—4.2 (1H, multiplet, AcO-CH), 2.7—1.1 (18H, multiplet+singlet (δ 1.93, OAc)).

Found: C, 66.1; H, 8.9%. Calcd for $C_{14}H_{22}O_4$: C, 66.1; H, 8.7%.

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5) R. H. Cornforth, J. W. Cornforth and G. Popjàk, *Tetrahedron*, **18**, 1351 (1962).