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Ring Opening Reactions of Dispiro[5.0.5.1.]trideca-1,5,8,12-tetraone

I. Reactions with Methanol and Ethanol[1]

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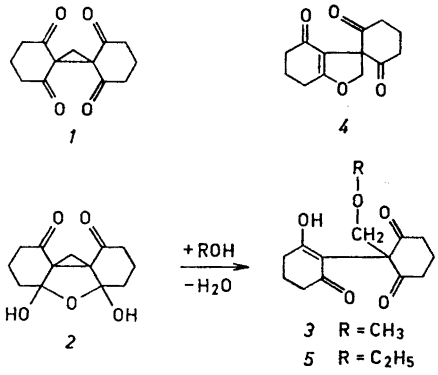
Dispiro[5.0.5.1.]trideca-1,5,8,12-tetraone undergoes ring opening addition reactions with methanol and ethanol in the dark and in the absence of catalyst. The alcohols exclusively attack the methylene group of the cyclopropyl ring.

The cyclopropane derivative, dispiro[5.0.5.1.]trideca-1,5,8,12-tetraone (*1*) which is obtained as its monohydrate *2* by intramolecular oxidative coupling of methylene-bis-1,3-cyclohexanedione as previously described [2,3] was found to react with ethanol even at room temperature and in the absence of catalyst.[3] The reaction which has now been studied in detail with methanol and ethanol was found to involve opening of the cyclopropane ring with formation of one free enolic hydroxyl group. The experiments, which were performed



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in order to establish the reactive site of the cyclopropyl ring in *1*, were carried out with the more readily available monohydrate *2*.

When compound *2* was refluxed with methanol for 24 h in the dark a single reaction product, $C_{13}H_{15}O_4(OCH_3)$, was formed by the addition of one molecule of methanol. The product shows IR bands at 1710 and 1630 cm^{-1} attributed to an isolated carbonyl group and an enone system, respectively. The UV spectrum indicates the presence of one enolisable 1,3-cyclohexanedione ring.[4] The NMR spectrum shows a singlet at δ 3.41 (3H) assigned to a methoxy group. An AB quartet (3.97 and 4.15 ppm, $J_{AB} = 10$ cps) collapsing into a singlet on the addition of trifluoroacetic acid is attributed to a methylene group between an ether function and a 1,3-cyclohexanedione ring. The residual protons appear at δ 6.30 (1H, OH) and as a poorly resolved multiplet in the region δ 1.6 – 2.8 (12 H). This NMR spectrum is consistent only with an addition product with structure *3*, resulting from an initial attack of the alcohol on the methylene group. The alternative point of attack, on the spiro-carbon, would yield a product with a methylene bridge between two 1,3-cyclohexanedione rings. Methylene bridge protons of that type appear around δ 3.1 – 3.2.[3,5] A tentative explanation for the non-equivalence of the methylene protons at δ 3.97 and δ 4.15 is that the rotation of the CH_2-group is restricted due to a hydrogen bond between the enol hydroxyl group and the ether group.

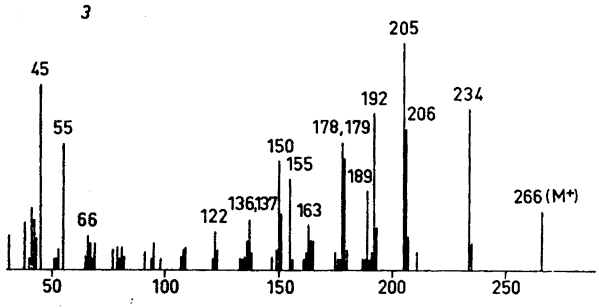

Fig. 1.

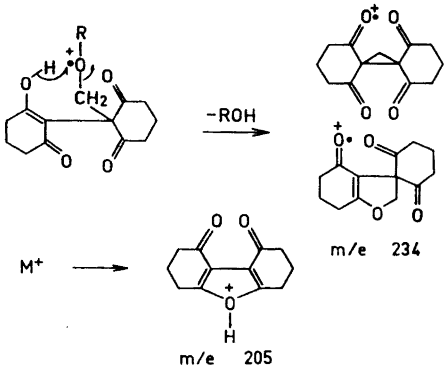

Fig. 2.

Further support for the assigned structure *3* was given by the mass spectrum (Fig. 1). The major fragmentation sequence (Fig. 2) starts with elimination of methanol to give *m/e* 234. This fragment is formulated as a mixture of the molecular ions of *1* and its isomer *4* [5] because of the close relationship between the mass spectrum of *3* (Fig. 1) and the mass spectra of *1*(Fig. 3) and *4* (Fig. 4).

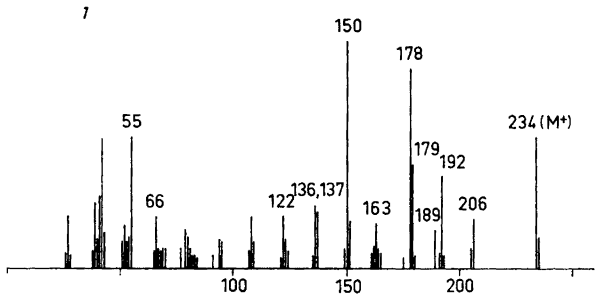

Fig. 3.

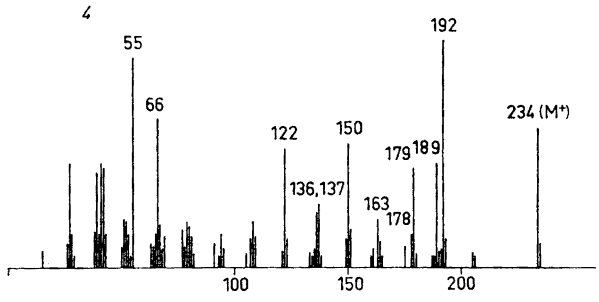

Fig. 4.

Deuterium labeling with CH_3OD shows that the enolisable proton is eliminated with the alcohol.

Three abundant fragments in the spectrum of *3* cannot, however, be related to the spectra of *1* and *4*, *viz.* *m/e* 45, *m/e* 155, and *m/e* 205. The presence of the peak *m/e* 45, which is virtually absent in the spectra of related *β*-dicarbonyl derivatives,[6] confirms the structural unit CH_3OCH_2-. The fragment *m/e* 155 is most likely formed through fission of the C–C bond between the rings.

The composition $C_{12}H_{13}O_3$ of the base peak *m/e* 205 has been verified by high resolution measurements. This fragment is formulated as a protonated furan derivative (Fig. 2), but its formation cannot easily be explained. The peak is shifted by one mass unit on deuteration with CH_3OD.

The ethanol addition product, $C_{15}H_{20}O_5$, shows IR, UV, NMR and mass spectra with striking similarities to those of *3* and was assigned the homologous structure *5*. In the NMR spectrum the ethoxy group gives rise to a triplet

($J = 7$ cps) at δ 1.14 (3H) and a quartet ($J = 7$ cps) at δ 3.53 (2H). The methylene protons between the ether group and the 1,3-cyclohexanedione ring exhibit an AB pattern similar to that shown by *3* with the absorption positions for protons A and B centered at δ 4.01 and δ 4.19 ($J_{AB} = 10$ cps), respectively. The hydroxyl proton appears at δ 6.38 (1H) and the remainder of protons give rise to a poorly resolved multiplet at δ 1.6–2.8 (12H).

The mass spectral fragmentation patterns are the same as outlined for compound *3* with *m/e* 45 and *m/e* 155 shifted to *m/e* 59 and *m/e* 169, respectively (Fig. 5).

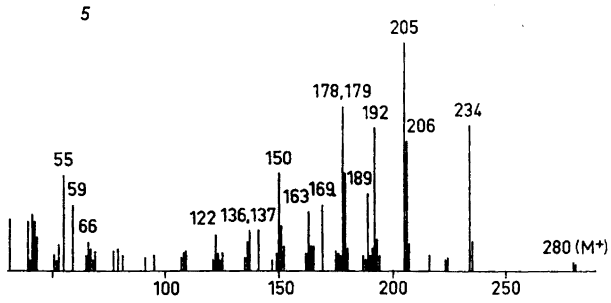

Fig. 5.

It is noteworthy that neither *3* nor *5* gives a doublet in the IR spectrum in the region 1700–1750 cm^{-1} typical for many 2,2-disubstituted 1,3-cyclohexanediones.[3,7]

The results presented show that the dispirocyclopropane derivative *1* undergoes ring opening addition reactions in the dark and under neutral conditions with methanol and ethanol, which exclusively attack the methylene group.

Similar ring openings of cyclopropane derivatives activated through the introduction of electron-withdrawing substituents on the ring have been reported in several cases.[8–18] The reactions have mostly been performed under strongly basic conditions and at elevated temperatures. The mechanism suggested for this type of reaction involves an initial nucleophilic attack on one of the carbon atoms of the ring to form a stabilized open-chain carbanion.[14]

Cyclopropyl rings which are incorporated into highly strained polycyclic systems show still greater reactivity.[19,20] Thus, Dauben and Willey [19] describe a cyclopropyl derivative obtained by irradiation of $\Delta^{3,5}$-cholestadiene which reacts with ethanol even at room temperature in the dark. Gassman [21] attributes this extraordinary reactivity to a so-called "twist" bent cyclopropyl bond which is thought to have less orbital overlap than normal cyclopropyl "symmetrically" bent bonds.

It has also been reported that protic compounds such as methanol, water, and acetic acid add to cyclopropyl derivatives in a heterolytic fashion under photochemical conditions.[22]

Further studies on the ring opening reactions of *1* are in progress.[5]

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. IR spectra were recorded on a Perkin-Elmer No. 221 or a 257 instrument. UV spectra were measured in 99.5 % ethanol with a Beckman DK 2 spectrophotometer. The NMR spectra were obtained on a Varian A-60 spectrometer using 10 % $CDCl_3$ solutions with tetramethylsilane as internal standard. Chemical shifts are given in δ(ppm) units. The mass spectra were recorded on an LKB 9000 instrument. The microanalyses were performed at A. Bernhardt, Microanalytisches Laboratorium, Elbach über Engelskirchen, West Germany.

Chromatographic investigations. All reactions were followed by TLC on silica gel HF plates with 1,2-dichloroethane-methanol in different proportions as solvents. The spots were detected as earlier described.[3]

Addition of methanol to the hydrate 2. The hydrate *2* (400 mg, 1.6 mmol) was refluxed in methanol (25 ml, *p.a.*). After 24 h when all crystalline material had dissolved, the solvent was removed and the solid residue recrystallized from ethanol to yield the enol *3* (340 mg, 80 %) as plates, m.p. 154—155°C, λ_{max} in acidic solution 264 nm (ε 12 500), λ_{max} in basic solution 288 nm (ε 20 000), ν_{max} ($CHCl_3$) 3380 (br), 1710 (s), 1630 (s), 1400, 1163 cm^{-1}. (Found: C 63.2; H 6.85; O 30.2; OCH_3 12.1. $C_{13}H_{15}O_4(OCH_3)$ requires C 63.2; H 6.81; O 30.0; OCH_3 11.7).

Addition of ethanol to the hydrate 2. The hydrate *2* (252 mg, 1.0 mmol) was refluxed in ethanol (10 ml, abs.) for 65 h. The solvent was removed and the solid residue recrystallized from ethyl acetate to yield the enol *5* (231 mg, 83 %) as needles, m.p. 129—130°C, λ_{max} in acidic solution 263 nm (ε 13 100), λ_{max} in basic solution 287 nm (ε 19 000), ν_{max} ($CHCl_3$) 3340 (br), 1712 (s), 1628 (s), 1397, 1164 cm^{-1}. (Found: C 64.2; H 7.16; O 28.7. $C_{15}H_{20}O_5$ requires C 64.3; H 7.19; O 28.5).

4,5,6,7-Tetrahydro-spiro[benzofuran-3(2H),1'-cyclohexane]-2',4,6'-trione (4). Compound *4* was prepared in this laboratory as described elsewhere.[5]

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