Tetrahedron. Vol. 32, pp. 2113 to 2115 Pergamon Press 1976. Printed in Great Britain

THERMAL REARRANGEMENT OF 2-OXABICYCLO[2.2.2]OCT-5-ENO-3-CARBOXYLIC ACIDS

O. ACHMATOWICZ JR.,* J. JURCZAK and J. S. PYREK
Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warszawa, Poland

(*Received in the UK* 17 *February* 1976; *Accepted for publication* 8 *March* 1976)

Abstract—The decarboxylation of 2-oxabicyclo[2.2.2]oct-5-eno-3,3-dicarboxylic acid, obtained by hydrolysis of the Diels–Alder adduct of diethyl mesoxalate with cyclohexa-1,3-diene, gave two stereoisomeric γ-lactones of 2-hydroxy-1,2,5,6-tetrahydromandelic acid.

INTRODUCTION

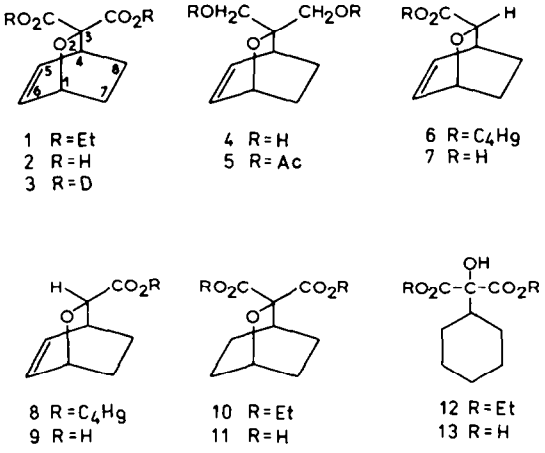
Reactions of ethyl mesoxalate and butyl glyoxylate with cyclohexa-1,3-diene yield esters of 2-oxabicyclo[2.2.2]oct-5-ene-3,3-dicarboxylic[1] and 3-carboxylic[2] (endo and exo) acids, respectively. It was later suggested that butyl glyoxylate gives also products of the ene reaction.[3] Examples of the ene reaction with dienes are not common and are limited to ethyl azodicarboxylate,[4] benzyne,[5] and singlet oxygen.[6] Examples of the ene reaction with dienophiles with active C=O groups are not known.[7] Therefore it appeared to be of interest to re-examine products arising from the reaction of butyl glyoxylate, and the related dienophile ethyl mesoxalate, with cyclohexa-1,3-diene.

We have found that thermal condensation of butyl glyoxylate and cyclohexa-1,3-diene gives solely products of the Diels–Alder reaction.[8] It has been also demonstrated that compounds which seemingly were derived from the products of the ene reaction,[3] namely esters of di- and hexahydromandelic acid, resulted from splitting of the allylic ether linkage in the 2-oxabicyclo[2.2.2]oct-5-ene system by acids and during catalytic hydrogenation, respectively.[8] In the present paper we describe analogous transformations of the ethyl mesoxalate and cyclohexa-1,3-diene adduct as well as thermal rearrangement of 2-oxabicyclo[2.2.2]oct-5-ene system with one or two carboxylic groups at C-3.

RESULTS AND DISCUSSION

Diethyl mesoxalate heated in a sealed tube at 120°C with cyclohexa-1,3-diene afforded the diethyl ester of 2-oxabicyclo[2.2.2]oct-5-ene-3,3-dicarboxylic acid **1**[1] as a single product (TLC). Reduction of **1** with lithium aluminium hydride gave diol **4**, and catalytic hydrogenation afforded two products in ratio 3:1. The latter on the basis of their analytical and spectral data were identified as dihydro derivative **10** and diethyl cyclohexyltartronate **12**. The structures of compounds **10** and **12** were confirmed by hydrolysis and decarboxylation which resulted in 2-oxabicyclo[2.2.2]oct-3-carboxylic and hexahydromandelic acid, respectively, identical with those obtained by catalytic hydrogenation and subsequent hydrolysis of adducts **6** or **8**.[8]

Alkaline hydrolysis of adduct **1** gave dicarboxylic acid **2**, which was characterized as its monohydrate. Attempted preparation of monocarboxylic acid endo **7** and/or exo **9** from **2** by decarboxylation failed. Though compounds **7** and **8** sublimed readily in vacuum without decomposition, dicarboxylic acid **2** heated above its m.p. under reduced pressure underwent decarboxylation with concomitant opening of the bicyclic moiety. From the reaction mixture two compounds, **14** and **15** in the ratio 9:1, were isolated by column chromatography. The same compounds could be obtained by heating endo **7** and exo **9** acids at 150°C under atmospheric pressure. The endo acid **7** was quantitatively converted into the major decarboxylation product **14**, whereas exo acid **9** gave minor decarboxylation product **15**.



1 R=Et
2 R=H
3 R=D

4 R=H
5 R=Ac

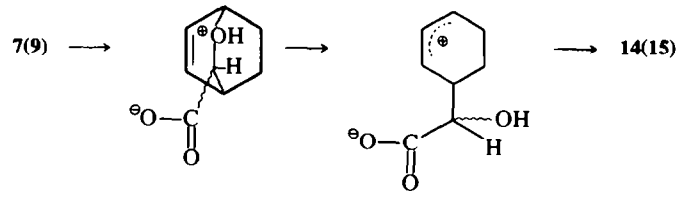
6 R=C_4H_9
7 R=H

8 R=C_4H_9
9 R=H

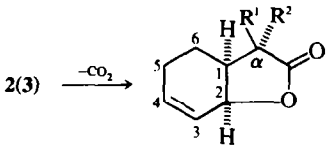
10 R=Et
11 R=H

12 R=Et
13 R=H

Both compounds **14** and **15** analysed correctly for $C_8H_{10}O_3$ and their IR spectra indicated the presence of hydroxyl group, double bond and 5-membered lactone. In their ^{1}H-NMR spectra, signals appeared corresponding to two vinyl and four aliphatic protons. Three other signals could be assigned to $\rangle$CHOCO, –CH/OH/CO and $\rangle$CH groupings. On the basis of the above data the structures of stereoisomeric lactones **14** and **15** were ascribed to the decarboxylation products of acid **2**. They arose from the acid **7** and **9** as the results of an allylic ether cleavage followed by the closure of the favorable γ-lactone ring probably via an allylic carbocation:



In the case of the acid **2** decarboxylation preferably on the exo-side proceeds that rearrangement:



14: $R^1 = OH$, $R^2 = H$
15: $R^1 = H$, $R^2 = OH$
16: $R^1 = OH$, $R^2 = D$
17: $R^1 = D$, $R^2 = OH$

The configuration of the hydroxyl group in lactones **14** and **15** followed from their correlation with acid **7** and **9**, respectively. Constitution and configuration of both lactones were assigned on the basis of the coupling constants in their ^{1}H–NMR spectra. Also their preferred conformations were deduced.

Coupling constants and unequivocal signal assignment was achieved by extensive decoupling experiments in the spectra of lactones **14** and **15** as well as their d_1-derivatives **16** and **17**. The latter were obtained by decarboxylation of d_2-acid **3**.

In the ^{1}H–NMR spectrum of lactone **15** large coupling constants $J_{1\alpha} = 9.5$ Hz and $J_{12} = 7.5$ Hz indicated *trans*-axial relation of H-1 and H-α, and very small torsion angle between C–(H-1) and C–(H-2) bonds. The signal of H-2 was a doublet (splitting 7.5 Hz) of poorly-resolved quartets with about 7.5 Hz half-height width each. These quartets are probably due to the small, nearly equal vicinal, allylic and homoallylic couplings of H-2 with H-3, H-4 and H-5pax, respectively. The foregoing coupling constants are consistant with pseudoaxial position of H-2. Finally, small values of $J_{1\delta}$ and $J_{1\delta'}$ show that (C-1)–H bond bisects angle between H-6 and H-6'. These data support the assigned structure of lactone **15** in conformation **19**.

In the ^{1}H–NMR spectrum of lactone **14** $J_{1\alpha} = 7.5$ Hz, smaller than analogous value for lactone **15**, indicated *cis* arrangement of H-1 and H-α. From the couplings $J_{12} = 4.4$ Hz and $J_{23} = 4.6$ Hz it was inferred that torsional angle between H-1 and H-α is small, however larger than corresponding angle in lactone **15**, and that H-2 is pseudoequatorial (relatively to the 6-membered ring). The exceptionally large coupling $J_{16a} = 13.6$ Hz pointed to the *trans*-diaxial relation of H-1 and H-6a. On the basis of the foregoing data for, lactone **14** followed conformation **18**, consistent with the upfield shift of H-6a due to its relative location to the double bond. Presently reported facile thermal rearrangement of 2-oxabicyclo[2.2.2]oct-5-eno-3-carboxylic and 3,3-dicarboxylic acids, readily available from the Diels–Alder adducts of glyoxylic or mesoxalic acid esters, could be utilized as a convenient entry to the synthesis of some sesquiterpene lactones.[9]

EXPERIMENTAL

B.ps refer to air-bath temperatures. M.ps (uncorrected) were determined on a Kofler block. The ^{1}H–NMR spectra were obtained on a Varian HR-60/IL unit at 60 MHz and on a Jeol JNM-100-4H instrument at 100 MHz. The IR spectra were taken with a Unicam SP-200 spectrophotometer on films for liquids and KBr discs for solids. For column chromatography silica gel Merck (0.05–0.2 mm or under 0.08), and for TLC silica gel G (Merck) were used. Solutions were dried over anhydrous $MgSO_4$ and solvents were removed under reduced pressure on a rotary evaporator. All reactions and chromatographic separations were monitored in TLC and/or ^{1}H–NMR.

Diethyl ester of 2-oxabicyclo[2.2.2]oct-5-ene-3,3-dicarboxylic acid **1**

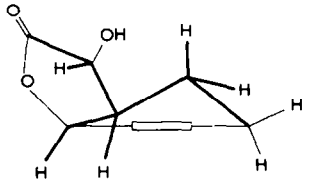
A mixture of diethyl mesoxalate (27.6 g, 0.15 mole) and cyclohexa-1,3-diene (13.0 g, 0.163 mole) was heated in a sealed tube at 120°C for 24 h. Distillation of the reaction mixture gave **1** (33.0 g, 86.5%) b.p. 120–124°C/0.4 torr. Found: C, 61.45; H, 7.25. $C_{13}H_{18}O_5$ requires: C, 61.40; H, 7.14%. IR: 1742 (C=O), 1260, 1220 (C–O–C ester), 1085, 1070 (C–O–C ether), 705 cm^{-1} (*cis* CH=CH); ^{1}H–NMR ($CDCl_3$): δ6.6–6.3 (m, 2H, H-5 and H-6), 4.65 (m, 1H, H-1), 4.25 and 4.15 (2 × q, 2 × 2H, 2 × $CO_2CH_2CH_3$), 3.40 (m, 1H, H-4), 2.3–1.4 (m, 4H, H-7 and H-8), 1.30 and 1.25 (2 × t, 2 × 3H, 2 × $CO_2CH_2CH_3$).

3,3-*Dihydroxymethyl-2-oxabicyclo*[2.2.2]*oct-5-ene* **4**

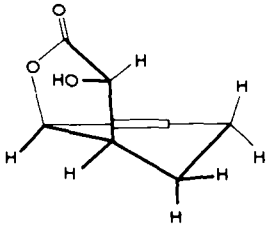
Lithium aluminium hydride reduction of **1** in ether solution at room temp. and work-up yielded **4** (85%) b.p. 107°C (0.4 torr). Found: C, 63.41; H, 8.25, $C_9H_{14}O_3$ requires: C, 63.51; H, 8.29%; IR: 3400 (OH), 1050, 1020 (C–O–C ether), 720 cm^{-1} (*cis* CH=CH); ^{1}H–NMR ($CDCl_3$): δ6.6–6.25 (m, 2H, H-5 and H-6), 4.35 (m, 1H, H-1), 3.65 and 3.35 (AB system and s, 2 × 2H, 2 × CH_2O), 2.75 (m, 1H, H-4), 2.1–1.1 (m, 4H, H-7 and H-8).

3,3-*Diacetoxymethyl-2-oxabicyclo*[2.2.2]*oct-5-ene* **5**

Treatment of **4** with a mixture of pyridine-acetic anhydride (1:1) at room temp. followed by the usual work-up, gave **5** (91%) b.p. 111°C/0.4 torr. Found: C, 61.27; H, 7.14, $C_{13}H_{18}O_5$ requires: C, 61.40; H, 7.14%; IR: 1740 (C=O), 1250 (C–O–C ester), 1040 (C–O–C ether), 702 cm^{-1} (*cis* CH=CH); ^{1}H–NMR ($CDCl_3$): δ6.55–6.3 (m, 2H, H-5 and H-6), 4.41 (m, 1H, H-1)), 4.15 (AB, 2H,



18



19

CH_2O), 3.85 (s, 2H, CH_2O), 2.65 (m, 1H, H-4), 2.08 and 2.02 (2 × s, 2 × 3H, 2 × $OCOCH_3$), 2.1–1.1 (m, 4H, H-7 and H-8).

Catalytic hydrogenation of adduct **1**. *Diethyl esters of 2-oxabicyclo[2.2.2]octa-3,3-dicarboxylic acid* **10** *and cyclohexyltartronic acid* **12**

Platinum oxide (50 mg) was suspended in ethyl acetate (20 ml) and shaken under hydrogen; after 0.5 h adduct **1** (0.7 g) in ethyl acetate (20 ml) was added and shaking was continued till absorption ceased. The reaction mixture comprised two compounds (TLC) which were separated by column chromatography. Elution with benzene–ether (95:5) gave **12** (0.12 g, 17%) b.p. 130°C/0.1 torr. Found: C, 60.34; H, 8.44, $C_{13}H_{22}O_5$ requires: C, 60.44; H, 8.59%; IR: 3500 (OH), 1740 (C=O), 1240, 1220 cm^{-1} (C–O–C ester); ^{1}H-NMR ($CDCl_3$): δ 4.25 (q, 4H, 2 × CO_2CH_2 CH_3), 2.30 (m, 1H, CH), 1.9–1.1 (m, 10H, 5 × CH_2), 1.30 (t, 6H, 2 × $CO_2CH_2CH_3$), and subsequently **10** (0.37 g, 53%) b.p. 139°C/0.6 torr. Found: C, 60.86; H, 7.82, $C_{13}H_{20}O_5$ requires: C, 60.92; H, 7.87%; IR: 1740 (C=O), 1200 (C–O–C ester), 1065 cm^{-1} (C–O–C ether); ^{1}H-NMR ($CDCl_3$): δ 4.24 (q, 4H, 2 × $CO_2CH_2CH_3$), 4.10 (m, 1H, H-1), 2.47 (m, 1H, H-4), 2.2–1.2 (m, 8H, H-5, H-6, H-7 and H-8), 1.29 (t, 6H, 2 × $CO_2CH_2CH_3$).

Hydrolysis of esters **10** and **12** carried out as in case of **1**, and subsequent decarboxylation of resulting acids **11** and **13**, afforded 2-oxabicyclo[2.2.2]octa-3-carboxylic and hexahydromandelic acid, respectively, identical with the samples obtained previously.[8]

2-Oxabicyclo[2.2.2]oct-5-eno-3,3-dicarboxylic acid **2**

Ester **1** dissolved in 5% methanolic KOH, left for 12 h at room temperature, neutralized with Amberlite CG-50 (100–200 mesh, form H^+), then evaporated gave quantitative yield of **2** m.p. 127–130°C after recrystallization from ethanol–water. Found: C, 50.00; H, 5.54, $C_9H_{10}O_5 \cdot H_2O$ requires: C, 50.00; H, 5.60%; IR: 3330, 3100 (OH), 1760, 1725 cm^{-1} (CO_2H); ^{1}H-NMR ($CDCl_3$): δ6.6–6.4 (m, 2H, H-5 and H-6), 4.7 (m, 1H, H-1), 3.45 (m, 1H, H-4), 2.2–1.2 (m, 4H, H-7 and H-8).

Deuterated acid **3** was obtained by exchange with D_2O: for 1 g of **2**, 6 × 0.5 ml of D_2O; IR: 2600, 2280 cm^{-1} (OD).

Decarboxylation of acid **2**. *Lactones* **14** *and* **15**

Acid **2** (1 g, 5 mmole) heated at 140°C/0.3 torr (sublimation) gave product comprising two compounds (TLC) which were separated by column chromatography. Elution with benzene–ether (9:1) afforded first lactone **15** (65 mg, 8.5%) m.p. 97–99°C. Found: C, 61.97; H, 6.54, $C_9H_{10}O_3$ requires: C, 62.32; H, 6.54%; IR: 3500 (OH), 1760 (5-membered lactone), 1640 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$): δ5.95 (m, 1H, H-4), 5.77 (m, 1H, H-3), 4.98 (m, 1H, H-2), 4.29 (d, 1H, H-α), 2.70 (m, 1H, H-1), 2.35–1.50 (m, 4H, H-5a, H-5e, H-6a and H-6e). $J_{1\alpha}$ = 9.5 Hz, J_{12} = 7.5 Hz, $J_{16} \sim J_{16'}$ = 3.8 Hz, J_{34} = 10.0 Hz. Further elution with the same solvent gave lactone **14** (590 mg, 77%) m. p. 88–90°C. Found: C, 62.55; H, 6.83. $C_9H_{10}O_3$ requires: C, 62.32; H, 6.54%; IR: 3500 (OH), 1760 (5-membered lactone), 1640 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$): δ6.20 (m, 1H, H-4), 5.90 (m, 1H, H-3), 4.72 (d, 1H, H-α), 4.70 (t, 1H, H-2), 2.70 (m, 1H, H-1), 2.45–1.70 (m, 3H, H-5a, H-5e, and H-6e), 1.22 (m, 1H, H-6a). $J_{1\alpha}$ = 7.5 Hz, J_{12} = 4.4 Hz, J_{16a} = 13.6 Hz, J_{16e} = 4.4 Hz, J_{34} = 10.0 Hz.

Decarboxylation of acid **3**. *Lactones* **16** *and* **17**

According to the procedure described in the previous experiment from acid **3** lactones **16** and **17** were obtained. Compounds **16** and **17** had IR and ^{1}H-NMR spectra consistent with assigned structures.

REFERENCES

[1]O. Achmatowicz and A. Zamojski, *Roczniki Chem.* **35**, 1251 (1961).

[2]Yu. A. Arbuzov, B. M. Klimov and E. I. Klimova, *Dokl. Akad. Nauk SSSR* **142**, 341 (1962).

[3]Yu. I. Smushkevich, V. M. Belov and A. Ya. Akimova, *Zhur. Org. Khim.* **3**, 1036 (1967).

[4]H. M. R. Hoffmann, *Angew. Chem. Internat. Ed.* **8**, 556 (1969).

[5]A. M. Braun, *J. Org. Chem.* **35**, 1208 (1970); P. Crews and J. Beard, *Ibid.* **38**, 522 (1973); P. Crews and J. Beard, *Ibid.* **38**, 529 (1973).

[6]E. Klein and W. Rojahn, *Tetrahedron* **21**, 2173 (1965).

[7]B. F. Gillis, in *1,4-Cycloaddition Reaction* (Edited by J. Hamer), pp. 143–177. Academic Press, New York (1967).

[8]O. Achmatowicz Jr., J. Jurczak and J. S. Pyrek, *Roczniki Chem.* **49**, 1831 (1975).

[9]T. K. Devon and A. I. Scott, *Handbook of Naturally Occuring Compounds*, Vol. II. Academic Press, New York (1972).