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PROPELLANES—LXXVI

STEPWISE REDUCTION OF [4.3.3]PROPELLANE-8,11-DIONE†

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Abstract—The title diketone **1** was converted via the diketal **5** into a monoketal **6** which was then reduced to afford a mixture of two epimeric ketal-alcohols **7** and **8**. Each of the corresponding keto-alcohols **9** and **10** was then reduced to give a mixture of *syn-anti*-diol **2** on the one hand and either the *syn-syn*-diol **3** or the *anti-anti*-diol **4**, respectively, incidentally proving the configurations of the ketal-alcohols. Catalytic reduction of **1** with Rh and Ru gives a mixture of **9** and **10**, and a mixture of **2**, **3**, and **4**, respectively.

The title dione **1** has been reduced with lithium aluminium hydride[1,2] and with sodium borohydride,[2] in each case giving a mixture of the three possible diols **2–4**, albeit in different ratios.[2] We wished to determine whether or not stepwise reduction might give further control of the product ratio. The dione was therefore converted into the diketal **5** thence into the mono-ketal monoketone **6** by *trans*-ketalization.

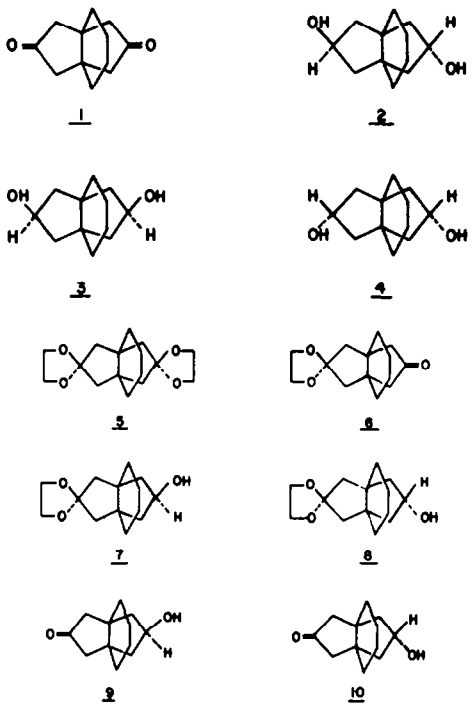
1,4-Butanediol which served well in the case of 1,4-cyclohexanedione[3] was, not surprisingly, unselective in the present case so that the more standard procedure of blocking with ethylene glycol was used.

Reduction of **6** was carried out with both lithium aluminium hydride and with sodium borohydride, affording mixtures of the *syn* and the *anti* ketal-alcohols **7** and **8**.

Although these substances could be partly separated by flash chromatography (Experimental), their properties were rather similar and a mixture of **7** and **8** formed the largest fraction. This was treated with acid in order to form the free keto-alcohol which could be more easily separated to afford pure **9** and **10**. Reduction of the ketols **9** and **10** gave mixtures of **2** + **3** and **2** + **4**, respectively, thus proving the configurations of the alcohols **7** and **8** by comparison with the diols **2–4** obtained earlier.[1,2]

One therefore has several options for the preparation of the *syn-syn*-diol **3** and the *anti-anti*-diol **4**, albeit in each case within a mixture. One may reduce the diketone **1** directly and obtain **2** + **3** + **4**,[1,2] or one may carry out stepwise reduction and obtain **3** + **2** or **4** + **2** as shown herein.

Since we are more interested in the *syn-syn*-diol **3** for reasons already discussed,[2] it is clear that stepwise reduction of **1** via **6**, followed by removal of the ketal blocking group and further reduction to diol is less efficacious than direct reduction of **1**. On the other hand, more *anti-anti*-diol **4**, if this were desired, may be obtained in larger amounts by stepwise reduction. We compare only the figures obtained using $NaBH_4$ as reducing agent because direct reduction of **1** with this reagent gave **2**:**3**:**4** in the ratio 36.7% : 40.8% : 22.5% (as compared to 45.1%: 18.3%: 36.6% using $LiAlH_4$).[2] Sodium borohydride reduction of **6** gives **7**:**8** in the ratio 40.8%:59.2%. When the corresponding ketols are reduced **9** affords **2**:**3** in the ratio of 37.7%:63.3% but owing to the first step the overall yield of **3** is only 26% as compared to 40.8% by direct reduction. On the other hand, **10** gives **2**:**4** in the ratio of 11.5%:88.5%. The overall yield of **4** is thus 45% as compared to 22.5% by direct reduction.



It is not surprising that for stereoelectronic reasons the monoketal **6** has hydride ion delivered to it from the face of the free CO group which is *syn* to the cyclohexane ring rather than *anti* to it for the latter is more proximate to the ketal. Thus, more ketal-*anti*-

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ol **8** and less **7** are obtained. By the same token the free *anti*-ketol is attacked by hydride ion from the side *syn* to the cyclohexane ring (rather than *syn* to the OH), giving largely the *anti–anti*-diol **4**. The CO group of the *syn*-ketol **9** undergoes about twice as much attack from the face *anti* to the cyclohexane ring, affording **3:2** as stated above, in the ratio 63.3%: 37.7%.

Clearly we could not risk the possibility that someone might have the idea that catalytic reduction of **1** might occur in a template coordinating both CO groups in a manner which would permit delivery of H from the lower face of each CO function. If such a possibility existed one might get a very high yield of **9** as compared to **10** or of **3** as compared to **2** and **4**. Thus we reduced **1** with Rh/C and Ru/C claimed to be the catalysts of choice for the hydrogenation of ketones in a neutral or basic medium.[4] Our implicit hope was unfounded. Mixtures of isomers were obtained in the ratios recorded in the Experimental. It is nevertheless noteworthy that selective reduction of only one CO group in **1** may be accomplished with Rh/C (H uptake ceases after one CO group is reduced) in contradistinction, in this respect, to Ru/C.

EXPERIMENTAL

Ketalization of **1**. A mixture of **1** (2.92 g), ethylene glycol (4.7 g), and *p*-toluenesulfonic acid (0.18 g) in dry benzene (150 ml) was heated under reflux with stirring using a Dean–Stark water separator for 48 hr. After cooling, washing with NaOH and with H_2O, the solvent was removed, affording the *bis* ketal **5** (2.84 g; 67%), m.p. 80–81° (hexane). (Found: M.W. 280.1685. $C_{15}H_{24}O_4$ requires 280.1674.) IR($CHCl_3$): 3020–2080 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ 3.8 (s, 8 CH_2O); 2.0 (s, 8 cyclopentane H); 1.7–1.4 (m, 8 cyclohexane H). MS: 280 (M^+, 100); 224(32); 179(20); 139(47); 162(82); 113(35).

Transketalization. A mixture of **5** (2.84 g), **1** (1.95 g), *p*-TsOH (0.11 g) in dry benzene (150 ml) was heated and under reflux as above for 48 hr. After similar workup the mixture of **5** and **6** was separated on a column of basic alumina (Merck, 70–230 mesh, 190 g), using benzene:hexane (1:4) as eluant. After a fraction of **5** (0.84 g), benzene:hexane (2:3) gave **6** (3.96 g; 83%) m.p. 49–50: (Found: M.W. 236.1426. $C_{14}H_{20}O_3$ requires M.W. 236.1412.) IR($CHCl_3$): 3000–2870, 1745 cm^{-1}. ^{1}H-NMR($CDCl_3$): 3.8 (s, 4 CH_2O); 2.4–2.2 (m, 4 CH_2CO); 2.1–1.9 (m, 4 cyclopentane H); 1.6–1.3 (m, 8 cyclohexane H). MS: 236 (M^+, 81); 180(41); 179(33); 178(31); 139(40); 126(78); 119(21); 105(49); 86(100).

Compund **5** could be separated preparatively from **6** using a Varian aerograph instrument with TCD detector, 250°, 200 mA, carrier gas helium 60 ml/min and a 5′ × $\frac{1}{4}$″ stainless steel column with chromosorb w, 60–80 mesh coated with 20% SE 30. Injection: 270°, chart speed 200 mm/hr. **6** appeared at 21.5 min and **5** at 29 min.

Reduction of **6**. $NaBH_4$ (1.06 g) was added portionwise at r.t. with stirring to a soln of **6** (1.5 g) in dry MeOH (160 ml) during 40 min. Further stirring was continued for 24 hr at r.t. After addition of water (15 ml), extraction with CH_2Cl_2 (3 × 40 ml) and drying (Na_2SO_4), removal of solvent gave a mixture of **7** and **8** (1.13 g; 72%). Attempted separation by flash chromatography using a column (15 cm × 20 mm dia.) of silica (Art 9385, Kieselgel 60, 230–400 mesh, Merck) under N_2 pressure with EtOAc:hexane (5:4) was not efficient. Nevertheless, pure fractions of **7** (191 mg) and **8** (72 mg) were separated. A larger fraction of **7** + **8** remained (see below).

Compound **7**. M.p. 82–83° (hexane–EtOAc). (Found: M.W. 238.1578. $C_{14}H_{22}O_3$ requires 238.1568.) IR($CHCl_3$): 3620, 2950 cm^{-1}. ^{1}H-NMR($CDCl_3$): 4.8–4.2 (br m, CHOH); 4.0–3.8 (m, 4 CH_2O); 2.4–2.0 (m, 4 CH_2C ); 2.0–1.7 (m, 4 CH_2CHOH); 1.7–1.3 (m, 8 cyclohexane H). MS: 238 (M^+, 48); 182(46); 151(55); 126(27); 113(28); 87(100).

Compound **8**. M.p. 34–35° (hexane–EtOAc). (Found: M.W. 238.1576.) IR($CHCl_3$); 3620, 2950 cm^{-1}. ^{1}H-NMR($CDCl_3$): 4.6–4.2 (br m, CHOH); 4.0–3.8 (m, 4 CH_2O); 2.5–2.0 (m, 4 CH_2C ); 2.0–1.7 (m, 4 CH_2CHOH); 1.7–1.3 (m, 8 cyclohexane H). MS: 238 (M^+, 70); 182(52); 180(20); 151(44); 126(32); 118(27); 113(38); 87(100).

Ketols **9**, **10**. The fraction of unseparated **7** + **8** (above, 345 mg) was allowed to stand overnight in a soln of MeOH (10 ml) and HCl (5%; 1 ml). After workup **9** + **10** (260 mg; 92%) was obtained. This was separated by flash chromatography on silica (as above) yielding a further quantity of **7** (14 mg) and of **8** (186 mg).

Compound **9**. Oil. (Found: M.W. 194.1265. $C_{12}H_{18}O_2$ requires M.W. 194.1306.) IR: 3620, 2950, 1745 cm^{-1}. ^{1}H-NMR: 5.5–5.0 (br m, CHOH); 2.5–2.2 (m, 4 CH_2CO); 2.2–1.7 (m, 4 CH_2CHOH); 1.7–1.4 (m, 8 cyclohexane H). MS: 194(M^+, 4); 176(40); 137(23); 136(97); 134(27); 133(35); 119(43); 118(100); 107(24); 105(33).

Compound **10**: Oil (Found: M.W. 194.1417.) IR($CHCl_3$): 3620, 2950, 1745 cm^{-1}. ^{1}H-NMR($CDCl_3$): 4.6–4.2 (br m, 1 CHOH); 2.5–2.3 (m, 4 CH_2CO); 2.2–1.7 (m, 4 CH_2CHOH); 1.7–1.4 (m, 8 cyclohexane H). MS: 194(M^+, 16): 176(14); 136(100); 135(18); 134(21); 119(26); 118(37); 107(16); 105(20).

Reduction of **9**. (a) Reduction of **9** (85 mg) with $NaBH_4$ (41.4 mg) as above gave a mixture of **2** and **3** (83.1 mg) which afforded on column chromatography as described previously[2] (30.2 mg; 37.7%) and **3** (52 mg; 63.3%), m.p. 139–140° and 159–160°, respectively. (Lit. m.p. 137–139°,[1] 140°,[2] and 163–164°,[1] 164°,[2] respectively.)

(b) Reduction of **9** (73 mg) with $LiAlH_4$ (24.5 mg) in dry ether (10 ml) during 24 hr at r.t. and the usual workup gave a mixture of **2** and **3** (50 mg; 68.5%). After chromatography as above **2** (19 mg; 37.2%) and **3** (32 mg; 62.8%) were isolated.

Reduction of **10**. (a) Compound **10** (186 mg) and $NaBH_4$ (91 mg) were reacted as above affording **2** + **4** (166.4 mg; 88.5%). Chromatography as above gave **2** (34.8 mg; 23.3%), m.p. 139–140° and **4** (115.1 mg; 76.7%), m.p. 120–121°. (Lit. m.p. 120–122°,[1] 122–123°.[2])

(b) Compound **10** (51.3 mg) and $LiAlH_4$ (15.8 mg) gave as above a mixture of **2** + **4** (46.3 mg; 90%). Chromatography as above gave **2** (5.4 mg; 11.5%) and **4** (40.8 mg; 88.5%).

Catalytic reduction of **1**. (a) The diketone **1** (192 mg) in dry MeOH (25 ml) was reduced under pressure (4 atm) with Rh (5% on carbon; 400 mg) during 4.5 hr at r.t. After workup the NMR spectrum of the mixture showed the presence of **9** and **10** in the ratio of 1:1.2. Only one CO group was reduced.

(b) Compound **1** (192 mg) in dry MeOH (25 ml) was reduced under pressure (4 atm) with Ru (5% on carbon; 400 mg) during 4.5 hr at r.t. After workup the NMR spectrum of the mixture showed the presence of **2**, **3** and **4** in the ratio of 1.13:1:1.

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