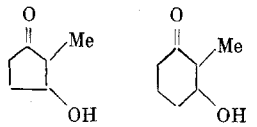
REDUCTION OF β-DICARBONYL COMPOUNDS WITH SODIUM BOROHYDRIDE

N. K. Levchenko, G. M. Segal', and I. V. Torgov

UDC 542.941:547.444

While synthesizing some steroid derivatives the need arose of obtaining the cyclic β-hydroxy ketones (I) and (II).

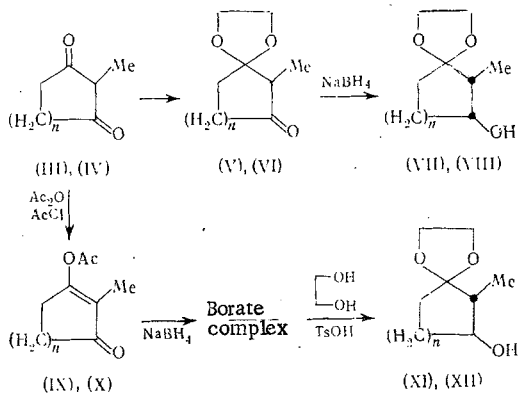


(I) (II)

The reduction of the corresponding β-diketones (III) and (IV) does not lead to the desired result, since the reaction is nonselective and gives a difficultly separable mixture of compounds. The reduction of the enol ethers of diketones leads only to cyclic α,β-unsaturated ketones [1].

We selected the path of selective protection of the keto group by ketalization or enolacetylation, with subsequent reduction of the ketals or enol acetates with $NaBH_4$.

Monoethylene ketals (V) and (VI) are formed in good yields using an equimolar ratio of the diketone and ethylene glycol, with a rapid removal of the formed water from the reaction sphere, which is achieved by azeotropic distillation and drying the recycled solvent (the use of the conventional Dean—Stark head does not accomplish the purpose).



(III), (IV) (V), (VI) (VII), (VIII)

(IX), (X) (XI), (XII)

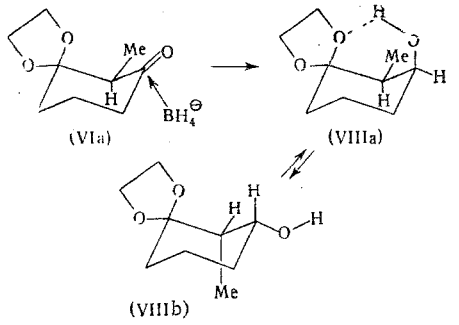
$n = 1$ (III), (V), (VII), (IX), (XI); $n = 2$ (IV), (VI), (VIII), (X), (XII)

The reduction of ketals (V) and (VI) with $NaBH_4$ at −30°C gives hydroxy ketals (VII) and (VIII). A similar reduction of enol acetates (IX) and (X) leads to high-melting crystalline borate complexes, from which the isolation of the ketals themselves is difficult. Still, when these complexes are heated in benzene under ketalization conditions (ethylene glycol, TsOH) the crystalline hydroxy ketals (XI) and (XII) can be isolated, which differ from hydroxy ketals (VII) and (VIII). As a result, the two paths lead to different stereoisomers.

M. M. Shemyakin Institute of the Chemistry of Natural Compounds, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 12, pp. 2757-2762, December, 1974. Original article submitted April 5, 1974.

In harmony with the Cram rule [2], when monoketal (VI) is reduced the C atom of the CO group should be attacked by the BH_4^- anion from the side of the smallest substituent at C_2. As follows from the molecular model, in the thermodynamically favorable conformation (VIa) the approach to C_1 is partially shielded by the equatorial CH_3 group, and partially by the ketal group, which determines the formation of the cis-isomer of (VIII) as the (VIIIa) conformation.

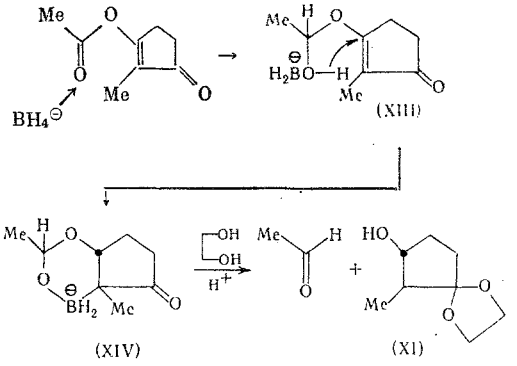
The other equilibrium conformation (VIIIb) apparently makes an insignificant contribution to the structure of hydroxy ketal (VIII), since, in contrast to (VIIIa), it is not stabilized by an intramolecular hydrogen bond between the axial OH group and the O atom of the dioxolane ring.



(VIa) (VIIIa) (VIIIb)

Actually, the IR spectrum of hydroxy ketal (VIII), taken as a film, has a broad absorption band of the OH group at 3200-3530 cm^{-1}, with a maximum at 3400 cm^{-1} [3]. Two bands appear when the concentration is reduced to $3.2 \cdot 10^{-3}$ mole/liter: a broad band at 3340-3450 with a maximum at 3390 cm^{-1}, and a narrow band at 3539 cm^{-1}. The first band must be assigned to the hydroxyl absorption of dimers, since the second band testifies to the intramolecular OH ... O hydrogen bond. The intensity of the first band decreases at a concentration of $6.3 \cdot 10^{-4}$ mole/liter, while the intensity of the second band increases sharply.

The reduction of ketal (V) and enol acetate (IX), which were obtained from 2-methyl-1,3-cyclopentadione (III), gives similar results. The formation of the isomeric hydroxy ketals (XI) and (XII) when enol acetates are reduced (with subsequent ketalization) can be explained on the example of enol acetate (IX).



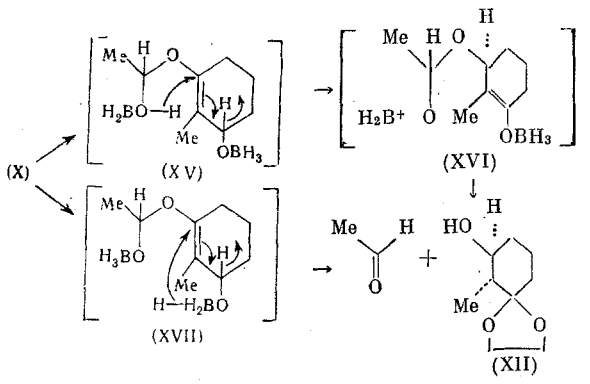
(XIII) (XIV) (XI)

The transition compound (XIII) is formed when the enol acetate grouping is attacked by hydride ion due to the bimolecular addition of the BH_4^- anion to the electrophilic C atom of the CO group. This compound can rearrange to the cyclic borate complex (XIV), which on acid hydrolysis in the ketalization process undergoes inversion at C_2 to give the trans-diequatorial isomer (XI). This scheme is supported by the formation of the stable borate complex, and also by the formation of acetaldehyde in the ketalization process.

Another reduction path is also possible, which apparently takes place in the case of enol acetate (X). Here attack by the anion can occur at both functions, which should lead to complex (XV), which then gives the transition intermediate compound (XVI) or (XVII) as the result of hydride (see Scheme 1).

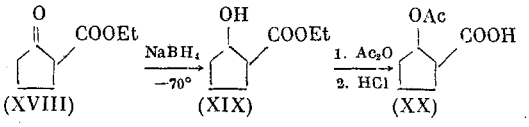
Acetaldehyde and hydroxy ketal (XII) were also obtained from the borate complex formed in this case by hydrolysis in the ketalization process.

We also studied the hydride reduction of 2-carbethoxy-1-cyclopentanone (XVIII). In contrast to the previously obtained results [4], it was shown that keto ester (XVIII) is smoothly reduced by $NaHB_4$ at low



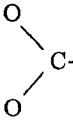
Scheme 1

temperatures (−70°) to give the liquid 2-carbethoxy-1-cyclopentanol (XIX).



Hydroxy ester (XIX) gives the phenylurethan with mp 88-89°, which corresponds to the cis-isomer [5]. Consequently also in this case the reduction of ester (XVIII) proceeds in harmony with the Cram rule. The cis-isomer (XIX) was also characterized by its conversion to the crystalline hydroxy acid acetate (XX).

EXPERIMENTAL METHOD

2-Methyl-1,3-cyclopentanedione Ethylene Ketal (V). A mixture of 10.3 g of 2-methyl-1,3-cyclopentanedione (III) and 4.3 g of ethylene glycol in 150 ml of absolute benzene was refluxed in the presence of 0.6 g of p-toluenesulfonic acid for 4 h in a Soxhlet apparatus (the cartridge was filled with anhydrous $CaCl_2$). After the usual workup and removal of the solvent in vacuo we obtained 12 g (85%) of ketal (V) with mp 123-124° (from ether); mol. wt. 156 (by mass spectrometry). Found: C 57.89; H 7.77%. $C_8H_{12}O_3 \cdot 0.5H_2O$. Calculated: C 58.17; H 7.93%. Infrared spectrum (KBr pellet, ν_{max}, cm^{-1}): 3500-3200 (chelated OH group), 1750 (cyclopentanone), 1695 and 1600 (—COCH-C$\langle$), 1068, 1100, 1260 (ketal grouping). NMR spectrum (C_5D_5N, δ, ppm): 1.9 s (CH_3), 4.03 ($-OCH_2CH_2O-$), 4.32 ().

Substantial amounts of diethylene ketal, with mp 194-195°, are formed if the ketalization is run without azeotropic distillation of the water or with excess ethylene glycol. $C_{10}H_{16}O_4$, mol. wt. 200 (by mass spectrometry). The absorption band, characteristic for the CO group, is absent in the IR spectrum of the diketal. NMR spectrum (C_5D_5N, δ, ppm): 1.9 (CH_3-), 4.07 ($-OCH_2CH_2O-$).

Reduction of Ketal (V). To a solution of 12 g of ketal (V) in 120 ml of methanol at −30° was added in 40 min a solution of 1.6 g of $NaBH_4$ in 70 ml of 57% methanol. The stirring at −30° was continued for 6 h. After the usual workup and extraction with $CHCl_3$ we obtained 11.3 g (96%) of hydroxy ketal (VII) with mp 70-72° (from ether), mol. wt. 158 [by mass spectrometry, an intense peak was also observed that corresponded to the fragment with m/e 140 ($M^+ - H_4O$)]. Found: C 60.74; H 8.92%. $C_8H_{14}O_3$. Calculated: C 60.40; H 9.00%. Infrared spectrum (KBr pellet, ν_{max}, cm^{-1}): 3200-3530 (OH) (CCl_4, $3.2 \cdot 10^{-3}$ mole/liter); 3340-3450 (dimeric absorption of OH group; 3539 (intramolecular H bond) CCl_4, $6.3 \cdot 10^{-4}$ mole/liter); 3540 (H bond), 3395 (weak intensity). NMR spectrum (C_5D_5N, δ, ppm): 1.72 (CH_3-), 2.57 m (> CH—OH), 4.03 m ($-OCH_2CH_2O-$).

The acetylation of the hydroxy ketal (VII) gives the acetate (oil), which was purified by chromatographing on silica gel in the system: 1:1 benzene—petroleum ether. Infrared spectrum (as a film): 1748 and 1242 cm^{-1} (CH_3COO-).

Enol Acetate (IX). A solution of 5 g of diketone (III) in 75 ml of Ac_2O and 25 ml of AcCl was refluxed for 3.5 h. Vacuum-distillation gave 5.5 g (81%) of enol acetate (IX), bp 129-130° (12 mm): n_D^{21} 1.4880, cf. [6]. Infrared spectrum (as a film): 1782 (vinyl acetate group), 1672 cm^{-1} (> C = C—CO—).

Hydroxy Ketal (XI). To a solution of 1.54 g of enol acetate (IX) in 15 ml of methanol at −30° was added 0.82 g of $NaBH_4$ in 5 ml of 57% methanol in 30 min, and the stirring was continued at −30° for 2 h. The reaction mixture was cautiously acidified with dilute HCl solution to pH 6, and then stirred for another hour. The excess methanol was vacuum-distilled. The residual aqueous solution deposited 1.39 g of the borate complex (XIII) with mp 355°. Found: B_2O_3 21.10%. $C_8H_{14}O_3B$. Calculated: B_2O_3 20.85%.

A suspension of 0.5 of the borate complex (XIII) in 30 ml of absolute benzene was refluxed in a Soxhlet apparatus (equipped with a cartridge filled with $CaCl_2$) for 3 h with 1 g of ethylene glycol and 30 mg of p-toluenesulfonic acid. After the usual workup we obtained 0.2 g of an oil, which was chromatographed on silica gel. The low-polar products were eluted with benzene and benzene—$CHCl_3$ mixtures. Elution with ether gave 130 mg of hydroxy ketal (XI) with mp 150-151°, $C_8H_{12}O_3$, mol. wt. 158 (by mass spectrometry, a peak with m/e 140 ($M^+ - H_2O$) was also observed). Infrared spectrum (KBr pellet): 2520-3200 cm^{-1} (OH), the CO absorption band is absent. NMR spectrum (C_5D_5N, δ, ppm): 1.90 (CH_3—), 3.82, 4.03 (—OCH_2CH_2O—), 2.34 (> CH—OH).

Ethylene Ketal (VI). Obtained in the same manner as (V) in 78% yield, mp 182-183° (from ether). Infrared spectrum (KBr pellet): 2400-3250, 1648, 1600 cm^{-1}. NMR spectrum (C_5D_5N, δ, ppm): 1.83 (CH_3—), 2.12 (CH_2CO), 3.61 (), 4.04 (—OCH_2CH_2O—).

Enol Acetate (X). Obtained in the same manner as (IX) in 98% yield, bp 163-164° (25 mm); n_D^{23} 1.4848; mol. wt. 168 (by mass spectrometry). Infrared spectrum (as a film): 1763, 1673 cm^{-1}. Based on the mass spectral data, the fraction with bp above 164° (traces) was a mixture of enol acetate (IX) and 2-methyl-$\Delta^{1,3}$-cyclohexadiene-1,3-diol diacetate (M^+ 210).

Hydroxy Ketal (VIII). Obtained from ketal (VI) in 50% yield, mp 90-90.5° (from CCl_4). It was purified by chromatographing on silica gel in the system: 1:1 octane—benzene, and before recrystallization had n_D^{23} 1.4868. $C_9H_{16}O_3$, mol. wt. 172 (by mass spectrometry, a peak with m/e 154 ($M^+ - H_2O$) was observed). Infrared spectrum (as a film): 3500, 1120, 1100, 1075, 1035 cm^{-1}; absorption appears at 3531 cm^{-1} (intramolecular H bond) in dilute CCl_4 solutions.

Hydroxy Ketal (XII). The reduction of 6.2 g of enol acetate (X) was run the same as the reduction of (IX). We obtained 3.2 g of the borate complex with mp above 355° (Found: B_2O_3 48%).

A mixture of 1 g of the borate complex, 2 g of ethylene glycol, 60 mg of p-toluenesulfonic acid, and 50 ml of benzene was refluxed in a Soxhlet apparatus (equipped with a cartridge filled with $CaCl_2$) for 7 h. After the usual workup, the product (0.74 g) was chromatographed on silica gel in a 1:1 benzene—$CHCl_3$ mixture. We eluted 240 mg of hydroxy ketal (XII) as an oil, $C_2H_{16}O_3$, mol. wt. 172 (by mass spectrometry, a peak with m/e 154 ($M^+ - H_2O$) was also observed). Infrared spectrum (as a film): 3400, 1085, 1050 cm^{-1} NMR spectrum (C_5D_5N, δ, ppm): 1.21 (CH—OH), 3.61 (CH—OH), 3.67, 4.04 (—OCH_2CH_2O—).

Hydrolysis of Borate Complex (XIII). A mixture of 1 g of complex (XIII), 2 g of ethylene glycol, 60 mg of p-toluenesulfonic acid, and 200 ml of xylene was refluxed, with the simultaneous distillation of the xylene (fresh xylene was added in order to maintain a constant volume of the reaction mass), for 30 h. The distillate was collected in a receiver that contained a solution of 1 g of 2,4-dinitrophenylhydrazine in 65 ml of HCl and 30 ml of methanol. To the distillate was added another 50 ml of dilute HCl solution (1:1) and the mixture was refluxed for 8 h. The mixture was evaporated in vacuo, water was added to the residue, and the mixture was extracted with ethyl acetate. The extract was worked up in the usual manner to give a product that was chromatographed in a thin layer of silica gel (ethyl acetate). The zone with R_f 0.85 was eluted with ethyl acetate. Evaporation of the eluate gave 0.1 g of the acetaldehyde dinitrophenylhydrazone with mp 148-150°.

Reduction of Keto Ester (XVIII). To a solution of 3.3 g of keto ester (XVIII) in 50 ml of ethanol, containing 20 mg of NaOH, at −70°, was added a solution of 1.7 g of $NaBH_4$ in 20 ml of 60% ethanol. The stirring was continued at −70° for 6 h. The mixture was decomposed at 0° with water, and then acidified with 3 ml of AcOH. The product was extracted with ether. The extract was worked up in the usual manner to give 3 g (90%) of hydroxy ester (XIX) as an oil, n_D^{18} 1.4598. Infrared spectrum (as a film, ν_{max}, cm^{-1}): 3460, 1736, 1235 (CCl_4 $3 \cdot 10^{-4}$ mole/liter), 3680 (H bond), 3533 (weak absorption), 1742, 1250. Mass spectrum (m/e): 158 (M^+, 100), 140 ($M^+ - H_2O$, 13), 113 (M^+ —OEt, 35), 95 ($M^+ - H_2O$—OEt, 22%).

Hydroxy ester (XIX) when refluxed with phenyl isocyanate in petroleum ether (bp 70°) for 5-6 h gave the phenylurethan with mp 88-89° (from petroleum ether), cf. [6].

Saponification of Hydroxy Ester (XIX). A mixture of 9 g of hydroxy ester (XIX), 160 ml of methanol, 6.35 g of KOH, and 40 ml of water was refluxed for 2 h. The methanol was removed in vacuo. The residue was treated with water, the neutral compounds were extracted with ethyl acetate, and the remainder was acidified with HCl. Extraction with ethyl acetate gave 7 g of the hydroxy acid, which without further purification was acetylated (by refluxing with 50 ml of Ac_2O for 2 h). We isolated 6.5 g of the hydroxy acid acetate (XX), which gives a stable hydrate with mp 148-150° (from water). Found: C 49.92; H 6.99%. $C_8H_{12}O_4 \cdot H_2O$. Calculated: C 50.32, H 7.12%. Infrared spectrum (KBr pellet, ν_{max}, cm^{-1}): 2500-3300, 1695 and 928 (COOH), 1720 and 1193 (CH_3COO—).

CONCLUSIONS

The reduction of the monoethylene ketals of cyclic β-diketones and the enol acetates of β-diketones with sodium borohydride is stereospecific, but proceeds with the formation of different isomers of the hydroxy ketals.

LITERATURE CITED

1. W. F. Gannon and H. O. House, Organic Syntheses, 40, 14 (1960).
2. D. J. Cram and K. B. Koecky, J. Am. Chem. Soc., 81, 2748 (1959).
3. L. J. Bellamy, Infrared Spectra of Complex Molecules [Russian translation], IL (1963), p. 137.
4. E. Buchta and H. Bayer, Ann. Chem., 573, 227 (1951).
5. J. Pascual and J. Castells, J. Am. Chem. Soc., 74, 2899 (1952).
6. G. V. Kondrat'eva, G. A. Kogan, T. M. Fadeeva, and S. I. Zav'yalov, Izv. Akad. Nauk SSSR, Ser. Khim., 1964, 1648.