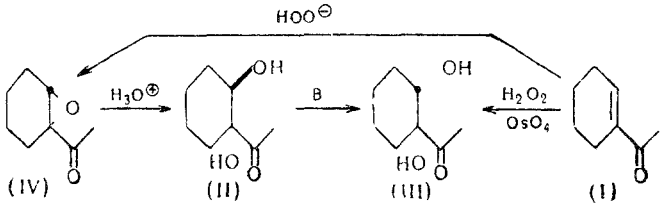
COMMUNICATION 12. DIFFERING STABILITIES OF cis- AND trans-1-ACETYL-1,2-CYCLOHEXANEDIOLS*

A. M. Moiseenko and A A. Akhrem

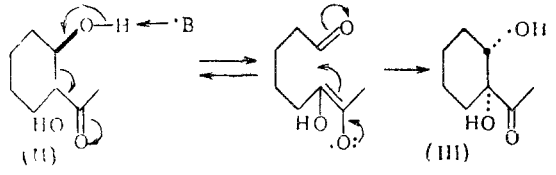
N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences, USSR

Translated from Izvestiya Akademii Nauk SSSR, Otdelenie Khimicheskikh Nauk, No. 6, pp. 1064-1070, June, 1963
Original article submitted February 16, 1963

One of us [1] has previously described the synthesis and reactions of the isomeric α-keto diols (II) and (III), which are models for the corticoid grouping of the ring of D,D-homosteroids. We now describe the further investigation of these compounds. Reaction of 1-acetylcyclohexene (I) with the hydroperoxide anion gives the keto epoxide (IV), the yield of which (45-75%) depends on the method of oxidation [1-4]. Epoxidation appears to be accompanied by profound degradation, for in the course of oxidation with alkaline hydrogen peroxide the pH of the reaction mixture falls from 10-9.5 to 8-7.5. This is evidence of the formation of acidic by-products even under optimum reaction conditions (low temperature of the reaction medium, following the progress of the oxidation by the disappearance of the ultraviolet characteristics of the unsaturated ketone). Actually, under these conditions the formation of appreciable amounts of acetic and adipic acids is observed. As already reported [1], epoxidation with alkaline hydrogen peroxide and with t-butyl hydroperoxide is slow, and by this means we did not succeed in obtaining a preparation of the keto epoxide (IV) that had a good elementary analysis. By thin-layer chromatography [5] on alumina we succeeded in showing that our sample of the keto epoxide, which had n_D^{25} 1.4655, was actually a mixture of the keto epoxide (IV) and 1-acetylcyclohexene (I), which were characterized by sharp R_f values of 0.61 and 0.52, respectively, in benzene. It is probable that Filler and co-workers [3] and Meinwald and Emerman [4] were dealing with such mixtures, for their samples of keto epoxide they give refractive indices of n_D^{25} 1.4650 and n_D^{22} 1.4633. Our mixture was separated by distillation through a column having a glass filling and of 40-plate efficiency. The epoxide (IV) then obtained, which had n_D^{25} 1.4641 and R_f 0.61, gave a good elementary analysis.

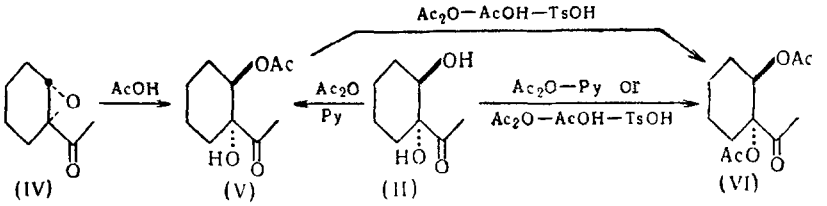


Acid hydrolysis of the keto epoxide led to the formation of the previously described [1] trans keto diol (II). Under the conditions of basic catalysis the latter underwent rearrangement into the cis isomer (III), which was prepared earlier [1] by the hydroxylation of 1-acetylcyclohexene (I) with osmium tetroxide. On the basis of various analogies reported in the literature, it was suggested [1] that such isomerization proceeds by a retro-aldol mechanism.



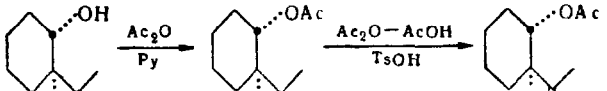
*This article is published in accordance with a resolution of the Conference of Chief Editors of Journals of the Academy of Sciences of the USSR of June 12, 1962, as a dissertation paper by A. M. Moiseenko.

The conversion of (II) into (III) takes place quantitatively when an attempt is made to purify the trans keto diol on commercial alumina of Grade II activity (which has a weakly alkaline reaction), using a slow elution procedure. Under these conditions the cis isomer is not affected. Moreover, isomerization is rapid in an aqueous-alcoholic solution of sodium carbonate. Under alkaline conditions the liquid trans monoacetate (V) behaves analogously. The latter was prepared by the acetolysis of the keto epoxide (IV) or by the acetylation of the trans keto diol (II). Acetylation goes under mild conditions and affects also the tertiary hydroxy group with formation of not only the monoacetate (V), but also the crystalline trans diacetate (VI), m.p. 63.5-64°. The resulting mixture of mono- and di-acetates can be separated chromatographically on silica gel. The diacetate (VI) was prepared also by the mild



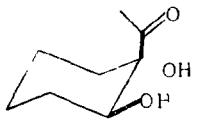
(IV) (V) (II) (VI)

acetylation of the monoacetate (V) in excess of acetic anhydride. Unlike the trans keto diol (II), under mild conditions the cis isomer (III) is acetylated only on the secondary hydroxyl with formation of the cis acetate (VII), m.p. 98.5-99.5°. Acetylation of the latter under severe conditions leads to the crystalline cis diacetate (VIII), m.p. 53-54°.



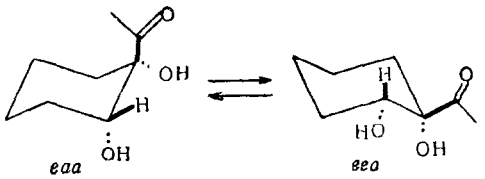
(III) (VII) (VIII)

The great difference in behavior between the tertiary hydroxyls of the isomeric keto diols in the acetylation reaction is in accord with NMR data for these compounds [1]; from these it follows that the trans keto diol exists in solution in the form of a single conformation (about 100% eea) with diequatorial hydroxy groups.



eea

On the other hand, the cis isomer exists in solution as an equilibrium mixture of two rotational isomers (conformers) in approximately 1 : 1 proportions.



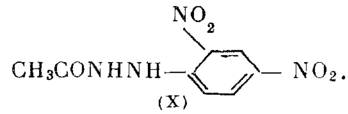
eaa *eea*

Thus, from the point of view of conformational analysis [6] the equatorial tertiary hydroxy group of the trans keto diol (II) should probably acetylate considerably more readily than that of the cis diol (III), in which at least 50% of the tertiary hydroxyls are axial. The reverse phenomenon is observed in the reaction of the trans (VI) and cis (VIII) diacetates with carbonyl reagents in glacial acetic acid solution at room temperature.

Acetylation of the two hydroxyls of the keto diols (II) and (III) probably does not affect the conformations of the diacetates (VI) and (VIII) substantially. If this is so, then in a solution of the trans diacetate (VI) the eea conformation with an axial keto group should predominate. Such a carbonyl would probably react considerably more slowly than an equatorial carbonyl, which will probably predominate in the eea conformation for the cis diacetate (VIII). Moreover, as can be seen by an examination of Stuart-Briegleb models, the axial carbonyl group in the eea

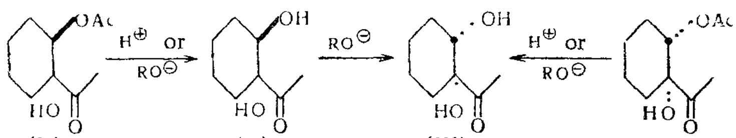
conformation of the trans diacetate (VI) is strongly screened by the acetyl groups, which hinder nucleophilic attack on the carbonyl center. Such steric limitations do not exist for the trans and cis monoacetates, which, like the cis diacetate (VIII), form carbonyl derivatives in good yield. It is probable that steric hindrance explains the fact that in the reactions of the trans diacetate (VI) with carbazic ester and with 2,4-dinitrophenylhydrazine under the same conditions, instead of the expected hydrazones, the N-acetyl derivatives (IX) and (X)

$CH_3CONHNHCO_2C_2H_5$
(IX)


(X)

were isolated in small amounts. It has been reported [7] that the hydrazide (X) is formed in quantitative yield by boiling 2,4-dinitrophenylhydrazine in 90% acetic acid for 18 hours [7].

Hydrolysis of the trans acetate (V) in an acid medium gives a good yield of the trans keto diol (II). Alkaline hydrolysis of (V) under mild conditions gives the trans keto diol (II), but under more severe conditions it leads to the formation of the more stable cis isomer (III).


(V) (II) (III) (VII)

The acid or alkaline hydrolysis of the cis monoacetate (VII) gives the cis keto diol (III) in good yield.

EXPERIMENTAL

1-Acetyl-1,2-epoxycyclohexane (IV)

69 ml of 3.65 N NaOH was added over a period of 40 minutes to a vigorously stirred solution of 30 g of 1-acetylcyclohexene and 36 ml of 40% H_2O_2 in 350 ml of methanol, external cooling being applied so that the temperature of the reaction mixture did not rise above 40°. When the evolution of heat stopped, the solution was stirred at room temperature and samples were taken periodically and tested for acetylcyclohexene content by determining their ultraviolet spectrum (EtOH, λ_{max} 233.5 mμ, ε 12020). 55 minutes after the start of the reaction analysis showed that the amount of unsaturated ketone present was only 8.1% of its initial value. After 55 minutes more its content had fallen to 7.8%, and the reaction was stopped by neutralizing the mixture to pH 7. The reaction mixture was poured into 700 ml of water and extracted with ether. The ether extract (A) was dried with anhydrous sodium sulfate. The aqueous layer was acidified to pH 2.5 with dilute sulfuric acid and was continuously extracted with ether for 75 hours. The ether extract then obtained (B) was dried with anhydrous sodium sulfate. After the removal of ether in a vacuum, acetic acid (1.7 g) was distilled off and was characterized as its silver salt. The residue consisted of 3.8 g of adipic acid, m.p. 149-151° (from benzene), undepressed by admixture with a known sample.

From the ether extract (A) after removal of solvent and vacuum fractionation we obtained 17.4 g of a substance having b.p. 56-58° (3 mm) and n_D^{25} 1.4655, whose chromatogram (alumina of Grade II activity, development with iodine) indicated the presence of the original ketone (R_f 0.52) and its epoxide (R_f 0.61). The combined product from eight experiments (139 g) was fractionated through a column having a glass filling and having an efficiency of 40 theoretical plates. The fractions obtained were I (30.5 g), b.p. 39-41° (2.5-3 mm) and n_D^{25} 1.4700, II) b.p. 40-42° (2 mm) and n_D^{25} 1.4650, 32.7 g, III (59.9 g), b.p. 41.5-42.9° (2.5 mm) and n_D^{25} 1.4641. The residue in the still (13.4 g) had b.p. 39-40° (2 mm) and n_D^{25} 1.4611. Fraction III was pure 1-acetyl-1,2-epoxycyclohexane (IV), d_4^{25} 1.0483, Found MR_D 36.91, Calculated MR_D 37.10, R_f 0.61. Found C 68.52, H 8.68%. $C_8H_{12}O_2$. Calculated: C 68.54, H 8.63%, $\nu_{C=O}$ 1715 cm^{-1} (in $CHCl_3$).

trans-1-Acetyl-1,2-cyclohexanediol (II)

A heterogeneous mixture of 7 g of the keto epoxide (IV), 55 ml of water, and 20 drops of concentrated sulfuric acid was heated for two hours in a boiling water bath. The mixture was cooled to 0°, neutralized with sodium bicarbonate, and extracted with ether. The extract was dried with anhydrous sodium sulfate, ether was distilled off, and the oily residue was vacuum-distilled. We obtained 5.4 g of a thick colorless liquid, b.p. 98-103° (2.5 mm) and n_D^{25} 1.4894, which crystallized out on standing. Recrystallization from a mixture of diethyl ether and petroleum ether

(b.p. 40-60°) gave 5.1 g of the trans keto diol (II) in the form of rosettes of crystals, m.p. 58.5-59°, undepressed by admixture of a known sample. A mixture with the cis keto diol (I) melted over the range 39-51°. A similar result was obtained by the hydrolysis of the epoxide in the solution obtained by the homogenization of the above reaction mixture with 50 ml of dioxane.

Isomerization of the trans Keto Diol (II) into the cis Keto Diol (III)

1.7 g of the trans keto diol (II) and 1 g of sodium carbonate were dissolved in 85 ml of 30% aqueous methanol, and the mixture was left at room temperature for ten hours, neutralized with 10% sulfuric acid, vacuum-evaporated, and extracted with ether. The usual treatment of the ether extract gave 1.5 g of crystals (prisms), which after recrystallization from an ether-hexane mixture had m.p. 77.5-78°, undepressed by admixture of a known sample of the cis keto diol (III) [1]. The chromatogram of the mother liquors revealed no spots due to the original trans diol (II).

A solution of 1 g of the trans keto diol (II) in 20 ml of ether was applied to a chromatographic column containing a 100 g layer of commercial alumina of Grade II activity. The column was left overnight at room temperature, and elution was then carried out with 1 liter of a 4:1 mixture of ether and hexane, after which removal of solvent and recrystallization gave 850 mg of the cis diol (III).

The same result was obtained by the vigorous stirring of 1 g of the trans diol (II) with 100 g of alumina of Grade II activity in 200 ml of ether for 12 hours. Under these conditions the cis diol (III) is not affected.

trans-2-Acetoxy-1-acetylcyclohexanol (V)

15 g of the keto epoxide (IV) was refluxed in 53 ml of glacial acetic acid for four hours. The reaction mixture was vacuum-evaporated, diluted with 30 ml of water, and extracted with ether. The extract was washed with saturated sodium bicarbonate solution and dried with anhydrous sodium sulfate. After removal of ether and unchanged epoxide (8.3 g) we obtained 6.5 g of a substance of b.p. 83-90° (2 mm) and n_D^{25} 1.4684. By chromatography of the latter on 150 g of silica gel containing 17% of water (eluate: 70:30 ether-hexane mixture saturated with water, 700 ml) we isolated 5.4 g of trans-2-acetoxy-1-acetylcyclohexanol (V) as a colorless liquid, b.p. 94-96. (2.5-3 mm), n_D^{25} 1.4657, d_4^{25} 1.1197, found MR 49.49, calculated MR 49.37. Found: C 60.06, H 8.03%. $C_{10}H_{16}O_4$. Calculated. C 59.98, H 8.05%, ν_{OAC} 1737 cm^{-1}, $\nu_{C=O}$ 1712 cm^{-1} (shoulder), ν_{OH} 3459 cm^{-1} (broad band) (in $CHCl_3$).

The 2,4-dinitrophenylhydrazone formed light-yellow needles of m.p. 135-135.5° (from alcohol). Found C 50.45, H 5.28, N 14.79%. $C_{16}H_{20}O_7N_4$. Calculated: C 50.52; H 5.30, N 14.73%.

9 g of the trans keto diol (II) was dissolved in 50 ml of pyridine, 10 ml of acetic anhydride was added, and the mixture was left overnight at room temperature, it was then diluted with 100 ml of water and extracted with ether. The extract was shaken with 5% hydrochloric acid solution, washed with water until neutral, and dried with anhydrous sodium sulfate. Ether was removed, and two vacuum fractionations gave 8 g of a substance of b.p. 95-99° (2.5 mm) and n_D^{25} 1.4640, the chromatogram of which had spots of the trans monoacetate (V) and of the corresponding diacetate (VI). The mixture was separated chromatographically under the conditions indicated above. We obtained 4.0 g of the monoacetate and 3.7 g of the diacetate.

trans-1,2-Diacetoxy-1-acetylcyclohexane (VI)

A solution of 1 g of the trans acetate (V) and 2 ml of acetic anhydride in 40 ml of pyridine was left at room temperature for 15 hours. The mixture was vacuum-concentrated, diluted with water, and extracted with ether. The usual treatment of the extract gave 1.1 g of trans-1,2-diacetoxy-1-acetylcyclohexane (VI) in the form of plates, m.p. 63.5-64° (from pentane). Found. C 59.89, H 7.60%. $C_{12}H_{18}O_5$. Calculated: C 59.50, H 7.50%. ν_{OAC} 1741 cm^{-1}, $\nu_{C=O}$ 1718 cm^{-1} (shoulder) (in $CHCl_3$). An analogous result was obtained in the acetylation of 1 g of the trans monoacetate (V) in 30 ml of glacial acetic acid by the action of 3 ml of acetic anhydride in presence of 300 mg of p-toluenesulfonic acid monohydrate at room temperature for 12 hours.

3.1 g of the trans diol (II), 10 ml of acetic anhydride, and 900 mg of p-toluenesulfonic acid monohydrate in 60 ml of glacial acetic acid was left at room temperature for 20 hours. After the usual treatment we obtained 3.1 g of the diacetate (VI).

Reaction of the Diacetate (VI) with Ethyl Carbazate. When we attempted to prepare the ethoxycarbonylhydrazone by the reaction of 2.4 g of the diacetate (VI) with 1.2 g of $H_2NNHCO_2C_2H_5$ in 45 ml of glacial acetic acid at room temperature for 40 hours, after the usual treatment we isolated 600 mg of ethyl 3-acetylcarbazate (IX), m.p. 93.5-94.5° (from an ether-hexane mixture). Found: C 41.08, H 6.93, N 19.37%. $C_5H_{10}O_3N_2$. Calculated: C 41.09, H 6.90, N 19.17%.

Reaction of the Diacetate (VI) with 2,4-Dinitrophenylhydrazine. Analogously, from 800 mg of (VI) and 660 mg of 2,4-dinitrophenylhydrazine we isolated 430 mg of acetic 2,4-dinitrophenylhydrazine (X), m.p. 196.5-197.5° (from alcohol). Found: C 40.17, H 3.57, N 23.30%. $C_8H_8O_5N_4$. Calculated: C 40.00, H 3.36, N 23.33%.

cis-2-Acetoxy-1-acetylcyclohexanol (VII)

A mixture of 750 mg of the cis keto diol (III) and 0.45 ml of acetic anhydride in 20 ml of pyridine was left at room temperature overnight. By the usual treatment we obtained 710 mg of cis-2-acetoxy-1-acetylcyclohexanol (VII) in the form of plates, m.p. 98.5-99.5° (from an ether-hexane mixture). Found: C 60.01, H 8.13%. $C_{10}H_{16}O_4$ Calculated: C 59.98, H 8.05%, ν_{OAC} 1729 cm^{-1}, $\nu_{C=O}$ 1712 cm^{-1} (shoulder), νOH 3440 cm^{-1} (broad band) (in CCl_4).

The 2,4-dinitrophenylhydrazone formed light-yellow needles, m.p. 179.5-180.5° (from alcohol). Found: C 50.81, H 5.58, N 14.60%. $C_{16}H_{20}O_7N_4$. Calculated C 50.52, H 5.30, N 14.73%.

cis-1,2-Diacetoxy-1-acetylcyclohexane (VIII)

A mixture of 2.8 g of the cis acetate (VII), 900 mg of p-toluenesulfonic acid monohydrate, and 15 ml of acetic anhydride in 30 ml of glacial acetic acid was heated in a boiling water bath for 90 minutes. After removal of solvent, neutralization, and the usual treatment, we obtained 2.8 g of cis-1,2-diacetoxy-1-acetylcyclohexane in the form of plates, m.p. 53-54° (from pentane). Found C 59.57, H 7.43%. $C_{12}H_{18}O_5$. Calculated C 59.50, H 7.50%. ν_{OAC} 1747 cm^{-1}, $\nu_{C=O}$ 1725 cm^{-1} (shoulder) (in chloroform).

The ethoxycarbonylhydrazone formed colorless needles, m.p. 115.5-116° (from an ether-hexane medium). Found: C 54.80, H 7.43, N 8.90%. $C_{15}H_{24}O_6N_2$. Calculated C 54.86, H 7.37, N 8.53%.

Hydrolysis of the cis Acetate (VII)

1.5 g of the cis acetate (VII), 1 ml of water, and 1 ml of concentrated hydrochloric acid in 100 ml of methanol was left at room temperature for three days. After the removal of solvent, neutralization, and the usual treatment, we obtained 1.1 g of the cis keto diol (III). Chromatography of the mother liquors showed that traces of the original cis acetate (VII) were present. A solution of 2 g of the cis acetate (VII) and 0.6 g of potassium hydroxide in 25 ml of methanol was refluxed for 45 minutes. After neutralization and the usual treatment we obtained 1.4 g of the cis keto diol (III).

Hydrolysis of the trans Acetate (V)

A solution of 1 g of the trans acetate (V), 1 ml of water, and 1 ml of concentrated hydrochloric acid in 70 ml of methanol was refluxed for 2.5 hours. After removal of solvent, neutralization, and the usual treatment we obtained 700 mg of the trans keto diol (II), which melted without depression in admixture with a known sample. Chromatography of the mother liquors did not reveal the presence of any cis keto diol.

A solution of 1.89 g of the trans acetate (V) in 10 ml of methanol was added to a solution of sodium methoxide prepared from 220 mg of sodium and 20 ml of methanol. The mixture was heated in a stream of nitrogen at 45° for 50 minutes and was then neutralized with acetic acid and vacuum concentrated. The residue was treated with 30 ml of water and extracted with ether. The usual treatment of the extract gave 1.27 g of the trans diol (II), identical to a known sample. Chromatography of the mother liquors showed that traces of the cis diol (III) were present.

4 g of the trans acetate (V) was dissolved in 50 ml of ethanol containing 80 mg of potassium hydroxide, and the solution was heated (in a water bath at 50°) for 90 minutes. After neutralization and the usual treatment we obtained 2.95 g of a mixture of trans and cis keto diols. 500 mg of this mixture was subjected to preparative separation on an unbound layer of silica gel containing 19% of water, thickness 2 mm on three 20 × 33 cm plates. Separation was attained by two chromatographic treatments in the aqueous ether – hexane (55 · 45) system with intermediate drying of the plates. In this way we obtained 421 mg of the trans keto diol (II) and 43 mg of the cis isomer (III), which indicates that the ratio of the amounts of the products in the mixture was about 10 : 1.

1.5 g of the trans acetate (V) was dissolved in 80 ml of 5% aqueous ethanol containing 700 mg of sodium hydroxide. The mixture was heated in a boiling water bath for 3.5 hours. After neutralization and the usual treatment we obtained 1.0 g of the cis keto diol (III), which melted without depression in admixture with a known sample.

SUMMARY

1. The acetolysis of 1-acetyl-1,2-epoxycyclohexane (IV) with glacial acetic acid gives the trans diol monoacetate (V).

2. A study was made of the stabilities of the isomeric acetylcyclohexanediols (II) and (III) under alkaline and acid conditions. Under alkaline conditions the trans acetylcyclohexanediol (II) and its monoacetate (V) are converted into the cis acetylcyclohexanediol (III). Under these conditions the latter is not isomerized into the trans isomer.

3. Some observations are made relating to the possible causes of the different behaviors of substances of the trans and cis series in acetylation and reactions leading to carbonyl derivatives.

LITERATURE CITED

1. A. A. Akhrem, Izv. AN SSSR. Otd. khim. n. 845 (1962).
2. A. A. Akhrem, Doctorate Dissertation, Moscow, 1958-1959, M. I. Batuev, A A. Akhrem, and A. D Matveeva, Dokl. AN SSSR 129, 1038 (1959).
3. R. Filler, B. Camara, and S. Naqvi, J. Amer. Chem. Soc. 81, 658 (1959).
4. J. Meinwald and S. L. Emerman, J. Amer. Chem. Soc. 78, 5087 (1956).
5. A. A. Akhrem and A. I. Kuznetsova, Uspekhi khimii 32, No. 7 (1963); A. A. Akhrem, A. I. Kuznetsova, Yu. A. Titov, and I. S. Levina, Izv. AN SSSR. Otd. khim. n. 657 (1962).
6. D. H. R. Barton and R. Cooxon, Quart. Rews 10, 44 (1956).
7. R. Abramovitch and K. Schofield, J. Chem. Soc. 2326 (1955).

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue

---