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1958

SovietRxiv

Abstract

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Chemistry

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INTRODUCTION OF DIOXYCARBONIC, GLYCERIC, AND OXYACETONE SIDE CHAINS INTO *ortho*-METHYLCYCLOHEXANONE AND THE STEREOCHEMISTRY OF THE COMPOUNDS FORMED THEREBY

Recently (^{1}) we described several methods for introducing oxygenated side chains into cyclic compounds on the basis of available acetylenic alcohols and their derivatives. As is known, the introduction of a dioxyacetone side chain constitutes an important task in the problem of the total and partial synthesis of corticosteroids in general, and of cortisone and its analogs in particular.

In studying the reaction of addition of bromohydric acid to tertiary acetylenic alcohols and their acetates, we found for the first time (^{1}) that in the case of tert.-acetylenic alcohols this reaction proceeds anomalously and leads to the formation of undefined dibromides instead of the expected dibromoketols.

In the present communication we briefly set forth the results of our investigations on the introduction of an oxygenated side chain into *ortho*-methylcyclohexanone (I).

Upon condensation of ketone I with acetylene under pressure (^{2}) in the presence of powdered caustic potash, 2-methyl-1-ethynylcyclohexanol is formed in high yield as two epimers: crystalline (II), m.p. 56–57°, and liquid (III), b.p. 75°/15 mm, n_D^{20} 1.4770. The ratio of the epimers is 3 : 2 and apparently depends on the conditions of synthesis (^{3}).

Earlier (^{4}) we showed that the crystalline acetylenic alcohol (II) has the cis configuration, while the liquid (III) is its trans isomer.

$$\mathrm{I} \xrightarrow{\mathrm{CH{\equiv}CH}} \mathrm{II} + \mathrm{III}$$

Upon acetylation of alcohols II and III with an excess of acetic anhydride, acetates IV and V, respectively, are formed in high yield.

On treatment of the cis-acetate IV with bromohydric acid, the normal addition reaction at the triple bond takes place and crystalline acetate of cis-1-(ω-dibromoacetyl)-2-methylcyclohexanol (VI) is formed in 95% yield.

$$\text{IV} \xrightarrow{\text{2HBr}} \text{VI, m.p. 90-90.5}^\circ \xrightarrow{\text{Ba(OH)}_2} \begin{cases} \text{VII, m.p. 149-150}^\circ, \\ \text{VIII, m.p. 128-129}^\circ. \end{cases}$$

On treatment of the acetate of the cis-dibromoketol (VI) with an aqueous solution of barium hydroxide hydrate, the intramolecular rearrangement described by us earlier (^{1}) occurs, giving, in about 50% yield, a mixture of two isomeric dioxycarboxylic acids (VII and VIII), which differ from one another in the configuration of the secondary hydroxyl. Acid VII is formed in the predominant amount. Acids VII and VIII, on treatment with an ethereal solution of diazomethane, give the methyl esters IX and X; on reduction of these with lithium aluminum hydride, triols XI and XII are formed.

$$\begin{array}{lclcl} \text{VII—m.p. 149-150}^\circ & & \text{IX—liquid} & & \text{XI—m.p. 88-88.5}^\circ \\ & \xrightarrow{\text{CH}_2\text{N}_2} & & \xrightarrow{\text{LiAlH}_4} & \\ \text{VIII—m.p. 128-129}^\circ & & \text{X—m.p. 73-74}^\circ & & \text{XII—m.p. 90-90.5}^\circ \end{array}$$

A mixed sample of the isomeric triols XI and XII melts at 50-55°.
Analogous transformations were also carried out with the trans-acetate V.

$$\text{V} \xrightarrow{\text{2HOBr}} \text{XIII} \xrightarrow{\text{Ba(OH)}_2} \begin{array}{l} \text{XIV—m.p. 156-156.5}^\circ \\ \text{XV—m.p. 109-110}^\circ \end{array}$$

Under the conditions described above, trans-dibromoketol (XIII) was obtained; on treatment of it with barium hydroxide hydrate, a mixture of two isomeric trans-dioxy acids (XIV and XV) with m.p. 156-156.5° and 109-110°, respectively, is formed in 50% yield.

The trans-acids XIV and XV were converted into their methyl esters XVI and XVII, on reduction of which with lithium aluminum hydride the triols XVIII and XIX were obtained:

$$\begin{array}{lclcl} \text{XIV—m.p. 156-156.5}^\circ & & \text{XVI—m.p. 91-91.5}^\circ & & \text{XVIII—m.p. 125-125.5}^\circ \\ & \xrightarrow{\text{CH}_2\text{N}_2} & & \xrightarrow{\text{LiAlH}_4} & \\ \text{XV—m.p. 109-110}^\circ & & \text{XVII—m.p. 33-34}^\circ & & \text{XIX—m.p. 88-88.5}^\circ \end{array}$$

A mixed sample of triols XI and XIX, which have the same m.p. 88-88.5°, gives a sharp depression and melts at 55-65°.

On catalytic selective hydrogenation of the cis-acetylenic alcohol II over a Pd catalyst, cis-2-methyl-1-vinylcyclohexanol (XX) was obtained in high yield; oxidation of it by Prilezhaev' s method with peracetic acid in chloroform gives, in 80% yield, a mixture of the isomeric glycidic alcohols XXI and XXII with m.p. 43-43.5° and liquid, respectively. Glycidic alcohol XXII was isolated in the larger amount.

$$\text{XX} \xrightarrow{CH_3CO_3H} \begin{array}{l}\text{XXI—m.p. } 43\text{-}43.5^\circ \\ \text{XXII—liquid}\end{array} \xrightarrow[H^+]{H_2O} \begin{array}{l}\text{XI—m.p. } 88\text{-}88.5^\circ \\ \text{XII—m.p. } 89\text{-}90^\circ\end{array}$$

Glycid XXI, m.p. 43-43.5°, on heating with acidified water is smoothly hydrolyzed to the triol (XI) described above, m.p. 88-88.5°. Upon hydrolysis of glycid XXII, a small amount of the triol XII described above, m.p. 89-90°, was isolated. The identity of the substances was confirmed by mixed-melting tests.

Upon oxidation of trans-2-methyl-1-vinylcyclohexanol (XXIII) with peracetic acid in chloroform, two crystalline glycidic alcohols (XXIV and XXV), epimeric at the asymmetric carbon atom of the oxidized side chain, were isolated. Glycid XXIV was isolated in the larger amount:

$$\text{XXIII} \xrightarrow{CH_3CO_3H} \begin{array}{c}\text{XXIV —m.p. } 73\text{-}74^\circ \\ \text{XXV —m.p. } 40\text{-}41^\circ\end{array} \xrightarrow[H^+]{H_2O} \begin{array}{c}\text{XVIII —m.p. } 125\text{-}125.5^\circ \\ \text{XIX —m.p. } 88\text{-}88.5^\circ\end{array}$$

Upon hydrolysis of glycid XXIV with acidified water, the triol XVIII described above, m.p. 125-125.5°, is formed in good yield; it was also obtained by reduction of the ester of trans-dioxy acid XVI with lithium aluminum hydride. Glycid XXV, on treatment with acidified water, is hydrolyzed with formation of triol XIX, m.p. 88-85°, which was not obtained by reduction of the ester of dioxy acid XVII. As follows from the experimental results, oxidation of the unsaturated alcohols XX and XXIII with peracetic acid does not proceed strictly selectively and leads to the formation of all the glycidic alcohol isomers predicted by theory (XXI, XXII, XXIV, and XXV). A mixture of glycid XXI, m.p. 43-43.5°, and XXV, m.p. 40-41°, melts at room temperature.

Upon catalytic selective hydrogenation over a Pd catalyst of cis-acetate IV and trans-acetate V, the acetates of cis-2-methyl-1-vinylcyclohexanol (XXVII) and trans-2-methyl-1-vinylcyclohexanol (XXVIII), respectively, were obtained.

Upon oxidation of cis-acetate XXVII with peracetic acid, a mixture of two epimeric triol monoacetates (XXIX and XXX), m.p. 99-100° and 57-58°, is formed.

The normal products of the oxidation reaction—the acetates of glycidic alcohol XXXI—were not isolated in this case.

$$\text{XXVII} \xrightarrow{CH_3CO_3H} \begin{array}{c}\text{XXIX —m.p. } 99\text{-}100^\circ \\ \text{XXX —m.p. } 57\text{-}58^\circ\end{array} \qquad \text{XXXI}$$

By alkaline hydrolysis of acetates XXIX and XXX it was shown that they contain one acetyl group. Thus, from the hydrolysis products of acetate XXIX, m.p. 99-100°, the triol XI described above, m.p. 88°, was isolated. Acetate XXX, m.p. 57-58°, on saponification gave the triol XII described above, m.p.

90–90.5°. A similar result was obtained also upon oxidation of trans-acetate XXVIII:

$$\text{XXVIII} \xrightarrow{CH_3CO_3H} \text{XXXIII} \qquad \text{XXXII}$$

In this case, instead of the expected glycidol acetate XXXII, a liquid mixture of monoacetates of isomeric triols XXXIII was isolated; upon hydrolysis of this mixture, two triols (XIX and XXVI) were obtained, with m.p. 86–87° and 111–112°, respectively. Triol XXVI was isolated in the larger amount.

The results obtained indicate that oxidation of acetates of tertiary vinyl alcohols with peracetic acid, unlike oxidation of the corresponding vinyl alcohols and acetates of allylic alcohols, proceeds differently and does not lead to the formation of the normal oxidation products—acetates of glycidol alcohols (1).

Conformational analysis (5), as is known, makes it possible to relate the stereochemistry of a molecule to its reactivity. It was therefore of interest, using the epimeric acetylenic alcohols II and III as an example, to study the hydration reaction of the triple bond, as well as the acetylation of the tertiary hydroxyl, in order to establish the dependence of the reaction rate on the equatorial or axial position of the substituent. Upon hydration of the cis alcohol II in methanolic solution in the presence of mercuric sulfate and sulfuric acid, the cis-α-ketol XXXIV, m.p. 37–38° (6), is formed in almost quantitative yield. The trans alcohol III is hydrated to the liquid trans-α-ketol XXXV at a somewhat higher rate, but in lower yield.

$$\text{II} \xrightarrow[H_2O]{HgSO_4} \text{XXXIV, m.p. 37–38°} \xrightarrow[\text{ether}]{CH_3COCl} \text{XXXVI}$$

$$\text{III} \xrightarrow[H_2O]{HgSO_4} \text{XXXV} \xrightarrow[H_2SO_4]{(Ac)_2O} \text{XXXVII}$$

A more pronounced difference is observed in the acetylation reaction of the hydroxyl group of the epimeric pair of α-ketols XXXIV and XXXV. Thus, the cis-α-ketol XXXIV is acetylated under mild conditions by boiling with an excess of acetyl chloride in ether. The trans-α-ketol XXXV is acetylated only by the action of acetic anhydride in the presence of concentrated sulfuric acid. In this process the acetates XXXVI and XXXVII are formed in almost quantitative yields. The result obtained indicates that in the cis-α-ketol XXXIV the tertiary hydroxyl apparently has an equatorial configuration, whereas in the trans-α-ketol XXXV the latter occupies an axial position (7). This conclusion is in agreement with data recently obtained in the study of combination light-scattering spectra (8).

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Received
21 XII 1957

CITED LITERATURE

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