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reaction scheme showing steroidal structures (I) → (II) → (III) → (IV)

Figure 1: reaction scheme showing steroidal structures (I) → (II) → (III) → (IV)

## Abstract

## Full Text

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# A NEW ONE-STAGE ROUTE TO THE SYNTHESIS OF STEROIDAL cis-16$\alpha$,17$\alpha$-DIOLS FROM $\alpha$-KETO EPOXIDES

*(Presented by Academician B. A. Kazansky, 16 XI 1964)*

We have previously shown ([1,2]) that the sterically anomalous opening of $\alpha$-keto epoxides (I) in acetic acid in the presence of nitrogen-containing reagents for a keto group, such as carbethoxyhydrazine, proceeds through the stage of formation of the $\alpha$-keto epoxide hydrazone (II), which under the reaction conditions, or upon treatment with acetic acid, undergoes *cis*-opening of the epoxy ring with formation of the hydrazone of the diol acetate (III).

In the course of proving the structure of the carbonyl derivative of the $\alpha$-keto epoxide (II), we replaced, in the reaction of the $\alpha$-keto epoxide (I) with the base, acetic acid by an aqueous dioxane solution of sulfuric acid, taken in an amount equivalent to the base. It was found that, as with acetic acid, the same hydrazone (II) is formed first, although more slowly, which confirmed the absence of incorporation of an acetoxy group into molecule (II). Further treatment of this compound with a solution of sulfuric acid led directly to the *cis*-diol (IV), bypassing the stage of the carbonyl derivative of the *cis*-diol. On the basis of these observations we developed ([3]) a new simple route for the synthesis of *cis*-diols (IV) from $\alpha$-keto epoxides (I), consisting in treatment of the $\alpha$-keto epoxides (I) with an aqueous dioxane solution of carbethoxyhydrazine sulfate. The reaction is carried out at room temperature in one stage without isolation of the hydrazone (II). The advantages of this method for the synthesis of *cis*-diols, in comparison with the usual ones ([4,5]), consist not only in reducing the number of stages, but also in the fact that it does not require the use of pyruvic acid for deprotection of the carbonyl group. The generality of the method was tested both for steroidal and for monocyclic compounds. Thus, from 16$\alpha$,17$\alpha$-epoxy-$\Delta^5$-pregnenol-3$\beta$-one-20 (V), upon treatment with an aqueous dioxane solution of carbethoxyhydrazine sulfate, $\Delta^5$-pregnenetriol-3$\beta$,16$\alpha$,17$\alpha$-one-20 (VI)—a key

product in the synthesis of 16-oxosteroids—was obtained in 78% yield.

(V) ⟶ (VI)

It is interesting to note that under the reaction conditions *D*-homoisomerization practically does not occur.

Analogous treatment of acetylcyclohexene oxide (VII) led to cis-1-acetylcyclohexanediol-1,2 (VIII) in 82.5% yield.

(VII) ⟶ (VIII)

The diols obtained proved to be identical with compounds obtained by the usual route ([4,6]).

## Experimental Part

Melting points were determined in a capillary. Infrared spectra were recorded on a UR-10 instrument. For thin-layer chromatography, KSK silica gel (100-150 mesh), prepared according to ([7]), was used. Chromatography was carried out in the ether—hexane system (4 : 1), with development by sulfuric acid ([7]).

**Carbethoxyhydrazone of 16$\alpha$,17$\alpha$-epoxy-$\Delta^5$-pregnenol-3$\beta$-one-20.** To a solution of 500 mg of 16$\alpha$,17$\alpha$-oxide (V) in 25 ml of dioxane was added a solution of 500 mg of carbethoxyhydrazine and 0.25 ml of conc. sulfuric acid in 25 ml of aqueous dioxane, and the mixture was left for 15 min at room temperature, then poured into 1 liter of water; the precipitate that separated was filtered off, washed with water, and dried. This gave 570 mg of a mixture, which was chromatographed on a column with 60 g of silica gel in a gradient benzene—ether system (1200 ml). The following fractions were isolated:
1) 320 mg of starting oxide (V), mp 186-190° (from aqueous methanol) ([2,4]);
2) 80 mg of carbethoxyhydrazone of 16$\alpha$,17$\alpha$-epoxy-$\Delta^5$-pregnenol-3$\beta$-one-20 (IX), mp 172-174° (from acetone—$C_6H_{14}$) ([4]);
3) 35 mg of carbethoxyhydrazone of the triol (X), mp 188-191° (from aqueous methanol) ([4]). The chromatogram showed the presence of traces of free triol (VI).

**Carbethoxyhydrazone of $\Delta^5$-pregnenetriol-3$\beta$,16$\alpha$,17$\alpha$-one-20.** To a solution of 50 mg of 16,17-oxide (V) in 3 ml of dioxane was added a solution of 8 mg of carbethoxyhydrazine and 0.005 ml of concentrated sulfuric acid in 3 ml of aqueous dioxane, and the mixture was kept for 2 h at room temperature. The chromatogram of the reaction mixture indicated the presence in it, in addition to the starting oxide (V), also of carbethoxyhydrazone of the oxide (IX) and carbethoxyhydrazone of the triol (X).

**$\Delta^5$-Pregnenetriol-3$\beta$,16$\alpha$,17$\alpha$-one-20.**
a) To a solution of 500 mg of 16$\alpha$,17$\alpha$-oxide (V) in 20 ml of dioxane was added a

solution of 500 mg of carbethoxyhydrazine and 0.25 ml of concentrated sulfuric acid in 25 ml of 85% aqueous dioxane, and the mixture was left for 20 h at room temperature. The reaction mass was then neutralized with a solution of 300 mg of soda, evaporated, and the residue was washed with water. After crystallization

from acetone–hexane there was obtained 400 mg (yield 78%) of $\Delta^5$-pregnenetriol-3$\beta$,16$\alpha$,17$\alpha$-one-20 (VI), mp 225; 234–236°, $[\alpha]_D^{20} - 85.8°$ (c 0.595 in $CHCl_3$); $R_f$ 0.46, IR spectrum 1700, 3300 $cm^{-1}$, identical with that of an authentic sample (2, 4).

b) To a solution of 100 mg of the carbethoxyhydrazone of the oxide (IX) in 10 ml of dioxane, 0.01 ml of concentrated sulfuric acid was added, and the mixture was left for 8 h at room temperature. The chromatogram showed the presence in the mixture of the free triol (VI), together with the starting carbethoxyhydrazone (IX).

**cis-1-Acetylcyclohexanediol-1,2 (VIII).** To a solution of 1.9 g of acetylcyclohexene oxide (VII) in 45 ml of dioxane, a solution of 1.5 g of carbethoxyhydrazine and 0.5 ml of concentrated sulfuric acid in 40 ml of 85% aqueous dioxane was added dropwise. The reaction mixture was kept for 12 h at room temperature, neutralized with sodium bicarbonate solution while cooling, evaporated, diluted with 50 ml of water, and extracted with ether. After drying and evaporation, the residue was crystallized from ether–hexane. There was obtained 1.77 g (yield 82.5%) of cis-1-acetylcyclohexanediol-1,2 (VIII), mp 76–77°, identical with an authentic sample (6).

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*Note: Figure translations are in progress. See original paper for figures.*