CORTICOSTEROID ANALOGS

COMMUNICATION 13. cis-OPENING OF 1-ACETYL-1,2-EPOXYCYCLOHEXANE*

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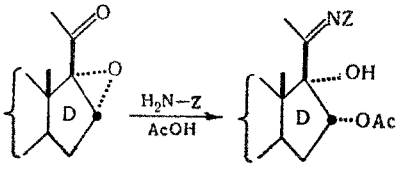
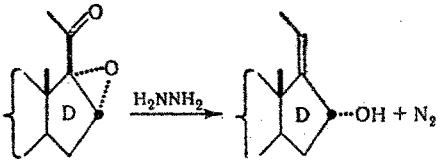
The introduction of a 16α-hydroxy group into the steroid molecule is of considerable interest because modified compounds of this kind have high physiological activity [1]. This problem has been solved in several ways; in particular by the reaction of keto epoxides with reagents for the carbonyl group. Some unsuccessful attempts to prepare carbonyl derivatives from keto epoxides by the standar procedure have been described in the literature [2]. However, in 1955 a method was patented for the synthesis of phenylhydrazones by the reaction of steroid keto epoxides with phenylhydrazine in a medium of glacial acetic acid [3]. Petrow and co-workers [4] investigated this reaction with ethyl carbazate and showed that cis-opening of the keto epoxide then occurred as follows;



Z = NHPh; $NHCO_2Et$

The mechanism of this reaction is unknown [5], but it is very probable that a reaction of this type is the reduction of keto epoxides to allyl alcohols with hydrazine hydrate in presence of acetic acid [6] or under the conditions of the Huang-Minlon reaction [7]. Here, for the oxygen function in the β-position the configuration of the original keto epoxide is preserved.



In the present investigation we studied the reactions of semicarbazide, ethyl carbazate, hydroxylamine, and 2,4-dinitrophenylhydrazine with 1-acetyl-1,2-epoxycyclohexane (I), which is a convenient model for the ring in D-homosteroids. The results are presented in Tables 1 and 2.

The reactions of the keto epoxide (I) with semicarbazide and with ethyl carbazide in acetic acid at room temperature lead to the formation of the semicarbazone (II) and the hydrazone (III), respectively. These compounds were obtained under identical conditions from the cis-monoacetate (IV) [8], which is readily regenerated by acid hydrolysis in the acetate buffer. This indicates that as a result of the reaction of reagents for carbonyl with the keto epoxide (I) under the given conditions, cis-opening of the epoxide ring occurs with the uptake of one molecule of acetic acid.

The cis hydrazone (III) then formed differed from the hydrazone (VI) prepared from the trans-monoacetate (V) [8, 9] under the same conditions as the hydrazone (III).

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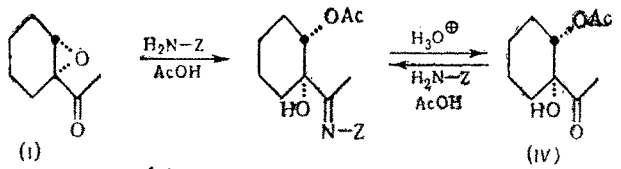
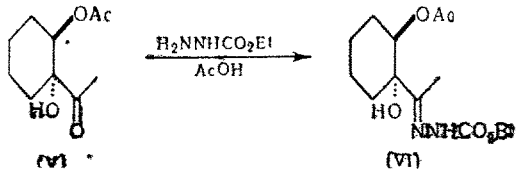
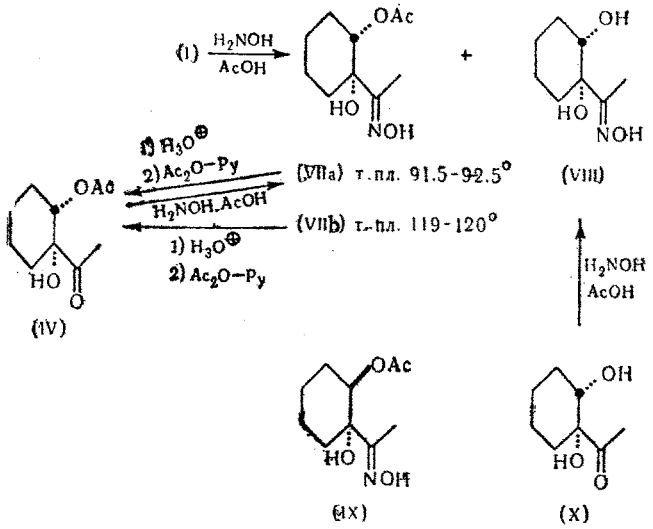




An analogous result was obtained in the reaction of the keto epoxide with hydroxylamine and with 2,4-dinitrophenylhydrazine. In the first case analysis of the reaction products with the aid of thin-layer chromatography on silica gel (containing 19% of water) showed the presence of three substances having R_f values of 0.63, 0.52, and 0.25 (in system 75 : 25 aqueous ether and hexane). The chromatographic separation of this mixture on silica gel gave (respectively) the cis keto diol monoacetate oxime (VIIa), m.p. 91.5-92.5°, and the isomeric oxime (VIIb), m.p. 119-120°, in about 1 : 1 proportions together with a small amount of the cis keto diol oxime (VIII). In their properties the oximes (VIIa) and (VIIb) differed from the oxime of the trans monoacetate (IX), m.p. 132.5-133.5° and R_f 0.69, obtained from (V), but the oximes (VIIa) and VIII) coincided in their properties in all respects with the products obtained by confirmatory synthesis from the corresponding ketones (IV) and (X) [8, 9]. The infrared spectra of both the oximes (VIIa) and (VIIb) had identical absorption bands in the region 1700-3000 cm^{-1} and differed in the positions of the absorption maxima of the hydroxy group. Under acid hydrolysis conditions the oximes (VIIa) and (VIIb) were converted into the cis keto diol (X), which was isolated as the monoacetate (IV).



On the basis of all these data we regard the oximes (VIIa) and (VIIb) formed in the opening of the keto epoxide (I) with hydroxylamine in acetic acid as an example of syn-anti isomerism. This phenomenon is observed neither in the case of the confirmatory synthesis of the carbonyl derivatives nor in the case of their formation from the keto epoxide and semicarbazide, ethyl carbazate, and 2,4-dinitrophenylhydrazine. This last reaction was investigated particularly carefully in view of the ease of separating and identifying the 2,4-dinitrophenylhydrazones formed. The main product, isolated from the reaction mixture in 72% yield, was the product of the cis-opening of the keto epoxide: the 2,4-dinitrophenylhydrazone (XI), R_f 0.50 (silica gel containing 19% of water; 70 : 30 aqueous ether and hexane), is undepressed in melting point by admixture of the sample obtained in the confirmatory synthesis from the cis monoacetate (IV). The latter was obtained in good yield by the acid hydrolysis of the hydrazone (XI) in presence of py-

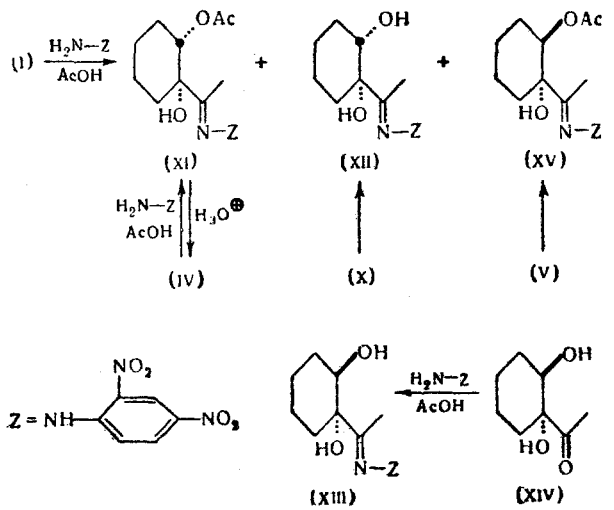
TABLE 1. Reaction of the Keto Epoxide (I) with Reagents for the Carbonyl Group in an Acetic Acid Medium

Compound	M.p., °C	Found, %			Formula	Calculated, %			Yield, %		Crystallization from
		C	H	N		C	H	N	from keto epoxide (I)	confirmatory synthesis	
II	196,5—198 (decomp.)	51.42	7.43	16.36	$C_{11}H_{19}O_4N_3$	51.35	7.44	16.33	63.5	89	30% EtOH
III	118—119	54.30	7.64	9.98	$C_{13}H_{22}O_5N_2$	54.53	7.75	9.78	48.4	97	Ether-hexane
VI	106—107	54.26	7.75	9.85					—	91	»
VII	a 91.5—92.5	55.59	8.12	6.71	$C_{10}H_{17}O_4N$	55.80	7.96	6.51	31.5	96	»
	b 119—120	55.78	8.00	6.76					29.3	—	»
IX	132.5—133.5	55.85	7.88	6.87	$C_8H_{15}O_3N$	55.47	8.73	8.09	—	92.5	»
VIII	101—102	55.16	8.70	7.88					7.0	45.8	»
XI	179,5—180,5	50.81	5.58	14.60	$C_{16}H_{20}O_7N_4$	50.52	5.30	14.73	71.7	96.5	EtOH
XV	135—135.5	50.45	5.28	14.79					0.7	94	Ditto
XII	188.5—189.5	49.49	5.05	16.42	$C_{14}H_{18}O_6N_4$	49.70	5.36	16.56	4.1	92	»
XIII	173—174	49.48	5.40	16.86					—	90	»

TABLE 2. Spectral Characteristics of Carbonyl Derivatives of 1-Acetyl-1,2-cyclohexanediol

Compound	Infrared spectrum, cm^{-1}: 1) in chloroform; 2) in mineral oil	Ultraviolet spectrum in ethanol: λ_{max}, mμ; ε
II	1) 1 700, 1 727 2) 3 128; 3 213; 3 316; 3 362; 3 490	227 11040
III	1) 1 725; 1 747 2) 3 105; 3 145; 3 227; 3 461	222.5 18 900
VI	1) 1 739 2) 3 110; 3 150; 3 230; 3 406	210 220 12 400 11 600
VIIa	1) 1 730; 2 865; 2 945; 3 415	—
VIIb	1) 1 735; 2 865; 2 945; 3 345	—
IX	1) 1 730; 2 865; 2 945; 3 400	—
VIII	1) 3 365	—
XI	1) 1 737 2) 3 093; 3 111; 3 314; 3 376; 3 492	359
XV	1) 1 739 2) 3 110; 3 320; 3 476	358
XII	2) 3 112; 3 300; 3 376	360
XIII	2) 3 109; 3 322; 3 376	362

ruvic acid. Analysis of the mother liquors with the aid of thin-layer chromatography on silica gel showed that, apart from unchanged 2,4-dinitrophenylhydrazine and the hydrazone (XI), they contained the 2,4-dinitrophenylhydrazone of the cis-diol (XII), R_f 0.24, identical with a known sample obtained by confirmatory synthesis from (X) and differing from the 2,4-dinitrophenylhydrazone (XIII), R_f 0.32, obtained from the trans keto diol (XIV) [8, 9]. In addition, the chromatogram of the mother liquors showed the presence of traces of the 2,4-dinitrophenylhydrazone of the trans keto diol monoacetate (XV), R_f 0.60, identical with the sample obtained by confirmatory synthesis from the trans monoacetate (V). The mixture of products, (XI), (XII), and (XV), was separated with the aid of preparative thin-layer chromatography (see Experimental).



Without concerning ourselves with the mechanism of the reaction observed, which leads to the cis-opening of the epoxide ring, we may explain the presence of a very small amount of the trans 2,4-dinitrophenylhydrazone (XV) by the usual opening of the keto epoxide (I) by means of acetic acid [8, 9] with subsequent (or simultaneous) formation of the derivative at the carbonyl group.

EXPERIMENTAL

Cis-opening of 1-Acetyl-1,2-epoxycyclohexane (I) by Means of Reagents for the Carbonyl Group: Reaction of the Keto Epoxide (I) with 2,4-Dinitrophenylhydrazine. 5.6 g of (I) and 8.0 g of 2,4-dinitrophenylhydrazine in 250 ml of glacial acetic acid were kept at room temperature for 28 hours. Acetic acid was then removed in a vacuum, and the yellow crystalline precipitate was washed on the filter with water and crystallized from alcohol. After two crystallizations we obtained 9.94 g of cis-2-acetoxy-1-acetylcyclohexanol 2,4-dinitrophenylhydrazone (XI) in the form of light-yellow needles, m.p. 179.5-180.5°. The evaporated mother liquors (2.6 g) were dissolved in 20 ml of methanol and subjected to preparative separation on ten plates (20 × 33 cm) carrying silica gel containing 19% of water, layer thickness 2 mm, in 60 : 40 aqueous ether and hexane. We obtained three fractions, and in the course of their isolation from the sorbent (with methanol) and the removal of solvent these became strongly resinified. The fractions were purified from resin by filtering their alcoholic solutions through a layer of alumina of activity II. As a result, from Fraction I we isolated 110 mg of trans-2-acetoxy-1-acetylcyclohexanol 2,4-dinitrophenylhydrazone (XV) in the form of yellow needles of m.p. 135-135.5° (from alcohol). From Fraction II we obtained 960 mg of the cis 2,4-dinitrophenylhydrazone (XI). From Fraction III we isolated 545 mg of cis-1-acetyl-1,2-cyclohexanediol 2,4-dinitrophenylhydrazone (XII) in the form of yellow needles, m.p. 188.5-189.5° (from alcohol).

By the same method [4] we prepared all the carbonyl derivatives of the ketones (IV), (V), (X), and (XIV), and we also carried out reactions of the keto epoxide (I) with bases of the carbonyl reagents. The bases of semicarbazide and hydroxylamine were prepared by a previously described method [10]. Ethyl carbazide base was synthesized by Diels's method [11].

Hydrolysis of cis-2-Acetoxy-1-acetylcyclohexanol 2,4-Dinitrophenylhydrazone (XI). A mixture of the 2,4-dinitrophenylhydrazone (XI) (4.2 g) and 7.1 g of freshly distilled pyruvic acid in 500 ml of 80% acetic acid was heated in a boiling water bath for three hours. The solution was then vacuum-evaporated to dryness, and the residue was treated with water (70 ml) and neutralized with saturated sodium bicarbonate solution. The insoluble yellow crystals were filtered off and washed on the filter with ether, which was then combined with the ether extract of the aqueous layer. After recrystallization from alcohol the yellow substance was found to be unchanged cis 2,4-dinitrophenylhydrazone (XI) (2.1 g). From the ether extract, after the usual treatment and recrystallization from a mixture of ether and hexane, we obtained 950 mg of the cis monoacetate (IV), which melted without depression in admixture with a known sample [8].

Hydrolysis of cis-2-Acetoxy-1-acetylcyclohexanol Oxime (VIIa) and (VIIb). A mixture of 850 mg of the cis oxime (VIIa) or its isomer (VIIb), 40 ml of 40% aqueous methanol, and 2 ml of concentrated hydrochloric acid was heated at the boiling point of the reaction mixture for seven hours. Solvent was removed in a vacuum, and the residue

was treated with 20 ml of water, neutralized with saturated sodium bicarbonate solution, and extracted with ether. The usual treatment of the extract gave 550 mg of a crystallizing oil, the chromatogram of which gave a spot for the cis keto diol (X). The product was treated with 15 ml of pyridine and 1 ml of acetic anhydride; it was then left at room temperature overnight. Pyridine and excess of acetic anhydride were removed in a vacuum, and the residue was treated with 20 ml of water and extracted with ether. The usual treatment of the ether extract gave 540 mg of the cis monoacetate (IV), identical with a known sample.

Hydrolysis of cis-2-Acetoxy-1-acetylcyclohexanol Semicarbazone (II). 2.21 g of freshly distilled pyruvic acid and 2.4 g of anhydrous sodium acetate were dissolved in 25 ml of glacial acetic acid and 2.5 ml of water, and the solution was added to 4.3 g of the semicarbazone (II) in 25 ml of glacial acetic acid. The mixture was heated for 3.5 hours in a boiling water bath, most of the solvent was then removed in a vacuum, and the residue was diluted with 50 ml of water and extracted with ether. As a result of the usual treatment of the ether extract and recrystallization of the product from a mixture of ether and hexane we obtained 2.6 g of the cis monoacetate (IV), which melted without depression in admixture with a known sample. The chromatogram of the mother liquors showed that traces of the cis keto diol (X) were present.

Under analogous conditions from 5.4 g of cis-2-acetoxy-1-acetylcyclohexanol (ethoxycarbonyl)hydrazone (III) we obtained 3.5 g of the cis monoacetate (IV) (93% yield).

SUMMARY

1. On reaction of 1-acetyl-1,2-epoxycyclohexane (I) with reagents for the carbonyl group in an acetic acid medium, cis-opening of the epoxide ring occurs with uptake of a molecule of acetic acid (main product) or of a molecule of water (side reaction).

2. In the case of 2,4-dinitrophenylhydrazine it was found that the formation of some product of the normal (trans-) opening of the epoxide ring could also be detected (0.7% yield).

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