TRANSFORMED STEROIDS

# 108.* CORRELATION OF OPENING REACTIONS OF 16,17α-CYCLOPROPANO-20-KETOSTEROIDS WITH THE CONFORMATIONS

A. V. Kamernitskii, A. M. Turuta, and Ngo Thi Mai An

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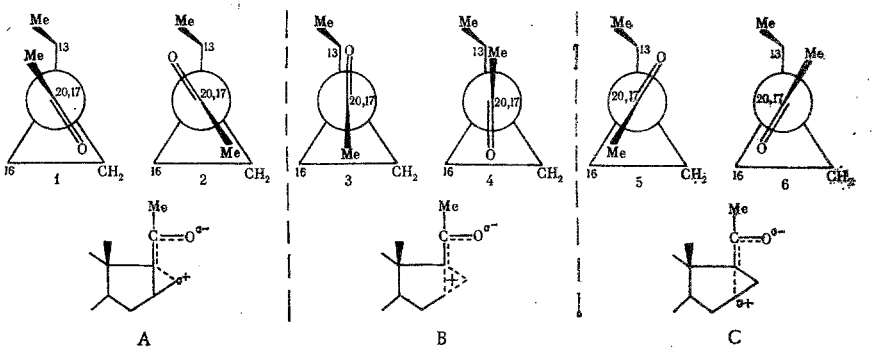
The properties of activated cyclopropanes and, in particular, of cyclopropyl ketones, have already been discussed in the literature [2-6]. The opinion was expressed that the direction of ring opening depends on the stereochemistry of the transition state and that the bond of the cyclopropane ring (CPR) that overlaps to the greatest degree with the π-electron system of the C=O group is cleaved [7]. The 16,17α-cyclopropano-20-ketosteroids, which are a very interesting model for studying problems of this type, have remained practically unstudied from this standpoint. Only the preparative aspect of the Birch reduction [8] and HHal additon [9, 10] reactions was studied. Here only the 16α-R-substituted (R = $CH_3$, $CH_2Cl$, $CH_2Br$, $CH_2I$) pregnenolones were isolated, which are formed by cleavage of the exo 17-C−$CH_2$ bond of the CPR. On the basis that these reactions have such a high stereospecificity, and taking the above said into account, it could be concluded that the preferred conformations are those in which only the exo bond (17-C−$CH_2$) overlaps with the π-electron system of the keto group (conformers 1 or 2). At the same time, a study of the circular dichroism (CD) spectra of 3'-H-cyclopropa[16,17α]pregn-5-en-3β-ol-20-one 3-acetate (I)




disclosed [11] that of the two bisectorial conformations, which satisfy the requirement of maximum conjugation of the keto group and the CPR [7, 12, 13] (conformers 3 and 4), only the s-transoid conformation 3 agrees with the experimental data, and apparently this conformation should be regarded as being the preferred in the ground state. In transoid conformer 3 the 17-C−16-C and 17-C−$CH_2$ bonds of the CPR, next to the keto group, have the same overlap with the π-shell of the carbonyl. In this situation, on the assumption that the conformations of the molecule in the ground and transition states are identical, a symmetrically polarized structure of the B type must be expected, and consequently a low regioselectivity of ring opening, i.e., cleavage of all three bonds of the ring is possible. To eliminate this contradiction, we studied the reaction of (I) [14] with thiocyanic acid (refluxing with KSCN or heating with pyridine thiocyanate in ethanol, pyridine or acetonitrile). In selecting the reagent we took into account its high reactivity (for example, (Ib), does not react with AcOH), and the convenience of identifying their desulfurization products. It was found that independent of the conditions (KSCN in AcOH or $C_5H_5N \cdot HSCN$ in pyridine or MeCN) the reaction of (Ia) with HSCN proceeds with opening of both the exo and endo α-bond of (I) and here thiocyanates (IIa) and (III) are formed in a 3-4:1 ratio. The reaction of (Ia) with $C_5H_5N \cdot HSCN$ in ethanol proceeds with partial hydrolysis of the 3-acetoxy group, which makes it difficult to separate the reaction mixture and quantitatively estimate the ratios of the products. The high selecti-

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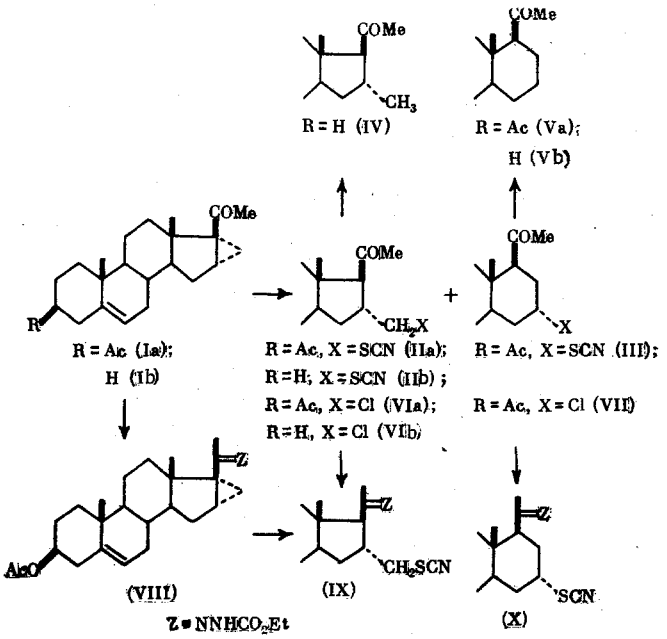
vity of the reaction indicates that in the transition state the C=O grouping is drawn out somewhat from the s-transoid conformation 3, which postulates a maximum electron delocalization [11]. Such a deviation (up to 30° on either side) leads to conformations 2 and 5, in which the C=O group is respectively conjugated with either the exo or endo cyclopropane bond.

The fact that the reaction of (Ia) with HSCN proceeds with the predominant formation of product (IIa) makes it possible to conclude that the exo 17-C−$CH_2$ α-bond of (I) has the best possibilities for conjugation, i.e., polarization of the A type, and consequently conformation 2,




is the preferred. Polarization of the C type, which leads to cleavage of the 17-C−16-C bond and the formation of product (III) is realized to much less degree. Other reaction products, in particular, those obtained by cleavage of the 16-C−$CH_2$ bond, are absent. Hence it follows that the symmetrically polarized structure B, which is realized in the bisectorial conformer 3, is not formed. Restriction of the analyses only to the transoid conformations 2, 3, and 5 is due to two reasons. First, the CD spectral data contradict the s-cisoid conformations of the molecule in the ground state [11]. Second, in the s-cisoid conformer 4, like in the gauche cisoid conformers 1 and 6 (deviation of 30° on either side), in view of the rigidity of a tetracyclic system a maximum degree of conjugation of the CPR with the C=O groups is impossible, since the geometry of these conformers does not correspond to the main requirement of conjugation, namely, that the planes of the p orbitals of the carbonyl group and the CPR have to be parallel. The performed analysis of the reaction products of (Ia) with HSCN makes it possible to conclude that a minimum deviation of the C=O group from the conformation of the s-transoid type 3 is observed in the transition state in the direction of a maximum overlap with the α-bonds of the CPR, in which connection the conformation equilibrium between the thus formed conformations of transoid type 2 and 5 is shifted toward the first.

The structure of products (II) and (III) follows from the physicochemical analysis results and the desulfurization data. Thiocyanates (IIa) and (III) have similar IR spectra (characteristic bands of the SCN group at 2160 $cm^{-1}$ and absorption of the carbonyl group at 1700 $cm^{-1}$). The PMR spectra of these compounds differ not only in the chemical shifts of the angular 18-$CH_3$ groups (respectively 0.61 and 0.88 ppm), but also in the position and intensity of the signals of the protons attached directly to the thiocyanato group. Thus, the two-proton signal of the $CH_2$ group in (IIa) and its hydroxy analog (IIb) appears as a broad singlet with δ 2.9 ppm, whereas the one-proton signal of 16-H in (III) appears as an unresolved, quite narrow band with δ 4.06 ppm ($W_{1/2}$ = 6 Hz), which makes it possible to assign the equatorial position to this proton. In general, the mass spectra of compounds (IIa) and (III) are identical, there is a strict repetition of the individual fragments, and only differences in the relative intensity of the peaks are observed. Thus, for example, in product (IIa) the $[M-HOAc]^+$ peak is most intense, whereas in thiocyanate (III) the $[M-HOAc-HSCN]^+$ fragment has the highest intensity. The ease of cleaving HSCN in thiocyanate (III) again indirectly confirms the axial α-configuration of the thiocyanato group. The desulfurization of thiocyanate (IIb) over Raney Ni leads to the 16α-methylpregnenolone (IV), while the desulfurization of thiocyanate (III) under analogous conditions, followed by hydrolysis of the obtained (Va), leads to the D-homoketone (Vb).

From the obtained data it follows that the character of the conjugation of the CPR with the C=O group determines the form of the intermediate cation and the structure of the formed products. It seems natural in such cases that the direction of the opening reactions and the quantitative composition of the products should remain unchanged when other nucleophilic reagents are used. As was mentioned above, the data given in [9, 10] on the opening of cyclopropyl ketones (I) by hydrogen halides do not confirm this. Consequently, we also studied the stereochemical aspect of the reaction of (Ia, b) with $C_6H_5N \cdot HCl$, taking into account the known advantages of this reagent in the opening reactions with HHal [15]. It was found that, contrary to [10], the reaction is not strictly specific, but it is regioselective, and gives a mixture of two chromatographically inseparable [in the reaction with Ia)] and difficultly separable [in the reaction with (Ib)] products, in which, based on the PMR spectroscopy data, the amount of the 16$\alpha$-chloromethylpregnenolone (VI), the cleavage product of the exo bond of the CPR, is 76%. In the PMR spectrum of this mixture, besides the intense singlet signals of the $CH_3$ protons of the 16$\alpha$-chloromethylketone (VI) with $\delta$ 0.61 ppm (18-$CH_3$), 0.94 (19-$CH_3$) and 2.08 (21-$CH_3$), are present singlet signals at 0.84, 0.92, and 2.1 ppm of the $CH_3$ protons of D-homoketone (VII), the intensity of which signals is 24% of the total intensity of the enumerated signals in pairs. A complete agreement of the positions of these signals and the chemical shifts, observed for D-homoketones (III) and (VII), makes it possible to conclude that the product, formed in smaller amounts when cyclopropane (I) is reacted with $C_5H_5N \cdot HCl$, has the D-homo structure and is the cleavage product of the endo bond of cyclopropane (I). A comparatively narrow signal at 4.54 ppm is present downfield in the NMR spectrum of (VII), which, in harmony with the above performed analysis for D-homoketone (III), was assigned to the equatorial proton at 16-C.

Replacing the 20-carbonyl group by the hydrazone fragment $N-NHCO_2Et$ does not change the general structural direction of opening the ring by thiocyanic acid, but in this case the reaction is regiospecific, with cleavage only of the exo bond of the ring, and from 3'-H-cyclopropa [16,17$\alpha$]pregn-5-en-3$\beta$-ol-20-one 3-acetate 20-carbethoxyhydrazone (VIII) by treatment with pyridine thiocyanate in MeCN is formed the 20-carbethoxyhydrazone (IX), which is identical with that obtained by the reaction of ketone (IIa) with carbethoxyhydrazine (CEH). The cleavage product of the endo 17-C–16-C bond of the ring, of hydrazone (VIII), was not detected. The reaction was run in the presence of CEH, since the hydrolysis of the hydrazone group to the keto group can be expected under these conditions. The strict structural direction of opening the ring in hydrazone (VIII) indicates a conformational rigidity of this system and a preferential conformation of the 1 or 2 type.

## EXPERIMENTAL

The melting points were determined on a Kofler block. The PMR spectra were taken on a Tesla BS-497 spectrometer (100 MHz) in $CDCl_3$ solution, and using HMDS as the internal standard. The IR spectra were obtained on a UR-10 instrument, while the mass spectra were obtained on a Varian MAT CH-6 instrument, with direct insertion of the sample into the ion source at an ionizing voltage of 70 eV.

16$\alpha$-Thiocyanatomethylpregn-5-en-3$\beta$-ol-20-one 3-Acetate (IIa) and 16$\alpha$-Thiocyanato-D-homopregn-5-en-3-$\beta$-ol-20-one 3-Acetate (III). A solution of 0.2 g of (Ia) and 0.8 g of KSCN in 6 ml of AcOH was heated for 33 h at 90°C. The mixture was diluted with water and the obtained precipitate was filtered, washed with water, and dried to give 0.2 g of product, from which we isolated by TLC ($SiO_2$, 2:3 ether–hexane) 0.01 g of unreacted (Ia) and 0.13 g of (IIa), mp 213-215° (from ether–hexane). Infrared spectrum ($\nu$, $cm^{-1}$, KBr): 1250, 1700, 1721, 2160. PMR spectrum ($\delta$, ppm): 0.61 s (18-$CH_3$), 0.95 s (19-$CH_3$), 1.96 s (3-OAc), 2.11 s (21-$CH_3$), 2.93 br. s ($CH_2SCN$), 4.52 br. (3-H). Mass spectrum (m/e): 369 $(M-HOAc)^+$, 310 $(M-HOAc-HSCN)^+$, 295 $(M-HOAc-HSCN-CH_3)^+$, 267 $(M-HOAc-HSCN-COCH_3)^+$, *260.4 (369→310).

In addition, we isolated 0.04 g of (III), mp 174-179° (from ether–hexane). Infrared spectrum ($\nu$, $cm^{-1}$, KBr): 1242, 1700, 1725, 2165. PMR spectrum ($\delta$, ppm): 0.88 s (18-$CH_3$), 0.93 s (19-$CH_3$), 1.96 s (3-OAc), 2.13 (21-$CH_3$), 4.06 br.l $W_{1/2}$ = 6 Hz (16-H), 4.52 br.l (3-H). Mass spectrum (m/e): 369$(M-HOAc)^+$, 310 $(M-HOAc-HSCN)^+$, 295 $(M-HOAc-HSCN-CH_3)^+$, *280,7 (310→295), *260.4 (369→310).

A solution of 0.1 g of (Ia) and 0.6 g of $C_5H_5N \cdot HSCN$ in 3 ml of dry $C_5H_5N$ was heated at 90° for 100 h. After the above described workup we obtained 0.1 g of a mixture, from which we isolated by TLC ($SiO_2$, 1:20 ether–$C_6H_6$) 0.06 g of 16$\alpha$-thiocyanate (IIa) and 0.014 g of D-homoketone (III), which were identical with those described above.

16$\alpha$-Thiocyanatomethylpregn-5-en-3$\beta$-ol-20-one (IIb). A solution of 0.1 g of (Ia) and 0.3 g of $C_5H_5N \cdot HSCN$ in 6 ml of EtOH was refluxed for 65 h. The solvent was evaporated, the residue was diluted with water, and the obtained precipitate was filtered and dried to give 0.06 g of (IIb), mp 162-166° (from ether) (TLC, 1:15 ether–$C_6H_6$). Infrared spectrum ($\nu$, $cm^{-1}$, KBr): 1060, 1358, 1690, 2160, 3550. PMR spectrum ($\delta$, ppm): 0.60 s (18-$CH_3$), 0.93 s (19-$CH_3$), 2.09 s (21-$CH_3$), 2.93 br.l ($CH_2SCN$), 3.45 br.l (3–H). Mass spectrum (m/e): 387

($M^+$), 369 $(M-H_2O)^+$, 328 $(M-HSCN)^+$, 310 $(M-HSCN-H_2O)^+$. Found: C 69.31; H 8.20; S 7.80; N 3.35%. $C_{25}H_{35}O_3SN$. Calculated: C 69.90; H 8.21; S 7.45; N 3.26%.

A solution of 0.008 g of (IIb) and 0.5 ml of $Ac_2O$ in 2 ml of $C_5H_5N$ was kept for 24 h at 20°. After the usual workup and recrystallization from an ether–hexane mixture we obtained 3-acetate (Ia) with mp 205-208°, which was identical with the above described.

16α-Methylpregn-5-en-3β-ol-20-one 3-Acetate (IV). A solution of 0.05 g of (IIa) in 5 ml of EtOH was refluxed with Raney Ni for 1 h. The catalyst was filtered, the solvent was evaporated, and the residue was recrystallized from an ether–hexane mixture to give 0.048 g of (IV), mp 177-182°, which was characterized as its 3-acetate [16], mp 180-182°, which did not depress the mixed melting point with an authentic sample.

D-Homopregn-5-en-3β-ol-20-one 3-Acetate (Va). A solution of 0.020 g of D-homoketone (III) in 1.5 ml of ethanol was refluxed with Raney Ni for 4 h. After an analogous workup we obtained 0.018 g of (Va), mp 184-185° (from ether). Infrared spectrum ($\nu$, $cm^{-1}$): 1250, 1370, 1455, 1705, 1735. PMR spectrum ($\delta$, ppm): 0.88 s (18-$CH_3$), 0.92 s (19-$CH_3$), 1.90 s (3-OAc), 2.03 s (21-$CH_3$), 4.49 br.l (3-H), 5.27 br.l (6-H). Mass spectrum (m/e): 312 $(M-HOAc)^+$, 297 $(M-HOAc-CH_3)^+$.

The hydrolysis of (Va) gave (Vb), mp 203-206° (from MeOH), $[\alpha]_D^{20}$ −28.3°; cf. [17].

16α-Chloromethylpregn-5-en-3β-ol-20-one 3-Acetate (VIa) and (16α-Chloro-D-homopregn-5-en-3β-ol-20-one 3-Acetate (VII). A solution of 0.25 g of (Ia) and 2.5 g of $C_5H_5N \cdot HCl$ in 100 ml of MeCN was refluxed for 32 h and then evaporated. The residue was diluted with water, and the precipitate was filtered and washed with water to give 0.26 g of a mixture, from which by repeated GLC and TLC we isolated 0.015 g of (Ia) 0.05 g of (Ib), and 0.1 g of (VIa), mp 159-162° (from MeOH). Infrared spectrum ($\nu$, $cm^{-1}$): 670, 1245, 1710, 1725. PMR spectrum ($\delta$, ppm): 0.61 s (18-$CH_3$), 0.94 s (19-$CH_3$), 2.08 s (21-$CH_3$), 3.38 q ($CH_2Cl$). Mass spectrum (m/e): 346 $(M+1-HOAc)^+$, 331 $(M+1-HOAc-CH_3)^+$, *316.65 (346→331).

In addition, we obtained 0.028 g of (VII), mp 203-210° (from MeOH). Infrared spectrum ($\nu$, $cm^{-1}$): 635, 1245, 1710, 1725. PMR spectrum ($\delta$, ppm): 0.84 s (18-$CH_3$), 0.92 s (19-$CH_3$), 1.96 s (3-OAc), 2.1 s (21-$CH_3$), 4.54 br.l ($W_{1/2}$ = 6 Hz) (16-H). Mass spectrum (m/e): 346 $M+1-HOAc)^+$, 331 $(M+1$ br.l $HOAc-CH_3)^+$, *316 *316.65(346→331).

16α-Chloromethylpregn-5-en-3β-ol-20-one. A solution of 0.05 g of cyclopropane (Ib) and 0.5 g of $C_5H_5N \cdot HCl$ in 2.5 ml of MeCN was refluxed for 28 h until all of the starting (Ib) had disappeared (checked by TLC, 1:10 ether–benzene). We obtained 0.047 g of a chromatographically inseparable mixture of two products, which, based on the PMR spectral data, contained 76% of 16α-chloromethylpregn-5-en-3β-ol-20-one, which was isolated by recrystallization from ether, mp 185-188°, c.f [10].

3'-H-Cyclopropa[16,17α]pregn-5-en-3β-ol-20-one 3-Acetate 20-Carbethoxyhydrazone (VIII). A solution of 1.5 g of (Ia) and 3 g of CEH in 75 ml of AcOH and 6 ml of $CHCl_3$ was kept for 3 days at 20°, partially evaporated in vacuo, the residue was diluted with water, and the obtained precipitate was filtered, washed with water, dried, and recrystallized from ether to give 0.95 g of 20-carbethoxyhydrazone (VIII), mp 190-195°. Infrared spectrum ($\nu$, $cm^{-1}$, KBr): 1042, 1260, 1520, 1712, 1736, 3300. PMR spectrum ($\delta$, ppm): 0.78 s (18-$CH_3$), 0.96 s (19-$CH_3$). 1.22 t ($CH_3$ of $OC_2H_5$ group), 1.74 s (21-$CH_3$), 1.94 s (3-OAc), 4.16 q ($CH_2$ of $OC_2H_5$ group), 7.43 (NH). Mass spectrum (m/e): 456 ($M^+$), 441 $(M-CH_3)^+$, *426.5 = (456→441), 396 $(M-HOAc)^+$, 381 $(M-CH_3-HOAc)^+$, 368 $(M-CH_3-CO_2C_2H_5)^+$, 323 $(M-HOAc-CO_2C_2H_5)^+$, 308 $(M-HOAc-CO_2C_2H_5-CH_3)^+$. Found: C 71.62; H 8.92; N 6.26%. $C_{27}H_{40}O_4N_2$. Calculated: C 71.05; H 8.77; N 6.10%.

16α-Thiocyanatomethylpregn-5-en-3β-ol-20-one 3-Acetate 20-Carbethoxyhydrazone (IX). A solution of 0.023 g of thiocyanate (IIa) and 0.035 g of CEH in 1.2 ml of glacial AcOH was kept overnight at 20°, diluted with water, and the obtained precipitate was filtered, washed with water, and dried to give 0.027 g of 20-carbethoxyhydrazone (IX), 182-184° (from ether–hexane). Infrared spectrum ($\nu$, $cm^{-1}$, KBr): 1215, 1250, 1722, 1748, 2155, 3345.

A solution of 0.05 g of 20-hydrazone (VIII), 0.15 g of $C_5H_6N \cdot HSCN$, and 0.05 g of CEH in 2.5 ml of MeCN was heated for 25 h at 90°. After the usual workup we obtained 0.05 g of product, which was purified by chromatography. Here we isolated 0.005 g of (VIII) and 0.040 g of (IX), mp 182-184° (from ether–hexane), which was identical with the above described.

16α-Thiocyanato-D-homopregn-5-en-3β-ol-20-one 3-Acetate 20-Carbethoxyhydrazone (X). A solution of 0.01 g of thiocyanate (III) and 0.015 g of CEH in 0.6 ml of glacial AcOH was kept overnight at 20°. After the above described workup we obtained 0.01 g of 20-hydrazone (X), mp 120-123° (from ether). Infrared spectrum ($\nu$, $cm^{-1}$, KBr): 1245, 1732, 2150, 3270.

## CONCLUSIONS

1. The opening of 16,17α-cyclopropano-20-ketosteroids by thiocyanic and hydrochloric acids proceeds with the cleavage of both the exo and endo α-bond of the three-membered ring; the obtained results correspond to a preference of conformations of the transoid type for this molecule in the transition state.

2. Replacing the 20-keto group by a hydrazone fragment qualitatively does not change the structural direction of the opening of the cyclopropane ring by thiocyanic acid.

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