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STEREOCHEMISTRY OF 8-HYDROXY-2-THIATRICYCLO$[7.3.1.0^{3,8}]$TRIDECAN-13-ONES

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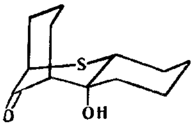
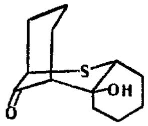
The configurations of two stereoisomers of 8-hydroxy-2-thiatricyclo$[7.3.1.0^{3,8}]$-tridecan-13-one formed as a result of the reaction of 2-chlorocyclohexanone with sodium sulfide were established by x-ray diffraction analysis and mass, IR, and PMR spectroscopy.

We have previously reported [1] that 8-hydroxy-2-thiatricyclo$[7.3.1.0^{3,8}]$tridecan-13-one (I) is formed as a crystalline substance with mp 102-103°C in the reaction of α-chlorocyclohexanone with Na_2S. We obtained the same compound by repeating the experiments of Backer and co-workers [2], who, however, assigned a bis(2-oxocyclohexyl) sulfide structure [1] to it. Subsequent studies showed that the indicated sample of ketol is, in fact, a mixture of two stereoisomers (α and β), which can be separated by repeated recrystallization. The aim of the present research was to determine the three-dimensional structures of these substances.

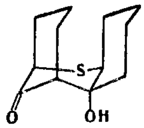
8-Hydroxy-2-thiatricyclo$[7.3.1.0^{3,8}]$tridecan-13-one can exist in the form of four stereoisomers IA-D:



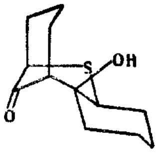
IA



IB



IC



ID

By means of x-ray diffraction analysis we have established that the α isomer of the ketol has structure IA (Fig. 1). To determine the three-dimensional structure of the β-ketol we made a comparative analysis of the mass, IR, and PMR spectra of both substances and also studied some of the chemical properties of the β isomer.

The mass spectra of the two ketols virtually coincide and contain an intense signal of a molecular ion (m/e 226). A comparison of their IR spectra, obtained from very dilute solutions, indicates the absence of an intramolecular hydrogen bond in the β-ketol; this makes it possible to exclude structure IC for it, in which this bond should be observed, as in structure IA (the $[O_{(2)}]H\ldots O_{(1)}$ bond length in the α-ketol is ∿2.2 Å).

The PMR spectrum of the β-ketol contains four groups of signals at 3.8 (1H), 3.2 (1H), 2.5 (1H), and 1.5-2.5 ppm (15H), and upon the whole coincides with the spectrum of the α isomer [3.9 (1H), 3.2 (1H), 2.6 (1H), and 1.5-2.5 ppm (15H)]. The signal at 2.5 ppm belongs to the proton of the OH group, since it vanishes when CD_3OD is added (in the spectrum of the α isomer this signal is observed at 2.6 ppm). The signals at 3.2 and 3.8 ppm can belong only to the protons of the CH groups adjacent to the sulfur atom. Their assignment can be made by comparing the multiplets at 3.9 and 3.8 ppm in the spectra of the α- and β-ketols. These multiplets, which are the X part of an ABX system (the $S{-}CH{-}CH_2{-}$fragment), have dif-

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Far Eastern State University, Vladivostok 690000. Pacific Institute of Bioorganic Chemistry, Far Eastern Science Center, Academy of Sciences of the USSR, Vladivostok 690022. Institute of Heteroorganic Compounds, Academy of Sciences of the USSR, Moscow 117312. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1044-1048, August, 1978. Original article submitted September 13, 1977.

0009-3122/78/1408-0836$07.50

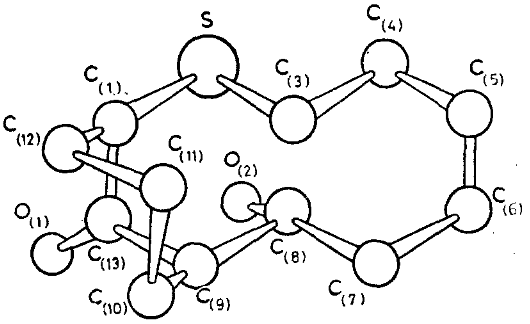
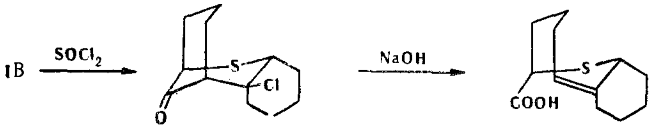


Fig. 1. Three-dimensional structure of α-ketol IA.

ferent widths (16 Hz in the case of the α isomer and 9 Hz in the case of the β isomer) and splittings (quartet and triplet, respectively) and consequently belong to protons with different orientations relative to the protons of the methylene group. They can only be 3-H protons and not 1-H protons, which are equatorial in all of the isomers. The position of the 3-H signal at relatively weak field as compared with 1-H can be explained by the steric effect of the cyclohexanone ring (the 11'-H...3-H distance in the α-ketol is $\sim$1.8 Å). The character of the splitting and the position of the signal of the 3-H proton in the spectrum of the β isomer (3.8 ppm, triplet) indicate its equatorial orientation with respect to the cyclohexane ring and its axial orientation with respect to the thiapyranone ring; this is possible only for structure IB.

To confirm this conclusion, we attempted to stereospecifically dehydrate the β-ketol by means of phosphorus oxychloride and thionyl chloride [3]. However, treatment with $POCl_3$ resulted in recovery of the starting compound, and β-chloroketone II is formed in quantitative yield under the influence of thionyl chloride in pyridine:



II III

The position of the signals of the 3-H and 1-H protons in the PMR spectrum of II and the character of their splitting are virtually the same as the position and character of splitting observed in the spectrum of the starting β-ketol, and the substitution reaction consequently proceeds with retention of the configuration at $C_{(8)}$. This fact makes it possible to exclude structure ID for the β-ketol, since dehydration in the latter case should proceed exceptionally readily because of the axial orientation of the OH group.

The hydrolysis of β-chloro ketone II to the α-ketol [with inversion of the configuration at $C_{(8)}$] could be yet another confirmation of structure IB for the β isomer. However, hydrolysis under the influence of Na_2CO_3 and CH_3COONa leads to the β-ketol, and the action of NaOH in aqueous alcohol unexpectedly led to rearrangement product III. The structure of acid III is confirmed by the IR, mass, and PMR spectra. The PMR spectrum of the product contains five groups of signals at 10.1, 5.2, 4.1, 3.6, and 1.5-2.5 ppm with an intensity ratio of 1:1:1:1:14. The singlet at 10.1 ppm belongs to the proton of the COOH group, since it vanishes when CD_3OD is added. The broad triplet at 5.2 ppm belongs to a vinyl proton, and the broadening is explained by long-range coupling of the vinyl proton with the allylic 3-H proton, which gives a signal at 4.1 ppm. The S—CH—COOH proton gives a triplet at 3.6 ppm.

EXPERIMENTAL

The IR spectra were obtained with a UR-20 spectrometer. The PMR spectra were recorded with a Bruker HX-90E spectrometer. The mass spectra were recorded with an MKh-1303 spectrometer.

Single crystals of the α-ketol grown from a solution in ethanol have monoclinic syngony. The unit cell parameters were determined with a Syntex $P2_1$ diffractometer: a = 8.6593(6) Å, b = 12.5269(12) Å, c = 11.3172(9) Å, β = 110.304(6)°, V = 1151.3, space group $P2_1/n$, z = 4, d_{calc} = 1.31 g/cm³, and F_{000} = 488.

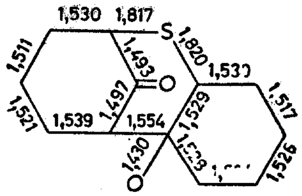


Fig. 2. Interatomic distances in the α-ketol (IA) molecule.

TABLE 1. Coordinates of the Atoms and Anisotropic Thermal Parameters (standard deviations)

Atom	x/a	y/b	z/c	B 11	B 22	B 33	B 12	B 13	B 23
S	0,1982 (9)	0,2560 (6)	0,0693 (8)	2,99 (4)	4,68 (4)	4,92 (4)	1,05 (3)	0,94 (3)	0,55 (3)
$C_{(1)}$	0,1579 (37)	0,1203 (26)	0,1076 (32)	2,13 (12)	5,01 (16)	4,37 (16)	−0,22 (11)	0,66 (12)	−0,49 (13)
$C_{(3)}$	0,4196 (34)	0,2696 (22)	0,1475 (29)	3,16 (13)	3,22 (13)	3,03 (14)	0,29 (10)	1,12 (11)	−0,12 (11)
$C_{(4)}$	0,4770 (42)	0,3679 (25)	0,0940 (35)	4,78 (17)	3,09 (14)	4,54 (18)	0,39 (13)	1,59 (14)	0,18 (18)
$C_{(5)}$	0,6570 (45)	0,3893 (27)	0,1686 (38)	5,23 (19)	3,63 (16)	5,41 (20)	−1,05 (13)	1,71 (15)	−0,03 (14)
$C_{(6)}$	0,7643 (42)	0,2927 (28)	0,1698 (38)	3,19 (15)	4,78 (17)	5,20 (19)	−1,01 (13)	1,36 (13)	−0,13 (14)
$C_{(7)}$	0,6996 (36)	0,1932 (26)	0,2146 (31)	2,75 (12)	3,79 (15)	3,72 (15)	−0,09 (11)	0,96 (11)	−0,12 (12)
$C_{(8)}$	0,5191 (31)	0,1715 (21)	0,1370 (25)	2,54 (12)	3,15 (12)	2,71 (12)	0,00 (9)	0,99 (9)	−0,22 (9)
$C_{(9)}$	0,4549 (34)	0,0664 (22)	0,1765 (27)	2,58 (12)	2,63 (12)	3,79 (14)	0,25 (10)	1,04 (10)	−0,44 (10)
$C_{(10)}$	0,4564 (39)	0,0564 (27)	0,3124 (30)	3,62 (15)	3,71 (15	3,74 (15)	−0,24 (12)	1,04 (12)	0,37 (12)
$C_{(11)}$	0,3224 (43)	0,1177 (30)	0,3417 (33)	5,19 (18)	5,52 (19)	3,53 (16)	−0,20 (14)	2,51 (14)	0,03 (14)
$C_{(12)}$	0,1552 (43)	0,1039 (34)	0,2409 (37)	3,70 (16)	5,93 (21)	6,41 (21)	0,12 (15)	2,94 (15)	0,40 (16)
$C_{(13)}$	0,2830 (34)	0,0469 (23)	0,0883 (23)	3,10 (13)	3,60 (14)	3,76 (14)	−0,46 (11)	1,29 (11)	−0,30 (12)
$O_{(1)}$	0,2452 (26)	−0,0263 (18)	0,0124 (23)	3,66 (10)	5,64 (12)	5,87 (13)	−0,98 (9)	1,40 (9)	−2,53 (10)
$O_{(2)}$	0,4971 (26)	0,1605 (17)	0,0064 (18)	3,74 (10)	4,63 (10)	2,76 (9)	0,18 (8)	1,42 (7)	−0,52 (8)

TABLE 2. Coordinates of the Hydrogen Atoms and Isotropic Thermal Parameters (standard deviations)

Atom	x/a	y/b	z/c	B
1-H	0,0714 (44)	0,1078 (26)	0,0520 (32)	4,37 (90)
3-H	0,4360 (26)	0,2791 (17)	0,2361 (23)	2,01 (48)
4-H	0,4730 (38)	0,3553 (25)	0,0056 (33)	5,01 (81)
4′-H	0,4028 (34)	0,4273 (23)	0,0977 (25)	3,96 (63)
5-H	0,6996 (42)	0,4485 (28)	0,1310 (33)	6,15 (87)
5′-H	0,6530 (44)	0,3987 (28)	0,2578 (37)	7,31 (97)
6-H	0,8718 (48)	0,3062 (28)	0,2205 (35)	7,11 (97)
6′-H	0,7596 (37)	0,2771 (24)	0,0310 (30)	4,22 (74)
7-H	0,7058 (33)	0,1952 (23)	0,3059 (29)	4,60 (71)
7′-H	0,7602 (34)	0,1326 (23)	0,2078 (25)	3,59 (67)
9-H	0,5193 (34)	0,0183 (23)	0,1606 (25)	2,39 (66)
10-H	0,5634 (43)	0,0732 (26)	0,3703 (31)	5,35 (81)
10′-H	0,4430 (36)	−0,0186 (27)	0,3261 (27)	4,50 (77)
11-H	0,3138 (36)	0,0951 (25)	0,4195 (31)	5,16 (78)
11′-H	0,3553 (36)	0,2002 (26)	0,3523 (27)	4,53 (71)
12-H	0,1097 (44)	0,0325 (29)	0,2461 (33)	5,32 (90)
12′-H	0,0673 (43)	0,1523 (27)	0,2505 (32)	6,14 (88)
H[O]	0,4308 (46)	−0,1200 (28)	−0,0047 (35)	5,44 (104)

The complete three-dimensional set of diffraction data consisting of 1399 nonzero independent reflections ($\sin \theta/\lambda \leqslant 0.545$) was obtained by the $2\theta/\omega$ method with a Syntex $P2_1$ diffractometer (Cu K_α emission and a graphite monochromator). Corrections for the Lorentz and polarization factors were introduced in the conversion of the intensities to structural factors. The structure of the α-ketol was determined by the heavy-atom method and refined by the method of least squares to an R factor of 4.2%. All of the calculations were made with an XTL system for the determination of crystal structures. The coordinates of the nonhydrogen atoms and their anisotropic thermal parameters are presented in Table 1. The coordinates of the hydrogen atoms and the isotropic thermal parameters are presented in Table 2. The conformation of the ketol molecule obtained on the basis of x-ray diffraction data

TABLE 3. Valence Angles in the α-Ketol Molecule

Atoms	Angle, deg	Atoms	Angle, deg	Atoms	Angle, deg
$C_{(1)}SC_{(3)}$	103,2	$C_{(7)}C_{(8)}C_{(9)}$	112,4	$C_{(10)}C_{(11)}C_{(12)}$	112,4
$SC_{(3)}C_{(4)}$	108,4	$C_{(9)}C_{(8)}C_{(3)}$	113,0	$C_{(11)}C_{(12)}C_{(1)}$	113,0
$SC_{(3)}C_{(8)}$	114,5	$C_{(9)}C_{(8)}O_{(2)}$	106,4	$C_{(12)}C_{(1)}S$	115,5
$C_{(4)}C_{(3)}C_{(8)}$	110,3	$C_{(3)}C_{(8)}O_{(2)}$	106,4	$C_{(12)}C_{(1)}C_{(13)}$	108,7
$C_{(3)}C_{(4)}C_{(5)}$	109,5	$C_{(7)}C_{(8)}O_{(2)}$	110,8	$SC_{(1)}C_{(13)}$	109,4
$C_{(4)}C_{(5)}C_{(6)}$	111,8	$C_{(8)}C_{(9)}C_{(13)}$	108,6	$C_{(1)}C_{(13)}C_{(9)}$	114,0
$C_{(5)}C_{(6)}C_{(7)}$	111,1	$C_{(8)}C_{(9)}C_{(10)}$	118,5	$C_{(1)}C_{(13)}O_{(1)}$	122,3
$C_{(6)}C_{(7)}C_{(8)}$	112,0	$C_{(10)}C_{(9)}C_{(13)}$	108,3	$C_{(9)}C_{(13)}O_{(1)}$	123,5
$C_{(7)}C_{(8)}C_{(3)}$	107,8	$C_{(9)}C_{(10)}C_{(11)}$	115,7		

is depicted in Fig. 1. The valence angles of the molecule are presented in Table 3. The interatomic distances are shown in Fig. 2.

Separation of the α and β Stereoisomers of 8-Hydroxy-2-thiatricyclo[7.3.1.$0^{3,8}$]tridecan-13-one. α-Ketol. A 30-g sample of the mixture of ketols (mp 102-103°C) [1] was dissolved by heating in 70 ml of ethanol, the resulting solution was cooled, and the precipitate was removed by filtration, washed, and recrystallized three times from ethanol to give 18.7 g of the α-ketol with mp 143-144°C and R_f 0.65 (Silufol, $CHCl_3$—CH_3OH, 50:1). IR spectrum ($CHCl_3$): 3590, 3525, 3410, 2950, 2872, and 1710 cm^{-1}. Found: C 63.5; H 7.9; S 14.1%. $C_{12}H_{18}O_2S$. Calculated: C 63.5; H 8.0; S 14.1%. The oxime had mp 183-184°C (from benzene). Found: C 59.4; H 8.0; N 6.0; S 13.2%. $C_{12}H_{19}NO_2S$. Calculated: C 59.7; H 7.9; N 5.8; S 13.3%.

β-Ketol. The filtrates after separation of the α-ketol crystals were combined and subjected to vacuum evaporation to give 11.3 g of crystals with mp 108-112°C. Four recrystallizations from CCl_4—cyclohexane (1:1) gave 7.6 g of the β isomer with mp 123-124°C and R_f 0.52 (Silufol, $CHCl_3$—CH_3OH, 50:1). IR spectrum ($CHCl_3$): 3600, 3400-3500, 2950, 2872, and 1710 cm^{-1}. Found: C 63.4; H 7.9; S 14.0%. $C_{12}H_{18}O_2S$. Calculated: C 63.5; H 8.0; S 14.1%. The oxime had mp 230-231°C (from propanol). Found: C 59.6; H 8.0; N 5.7; S 13.1%. $C_{12}H_{19}NO_2S$. Calculated: C 59.7; H 7.9; N 5.8; S 13.3%.

8-Chloro-2-thiatricyclo[7.3.1.$0^{3,8}$]tridecan-13-one (II). A solution of 7.14 g (0.06 mole) of thionyl chloride in 10 ml of dry pyridine was added dropwise in the course of 20 min at 0°C to a solution of 10 g (0.044 mole) of the β-ketol in 30 ml of dry pyridine, and the mixture was poured over crushed ice. The aqueous mixture was extracted with five 15-ml portions of petroleum ether, and extract was dried and vacuum evaporated to dryness to give 10.8 g of a colorless oil, which crystallized and was chromatographically homogeneous. An analytical sample (mp 40-42°C) was obtained by freezing out from petroleum ether. Found: C 58.3; H 7.0; S 12.9%. $C_{12}H_{17}ClOS$. Calculated: C 58.8; H 6.9; S 13.1%. IR spectrum ($CHCl_3$): 2950, 2870, and 1710 cm^{-1}. PMR spectrum ($CDCl_3$), δ: 4.23 (1H, t), 3.22 (1H, s), and 1.3-2.9 ppm (15H, m).

2-Thiabicyclo[6.4.$0^{1,8}$]dodec-7-ene-3-carboxylic Acid (III). A total of 6 ml of a 2 N solution of NaOH was added to a solution of 1 g (0.004 mole) of chloro ketone II in 12 ml of ethanol, and the mixture was stirred for 2 h, after which it was acidified with dilute hydrochloric acid (1:3), and the precipitate was removed by filtration, washed with water, dried, and recrystallized from benzene to give 0.85 g (92%) of a product with mp 149-151°C. IR spectrum ($CHCl_3$): 3500, 2950, 2870, and 1700-1740 cm^{-1}. Mass spectrum: m/e 226 (M^+). Found: C 64.0; H 8.4; S 14.0%. Equivalent 227. $C_{12}H_{18}O_2S$. Calculated: C 63.5; H 8.0; S 14.1%; equivalent 226.

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