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**An Absolute Configuration of (1R, 4R, 5R)-4-Methoxy-8-acetyl-
-7,7-dimethyl-6-thia-3,8-diazabicyclo[3.2.1]octan-2-one,
C₁₀H₁₆N₂O₃S***

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The crystal and molecular structure of the title compound was determined; its absolute configuration 1R, 5R was deduced from CD spectral data. Crystals are orthorhombic, space group $P2_12_12_1$ with: $a = 15.857(4)$, $b = 12.449(3)$, $c = 6.120(2)$ Å, $U = 1208.11$ Å³, $Z = 4$; $D_c = 1.35$ Mgm⁻³, $\mu(\text{MoK}\alpha) = 0.25$ mm⁻¹. The final $R = 0.048$ for 671 observed reflexions [$I > 3\sigma(I)$]. The conformation of the diazabicyclo [3.2.1] octane ring is boat-envelope-chair. Molecules are connected in an infinite chain by hydrogen bonds between N(3) amino and C(2) carbonyl groups [N—H...O, 2.881(8) Å].

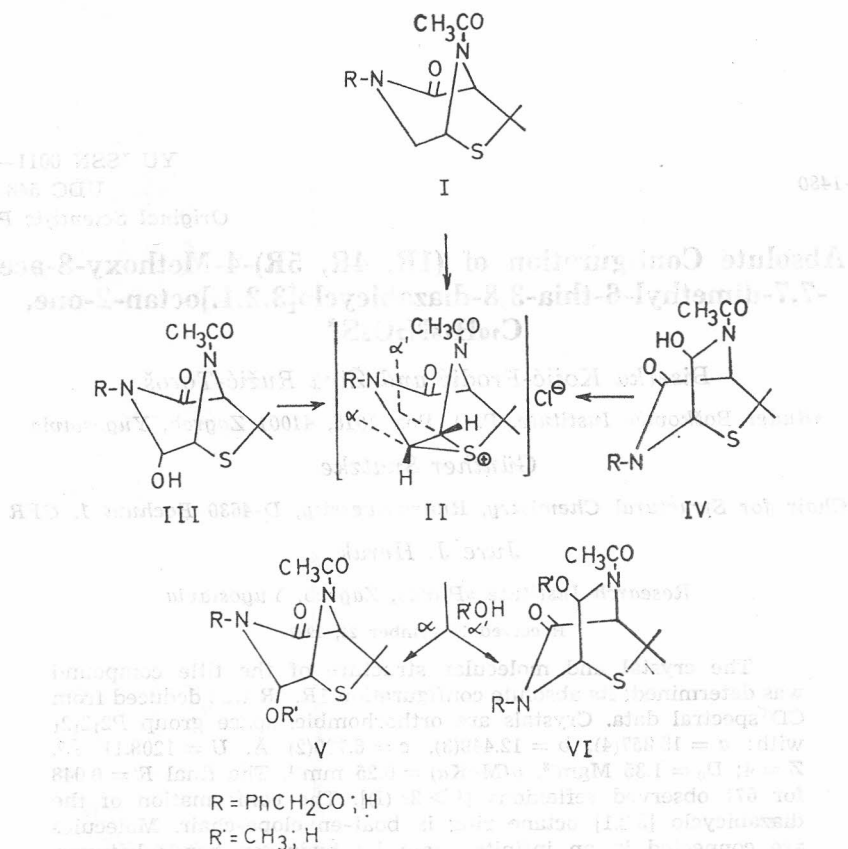
INTRODUCTION

In connection with the chemical transformation of penicillins the ring expansion of thiazolidine was studied.¹ Reaction of N⁸-acyl and N³,N⁸-diacyl derivatives of 6-thia-3,8-diazabicyclo[3.2.1]octan-2-ones(I) with PCl₅ or SO₂Cl₂ gave a chloroderivative, which upon addition of water yielded two isomers III and IV.¹

One of these isomers(III) was the starting compound I, substituted with a hydroxyl group at position C-4, while the other (IV) was 7-thia-2,5-diazabicyclo[2.2.2]octan-2-one, formed by rearrangement of I, due to expansion of the thiazolidine into the tetrahydrothiazine ring. In this reaction also nucleophilic substitution occurred at the position β to sulphur.

It was proposed that the ring expansion of thiazolidine and nucleophilic substitution occurred *via* the thiiranium ion II as a common intermediate. This was inferred from the fact that isomers (III or IV) in the repeated reaction with PCl₅ or SO₂Cl₂ gave the same chloro compound, which when treated with water or alcohol gave again the same mixture and ratio of products (V and

* Dedicated to Professor D. Grdenić on occasion of his 65th birthday.



VI).² The nucleophilic attack at the carbon α to sulphur explains the formation of isomers V, while the reaction at the α' C-atom leads to the isomers VI.

This mechanism is supported by the evidence of stereospecific introduction of a hydroxy or methoxy group giving only one stereoisomer as a reaction product. A recent X-ray crystallographic analysis³ of VI ($\text{R} = \text{PhCH}_2\text{CO}$, $\text{R}' = \text{H}$) established the absolute configuration 1*S*, 4*R*, 6*S* with a hydroxy group bonded at C(6) in a *E* position to sulphur. The absolute configuration of the compound V, ($\text{R} = \text{H}$; $\text{R}' = \text{CH}_3$) reported in this paper, was found to be 1*R*, 4*R*, 5*R*. An *E* orientation of the methoxy group to sulphur was also found.

EXPERIMENTAL

a) X-ray Data

Preliminary cell dimensions and the space group were determined from oscillation and Weissenberg photographs recorded with $\text{CuK}\alpha$ radiation; final cell dimensions were refined from diffractometer measurements (25 reflexions). Intensities were collected on a Philips PW1100 computer-controlled four-circle diffractometer in the ω -scan mode [scan width = $1.00^\circ(\Theta)$, scan speed = $0.025^\circ(\Theta) \text{ s}^{-1}$] with graphite monochromated $\text{MoK}\alpha$ radiation using a crystal $0.05 \times 0.09 \times 0.62 \text{ mm}$. 671 observed reflexions [$I > 3\sigma(I)$] in the range $2 < \Theta < 30^\circ$ were recorded and used in the

calculations. The data were corrected for background, Lorentz and polarization effects but not for absorption. The structure was solved with MULTAN 80⁴ (ABS FOM = 1.271, PSI ZERO = 1.651, RESID = 20.35). A subsequent difference synthesis located the remaining four atoms of the molecule. Refinement was by least squares minimizing $\sum w ||F_o| - |F_c||^2$ ($w = 1$). Anisotropic refinement and the resulting difference synthesis revealed the positions of the H atoms. A scale factor and atomic coordinates of the non-hydrogen atoms (145 variables) were refined. The H atoms were included in the structure factor calculations only. For the H atoms the isotropic thermal parameters were those of the bonded atoms plus one. Anisotropic thermal parameters were in the usual range: maximum values of U_{11} for C(11) and U_{22} for C(16) of 0.104(8) and 0.103(7) Å² were obtained, respectively. The final $R = 0.048$ for 671 observed reflexions with $I > 3\sigma(I)$. The R factor of both enantiomers is of the same value. Probably due to poor crystal quality application of Bijvoet pairs in the discrimination of the enantiomers was not successful.

Scattering factors given by Cromer and Mann⁵ and (for H) Stewart, Davidson and Simpson⁶ were used. An anomalous-dispersion correction was included for S⁷. The calculations were carried out on a Univac 1110 computer at the University Computing Centre in Zagreb with the XRAY system.⁸

b) CD Data

The CD was recorded with an ISA-dichrograph Mark III connected on line to a PDP-8/e computer, at room temperature at a concentration of 1.53 mMol/l.

Circular Dichroism

The CD was measured in acetonitril solution and showed Cotton effects at 252 (−3.50) and 207 nm ($\Delta \epsilon = +33.2$); it became strongly negative at shorter wavelengths. Whereas the first (negative) band comes from the thioether chromophore for which in the presence of the two strong perturbing amide groups no appropriate rule can be applied, the next two CD-bands of opposite signs are typical for a CD-couplet, which in this case must result from a chiral Davydov interaction between the strong $\pi^o \rightarrow \pi$ -transition moments of the two amide groups,⁹ similar *e.g.* to the α -helix of polypeptides, for which the first branch of the respective CD-couplet appears at 208 nm ($\Delta \epsilon$ appr. −10).¹⁰

In order to apply the point-dipole approximation one has for the calculation of such CD-couplets to »localize« the two transition dipoles in the chromophore. We have to this end taken the co-ordinates of $V(R = H, R' = CH_3)$ as obtained from the X-ray diffraction experiment, calibrated deliberately for the (1R, 5R)-stereoisomer. Assumption of a halfband width of 3000 cm⁻¹, band position of 202 nm and ϵ of 8000 (cf.¹¹) leads to a CD-couplet with values of 208 (+14.0) and 197 nm ($\Delta \epsilon = -14.9$); if the direction of the transition dipole is changed so as to conform with the values determined by Peterson and Simpson¹² the corresponding result is 207 (+10.4) and 197 nm ($\Delta \epsilon = -11.0$). These CD-values are smaller than those found; one must take into account, however, that actually the transition charges are not localized at the positions of the nuclei but above and below them. The point-dipole approximation is, therefore, very crude for interacting dipoles which are not farther apart than in V .

As NMR-measurements have shown¹ the N(8)-acetyl group in solution is not fixed in the E-configuration but can also adopt the Z-configuration. If the CD-couplets are calculated for this stereochemistry the ellipticities are smaller but they do not change their signs. Therefore, whatever the conformation present in solution, the CD-couplet for the (1R, 5R)-isomer is always positive; for its enantiomer with (1S, 5S)-stereochemistry the CD-couplet should then, of course, be negative. As a positive CD-couplet is observed for the (−)− $V(R = H, R' = CH_3)$, its absolute configuration must thus be (1R, 5R).

DESCRIPTION AND DISCUSSION OF THE STRUCTURE

The structural formula with the atom numbering is given in Figure 1. The final atomic coordinates for non-hydrogen atoms are listed in Table I.

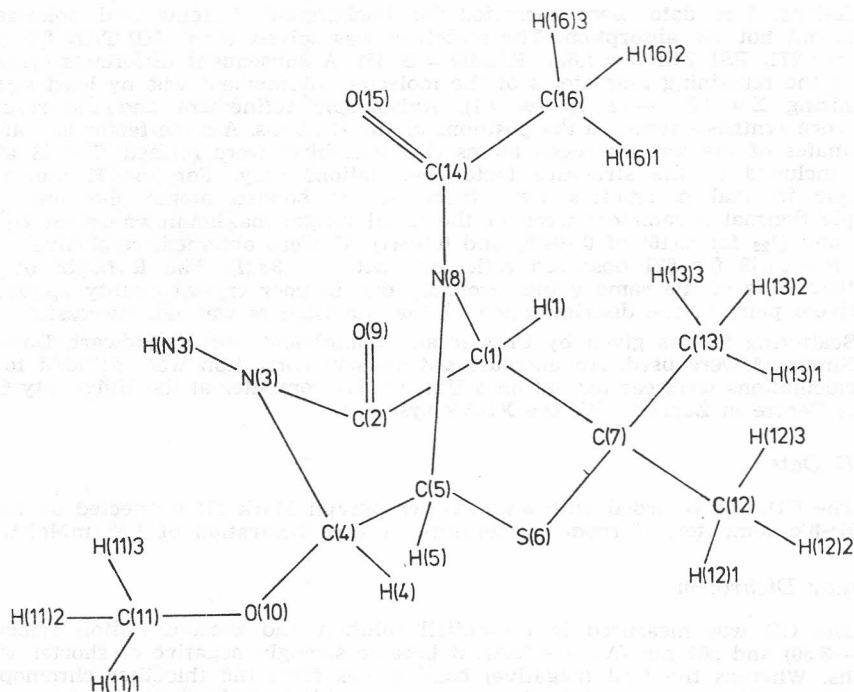


Figure 1. Structural formula with the atom numbering.

TABLE I

Final Atomic Coordinates($\times 10000$) and Isotropic Thermal Parameters($\times 100$) for Non-Hydrogen Atoms

	X	Y	Z	U (\AA^2)
C (1)	1445(4)	2569(5)	8598(10)	3.2(2)
C (2)	1890(4)	3632(5)	8303(11)	3.5(2)
N (3)	1805(4)	4132(4)	6394 (9)	4.5(3)
C (4)	1214(5)	3809(6)	4678(13)	5.1(4)
C (5)	886(4)	2685(5)	5076(11)	3,9(3)
S (6)	1745(1)	1697(1)	4703 (2)	4.8(4)
C (7)	1950(4)	1597(5)	7671 (9)	3.4(2)
N (8)	653(3)	2603(5)	7371 (8)	3.3(2)
O (9)	2353(3)	3980(3)	9765 (8)	5.1(4)
O(10)	520(3)	4530(4)	4673 (9)	6.8(4)
C(11)	303(6)	4913(7)	2574(15)	8.2(5)
C(12)	1581(5)	572(5)	8545(13)	4.9(3)
C(13)	2883(4)	1677(6)	8148(12)	5.3(4)
C(14)	-104(4)	2401(6)	8299(12)	4.1(3)
O(15)	-169(3)	2354(4)	10285 (9)	5.8(4)
C(16)	-842(5)	2269(8)	6851(15)	7.2(5)

Interatomic distances and angles are listed in Table II. The absolute configuration of the molecule is defined by the torsion angles listed in Table III. The molecular packing is illustrated in Figure 2.

TABLE II
Bond Distances (Å) and Angles (°)

a) For non-hydrogen atoms		C(12) — C(7) — C(13)	111.7(6)
C(1) — C(2)	1.511(9)	C(1) — N(8) — C(5)	106.2(5)
C(1) — C(7)	1.558(10)	C(1) — N(8) — C(14)	122.8(6)
C(1) — N(8)	1.463(8)	C(5) — N(8) — C(14)	130.0(6)
C(2) — N(3)	1.331(9)	C(4) — O(10) — C(11)	113.9(7)
C(2) — O(9)	1.236(9)	N(8) — C(14) — O(15)	120.1(6)
N(3) — C(4)	1.464(10)	N(8) — C(14) — C(16)	118.2(7)
C(4) — C(5)	1.513(11)	O(15) — C(14) — C(16)	121.7(7)
C(4) — O(10)	1.419(10)		
C(5) — S(6)	1.849(7)	b) For hydrogen atoms	
C(5) — N(8)	1.456(9)	C(1) — H(1)	1.09
S(6) — C(7)	1.849(6)	N(3) — H(N3)	1.11
C(7) — C(12)	1.502(10)	C(4) — H(4)	0.97
C(7) — C(13)	1.511(10)	C(5) — H(5)	1.09
N(8) — C(14)	1.353(9)	C(11) — H(11)1	1.14
O(10) — C(11)	1.413(11)	C(11) — H(11)2	1.07
C(14) — O(15)	1.222(10)	C(11) — H(11)2	1.02
C(14) — C(16)	1.477(11)	C(12) — H(12)1	0.97
		C(12) — H(12)2	1.02
C(2) — C(1) — C(7)	113.4(5)	C(12) — H(12)3	1.00
C(2) — C(1) — N(8)	108.3(5)	C(13) — H(13)1	0.95
C(7) — C(1) — N(8)	106.1(5)	C(13) — H(13)2	1.05
C(1) — C(2) — N(3)	117.9(6)	C(13) — H(13)3	1.07
C(1) — C(2) — O(9)	119.9(6)	C(16) — H(16)1	0.98
N(3) — C(2) — O(9)	122.1(6)	C(16) — H(16)2	1.09
C(2) — N(3) — C(4)	124.5(6)	C(16) — H(16)3	1.07
N(3) — C(4) — C(5)	111.0(6)		
N(3) — C(4) — O(10)	108.9(6)	C(2) — C(1) — H(1)	102
C(5) — C(4) — O(10)	108.6(6)	C(7) — C(1) — H(1)	109
C(4) — C(5) — S(6)	110.0(5)	N(8) — C(1) — H(1)	119
C(4) — C(5) — N(8)	107.9(6)	C(2) — N(3) — H(N3)	123
S(6) — C(5) — N(8)	105.0(5)	C(4) — N(3) — H(N3)	112
C(5) — S(6) — C(7)	93.1(3)	N(3) — C(4) — H(4)	108
C(1) — C(7) — S(6)	102.4(4)	C(5) — C(4) — H(4)	108
C(1) — C(7) — C(12)	109.2(5)	O(10) — C(4) — H(4)	101
C(1) — C(7) — C(13)	112.4(6)	C(4) — C(5) — H(5)	110
S(6) — C(7) — C(12)	109.8(5)	S(6) — C(5) — H(5)	104
S(6) — C(7) — C(13)	110.9(5)	N(8) — C(5) — H(5)	119

TABLE III
Torsion Angles (°)

C(7) — C(1) — C(2) — N(3)	83.6(8)
N(8) — C(1) — C(2) — O(9)	150.2(6)
C(1) — C(2) — N(3) — C(4)	10(1)
C(2) — N(3) — C(4) — C(5)	—15(1)
C(2) — N(3) — C(4) — O(10)	104.2(8)
N(3) — C(4) — C(5) — S(6)	—68.3(7)
N(3) — C(4) — C(5) — N(8)	45.7(8)
O(10) — C(4) — C(5) — S(6)	171.9(5)
C(4) — C(5) — S(6) — C(7)	98.7(5)
C(5) — S(6) — C(7) — C(1)	—12.7(5)
C(5) — S(6) — C(7) — C(12)	103.2(5)
C(5) — S(6) — C(7) — C(13)	—132.8(5)
S(6) — C(7) — C(1) — C(2)	—78.4(6)
S(6) — C(7) — C(1) — N(8)	40.3(5)
N(3) — C(4) — O(10) — C(11)	132.5(7)
C(5) — C(4) — O(10) — C(11)	—106.4(7)
C(5) — N(8) — C(14) — O(15)	179.3(7)
C(5) — N(8) — C(14) — C(16)	—2(1)

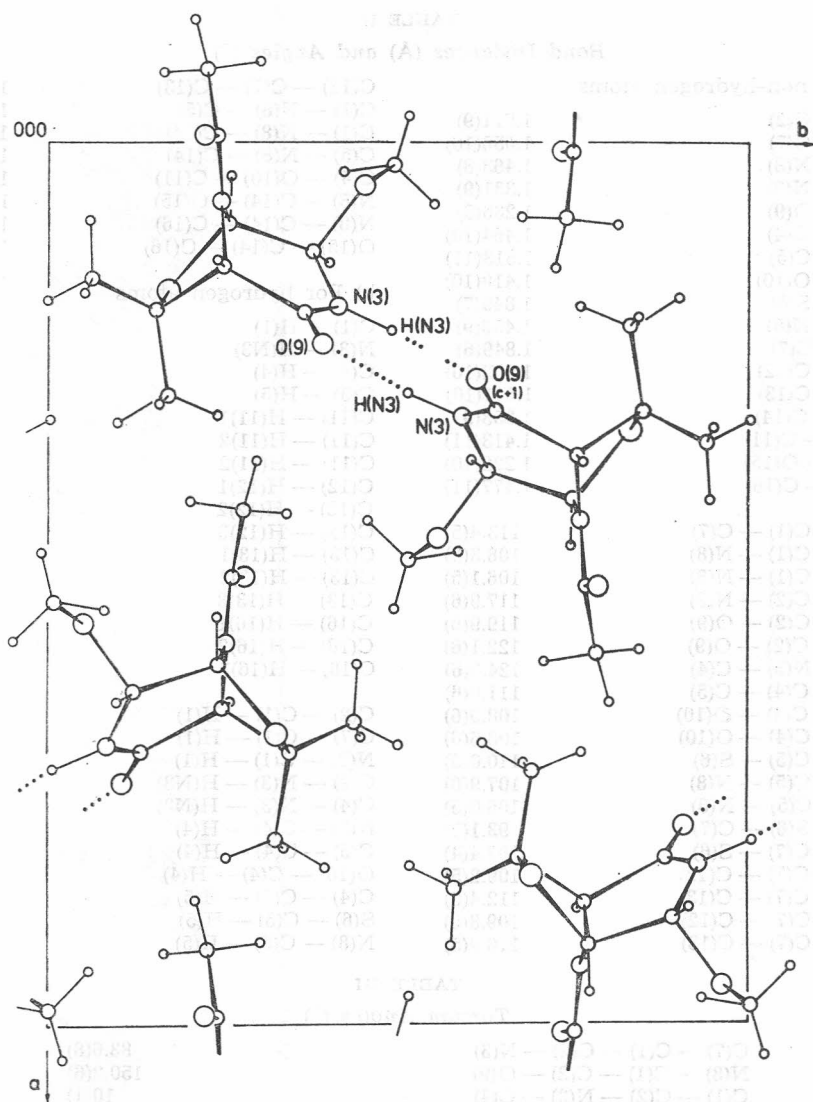


Figure 2. A view of the crystal structure along c showing hydrogen bonds between amino and carbonyl groups.

The C—C lengths for C in the sp^3 hybridization range from 1.502(10) to 1.558(10) Å. There are two categories of C to N bonds: the C—N bonds [C(1)—N(8), 1.463(8); C(4)—N(3), 1.464(10); C(5)—N(8), 1.456(9) Å] and N—C=O [C(2)—N(3), 1.331(9); C(14)—N(8), 1.353(9) Å]. The carbonyl bonds are 1.222(10) and 1.236(9) Å. The C—S bonds are symmetrical [1.849(6), 1.849(6) Å]. Bond angles are in accordance with the given atom type, hybridization and the requirements of the ring geometry. The pronounced deviations from normal values are C(1)—C(7)—S(6), 102.4(4) and C(1)—N(8)—C(5), 106.2(5)°.

The diazabicyclo [3.2.1] octane ring is puckered (Table III); the seven-membered ring with the sequence C(1), C(2), N(3), C(4), C(5), S(6), C(7), appears in a boat conformation. C(1), C(7), S(6), C(5), N(8) form a five-membered ring in an envelope conformation with the bridging N(8) lying out of four atom plane [0.638() Å]. The six-membered ring C(1), C(2), N(3), C(4), C(5), N(8) occurs in a distorted chair conformation; the displacements of N(3) and N(8) are 0.131(9) and 0.774(9) Å, respectively. The relative orientation of the methoxy group to S defined by the torsion angle S(6) — C(5) — C(4) — O(10), 171.9(5)°, is *trans*.

Molecules are connected in an infinite chain along *c* by the hydrogen bonds N(3) — H... O(9), 2.881(8) Å [\sphericalangle N(3) — H — O(9), 167°] between amino and carbonyl groups.*

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REFERENCES

1. J. J. Herak, M. Kovačević, and B. Gašpert, *Croat. Chem. Acta* **55** (1982) 327.
2. B. Gašpert, *Rad Jugosl. akad. znan. i umjet., kem.* **2** (1982) 75.
3. B. Kojić-Prodić, Ž. Ružić-Toroš, and J. J. Herak, *Acta Cryst.* **B37** (1981) 214.
4. P. Main, S. J. Fiske, S. E. Hall, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univ. of York, England, and Louvain, Belgium, 1980.
5. D. T. Cromer and J. B. Mann, *Acta Cryst.* **A24** (1968) 321.
6. R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.* **42** (1965) 3175.
7. D. T. Cromer and D. Liberman, *J. Chem. Phys.* **53** (1970) 1891.
8. J. M. Stewart, P. A. Machin, C. Dickinson, H. L. Ammon, H. Heck, and H. Flack, *The XRAY76 System*, *Tech. Rep. TR-446*. Computer Science Center, Univ. of Maryland, College Park, Maryland.
9. For a general discussion cf. e.g. N. Harada and K. Nakanishi, *Circular Dichroic Spectroscopy — Ectiton Coupling in Organic Stereochemistry* University Science Books, Mill Valley (1983).
10. Cf. e.g. E. R. Blout, in F. Ciardelli and P. Salvadori (eds.): *Fundamental Aspects and Recent Developments in Optical Rotatory Dispersion and Circular Dichroism*, Heyden, London (1973).
11. Cf. e.g. M. B. Robin: *Higher Excited States of Polyatomic Molecules*, Vol. 2, p. 122 ff, Academic Press, New York (1975).
12. D. L. Peterson and W. T. Simpson, *J. Amer. Chem. Soc.* **79** 2375 (1957).

* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the editorial board of *Croat. Chem. Acta*.

SAŽETAK

Apsolutna konfiguracija (1R, 4R, 5R)-4-metoksi-8-acetil-7,7-dimetil-tio-3,8-diazabicyklo[3.2.1]-oktan-2-ona, $C_{10}H_{16}N_2O_3S$

B. Kojić-Prodić, Ž. Ružić-Toroš, G. Snatzke i J. J. Herak

Određena je kristalna i molekulska struktura, a apsolutna konfiguracija 1R, 4R, 5R određena je iz spektra CD i rendgenskih podataka. Supstanca kristalizira u rompskom sustavu, prostorna grupa $P2_12_12_1$, parametri jedinične ćelije $a = 15,857(4)$, $b = 12,449(3)$, $c = 6,120(2)$ Å, $V = 1280.11$ Å³, $Z = 4$, $D_c = 1.35$ Mgm⁻³, μ (MoK α) = 0.25 mm⁻¹. Za 671 opaženih refleksa $[I > 3\sigma(I)]$ $R = 0,048$. Diazabicyklo [3.2.1]oktanski prsten ima konformaciju »boat-envelope-chair«. Molekule su povezane u beskonačne lance vodikovom vezom između amino- i karbonilnih skupina [N—H...O, 2.881(8) Å].