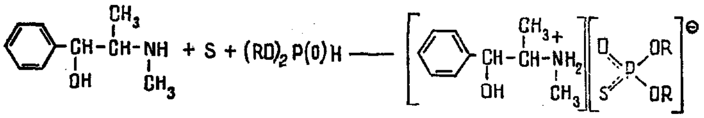
SYNTHESIS OF EPHEDRINE (DIALKYL PHOSPHOROTHIOATE)S. CRYSTALLOGRAPHIC STRUCTURE OF EPHEDRINE (DIETHYL PHOSPHOROTHIOATE)

K. M. Turdybekov, S. V. Lindeman, Yu. T. Struckov,
A. M. Gazaliev, S. D. Fazylov, M. Zh. Zhurinov, and
B. Zh. Zhumazhanova

UDC 548.73

The synthesis of ephedrine (dialkyl phosphorothioate)s has been effected. The method of their preparation and their properties are described. The IR and PMR spectra of ephedrine (dialkyl phosphorothioate)s and some results of an x-ray structural investigation of the spatial structure of ephedrine (diethyl phosphorothioate) are given.

Continuing investigations on alkaloid modification [1-3], we have synthesized ephedrine (O,O-dialkyl phosphorothioate)s by the following scheme:



where R in (I) is Me, in (II) Et and in III i-Pr.

It has been established that the reaction of ephedrine with dialkyl phosphorothioates in the presence of sulfur has a general nature and can easily be carried out in benzene with gentle heating. The salts obtained consist of colorless acicular crystals readily soluble in water, ethanol, and other solvents. The yields and physicochemical constants of ephedrine (dialkyl phosphorothioate)s are given in Table 1.

The fact that compounds (I-III) were salts was confirmed by the presence in the IR spectra of absorption bands in the 2400 and 2700 cm^{-1} regions due to the vibrations of N–H

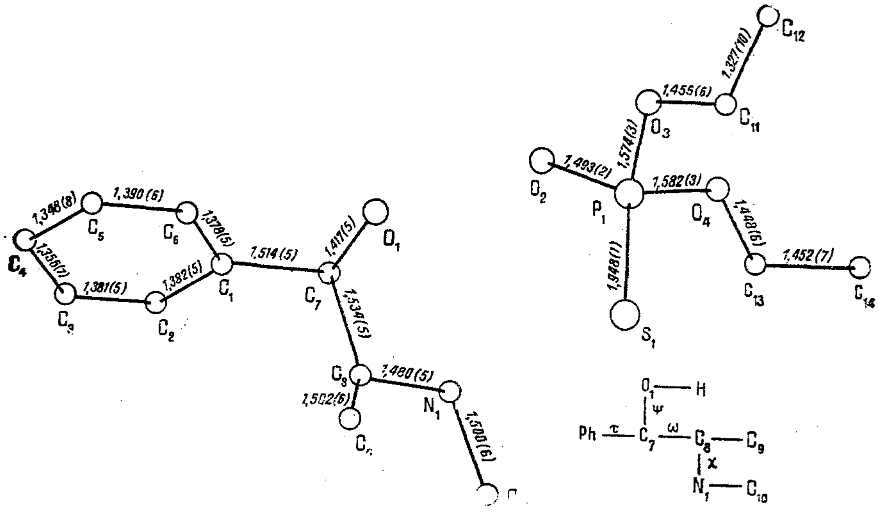


Fig. 1. Structure of the cation and the analog of the salt (II). Bond lengths are given.

Institute of Organic Synthesis and Coal Chemistry, Kazakh SSR Academy of Sciences, Karaganda. A. N. Nesmeyanov Institute of Heteroorganic Compounds, Moscow. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 88-91, January-February, 1989. Original article submitted February 28, 1988; revision submitted August 31, 1988.

TABLE 1. Physicochemical Constants of Ephedrine (Dialkyl Phosphorothioate)s

Compound	Empirical formula	Yield, %	mp, °C	Chemical shift, δ, ppm (J, Hz)				
				C–CH$_3$	N–CH$_3$	N–H	O–R	Ph
I	$C_{12}H_{22}NO_4PS$	91	105	1,0 d (J=7)	2,83 s	3,3 s	3,43 and 3,62 d (J=4)	7,3 m
II	$C_{14}H_{26}NO_4PS$	96	85	1,16 s	2,80 s	3,3 s	3,90 m	7,40 m
III	$C_{16}H_{30}NO_4PS$	93	145	1,22 d (J=6)	2,8 s	3,38 d	4,55 m	7,37 m

---

*R=CH_3 (I), R=CH_2 (II), R–CH (III). The results of elementary analysis for all the compounds corresponded to the calculated figures.

TABLE 2. Valence Angles ω, deg

Angle	ω	Angle	ω
anion		cation	
S1P1O2	117,0 (1)	C8N1C10	116,4 (4)
S1P1O3	112,6 (1)	C2C1C6	118,5 (4)
S1P1O4	112,2 (1)	C2C1C7	120,0 (3)
O2P1O3	105,1 (2)	C6C1C7	121,5 (4)
O2P1O4	108,7 (2)	C1C2C3	119,0 (5)
O3P1O4	99,6 (2)	C2C3C4	122,0 (6)
P1O3C11	120,7 (3)	C3C4C5	119,4 (5)
P1O4C13	124,2 (3)	C4C5C6	120,2 (5)
O3C11C12	114,3 (6)	C1C6C5	120,9 (5)
O4C13C14	109,9 (5)	O1C7C1	108,8 (3)
		O1C7C8	110,7 (3)
		C1C7C8	110,9 (3)
		N1C8C7	109,6 (3)

bonds of a group of the PNH_2^+ type in a secondary ammonium salt. Absorption bands were also observed in the following regions (cm^{-1}) 3200-3360 (OH), 2820-2940 (CH_{ar}), 1570-1600 (Ph), 950-1040 (P–O–C).

To confirm the structures of the salts synthesized, an x-ray structural study was made for the case of ephedrine (diethyl phosphorothioate) (II).

The structures of the cation and the anion in (II) are shown in Fig. 1. The bond lengths (Fig. 1) and valence angles (Table 2) in the cation are close to those found in the ephedrine salts $C_{10}H_{16}ON^+Cl^-$ (IV) [4], $C_{10}H_{16}ON^+H_2PO_4^-$ (V) [5], and $(C_{10}H_{16}ON^+)_2HPO_4^{2-}\cdot H_2O$ (VI) [6]. The O1 and N1 atoms depart from the plane of the benzene ring by 0.25 and −1.29 Å, respectively [in (IV), by 0.42 and −1.38 Å]. The torsion angles characterizing the molecular conformations of ephedrine and its derivatives (see Fig. 1) are: τ (C6C1C7-O1) = −12.2(4), ω (O1C7C8N1) = −71.0(4), ψ (C10N1C8C7) = −176.0(6), and χ (HO1C7C8) = −83.0(4)°.

The hydroxy group is located closer to the plane of the benzene ring than in (IV), where τ = −21°. The conformations relative to the C7–C8 and C8–N1 bonds (gauche and trans, respectively) are analogous to those found in (IV) (ω = −70°, χ = −170°), which is explained by the influence of the counter-ion forming with the hydroxy group of the cation O1—H... O2 (x, y, z) bond (O...O distance 2.71 Å, O–H...O angle 179.6°). There is also a hydrogen bond, N1–H...O2 (1x, 0.5 + y, −z) (N...O distance 2.75 Å, N–H...O angle 162.2°). In the crystal, cyclic associates of two cations and two anions alternating in a ring are formed through hydrogen bonds.

The phosphorus atom in the anion of (II) has a distorted tetrahedral coordination. The valence angles and bond lengths are the usual ones for cyclic compounds of tetracoordinated phosphorus [7]. The observed lengths of the C–C bonds of the ethoxy group are appreciably shortened relative to the usual value of 1.53-1.55 Å for an ordinary C_{sp^3}–C_{sp^3} bond [8], which is obviously connected with the large thermal vibrations of the C11, C12, C13, and C14 atoms of the terminal linear groups (B_{iso}^{eq} = 12, 12.8, and 10 Å^2, respectively).

TABLE 3. Coordinates of the Atoms ($\times 10^4$, for H $\times 10^3$)

Atom	x	y	z	Atom	x	y	z
anion				cation			
S1	2840 (1)	0	12001 (1)	O1	2599 (3)	−1679 (5)	9140 (2)
P1	1304 (1)	−1697 (2)	11771 (8)	N1	1996 (3)	2028 (5)	9785 (3)
O2	750 (3)	−1938 (5)	10682 (2)	C1	2863 (4)	−661 (6)	7416 (3)
O3	1713 (4)	−3612 (5)	12159 (2)	C2	2453 (5)	337 (7)	6565 (4)
O4	10 (3)	−1316 (5)	12480 (2)	C3	3057 (6)	−17 (9)	5625 (3)
C11	2390 (9)	−338 (1)	13176 (5)	C4	3998 (5)	−134 (1)	5514 (4)
C12	208 (1)	−542 (1)	13612 (6)	C5	4407 (5)	−2327 (8)	6348 (4)
C13	−491 (6)	438 (8)	12728 (5)	C6	3834 (5)	−2008 (7)	7294 (3)
C14	−729 (8)	56 (1)	13827 (5)	C7	2253 (4)	−267 (6)	8455 (3)
H11.1	350	−382	1314	C8	2826 (4)	1493 (6)	8891 (3)
H11.2	211	−281	1367	C9	4387 (5)	1449 (9)	9174 (4)
H12.1	248	−561	1436	C10	2357 (5)	3792 (7)	.0259 (4)
H12.2	229	−649	1317	HO1	212 (4)	−175 (7)	953 (2)
H12.3	91	−548	1370	HN1	121 (3)	214 (5)	957 (2)
H13.1	31	136	1255	HN2	208 (3)	137 (6)	1029 (2)
H13.2	−139	73	1231	H2	179 (4)	137 (6)	666 (2)
H14.1	−106	176	1406	H3	279 (4)	50 (3)	519 (3)
H14.2	21	22	1427	H4	435 (3)	−140 (6)	485 (3)
H14.3	−149	−40	1403	H5	519 (4)	−335 (7)	630 (3)
				H6	394 (4)	−280 (6)	780 (3)
				H7	113 (4)	−4 (6)	838 (3)
				H8	252 (3)	214 (4)	844 (2)
				H9.1	497 (4)	115 (7)	858 (3)
				H9.2	448 (4)	97 (7)	974 (3)
				H9.3	479 (5)	264 (7)	938 (3)
				H10.1	231 (4)	456 (6)	972 (3)
				H10.2	331 (6)	37 (1)	1056 (4)
				H10.3	128 (7)	39 (1)	1078 (5)

EXPERIMENTAL

Synthesis of Ephedrine (Dialkyl phosphorothioate)s. A mixture of ephedrine, sulfur, and a dialkyl phosphorothioite in a ratio of 1:1:1 in absolute benzene was heated with stirring until the sulfur had dissolved completely. After the solution had cooled, the crystals that had deposited were filtered off and were recrystallized from benzene–hexane.

IR spectra were taken on a Specord IR-71 spectrometer in KBr tablets, and PMR spectra on a Tesla BS-467 instrument at a frequency of 100 MHz in CCl_4 with hexamethyldisiloxane as internal standard.

The parameters of the cell and the intensities of 1943 reflections were measured on an SAD-4 automatic four-circle diffractometer (λMoK_α) with a graphite chromator at a ratio of rates of $\omega:\theta = 1.2:1$; $2\theta \leq 52°$. Crystals of ephedrine (O,O-diethyl phosphorothioate were monoclinic: $a = 9.427(3)$, $b = 7.553(1)$, $c = 12.953(3)$; $\beta = 92.28(2)°$; $v = 921.6$ Å^3; $M = 322$; $d_{calc} = 1.16$ g/cm^3; $C_{13}H_{25}NOPS$; sp. gr. $P2_1$. The calculations made use of 1271 independent reflections with $I \leq 3\sigma$. The structure was interpreted by the direct method, the system of coordinates being chosen in accordance with the known absolute conformation of ephedrine [4]. Refinement was carried out by full-matrix MLS first in the isotropic and then in the anisotropic approximation for the nonhydrogen atoms. The H atoms of the cation were revealed in a difference synthesis and were included in the refinement in the isotropic approximation. The positions of the H atoms of the anion were calculated and were not refined. The final divergence factors were $R = 0.039$ and $R_w = 0.047$. All the calculations were performed on a PDP-11/23 PLUS computer by the SDP-PLUS programs. The coordinates of the atoms are given in Table 3.

SUMMARY

Ephedrine (dialkyl phosphorothioate)s have been synthesized. An x-ray structural investigation has been made of the spatial structure of ephedrine (diethyl phosphorothioate).

LITERATURE CITED

1. M. Zh. Zhurinov, L. A. Mirkind, and M. Ya. Fioshin, Advances in the Electrochemistry of Organic Compounds [in Russian], Kazan' (1970), p. 42.
2. M. Zh. Zhurinov, M. Ya. Fioshin, and L. A. Mirkind, Electrokhimiya, 5, 1257 (1969).

3. M. Zh. Zhurinov, B. A. Serikbaev, M. Ya. Fioshin, and Kh. A. Aslanov, Uzb. Khim. Zh., No. 3, 53 (1970).
4. R. Bergin, Acta Crystallogr., B27, 381 (1971).
5. R. A. Hearn, G. R. Freeman, and C. E. Bugg, J. Am. Chem. Soc., 95, 7150 (1973).
6. R. A. Hearn and C. E. Bugg, Acta Crystallogr., B28, 3662 (1972).
7. N. G. Bokii, Yu. T. Struchkov, A. E. Kalinin, V. G. Andrianov, and T. N. Sal'nikov, Crystal Chemistry [in Russian], VINITI, Moscow (1977), p. 56.
8. L. E. Sutton, Tables of Interatomic Distances and Configuration in Molecules and Ions, Special Publication No. 18, The Chemical Society, London (1965), p. S14s.
9. B. A. Frenz, Computing in Crystallography, Delft University Press, Delft, Holland (1978), p. 64.

C-10 DIPEPTIDE DERIVATIVES OF COLCHICINE

E. O. Esbolaev, N. A. Aitkhozhina,
and L. A. Aleksandrova

UDC 547.944

The methyl esters of colchicidylglycyl-L-leucine, -L-phenylalanine, and -L-tryptophan and the ethyl esters of colchicidylglycylglycine, -L-isoleucine, -L-valine, -L-tyrosine, and -L-glutamic acid have been obtained by the condensation of colchicidylglycine and esters of amino acids. The structures of the compounds have been confirmed on the basis of their UV spectra and nuclear magnetic resonance spectra.

Colchicine is one of the most active compounds possessing cytotoxic activity. In spite of its high biological activity and its capacity for inhibiting the growth of many types of malignant cells, the use of colchicine in practical medicine is limited by its high toxicity. A broad spectrum of chemically modified analogs of colchicine has been obtained [1, 2]. Unfortunately, in the majority of cases, attempts to decrease its toxicity by changing its chemical structure have led to a considerable fall in, and sometimes to the loss of, biological activity [3]. The most effective of all known chemical derivatives of colchicine have proved to be thiocolchicine and colchicinamide [4, 5], which are less toxic than colchicine itself. Some amino acid derivatives of colchicine were obtained by V. V. Kiselev by the direct replacement of the C-10 methoxy group of the alkaloid by an amino group [6-8]. Colchicidylglycylglycine and colchicidylglycyl-D-valine have been synthesized similarly [9]. It has recently been shown that the introduction of amino acid residues into the structures of the alkaloids vinblastine [10] and ellipticine [11] leads to an increase in the efficacy of their action. The study of the chemotherapeutic properties of esters of the amino acid derivatives of vinblastine on the P388 and L1210 lines of tumor cells showed that what was important for the manifestation of activity was not only the nature of the amino acid residues but also the presence of the ester group [10]. The results of these investigations have created the prerequisites for the directed modification of certain low-molecular-mass biologically active compounds.

In the present paper we describe the synthesis of a number of C-10 dipeptide derivatives of colchicine. To obtain methyl and ethyl esters of colchicidylglycylamino acids we used cholicidylglycine (I) obtained by Kiselev's method [7] with some modifications. The structure of the compound obtained was confirmed by its UV and PMR spectra, TLC analysis, and electrophoretic mobility. In the UV spectra of (I) a shoulder appears at 408 nm on the band with its maximum at 354 nm due to the presence of a conjugated nitrogen atom in the structure of the molecule. When the solution under investigation was acidified, the

---

Institute of Molecular Biology and Biochemistry, Kazakh SSR Academy of Sciences, Alma-Ata. Institute of Molecular Biology, Academy of Sciences of the USSR, Moscow. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 91-95, January-February, 1989. Original article submitted March 10, 1988.

0009-3130/89/2501-0080 $12.50