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TOSYLATE OF ETHYL 3-AMINO-2-PHENYLIODONIOCROTONATE: SYNTHESIS, CRYSTAL STRUCTURE, AND SYNTHESIS OF HETEROCYCLIC COMPOUNDS BASED ON IT

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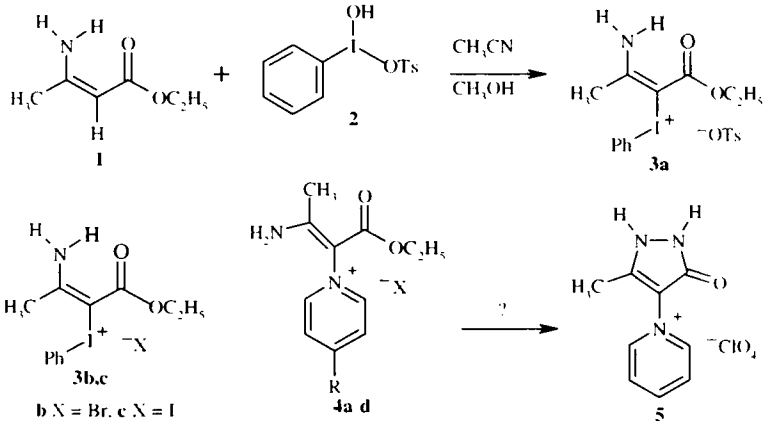
Ethyl 3-aminocrotonate, when reacted with hydroxy(tosyloxy)iodobenzene, forms the tosylate of ethyl 3-amino-2-phenyliodoniocrotonate which crystallizes well in up to 80% yield. X-ray analysis confirms the structure of the phenyliodonium salt, revealing intramolecular and unusual intermolecular hydrogen bonds, stabilizing the compound in the crystalline state. Reaction with pyridine, its 4-substituted derivatives, and 4,4'-bipyridine yields tosylates of 2-pyridinio-substituted ethyl 3-aminocrotonates. ^{1}H NMR and IR spectra support formation of an intramolecular hydrogen bond for the E-isomer, and iodonium salts in the case of pyridinium salts for the Z-isomer. The UV spectra of the pyridinium salts show an intramolecular charge transfer band.

Keywords: aminocrotonate ester, pyridinium salts, phenyliodonium salts, crystal structure.

Alkenyl(phenyl)- and alkynyl(phenyl)iodonium salts, synthesized and studied mainly in the past decade, have stimulated increased interest among synthetic chemists because of their high reactivity toward nucleophilic reagents [1, 2]. Mainly the alkenyl(phenyl)iodonium salts have been synthesized, containing alkenyl groups without electron-donor (alkoxy, dialkylamino) substituents in the β-position. These compounds are not very stable and rapidly decompose during storage [2, 3].



a R = H, X = Tos; **b** R = H, X = ClO_4;
c R = 4-pyridyl, X = ClO_4; **d** R = $N(CH_3)_2$, X = Tos

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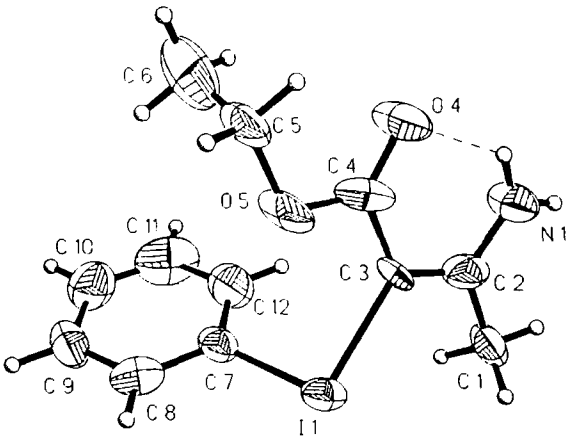

Fig. 1. Three-dimensional model for the cation of salt **3a** with thermal vibration ellipsoids for non-hydrogen atoms.

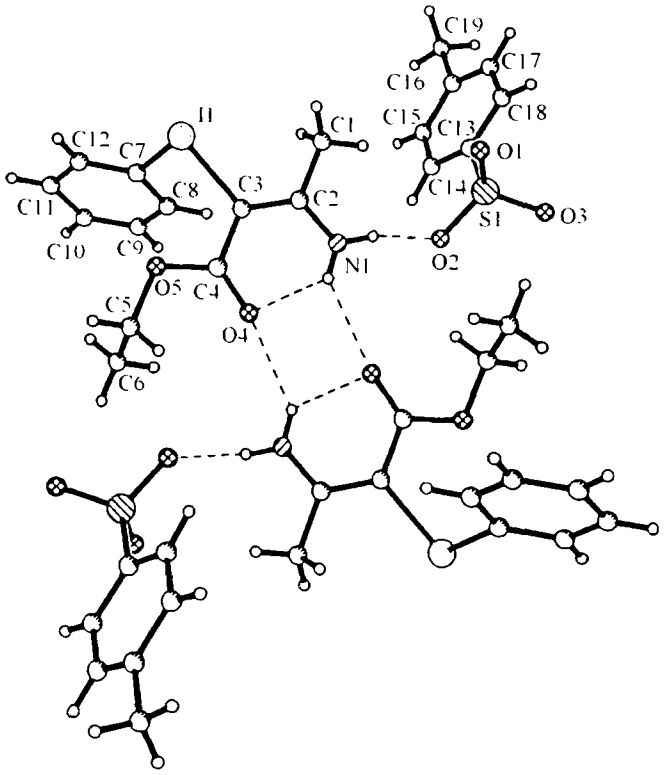

Fig. 2. Structure of the dimer of salt **3a** with hydrogen bonds and numbering of atoms.

Our group synthesized and studied the first stable cycloalkenyl(phenyl)iodonium salts, containing a carbonyl and also an alkoxy or amino group, or more precisely salts of 3-alkoxy-2-phenyliodonio- or 3-aminocyclohex-2-enones (enol esters and imines of dimedone) [4-7]. Phenyliodonium derivatives of acyclic enaminones had not been synthesized until we began our work.

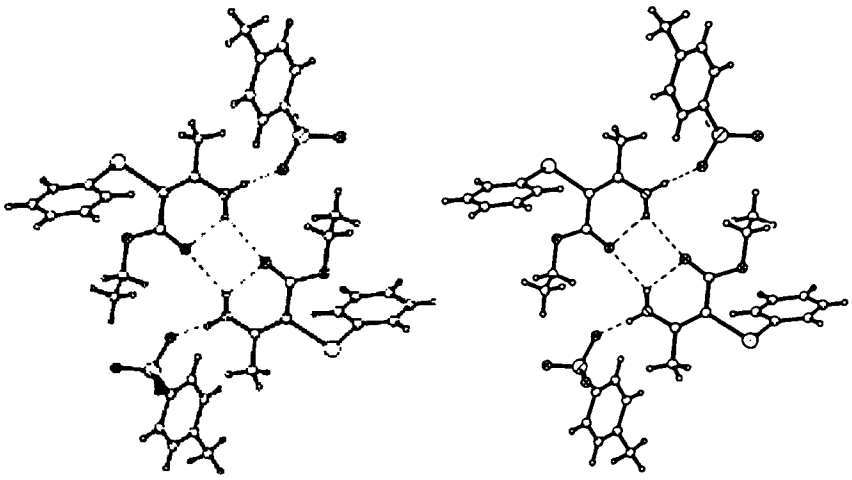

Fig. 3. Stereoscopic representation of the dimer of salt **3a**.

With the objective of obtaining phenyliodonium derivatives of 3-aminocrotonic ester (the imine of acetoacetic ester **1**, the simplest representative of enaminocarbonyl compounds), we studied the reaction of ester **1** with [hydroxy(tosyloxy)iodo]benzene (**2**), which has been intensively studied as an oxidizing agent and an intermediate in synthesis of phenyliodonium salts [8]. Phenyliodosyltosylate **2** was obtained in 1969 in our laboratory for the first time [5] and subsequently was studied in detail in the groups of G. F. Koser and R. M. Moriarty [8]. In our group, we found that the ethyl ester of dimedone and the imine of dimedone easily react with compound **2**, forming the corresponding phenyliodonium salts [5-7]. We found that the 3-aminocrotonate **1** reacts with phenyliodosyltosylate in acetonitrile solution in the presence of 5% methanol at 40°C unexpectedly easily, and the pure tosylate of ethyl 3-amino-2-phenyliodoniocrotonate **3a** is crystallized in up to 80% yield. In 1997, Papoutsis et al. independently carried out an analogous reaction with methyl 3-aminocrotonate in methylene chloride solution at room temperature; the corresponding phenyliodonium tosylate was obtained in 73% yield [9].

Compound **3a** forms large colorless crystals, which after a single crystallization are suitable for X-ray study. They are unstable in the X-ray beam and gradually decompose. Nevertheless, we were able to solve its complete crystal structure (Figs. 1-3; Tables 1-3). The crystal structure of the phenyliodonium salt **3a** is basically similar to the structure of the ethyl ester of 3-amino-2-cyanocrotonic acid [10]. Phenyliodonium and amino groups are located in the *E*-position and consequently an intramolecular hydrogen bond is formed. An interesting structural element is the dimer created as a result of the two hydrogen bonds. One of the hydrogen atoms of the amino group forms two hydrogen bonds (intramolecular and intermolecular), while the second forms an intermolecular hydrogen bond with the oxygen atom of the sulfonate anion. All three hydrogen bonds, judging from their lengths, are strong (especially the intramolecular hydrogen bond). This strong intermolecular interaction in the crystal probably stabilizes the phenyliodonium salts with aliphatic residues, which are usually not very stable during storage.

Tosylate **3a** is moderately soluble in water and very soluble in methanol. It can be crystallized from water, but boiling aqueous solutions causes decomposition with liberation of iodobenzene. Decomposition proceeds rapidly with crystallization of samples that have been stored for a long time. We assume that decomposition is promoted by the presence of small amounts of acids, causing hydrolytic cleavage of the amino group. This also explains the need to use completely anhydrous solvents in synthesis of the tosylate, otherwise the reaction leads to the ammonium tosylate and the target product cannot be isolated. The bromide **3** and the unstable iodide **3c** can be precipitated from aqueous solutions of the tosylate by addition of potassium bromide or iodide.

TABLE 1. Coordinates of Nonhydrogen Atoms in the Crystal Tosylate of Ethyl 3-Amino-2-phenyliodoniumcrotonate **3a**

Atom	x	y	z
I1	0.12623(7)	0.11375(7)	0.14306(7)
S1	0.0306(4)	0.2448(3)	0.8112(3)
C1	0.0067(14)	0.3950(11)	0.1756(15)
C2	0.1695(13)	0.3873(14)	0.1194(13)
C3	0.2422(12)	0.2768(9)	0.1028(11)
C4	0.3982(14)	0.2677(15)	0.0571(13)
C5	0.5978(15)	0.1355(13)	0.0240(23)
N1	0.2386(13)	0.4930(11)	0.0879(12)
O4	0.4781(10)	0.3569(9)	0.0258(11)
O5	0.4436(10)	0.1492(8)	0.0563(13)
C7	0.1716(13)	0.0160(11)	0.3218(13)
C8	0.1854(15)	-0.1135(15)	0.3513(14)
C9	0.2163(17)	-0.1802(13)	0.4696(15)
C10	0.2319(18)	-0.1100(17)	0.5511(16)
C11	0.2164(20)	0.0146(21)	0.5202(15)
C12	0.1875(18)	0.0818(15)	0.4055(16)
C13	0.1732(13)	0.3091(12)	0.6599(13)
C14	0.1471(18)	0.3853(20)	0.5479(15)
C15	0.2622(29)	0.4320(15)	0.4313(18)
C16	0.4025(29)	0.3970(31)	0.4257(21)
C17	0.4220(21)	0.3206(21)	0.5357(26)
C18	0.3127(17)	0.2720(21)	0.6533(19)
C19	0.5280(40)	0.4513(38)	0.3008(26)
O1	0.0690(13)	0.2725(11)	0.9151(10)
O2	-0.0981(10)	0.3074(9)	0.7906(10)
O3	0.0287(12)	0.1108(9)	0.8257(11)
C6	0.6444(17)	0.1097(10)	0.1434(16)

TABLE 2. Bond Lengths (l), Bond Angles (ω) and Torsional Angles (τ) in the Crystal of Tosylate of Ethyl 2-Phenyliodonium-3-aminocrotonate **3a**

Bond	l, Å	Angle	ω, τ, deg.
I1 C3	2.062(10)	C3 I1 C7	96.1(5)
I1 C7	2.119(13)	C2 C3 C4	124.0(10)
C1 C2	1.52(2)	C3 C4 O4	123.0(13)
C2 N1	1.29(2)	C3 C2 N1	121.3(12)
C2 C3	1.39(2)	N1 H1···O4	129
C3 C4	1.45(2)	N1 H1···(O4)*	141
C4 O4	1.20(2)	C7 I1 C3 C2	-108.1(10)
N1 H1	0.86	C7 I1 C3 C4	72
O4···H1	2.05	C6 C5 O5 C4	86
O4···(H1)*	2.30	C3 I1 C7 C12	34
O2···H1	2.11	C3 I1 C7 C8	-146

* O4 and H1 atoms belong to the adjacent molecule.

When heated, tosylate **3a** easily reacts with pyridines. The reaction products were found to be the pyridinium salts **4**. So upon reaction with pyridine, the tosylate of ethyl 3-amino-2-N-pyridiniocrotonate (**4a**) was obtained. This compound occurs as yellowish crystals, readily soluble in water and methanol. The less soluble perchlorate **4b** is precipitated from aqueous solutions when treated with sodium perchlorate. Solutions of salts **4a** and **4b** have a yellowish color due to weak absorption at 330-335 nm (the spectrum was taken for **4a**, Table 3).

TABLE 3. IR and UV Spectra for Compounds **3** and **4**

Compound	IR spectrum, ν_{max}		UV spectrum	
	1500-1800 cm^{-1}	2400-3600 cm^{-1}	solvent	λ_{max}, nm (ε, $l \cdot mole^{-1} \cdot cm^{-1}$)
3a	1600	3180, 3330		
4a	1528, 1632, 1668	3068, 3128, 3208, 3380	H_2O CH_3CN $CHCl_3$	221 (10370), 263 (12630), 330-335 (800), 223 (17810), 262 (20580), 338 (1260) 263 (18540), 352 (940)
4b	1501, 1629, 1677	3080, 3127, 3375, 3427		
4c	1548, 1598, 1634, 1690	3120, 3220, 3290, 3430	H_2O CH_3CN $CHCl_3$	267 (27680), 361 (2100), 267 (33560), 364 (2040), 267 (19160), 372 (1250)
4d	1520, 1632, 1674	2980, 3100-3350	CH_3CN	220 (20580), 284 (29240)

TABLE 4. ^1H NMR Spectra of Compounds **3** and **4**

Compound	Solvent	Chemical shift, ppm
3a	DMSO-d_6	9.03 (1H, s, NH); 8.91 (1H, s, NH); 7.93-7.07 (9H, m, H_{arom}); 4.11 (2H, q, CH_2O); 2.47 (3H, s, CH_3); 2.27 (3H, s, CH_3-Tos); 1.16 (3H, t, $C\underline{H}_3CH_2$)
3b	DMSO-d_6	8.96 (1H, s, NH); 8.77 (1H, s, NH); 7.86-7.43 (5H, m, H_{arom}); 4.00 (2H, q, CH_2O); 2.41 (3H, s, CH_3); 1.07 (3H, t, $C\underline{H}_3CH_2$)
	CH_3OH-d_4	7.91-7.56 (5H, m, H_{arom}); 4.19 (2H, q, CH_2O); 2.54 (3H, s, CH_3); 1.23 (3H, t, $C\underline{H}_3CH_2$)
4a	DMSO-d_6	9.10-8.20 (7H, m, H_{Py}, NH_2); 7.35-7.10 (4H, m, H_{arom}); 4.05 (2H, q, CH_2O); 2.30 (3H, s, CH_3-Tos); 1.73 (3H, s, CH_3); 1.07 (3H, t, $C\underline{H}_3CH_2$)
4b	DMSO-d_6	9.04-8.18 (7H, m, H_{Py}, NH_2); 4.04 (2H, q, CH_2O); 1.73 (3H, s, CH_3); 1.05 (3H, t, $C\underline{H}_3CH_2$)
	+ H_2O-d_2	8.90-8.13 (5H, t, H_{Py}); 1.75 (3H, s, CH_3); 1.07 (3H, t, $C\underline{H}_3CH_2$)
4c	DMSO-d_6	9.16-8.09 (10H, m, H_{Py}, NH_2); 4.09 (2H, q, CH_2O); 1.82 (3H, s, CH_3); 1.07 (3H, t, $C\underline{H}_3CH_2$)
4d	DMSO-d_6	8.23 (2H, br. s, NH_2); 7.79-7.16 (8H, m, H_{arom}); 4.16 (2H, q, CH_2O); 3.31 (6H, s, $(CH_3)_2N$); 2.36 (3H, s, CH_3-Tos); 1.93 (3H, s, CH_3); 1.18 (3H, t, $C\underline{H}_3CH_2$)

This absorption probably is due to intramolecular charge transfer from the electron-donor aminocrotonate residue to the electron-acceptor pyridinium. Such a hypothesis finds support in the fact that the perchlorate of ethyl 3-amino-2-N-(4,4'-bipyridinio)crotonate **4c**, containing a stronger electron-acceptor residue (the bipyridinium cation), has a deeper yellow color and in aqueous solution absorbs in the 360 nm region (Table 3). If the 4'-dimethylaminopyridinium residue (a weaker electron-acceptor) is available in the molecule (compound **4d**), then the charge transfer band has a hypsochromic shift and is hidden under the strong absorption band at 284 nm. We also observe a bathochromic shift of the charge transfer band as we go from a polar solvent (water) to a less polar solvent (acetonitrile and chloroform). Compound **4c** is obtained similarly to **4a** by treatment of the iodonium tosylate **3a** with 4,4'-bipyridine followed by precipitation of the yellow perchlorate from aqueous solutions. The iodonium tosylate reacts readily with 4-dimethylaminopyridine: the almost colorless tosylate of ethyl 3-amino-2-N-4'-(dimethylamino)pyridiniocrotonate (**4d**) is obtained. The ^1H NMR and IR spectra of compounds **4** reveal significant differences compared with the spectra of the phenyliodonium derivatives. Thus the chemical shifts of the amino group protons undergo displacements from 9 to 8.2 ppm, and overlap with signals from the protons in the 3 and 5 positions of the pyridinium residue, which is observed during deuteration. The position of the signals from the methyl group of the crotonate residue changes from 2.41-2.47 ppm to 1.73-1.93 ppm (Table 4). In the IR spectrum of compound **3a**, we observed broad absorption with a maximum at 1600 cm^{-1}; compound **4** in this region has 3 maxima (Table 3).

The data presented suggest a change in the molecular configuration: in salts **4**, the pyridinium residue and the amino group are found in the *Z*-position, where there is no intramolecular hydrogen bond.

With the objective of obtaining the corresponding pyrazolones based on the pyridinium derivatives **4**, we carried out the reaction of perchlorate **4b** with hydrazine hydrate in methanol or acetic acid solution. After treatment of the reaction products, we were able to isolate a novel compound, the correspondence of which to the perchlorate of N-[3(2H)-oxo-5-methylpyrazol-4-yl]pyridinium (**5**) we studied.

EXPERIMENTAL

The IR spectra were taken on a Specord M-80 in a suspension with vaseline oil (1500-1800 cm^{-1}) and hexachlorobutadiene (2400-3600 cm^{-1}). The ^1H NMR spectra were recorded on a Bruker WH-90/DS, internal standard TMS; the UV spectra were recorded on a Specord M-40.

X-ray Diffraction Analysis. Single crystals of compound **3a** were grown from an acetonitrile solution with slow cooling. Crystals of **3a** are of triclinic syngony, space group *P*1, $Z = 2$. A single crystal (0.10 × 0.15 × 0.25) was used to measure the intensities of 2791 independent reflections on a Syntex-P21 four-circle automatic diffractometer. The unit cell parameters of the crystal were: $a = 9.835(1)$, $b = 11.042(2)$, $c = 11.038(2)$; Å, $\alpha = 72.63(1)°$, $\beta = 70.65(1)°$, $\gamma = 85.42(1)°$; unit cell volume $V = 1079.2(3)$ $Å^3$; $F(000) = 504$; $\mu = 1.608$ mm^{-1}; $D_x = 1.549(1)$ g/cm^3. The position of the iodine atoms was determined from the three-dimensional Patterson function. Other non-hydrogen atoms were found by two successive Fourier syntheses. The structure was least-squares refined in the full-matrix anisotropic approximation. The coordinates of the hydrogen atoms were calculated geometrically. The final *R* factor was equal to 0.0747. All the calculations were performed using the program SHELXL-93 [11].

Tosylate of Ethyl 3-Amino-2-phenyliodoniocrotonate (3a). Phenyliodosotosylate **2** (4 g, 10.2 mmol) was dissolved in a mixture of anhydrous acetonitrile (50 ml) and methanol (2.5 ml) with heating up to 50-60°C. The solution was quickly filtered, and at 40-45°C, ethyl 3-aminocrotonate (1.5 g, 10.8 mmol) was added to it. The material was dissolved, and after a certain time crystallization of the product began. The mixture was allowed to stand in a refrigerator for 24 h; large lustrous crystals were filtered and washed with ether. Yield 4 g (78%); mp 109-111°C (decomp.). The compound did not require purification for all further operations. It was recrystallized from acetonitrile or water. When crystallized from water at a temperature no higher than 80-90°C, the yield of crystals was 50%, decomposition temperature 112-114°C. Found, %: C 45.73; H 4.90; I 25.4; N 3.23; S 6.70. $C_{19}H_{22}INO_5S$. Calculated, %: C 45.34; H 4.41; I 25.21; N 2.78; S 6.37.

Bromide of Ethyl 3-Amino-2-phenyliodoniocrotonate (3b). Tosylate **3a** (0.2 g) was dissolved in water (15 ml) at 50°C and filtered; a solution of sodium bromide (1 g) in water (3 ml) was added. The mixture was allowed to stand in a refrigerator. The colorless crystals gradually decomposed during storage. Found, %: C 35.00; H 3.63; I 30.68; N 3.60. $C_{12}H_{15}BrINO_2$. Calculated, %: C 34.98; H 3.67; I 30.80; N 3.40.

Tosylate (4a) and Perchlorate (4b) of Ethyl 3-Amino-2-N-pyridiniocrotonate. Phenyliodonium tosylate **3a** (0.5 g, 1 mmol) and pyridine (0.2 ml) in acetonitrile (5 ml) were boiled for 30 min. A part of acetonitrile (3 ml) was evaporated, and the residue was diluted with absolute ether (10 ml). The oil separated upon cooling slow crystallized. It was recrystallized from a 5:1 ethyl acetate–ethanol mixture and then dried at 80-90°C. Yield of faintly yellowish, lustrous crystals of tosylate **4a** 56%; mp 161-162°C. Found, %: C 57.06; H 5.75; N 7.39. $C_{18}H_{22}N_2O_5S$. Calculated, %: C 57.13; H 5.86; N 7.40.

To obtain perchlorate, the oil which separated out after addition of the ether was dissolved in a small amount of water and sodium perchlorate was added. Almost colorless large crystals was obtained. The compound can be recrystallized from water; mp 147°C. Judging from the IR spectra and the chlorine content, perchlorate **4b** forms a crystal hydrate. Found, %: Cl 11.65. $C_{11}H_{17}ClNO_7$. Calculated, %: Cl 11.41.

Perchlorate of Ethyl 3-Amino-2-N-(4,4'-pyridinio)crotonate (4c·2H$_2$O). Phenyliodonium tosylate **3a** (0.5 g, 1 mmol) and 4,4'-bipyridine (0.16 g, 1 mmol), and acetonitrile (2 ml) were boiled for 10-15 min. The reaction mixture was cooled down and diluted with ether (20 ml). A yellow oil was formed, which was then

dissolved in water (2 ml) and filtered; sodium perchlorate was added to the filtrate. The yellow oil obtained upon cooling slowly crystallized, yield 0.15 g (36%). The compound was crystallized from water, yellow crystals; mp 168-170°C. Found, %: C 46.15; H 4.85; N 9.95. $C_{16}H_{22}ClN_3O_8$. Calculated, %: C 45.78; H 5.28; N 10.01.

Tosylate of Ethyl 3-Amino-2-(4'-dimethylamino)pyridiniocrotonate (4d·H$_2$O). Phenyliodonium tosylate **3a** (0.5 g, 1 mmol) and 4-dimethylaminopyridine (0.15 g, 1.2 mmol) in acetonitrile (2 ml) were boiled for 5-10 min. After this was cooled down, ether (10 ml) was added. The oil formed slowly crystallized. Yield of crude product: 0.32 g. The product was purified by crystallization from a 20:1 ethyl acetate–ethanol mixture. In a refrigerator, the compound crystallized very slowly, light beige crystals, yield 0.15 g; mp 92-94°C. Found, %: C 55.00; H 6.60; N 9.58. $C_{20}H_{29}N_3O_6S$. Calculated, %: C 54.65; H 6.65; N 9.56.

REFERENCES

1. P. J. Stang, *Angew. Chem. Int. Ed. Engl.*, **31**, 274 (1992).
2. P. J. Stang and V. V. Zhdankin, *Chem. Rev.*, **96**, 1123 (1996).
3. M. Ochia, M. Kunishima, K. Fuji, M. Shiro, and Y. Nagao, *J. Chem. Soc. Chem. Commun.*, 1076 (1988).
4. O. Ya. Neiland, *Izv. Akad. Nauk LatvSSR, Ser. Khim.*, No. 5, 589 (1964); *Chem. Abstr.* **62**:7661 (1965).
5. O. Ya. Neiland and B. Ya. Karele, *Zh. Org. Khim.*, **6**, 885 (1970).
6. B. E. Arena and O. Ya. Neiland, *Zh. Org. Khim.*, **17**, 2114 (1981).
7. B. E. Arena, O. Ya. Neiland, and R. B. Kampare, *Zh. Org. Khim.*, **18**, 995 (1982).
8. R. M. Moriarty, R. K. Vaid, and G. F. Koser, *Synlett*, **365** (1990).
9. I. Papoutsis, S. Spyroudis, and A. Varvoglis, *Tetrahedron*, **54**, 1005 (1998).
10. K. Szulzevskiy, B. Schulz, S. Kulpe, and J. Kreutzmann, *Acta Crystallogr. C*, **40**, 280 (1984).
11. G. M. Sheldrick, *SHELXL-93*, Program for the Refinement of Crystal Structures (1993), University of Göttingen, Germany.