S- and *Se*-Dimethylarsino Derivatives of Thio- and Selonopyrimidines and Purines

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The synthesis of dimethylarsinothio- and dimethylarsinoselonopyrimidines and -purines which utilizes diethylaminodimethylarsine is described. A series of these derivatives, with different substituents on the heterocyclic ring, has been investigated by infrared, nmr, and mass spectroscopic methods. Attempts to prepare *O*- or *N*- arsinous acid derivatives from oxy- and aminopyrimidines were unsuccessful.

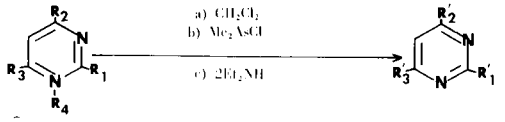
Recently, there has been an increasing accumulation of reports citing the isolation and characterization of several thiopyrimidines and thionucleosides from natural sources. Thus, 6-(4-hydroxy-3-methyl-2-butenylamino)-2-methylthio-9-β-D-ribofuranosylpurine (1), (methyl 2-thiouridine-5-acetate) (2), and various other thionucleosides have been isolated from a variety of t-RNA's (3). The work described in this paper was initiated as a result of the report of Sagan, *et al.* (4), which utilized the reaction between an -OH, -SH, or -SeH group and a dialkylaminodialkylarsine. The arsinous acid esters produced in this reaction possess the following order of hydrolytic stability: $R_2AsSeR' >> R_2AsSR' > R_2AsOR'$ (5). The dialkylalkoxyarsines, R_2AsOR', have a C-O-As bond which has been postulated to exist in sugar arsenates (6). They are exceedingly moisture sensitive whereas the dialkyl(alkylseleno)arsines and the dialkyl(alkylthio)arsines can be handled in the atmosphere (4,5,7).

Thiopyrimidines and thiopurines would be interesting substrates for condensation with Et_2NAsR_2, since, in the tautomeric -SH form, they have only one active site. It was felt that dialkylaminodialkylarsines could serve as useful probes in the preparation of specific derivatives of -SH (-SeH) groups in nucleic acids. Furthermore, a knowledge of the mass spectral fragmentation patterns of the dimethylarsino derivatives could serve for the purpose of identifying the sulfur (selenium) containing bases in nucleic acids.

Results and Discussion.

The approach to the synthesis of the dimethylarsinothio- and -selonopyrimidines (**2**) is presented in Scheme I. Diethylaminodimethylarsine was prepared *in situ* by the addition of two equivalents of diethylamine to dimethylchloroarsine. The reagent, immediately following its preparation was allowed to react with the thio- or selenopyrimidines. The product was washed several times with water, and then purified by recrystallization or distillation.

Scheme I



1

	R_1	R_2	R_3	R_4
1a	-SH	-H	-H	
b	-SH	-SH	-H	
c	-SH	-SH	-Me	
d	-SH	-SH	-Pr	
e	-SH	-SH	-SH	
f	-SeH	-SeH	-H	
g	-SH	-OH	-H	
h	-SH	-OH	-OH	
i	-SH	$-NH_2$	-H	
j	-O	-SH	-H	-Me
k	-O	-SH	-H	-Et

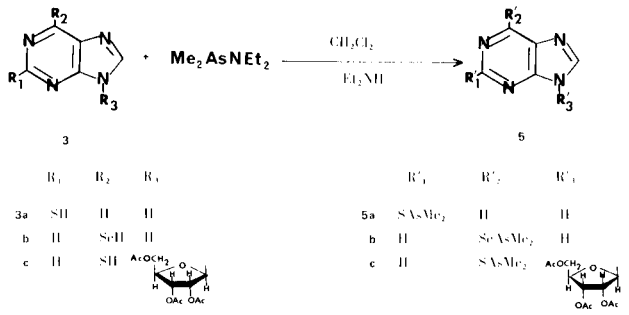
2

	R'_1	R'_2	R'_3
2a	$-SAsMe_2$	-H	-H
b	$-SAsMe_2$	$-SAsMe_2$	-H
c	$-SAsMe_2$	$-SAsMe_2$	-Me
d	$-SAsMe_2$	$-SAsMe_2$	-Pr
e	$-SAsMe_2$	$-SAsMe_2$	$-SAsMe_2$
f	$-SeAsMe_2$	$-SeAsMe_2$	-H

g, h, i, j, and k did not yield stable derivatives

The procedure followed in the preparation of the dimethylarsinothio- and -selenopurines (**5**) is given in Scheme 2. The procedure differed from that used for the preparation of the dimethylarsinothio- and -selonopyrimidines in that the diethylaminodimethylarsine was actually separated and purified prior to its condensation with the purines. This was done in order to eliminate the formation of amine hydrochloride and made it possible to recrystallize the product without a preliminary water wash. The aqueous solubilities of the bases made this procedure desirable. The physical properties and analytical data for these compounds are given in Table I. Pertinent spectral data are presented in Tables II, III, and IV.

Scheme II



No difficulty was encountered in the preparation of the *S*-thioarsinous or *Se*-selonarsinous acid esters. However, all attempts to prepare *O*- or *N*-arsinous acid derivatives from oxy- and aminopyrimidines were completely unsuccessful. This is attributed to the extreme hydrolytic instabilities of C-O-As and C-N-As bonds in air. However, it was not possible to isolate such derivatives, even when an SH- group was present on the base, (Scheme I, g-k).

Nuclear Magnetic Resonance Spectroscopy.

The ^1H chemical shifts for the compounds prepared are listed in Table II. The protons of the methyl groups

TABLE I

Analytical Data

	Name	Elemental Analysis (Found) Calcd.	Yield	M.p., °C	B.p., °C
2a	*S*-Dimethylarsino-2-thiopyrimidine	(C, 33.56; H, 4.15) C, 33.33; H, 4.17	57%		114 at 1.3 mm Hg
2b	*S,S'*-Bis(dimethylarsino)-2,4-dithiopyrimidine	(C, 27.44; H, 4.03) C, 27.12; H, 3.95	60%	46-48	
2c	*S,S'*-Bis(dimethylarsino)-2,4-dithio-6-methylpyrimidine	(C, 29.74; H, 4.42) C, 29.51; H, 4.37	78%		168 at 0.1 mm Hg
2d	*S,S'*-Bis(dimethylarsino)-2,4-dithio-6-propylpyrimidine	(C, 33.33; H, 5.10) C, 33.50; H, 5.08	68%		160 at 0.1 mm Hg
2e	*S,S',S''*-Tris(dimethylarsino)-2,4,6-trithiopyrimidine	(C, 24.74; H, 3.97) C, 24.59; H, 3.89	55%	48-50	
5a	*S*-Dimethylarsino-2-thiopurine	(C, 32.61; H, 3.75) C, 32.81; H, 3.52	32%	173-175	
5c	*S*-Dimethylarsino-6-thio-2',3',5'-triacetylpurine Riboside	(C, 41.90; H, 4.59) C, 42.02; H, 4.47	26%	101-103	
2f	*Se,Se'*-Bis(dimethylarsino)-2,4-diselenopyrimidine	(C, 21.79; H, 2.98) C, 21.53; H, 3.12	63%		
5b	*Se*-Dimethylarsino-6-selenopurine		10%		

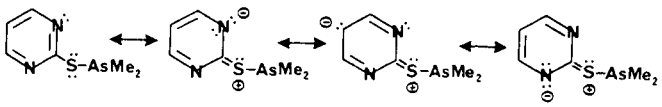
TABLE II

^1H Chemical Shifts (a) and Observed Infrared Frequencies Assigned to Chalcogen-Arsenic Modes in Dimethylarsinothio- and -selenopyrimidines and Purines

Compounds	Solvent	Nmr $(CH_3)_2As$	Nmr H(4); H(6)	Nmr H(5)	Nmr H(8)	Ir (cm^{-1}) C-As	Ir (cm^{-1}) S-As	Ir (cm^{-1}) Se-As
2a	$CDCl_3$	1.47s	8.50d	7.00t		584	398	
2b	$CDCl_3$	1.45s	8.06d	6.90d		580	398	
2c	$CDCl_3$	1.46s		6.90s		585	400	
2d	$CDCl_3$	1.46s		6.84s		584	392	
2e	$CDCl_3$	1.45s		6.95s		585	400	
2f	$CDCl_3$	1.53s	8.05d	7.15d		582		270
5a	d_6-DMSO	1.60s	8.95s		8.52s	584	394	
5b						585		272
5c	d_6-DMSO	1.57s	8.72s		8.27s	585	387	

(a) Tetramethylsilane was used as the internal standard. Chemical shifts reported in δ units. The letter immediately following the [illegible] value of the chemical shift designates multiplicity, *i.e.*, s for singlet, d for doublet, t for triplet.

bonded to the arsenic atom are shifted slightly downfield compared with the chemical shifts observed for aliphatic thioarsines (5,8). An interesting trend in the chemical shift of the H(5) proton is noted. As the number of arsinothio groups on the ring increases, the H(5) proton moves upfield. This is indicative of an increase in electron density. Position 5 of the pyrimidine ring is naturally electron rich compared to the 2,4 or 6 positions (9). Consequently, any donation of electrons to the ring system will serve to proportionally increase the electron density at this position. In this case, sulfur could function as an electron donor and bring about an increase in the electron density at position 5. The postulated resonance structures are:



In the proposed resonance structures, a formal positive charge is associated with the sulfur atom. This increases the electronegativity difference between the sulfur and arsenic atoms, which in turn, draws electrons from the dimethylarsino moiety toward the S atom. This would explain the observed downfield shift in the dimethylarsino protons. The nmr spectra (Table II) of the arsinothiopurines exhibit a slight downfield shift in the methylarsino protons relative to the pyrimidine derivatives. This may be attributed to the use of DMSO as the solvent.

In the case of *Se*,*Se*′-bis(dimethylarsino)-2,4-diselenopyrimidine the ring protons display chemical shifts similar to those noted for the arsinothiopyrimidines. This would indicate that similar resonance structures are operative in the case of the selenium compound. The chemical shift of the arsinomethyl protons, 1.53 δ, is even further downfield than in the corresponding thio compounds. This suggests that there may exist a larger degree of back donation from the arsenic through a π bond to the Se 4d orbitals than exists in the As-S compounds. Arsenic and selenium, have more closely matched energy levels than do arsenic and sulfur. Thus, any bonding of the As-Se π type should be stronger. However, as will be pointed out subsequently, the infrared data are inconsistent with this argument.

Infrared Spectroscopy.

The ir bands of interest for the compounds are presented in Table II. The As-C stretching frequency has been reported at 552-585 cm^{-1} and the As-S stretch in molecules of the type R_2AsSR' at 380-390 cm^{-1} (5). The value for an "isolated" arsenic-sulfur double bond has been calculated to be 555 cm^{-1} (10) and has been observed in the region 470-490 cm^{-1} in molecules of the type R_3AsS. Similar calculations give a value of 372 cm^{-1} for an "isolated" As-S single bond. All of the thioarsino compounds which are the subject of this study absorb in the region 387-400 cm^{-1}. This is very close to the value which would be expected for an arsenic-sulfur single bond.

All of the spectra were characterized by a medium to strong absorption in the range of 580-585 cm^{-1}. These bands fall in the region where arsenic-carbon stretching frequencies (552-585 cm^{-1}) are expected (5). Netzel (11) reported an out-of-plane ring deformation for pyrimidines near 450 cm^{-1} which may be used to identify pyrimidine compounds. The compounds prepared in this research had an absorption in this region as well.

The As-Se absorption in compounds of the type R_2AsSeR' has been located in the 268-280 cm^{-1} region (5). The arsenic-selenium bond stretching frequency was calculated (12) to lie between 388-277 cm^{-1}. In the case of *Se*,*Se*′-bis(dimethylarsino)-2,4-diselonopyrimidine, this absorption is observed at 270 cm^{-1}. *Se*-Dimethylarsino-6-selenopurine also absorbs in this region. Thus, the ir data suggest that little, or no, double bond character exists in these cases, as well. The observed As-Se stretching vibration is very close to that expected for an "isolated" As-Se single bond (277 cm^{-1}). Absorptions at 580 cm^{-1} and 585 cm^{-1} were observed for the C-As stretching vibrations.

It is our feeling that the As-S and As-Se bonds, in molecules of the type R_2AsXR' (X = S or Se), as is indicated by the ir data, are essentially single, covalent bonds with very little π bond character. In this regard, it is interesting to point out that the As(III)-S bond distance in tetramethyldiarsine disulfide, 2.28 Å is only 0.03 Å smaller than that calculated from the sum of covalent single bond radii (13). The downfield shift in the nmr spectra of the ^1H arsinomethyl protons is more likely due to the hyperconjugation effects of methyl groups.

Mass Spectroscopy.

Listed in Table III are the high-mass ions which were observed to form in significant amounts in the mass spectra of this group of compounds. The formation of the molecular ion occurs in all cases, but its intensity varies. Also, as noted from examination of Table III, the loss of methyl group(s) from the $As(CH_3)_2$ moiety is highly characteristic of this group of derivatives.

All of the thiopyrimidines were observed to yield ions formed by a process involving the loss of the $SAsMe_2$

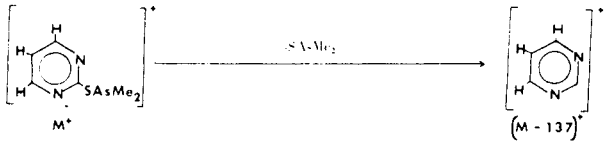


TABLE III

Pertinent Mass Spectral Data

Compound (a)	Significant High-Mass Ions	High-Resolution Measurements (b)	Elemental Compositions
2a (216)	M M-15 M-30	215.9707 (1.9 ppm)	$C_6H_9N_2SAs$
2b (352)	M M-15 M-30 M-45	336.8793 (1.5 ppm)	$C_7H_{11}N_2S_2As_2$
2c (366)	M M-15 M-30 M-45	350.8965 (3.1 ppm)	$C_8H_{13}N_2S_2As_2$
2d (394)	M M-15 M-30 M-45	378.9258 (2.5 ppm)	$C_{10}H_{17}N_2S_2As_2$
2e (488)	M M-15 M-45	472.8117 (1.9 ppm)	$C_9H_{16}N_2S_3As_3$
2f (448)	M M-15 M-30 M-45	447.7923 (0.5 ppm)	$C_8H_{14}N_2As_2Se_2$
5a (256)	M M-15 M-30	240.9527 (1.2 ppm)	$C_6H_6N_4SAs$
5c (514)	M M-15		

(a) Nominal molecular mass, M, given in parentheses. (b) Experimental values are given. Errors are shown in parentheses.

group without cleavage of the heterocyclic ring, as shown. As the number of thiodimethylarsino groups on the ring increases, fragmentation of the heterocyclic ring, as indicated by the distribution of the ions, appears to take place. The nature of the fragmentation products, due largely to the presence of the $-SAsMe_2$ or $-SeAsMe_2$ groups on the ring, differs from those reported by Rice, *et al.* (14) and Biemann and McCloskey (15) for simple purines and pyrimidines.

S-Dimethylarsino-6-thio-2′,3′,5′-triacetylpurine riboside displays a mode of fragmentation which differs from that of the other compounds (Figure 1). The molecular ion, which is found in less than 1% abundance, readily loses a methyl group from the dimethylarsino portion of the molecule creating a $(M-15)^+$ peak, m/e = 499. This ion then cleaves at the purine-sugar linkage producing an acetylated ribose ion, Q^+ (m/e = 259) and an *S*-methylarsino-6-thiopurine radical (B), which readily picks up one or two protons producing $(B+1)^+$, m/e = 241 and $(B+2)^+$ m/e = 242. $(B+1)^+$ and $(B+2)^+$ then undergo further fragmentation. The acetylated ribose underoges cleavage according to the scheme described by Budzikiewicz (16).

Details of the fragmentation pathways are not presently discussed, but are currently under more detailed study.

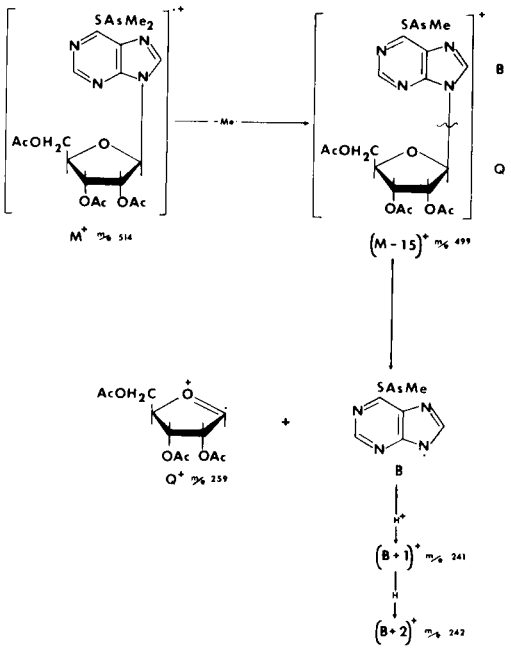
EXPERIMENTAL

The ir spectra were run on a Beckman Model IR-12 spectrophotometer. The nmr spectra were measured on a Varian Model T-60 spectrometer. TMS was used as the internal standard. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. The mass spectroscopic data were measured in the mass spectroscopic laboratory of the Department of Biochemistry and Biophysics, Texas A&M University on a CEC 21-110B High-Resolution Mass Spectrometer. The electron energy was 70 eV and the accelerating voltage was eight kV.

Samples were introduced with glass, direct-introduction probes at temperatures ranging from 20-70° for the pyrimidine derivatives and from 125-210° for the purine derivatives. The ion-source temperature was varied from 180-230°.

Figure 1

Fragmentation Pattern for S-Dimethylarsino-6-thio-2',3',5'-triacetylpurine Riboside



Starting Materials.

The dimethylchlorarsine was prepared by the method of Van der Kelen (17). The starting purines and pyrimidines (1a,c,d; 3a,b,c) were obtained from Sigma Chemical Company, Nutritional Biochemical Corporation, Schwarz Bio-Research, Inc., and K & K Laboratories, Inc. The other starting thiopyrimidines were prepared according to procedures described by Elion *et al.* (18,19) and Fox *et al.* (20).

General Synthesis of Dimethylarsinothio- and -selenopyrimidines.

An equivalent amount of dimethylchloroarsine was added to a well-stirred suspension of the appropriate thiopyrimidine in methylene chloride. This suspension was then treated dropwise with two equivalents of diethylamine. The resulting solution was extracted with three portions of cold water to remove any unreacted thiopyrimidine and amine hydrochloride. The organic layer was dried over magnesium sulfate, filtered, and the solvent removed *in vacuo*. The product was then purified.

S-Dimethylarsino-2-thiopyrimidine (**2a**).

Dimethylchloroarsine (12.46 g., 0.089 mole) and diethylamine (12.99 g., 0.178 mole) were added to 2-thiopyrimidine (10 g., 0.089 mole) in methylene chloride. The *S*-dimethylarsino-2-thiopyrimidine was distilled at 114° at 1.3 mm Hg. The clear yellow liquid was obtained in 57% yield.

S,S'-Bis(dimethylarsino)-2,4-dithiopyrimidine (**2b**).

2,4-Dithiouracil (4 g., 0.028 mole) was treated with dimethylchloroarsine (7.9 g., 0.056 mole) and diethylamine (8.2 g., 0.112 mole). The oily product crystallized upon cooling. The *S,S'*-bis-(dimethylarsino)-2,4-dithiopyrimidine was recrystallized from a 50-50 mixture of hot chloroform and petroleum ether. The pale yellow crystals were collected in 60% yield. The melting point was 46-48°.

S,S'-Bis(dimethylarsino)-2,4-dithio-6-methylpyrimidine (**2c**).

A suspension of 6-methyl-2,4-dithiouracil (2.0 g., 0.013 mole) in methylene chloride was stirred well. Dimethylchloroarsine (3.54 g., 0.025 mole) and diethylamine (3.68 g., 0.09 mole) were added. The *S,S'*-bis(dimethylarsino)-2,4-dithio-6-methylpyrimidine was distilled at 168° at 0.01 mm Hg. The clear yellow liquid was obtained in 78% yield.

S,S'-Bis(dimethylarsino)-2,4-dithio-6-propylpyrimidine (**2d**).

A methylene chloride solution of 6-propyl-2,4-dithiouracil (0.5 g., 0.003 mole) was treated with dimethylchloroarsine (0.84 g., 0.006 mole) and diethylamine (0.87 g., 0.012 mole). The *S,S'*-bis(dimethylarsino)-2,4-dithio-6-propylpyrimidine distilled at 160° at 0.1 mm Hg. The clear yellow liquid was obtained in 68% yield.

S,S',S''-Tris(dimethylarsino)-2,4,6-trithiopyrimidine (**2e**).

2,4,6-Trithiobarbituric acid (0.38 g., 0.0022 mole) was mixed in methylene chloride with dimethylchloroarsine (0.936 g., 0.0067 mole) and diethylamine (0.978 g., 0.0134 mole). The product crystallized upon refrigeration. The solid was recrystallized from a 50-50 mixture of hot chloroform and petroleum ether. The pale yellow crystals of *S,S',S''*-tris(dimethylarsino)-2,4,6-trithiopyrimidine were collected in 55% yield. Their melting point was 48-50°.

Se,Se'-Bis(dimethylarsino)-2,4-diselonopyrimidine (**2f**).

Dimethylchloroarsine (1.68 g., 0.012 mole) was added to a well stirred suspension of 2,4-diselonopyrimidine (1.42 g., 0.006 mole) in methylene chloride. This mixture was treated dropwise with diethylamine (1.51 g., 0.024 mole). The resulting clear solution was extracted with three portions of water and the aqueous layer discarded. The organic layer was dried over magnesium sulfate, filtered, and concentrated to a thin syrup *in vacuo*. Attempted distillation resulted in thermal decomposition. Instead, the *Se,Se'*-bis(dimethylarsino)-2,4-diselonopyrimidine was purified by extraction with water to remove excess 2,4-diselenopyrimidine, and then by washing the resultant syrup with ether, in which the desired product dissolved leaving a residue of impurities including cacodylic acid. The yellow oil was then subjected to reduced pressure for 6 hours to remove volatile impurities. The *Se,Se'*-bis(dimethylarsino)-2,4-diselenopyrimidine was obtained in 63% yield.

General Synthesis of Dimethylarsinothio- and -selenopurines.

Because of greater solubility of these purines in water, the procedure used in the preparation of arsinothiopyrimidines was altered slightly. Diethylaminodimethylarsine was first prepared under an atmosphere of nitrogen by the addition of dimethylchloroarsine (3.50 g., 0.025 mole) to a well-stirred solution of diethylamine (3.15 g., 0.050 mole) in anhydrous diethyl ether (21). The precipitated amine hydrochloride was removed by filtration under nitrogen and the clear filtrate concentrated *in vacuo*. The diethylaminodimethylarsine was distilled at 60-61° at 35 mm Hg and stored under dry nitrogen. The diethylaminodimethylarsine was then added to a well-stirred suspension of the thio- or -selenopurine in methylene chloride solution. The reaction mixture was concentrated *in vacuo* and crystallized upon refrigeration. The products were then recrystallized from chloroform.

S-Dimethylarsino-2-thiopurine (**5a**).

2-Thiopurine (0.25 g., 0.0016 mole) was stirred in methylene chloride and diethylaminodimethylarsine (0.28 g., 0.0016 mole) was added. The reaction mixture was concentrated *in vacuo* and

crystallized upon cooling. The *S*-dimethylarsino-2-thiopurine was recrystallized from chloroform and obtained in 32% yield. The crystals melted at 173-175°.

Se-Dimethylarsino-6-selonopurine (**5b**).

6-Selenopurine (0.1 g., 0.0005 mole) was permitted to react with dimethylaminodimethylarsine (0.09 g., 0.0005 mole). The product was obtained in such a small quantity and elemental analysis was not attempted. Instead, its ir and mass spectra were used to characterize it. From these data the product was concluded to be *Se*-dimethylarsino-6-selenopurine.

S-Dimethylarsino-6-thio-2′,3′,5′-triacetylpurine Riboside (**5c**).

Dimethylchloroarsine (0.35 g., 0.0025 mole) was added to a well stirred suspension of 6-mercapto-2′,3′,5′-triacetylpurine riboside (1 g., 0.0025 mole) in methylene chloride. This suspension was then treated dropwise with diethylamine (0.32 g., 0.005 mole). The resulting clear solution was extracted with three portions of cold water and the aqueous layer discarded. The remaining organic layer was dried over magnesium sulfate, filtered, and concentrated to a gum *in vacuo*. The product crystallized upon scratching. The *S*-dimethylarsino-6-thio-2′,3′,5′-triacetylpurine riboside was recrystallized from a 50-50 mixture of chloroform and petroleum ether. The white crystals were obtained in 26% yield. Their melting point was 101-103°.

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