SYNTHESIS AND TRANSFORMATIONS OF SULFIDES OF THE THIOPHENE SERIES.

32.* SYNTHESIS AND PROPERTIES OF SOME (β-ETHOXYETHYL)-SUBSTITUTED MERCAPTO ALDIMINES AND CHELATES OF THE THIOPHENE SERIES

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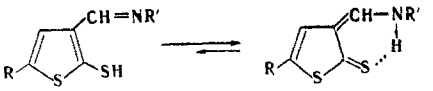
Several N-substituted 2-mercapto-5-(β-ethoxyethyl)-3-thenylidenimines and the corresponding chelate compounds with metals, which are readily soluble in organic solvents, were obtained. The synthesized compounds have a slight inhibiting effect on the liquid-phase oxidation of hydrocarbons.

It has been shown [2, 3] that the introduction of various types of substituents in the 5 position of the thiophene ring of mercapto aldimines I may serve as one of the practicable methods for varying their properties, as well as the properties of the chelates formed by them.



I a-d

I a R=H, alkyl, b R=$(CH_2)_nNR_2$; c R=$(CH_2)_2OH$; d R=$(CH_2)_2OC_2H_5$; R′=H, alkyl aryl n=1, 2

This is particularly true of their solubilities in polar and nonpolar organic solvents, which is one of the important conditions for the testing and practical utilization of the synthesized compounds. For example, the introduction of a diethylaminoethyl or β-hydroxyethyl group in the I molecule leads to ligands and chelates Ib, c that are quite soluble in alcohols.

In the present paper we describe the synthesis and properties of β-ethoxyethyl derivatives Id. The conversion of an alcohol group to an ether group serves, as is well known, as a convenient method for the protection of a hydroxy group in acidic and alkaline media and, in addition, is the determining factor in changing the physiological activity (for example, toxic, narcotic, and other properties) [4, 5]. The alkylation of the hydroxyethyl group of sulfide II was realized by the action of 2 equivalents of sodium in liquid ammonia on it with the subsequent addition of excess (2-4 moles) alkyl halide to the resulting mercaptide at −60 to −70°C. 5-Ethylthio-3-(β-ethoxyethyl)thiophene (IIIa) was obtained in up to 80% yields when ethyl bromide was used, while 5-methylthio-2-(β-methoxyethyl)thiophene (IIIb) was obtained with methyl iodide. The high yields of the ethers are evidently due to the presence in the reaction mixture of sodium amide, which is one of the products of cleavage of alkyl 2-thienyl sulfides by sodium in liquid ammonia and promotes the more nearly complete formation of an alkoxide [6]. In fact, we synthesized ether IIIa from hydroxyethyl sulfide II and ethyl bromide in the presence of 1 mole of previously prepared sodium amide in liquid ammonia. 2-(β-Methoxyethyl)thiophene is similarly formed from 2-thienylethanol and CH_3I. When sodium amide is absent, the yields of ethers via the Williamson method in liquid ammonia are usually low [6, 7].

*See [1] for Communication 31.

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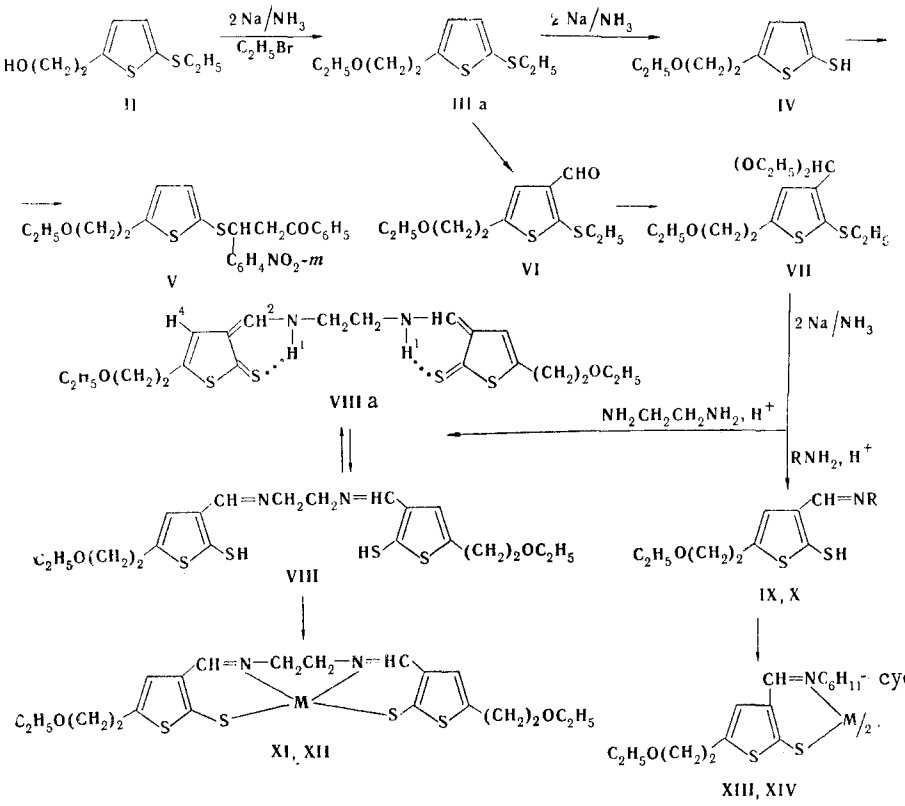
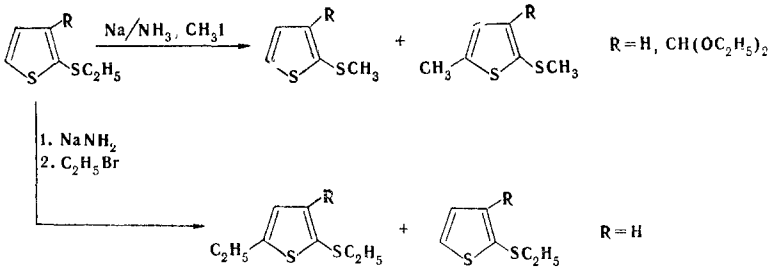


IX R = β-$C_{10}H_7$; X R = cyclo C_6H_{11}; XI M = Cu; XII, XIII M = Ni; XIV M = Co

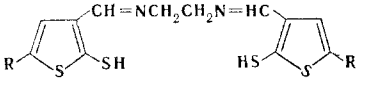
The method used for the synthesis of ethers of the II type makes it possible in one step to realize the etherification of the alcohol group and replace the grouping attached to the exocyclic sulfur atom. Exchange of the grouping also takes place readily by the successive action of Na/NH_3 and an alkyl halide in the case of alkyl 2-thienyl sulfides that do not contain a β-hydroxyethyl grouping such as, for example, ethyl 2-thienyl sulfide and 2-ethylthio-3-formylthiophene. In this case, in addition to exchange of the grouping attached to the exocyclic sulfur atom, we observed the formation of products of alkylation of the free α position of the thiophene ring; the ratio of the products [according to the results of gas–liquid chromatography (GLC)] ranged from 1:1 to 0.7:1.



This result is also evidently due to the presence of sodium amide in the reaction mixture. One should point out here the available data [8] on the alkylation of thiophene by alkyl halides in the presence of $NaNH_2$ in liquid ammonia. The effect of sodium amide in this process was also demonstrated in our experiments: The mixture formed in the reaction of ethyl 2-thienyl sulfide with 1 mole of sodium amide and subsequent reaction with excess ethyl bromide contains ethyl 2-thienyl and ethyl 5-ethyl-2-thienyl sulfides in a ratio of 1:1.

The action of sodium in liquid ammonia in β-ethoxyethyl sulfide IIIa gave mercapto ether IV, the structure of which was confirmed by the data from the IR spectrum and the formation from it of sulfide V by reaction with m-nitrobenzalacetophenone. Vilsmeier formylation of ether IIIa leads to 2-ethylthio-5-(β-ethoxyethyl)-3-formylthiophene (VI), which was converted to acetal VII. On the basis of the latter, by means of our previously described method, viz., by the successive action of sodium in liquid ammonia and subsequent reaction with primary amines, we obtained mercapto aldimines VIII-X, which are readily soluble in alcohols (MeOH and EtOH) and other organic solvents (ethyl acetate, $CHCl_3$, etc.). According to the data from the

the PMR spectrum (for VIII), the mercapto aldimines obtained, like their 5-alkyl-substituted analogs, exist in solution in thione amine form VIIIa. Some of the ligands and chelates (VIII, XI, XII, and XIV) examined here, as well as the previously described [2, 3, 9] mercapto aldimines with the general formula XV, which contain various substituents in the 5 position of the thiophene ring, were tested as possible inhibitors of the liquid-phase oxidation of hydrocarbons. It has been shown [10] that 2-mercapto-5-ethyl-3-thenylidenecyclohexylamine displays a dual function (inhibiting and catalyzing) in the initiated oxidation of isopropylbenzene. An estimate of the inhibiting activity of the examined compounds by the method in



XV a-d

a $R=C_2H_5$; b $R=CH_2CH_2OH$; c $R=CH_2N(CH_3)_2$; d $R=CH_2CH_2N(C_2H_5)_2$

[11] (at 60°C) showed that, regardless of the nature of the substituent in the 5 position, they all have a weak inhibiting effect (corresponding to an inhibitor with $K_7 \approx 3 \cdot 10^3$ liters/mole·sec), as well as weak catalytic properties. The latter were strongly expressed for ligand XVa and for β-ethoxyethyl-substituted chelates of copper and nickel (XI, XII).

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were obtained with a Varian DA-60-IL spectrometer with hexamethyldisiloxane as the internal standard; the chemical shifts are presented on the δ scale relative to tetramethylsilane. Analysis by GLC was carried out with an LKhM-8MD chromatograph with a flame-ionization detector with stainless steel columns: a) with a length of 2 m and a diameter of 3 mm and filled with 5% Apeizon L on Celite-545 modified (to a length of 0-1 m) with 0.35% Na_3PO_4 and 7% PFMS-4 on Chromosorb N-AW (to a length of 1-2 m) with helium as the carrier gas; b) with a length of 3 m and a diameter of 3 mm and filled with 5% SE-30 on Chromaton N-AW with nitrogen as the carrier gas.

5-Ethylthio-2-(β-ethoxyethyl)thiophene (IIIa). A) A 1.22-g (53 mg-atom) sample of Na was added gradually to 5 g (26.5 mmole) of 5-ethylthio-2-(β-hydroxyethyl)thiophene (II) in 10 ml of dry ether and 50 ml of liquid NH_3 at −70°C, after which 11.4 g (106 mmole) of ethyl bromide was added, during which a white precipitate formed immediately. The ammonia was evaporated, ether and water were added to the residue, and the ether layer was separated. The aqueous layer was extracted thoroughly with ether, and the ether extract was washed with water and dried with $MgSO_4$. The residual 4.95 g of light-colored oil was vacuum distilled to give 4.2 g (73.2%) of ether IIIa with bp 138°C (8 mm) and n_D^{20} 1.5398. Found: C 55.7; H 7.4; S 29.7%. $C_{10}H_{16}OS_2$. Calculated: C 55.5; H 7.4; S 29.6%.

5-Methylthio-2-(β-methoxyethyl)thiophene (IIIb). This compound, with bp 126°C (8 mm) and n_D^{20} 1.5600, was similarly obtained in 70% yield from alcohol II and CH_3I, yield 40%, bp 116°C (8 mm) and n_D^{20} 1.5600. Found: C 51.0; H 6.6; S 33.9%. $C_6H_{12}OS_2$. Calculated: C 51.0; H 6.4; S 34.0%.

B) A 3-g (32 mmole) sample of hydroxyethyl sulfide II was added at −50 to −60°C to 15.8 mmole of $NaNH_2$, obtained from 0.36 g of Na in 35 ml of liquid NH_3. After 10-15 min, 3.5 g (32 mmole) of ethyl bromide was added to the mixture (an oil collected on the bottom and walls of the flask), and the mixture was stirred for 30 min. The ammonia was evaporated, and the residue was worked up as described in method A to give 2.9 g of an oil containing, according to GLC data (column a at 220°C), ether IIIa and 10-15% of starting alcohol II. The ether [bp 140-148°C (8 mm) and n_D^{20} 1.5570] contained 4-5% of the starting alcohol after distillation.

2-(β-Methoxyethyl)thiophene. This compound was obtained as described above (see method B) from 1.5 g (12 mmole) of 2-(β-hydroxyethyl)thiophene, 0.46 g (12 mmole) of freshly prepared $NaNH_2$, and 2 ml (32 mmole) of CH_3I. After the usual workup, the ether extract yielded 1.1 g (69%) of 2-(β-methoxyethyl)thiophene containing 3-4% of the starting alcohol (GLC with column at 185°C); the principal product had bp 88-90°C (17 mm) and n_D^{20} 1.5410.* Found: C 59.5; H 7.1; S 22,4%. $C_7H_{10}OS$. Calculated: C 59.1; H 7.1; S 22.5%.

*2-(β-Methoxyethyl)thiophene, with bp 109°C (55 mm) and n_D^{20} 1.5118, was previously obtained in our laboratory by E. P. Zakharov by the method in [12] in 43% yield.

Action of Sodium in Liquid Ammonia and CH_3I on Ethyl 2-Thienyl Sulfide. A 0.96-g (41.6 mg-atom) sample of Na and 11.88 g (83 mmole) of CH_3I were added as described above to 3 g (20.8 mmole) of ethyl 2-thienyl sulfide in 30 ml of liquid NH_3. After the usual workup, the ether extract yielded 2.2 g of a light-colored oil, which, according to GLC data (column b at 138°C), was a mixture of methyl 2-thienyl sulfide (37%) with methyl 5-methyl-2-thienyl sulfide (63%).

Mixtures obtained by: 1) the action of Na/NH_3 and CH_3I on 2-ethylmercapto-3-formylthiophene diethylacetal [the product contained 55% of 2-methylmercapto-3-formylthiophene diethylacetal and 45% of 2-methylmercapto-5-methyl-3-formylthiophene diethylacetal (column b at 206°C] and by 2) the action of $NaNH_2$ and C_2H_5Br on ethyl 2-thienyl sulfide [the ratio of the reaction products, viz., ethyl 2-thienyl sulfide and ethyl 5-ethyl-2-thienyl sulfide, was 1:1 (column b at 138°C)] were similarly worked up and analyzed.

5-Mercapto-2-(β-ethoxyethyl)thiophene (IV). A 0.362-g (15.8 mg-atom) sample of Na was added gradually to 1.7 g (7.9 mmole) of ether IIIa in 2 ml of ether and 20 ml of liquid NH_3. A persistent blue coloration developed as the last portion of Na was being added. The excess sodium was decomposed with dry NH_4Cl, the ammonia was evaporated, and ether and water were added to the residue with cooling. The aqueous layer was separated and extracted thoroughly with ether. The ether extract was acidified with dilute HCl (1:1), and the liberated oil was extracted with ether. The extract was washed with water and dried with $MgSO_4$, and the ether was removed by distillation to give 1.1 g (74%) of mercapto ether IV with bp 112°C (5 mm) and n_D^{20} 1.5530. IR spectrum (in $CHCl_3$): 2550-2560 cm^{-1} (SH). Found: C 50.7; H 6.5; S 34.1%. $C_8H_{12}OS_2$. Calculated: 51.0; H 6.4; S 34.0%.

β-(3-Nitrophenyl)-5-[(β-ethoxyethyl)-2-thienylmercapto]propiophenone (V). This compound was obtained by the method in [13] from 0.3 g of ether IV and 0.4 mg of m-nitrobenzalacetophenone. After recrystallization from heptane, it had mp 69-71°C. Found: C 62.6; H 5.2; S 14.2%. $C_{23}H_{23}NO_4S_2$. Calculated: C 62.6; H 5.2; S 14.5%.

2-Ethylthio-5-(β-ethoxyethyl)-3-formylthiophene (VI). A 4.2-g (19.5 mmole) sample of ether IIIa was added gradually with water cooling in the course of 40 min to 5.3 g (39 mmole) of N-methylformanilide and 6.0 g (39 mmole) of $POCl_3$, and the mixture was heated with stirring at 50-60°C for 3-4 h. The viscous dark mass was hydrolyzed with water cooling, and the oil was extracted with ether. The ether extract was washed with dilute HCl (1:10), the aqueous extracts were extracted with ether, and the combined ether extract was washed with dilute HCl, aqueous $NaHCO_3$ solution, and water, and dried with $MgSO_4$. The ether was removed by distillation, and the residue was distilled to give 4 g (84%) of aldehyde VI with bp 179-180°C (6 mm) and n_D^{20} 1.5700. IR spectrum (thin layer): 1670 cm^{-1} (CO). Found: C 54.0; H 6.5; S 26.3%. $C_{11}H_{16}O_2S_2$. Calculated: C 54.0; H 6.6; S 26.2%. The 2,4-dinitrophenylhydrazone had mp 140.5-141.5°C (from alcohol and also from heptane). Found: C 48.1; H 4.6; S 15.86%. $C_{17}H_{20}N_4O_5S_2$. Calculated: S 48.1; H 4.7; S 15.1%.

2-Ethylthio-5-(β-ethoxyethyl)-3-formylthiophene Diethylacetal (VII). A mixture of 17.3 g (70 mmole) of aldehyde VI, 17 ml of ethyl orthoformate, 35 ml of absolute alcohol, and two to three drops of concentrated HCl was refluxed for 4 h, after which it was neutralized with a 10% solution of KOH in MeOH. The solvents were removed by vacuum distillation, and the residue was diluted with water. The aqueous mixture was extracted thoroughly with ether, the ether extract was washed with water and dried with $MgSO_4$, and the ether was removed by distillation. The residue was distilled to give 18.3 g (81.2%) of diethylacetal VII with bp 184°C (6 mm) and n_D^{20} 1.5170. Found: C 56.0; H 8.0; S 21.1%. $C_{15}H_{26}O_3S_2$. Calculated: C 56.5; H 8.2; S 20.6%.

N-Substituted 2-Mercapto-5-(β-ethoxyethyl)-3-thenylideneimines. A 0.725-g (31.5 mg-atom) sample of Na was added gradually at −70°C in a stream of argon to 5 g (15.7 mmole) of diethylacetal VII in 5 ml of dry ether and 50 ml of liquid NH_3 until a persistent blue coloration of the solution developed. The excess Na was decomposed with dry NH_4Cl, the NH_3 was evaporated, and ether and water were added to the residue. The aqueous layer was separated and extracted thoroughly with ether. The resulting aqueous alkaline solution (100 ml) was used for the synthesis of the mercapto aldimines (VIII-X):

1) A 3-ml sample of ethylenediamine was added to 30 ml of this solution, and the pH of the mixture was adjusted to 7-8 with HCl (1:1). The resulting yellow precipitate was removed by filtration, washed with water, and dried to give 0.55 g (46%) of N,N-bis[2-mercapto-5-(β-ethoxyethyl)-3-thenylidene]ethylenediamine (VIII). After recrystallization

from MeOH and ethyl acetate–heptane, the product had mp 165-167°C. PMR spectrum (in $CDCl_3$): 6.19 (1H, s, H_4), 7.75 (1H, d, J = 13 Hz, CH_2NH_1), and 13.36 ppm (1H, broad s, NH_1). Found: S 52.7; H 6.2; S 28.4%. $C_{20}H_{28}N_2O_2S_4$. Calculated: C 52.6; H 6.2; S 28.1%.

2) 2-mercapto-5-(β-ethoxyethyl)-3-thenylidene-β-naphthylamine (IX) was similarly obtained in 40% yield from 30 ml of an aqueous solution and a methanol solution of β-naphthylamine in the form of red crystals with mp 119-120°C (from alcohol and from heptane). Found: C 66.9; H 5.3; S 18.6%. $C_{19}H_{19}NOS_2$. Calculated: C 66.8; H 5.6; S 18.8%.

3) A 30-ml sample of the aqueous alkaline solution was treated with HCl up to pH ~ 8, as a result of which a dark oil was liberated. The water was decanted, and the oil was dissolved in methanol. A 2-ml sample of cyclohexylamine was added to the methanol solution, and the mixture was heated for a few minutes and filtered. The filtrate was evaporated *in vacuo*, and the residue was dissolved in ether. The ether solution was washed with water and dried with $MgSO_4$ to give 0.7 g of 2-mercapto-5-(β-ethoxyethyl)-3-thenylidenecyclohexylamine (X) in the form of a viscous uncrystallizable oil, which was used directly for the preparation of the chelate compounds.

Nickel Chelate (XIII) of 2-Mercapto-5-(β-ethoxyethyl)-3-thenylidenecyclohexylamine. A solution of 0.3 g of nickel acetate in methanol was added to 0.3 g of crude X in 10 ml of methanol; the solution darkened, and violet crystals of the chelate precipitated upon standing. The crystals were removed by filtration, washed with water, and dried to give 0.25 g (75%) of chelate XIII with mp 153-155°C (from alcohol). Found: C 55.5; H 6.6; Ni 9.5; S 19.7%. $C_{30}H_{44}NiN_2O_2S_4$. Calculated: C 55.3; H 6.8; Ni 9.0; S 19.7%.

Cobalt Chelate (XIV) of 2-Mercapto-5-(β-ethoxyethyl)-3-thenylidenecyclohexylamine. This compound was obtained by the procedure used to prepare chelate XIII; recrystallization of the product from heptane gave brown crystals with mp 173-175°C. Found: C 55.3; H 6.8; S 19.3%. $C_{30}H_{44}CoN_2O_2S_4$. Calculated: C 55.3; H 6.8; S 19.7%.

Nickel Chelate (XII) of N,N'-Bis[2-mercapto-5-(β-ethoxyethyl)-3-thenylidene]ethylenediamine. A methanol solution of 0.4 g (1.6 mmole) of nickel acetate was added to a solution of 0.3 g (0.66 mmole) of Schiff base VIII in ethyl acetate, after which heptane was added to the resulting brown solution, and the crystals that formed upon standing were removed by filtration and dried to give 0.2 g (60%) of chelate XII, which had mp 109-111°C after reprecipitation from solution in ethyl acetate by the addition of heptane. Found: C 46.4; H 5.2; Ni 11.9; S 25.0%. $C_{20}H_{26}N_2NiO_2S_4$. Calculated: C 46.8; H 5.1; Ni 11.4; S 25.0%.

Copper Chelate (XI) of N,N'-Bis[2-mercapto-5-(β-ethoxyethyl)-3-thenylidene]ethylenediamine. This chelate was obtained by the method used to prepare nickel chelate XII and was reprecipitated twice from solution in ethyl acetate by the addition of heptane to give a product with mp 127-128.5°C. Found: C 46.4; H 5.3; Cu 12.2; N 5.4; S 24.9%. $C_{20}H_{26}CuN_2O_2S_4$. Calculated: C 46.4; H 5.1; Cu 12.3; N 5.4; S 24.8%.

LITERATURE CITED

1. Ya. L. Gol'dfarb, M. A. Kalik, and V. K. Zav'yalova, Zh. Org. Khim., 15, 1540 (1979).
2. Ya. L. Gol'dfarb and M. A. Kalik, Izv. Akad. Nauk SSSR, Ser. Khim., No. 7, 1583 (1975).
3. Ya. L. Gol'dfarb and M. A. Kalik, Izv. Akad. Nauk SSSR, Ser. Khim., No. 7, 1578 (1976).
4. T. Jenkins and U. Hartung, The Chemistry of Organic Medicinal Preparations [Russian translation], Inostr. Lit., Moscow (1949), p. 138.
5. H. P. Kaufmann, Arzneimittel Synthese, Springer Verlag, Berlin–Göttingen–Heidelberg (1953), p. 606.
6. G. F. White, A. B. Morrison, and E. G. Anderson, J. Am. Chem. Soc., 46, 961 (1924).
7. H. Smith, Organic Reactions in Liquid Ammonia, F. Vieweg and Sohn, Braunschweig (1963), p. 63.
8. W. J. Zimmerschied and R. C. Arnold, USA Patent No. 2585292; Chem. Abstr., 47, 2776 (1953).
9. Ya. L. Gol'dfarb, M. A. Kalik, and A. A. Dudinov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 6, 1449 (1977).
10. T. V. Sirota, A. B. Gagarina, M. A. Kalik, Ya. L. Gol'dfarb, and N. M. Émanuél, Dokl. Akad. Nauk SSSR, 228, 896 (1976).
11. V. F. Tsepalov, A. A. Kharitonov, T. P. Gladyshev, and N. M. Émanuél, Kinet. Katal., 18, No. 5, 1261 (1977).
12. E. Müller, R. Heischkeil, and M. Bauer, Lieb. Ann. Chem., 677, 55 (1964).
13. Ya. L. Gol'dfarb, M. A. Kalik, and M. L. Kirmalova, Zh. Obshch. Khim., 37, 222 (1962).