SELENIDES OF THE THIOPHENE AND FURAN SERIES

COMMUNICATION 3. METALATION AND ACYLATION OF ALKYL 3-THIENYL SELENIDES

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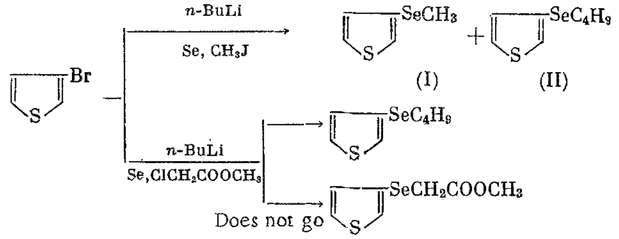
UDC 542.91:547.7

The sharp difference previously detected by us in the behavior of the alkyl 2-thienyl selenides and the corresponding sulfides of the thiophene series in the metalation reaction with n-butyllithium, and the parallelism in electrophilic substitution reactions [1-3], caused us to investigate the behavior of the alkyl 3-thienyl selenides along these lines. The observations made in this connection could supply data for ascertaining both the mechanism of the action of n-BuLi on selenides of the thiophene series and the orienting effect of the alkylseleno group.

We obtained a difficultly separable mixture of methyl 3-thienyl selenide (I) and butyl 3-thienyl selenide (II) in a ratio of approximately 3 : 1 (based on the GLC analysis data) by the reaction of 3-bromothiophene with n-BuLi and subsequent treatment of the formed 3-thienyllithium with selenium and CH_3I. The formation of (II) along with (I) probably occurs due to the alkylation of the Li salt of 3-thienylselenol with the butyl bromide that is formed in the process of metalating the 3-bromothiophene. A similar picture was also observed in the case of obtaining the new heteroaromatic system – thieno[3,2-b]selenophene [4]. Specifically, when 3-bromothiophene was reacted with n-BuLi, followed by treatment with selenium and methyl monochloroacetate, butyl 3-thienyl selenide (II) was formed in 66% yield, instead of the expected methyl ester of 3-thienylselenoacetic acid

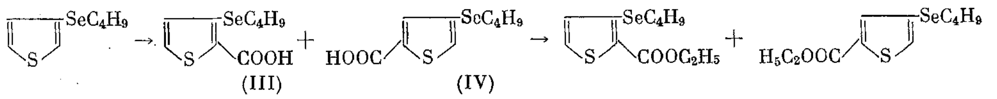


Analogous observations were made when 3-methylmercaptothiophene was obtained [5].

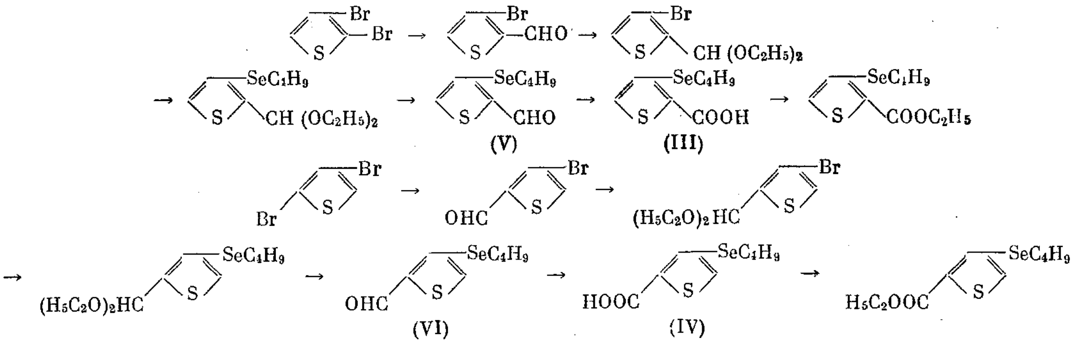
The pure (I) was obtained by us by the action of dimethyl diselenide, while (II) was obtained by the successive action of selenium and butyl bromide on 3-thienyllithium. A priori, it could be expected that the alkyl 3-thienyl selenides and the alkyl 2-thienyl selenides will differ in their behavior toward n-BuLi, since the S,Se-acetal fragment is present in the latter molecules. Actually, it was established that when 1 equiv. of n-BuLi is reacted with (II) under conditions analogous to those used for the reaction of alkyl 2-thienyl selenides with n-BuLi, i.e., at room temperature, elimination of the alkylseleno group fails to occur, and the metal atom replaces the α-hydrogen atom of the thiophene ring with the formation, after carbonation, of β-butylselenothiophenecarboxylic acid. In this connection we will mention that, based on the data given in [5], 3-methylmercaptothiophene metalates exclusively in the 2-position of the thiophene ring. Starting with these data and the fact that alkylmercapto and alkylseleno groups possess –I and +M effects, it could be assumed that the obtained β-butylselenothiophenecarboxylic acid has the structure of (III). However, GLC analysis of the esterification product, obtained by refluxing the carbonation product with ethyl alcohol in the presence of conc. H_2SO_4, disclosed that actually a mixture of two esters exists:

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 6, pp. 1296-1302, June, 1971. Original article submitted August 20, 1969.

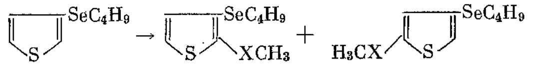
the ester of 3-butylseleno-3-thiophenecarboxylic acid (III) and the ester of 4-butylseleno-2-thiophenecarboxylic acid (IV)



We propose to determine the quantitative composition of the mixture of acids more accurately later. Acids (III) and (IV), and their ethyl esters, were obtained by "counter" synthesis by the following schemes:

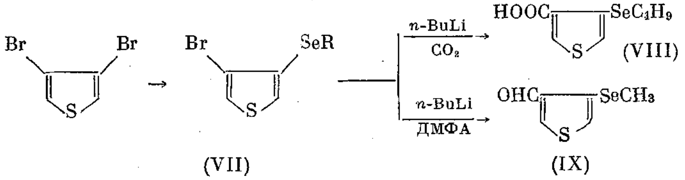


In order to ascertain if the formation of carboxylic acid (III) is due to steric hindrance, associated with the length of the side alkyl chain, or whether it depends on the nature of the heteroatom in the side chain, we studied the reaction of n-BuLi with methyl 3-thienyl selenide (I). It proved that also in this case a mixture of two acids is formed: 3-methylseleno-2-thiophenecarboxylic acid and 4-methylseleno-2-thiophenecarboxylic acid. Consequently, the formation of two acids, and not of one, as in the case of 3-methoxythiophene [6] and 3-methylmercaptothiophene [5], is mainly influenced by the nature of the heteroatom in the side chain (possibly, by the value of the atomic radius of the heteroatom). A similar picture is also observed in the preparation not only of acids, but also of bis-selenides and selenido sulfides:



X = S, Se

It was shown by us in previous communications [2,3] that in alkyl 2-thienyl selenides where one of the hydrogen atoms of the thiophene ring is replaced by the bromine atom, when reaction is with n-BuLi there occurs either elimination of the alkylseleno group (in the case of the β-bromo derivative even at −70°C) or exchange of bromine atom by the metal atom, with a retention of the alkylseleno group in the ring (in the case of the α-bromo derivative). It was interesting to trace the direction of attack of n-BuLi on alkyl 3-thienyl selenides, in which the second β-position of the ring is occupied by a bromine atom, and to ascertain whether metalation occurs at one of the free α-positions of the ring or whether the bromine atom is replaced by the metal atom. It proved that in this case the action of n-BuLi is directed to the bromine atom, and neither the hydrogen atoms of the thiophene ring nor the alkylseleno group are involved



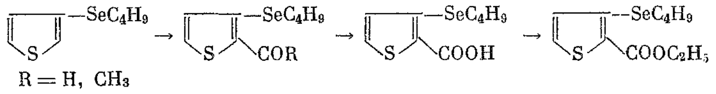
R = CH3 (a), C4H9 (b)

In support of such a reaction course are the difference in the melting points of compound (VIII) and the isomeric acids (III) and (IV), the nonidentity of the NMR spectra of aldehydes (IX), (V), and (VI), and also the NMR spectrum of compound (IX), which does not contradict the indicated structure. (The NMR spectra of the β-alkylseleno-substituted thiophenecarboxaldehydes will be given and discussed in our next communication.)

In the case of electrophilic substitution reactions, the same as for the alkyl 2-thienyl selenides, a parallelism is observed between the behavior of the alkyl 3-thienyl selenides and the corresponding sulfides

[7], and specifically, the acyl group enters exclusively into the α-position of the ring, adjacent to the alkyl selenide function. Thus, the formylation and acetylation of butyl 3-thienyl selenide respectively gave 3-butylseleno-2-thiophenecarboxaldehyde and 3-butylseleno-2-acetothienone. Based on the GLC analysis data, the acylation products do not contain any impurities.

As confirmation of the fact that the acyl group enters the 2-position of the thiophene ring can serve the transformation of the formyl and acetyl derivatives to 3-butylseleno-2-thiophenecarboxylic acid, which proves to be identical with the acid (III), obtained by "counter" synthesis, as indicated above. Esterification of the acids, formed in the oxidation of the formyl and acetyl derivatives, gave the ethyl ester of 3-butylseleno-2-thiophenecarboxylic acid, which was identical with the ethyl ester of acid (III).



EXPERIMENTAL METHOD

Analysis by the GLC method was carried out under the conditions described in the previous communication [3].

Butyl 3-Thienyl Selenide (II). To 160 ml of an ether solution of 19.2 g of n-BuLi, in a N_2 atmosphere, at −70°C, was added a solution of 48.9 g of 3-bromothiophene in 300 ml of absolute ether. The mixture was stirred at −70° for 2 h (the deposition of a white precipitate of 3-thienyllithium was observed). Then at −70° was added 23.7 g of finely pulverized Se and the temperature of the mixture was raised up to −20°. Then the mixture was stirred at −20° for 1-2 h (until all of the Se had reacted) and, at the same temperature, to the mixture was added 27.4 g of C_4H_9Br. After stirring at room temperature for 1 h, the reaction mass was treated at −10° with 300 ml of 25% NH_4Cl solution. The ether layer was separated, and the aqueous layer was extracted three times with ether. The combined extracts were washed with water and then dried over $CaCl_2$. After a double distillation we obtained 49 g (74.5% yield) of (II); bp 133-135° (20 mm); n_D^{20} 1.5730. Based on the GLC data, after the first distillation (II) contained 1% of an impurity, apparently butyl 2-thienyl selenide. Based on the GLC data, after the second distillation (II) did not contain any impurities. Found: C 43.55; 43.41; H 5.31; 5.58%. $C_8H_{12}SSe$. Calculated: C 43.83; H 5.52%.

Methyl 3-Thienyl Selenide (I). To a solution of 3.2 g of n-BuLi in 27 ml of absolute ether at −70°, in a N_2 atmosphere, with stirring, was added a solution of 8.2 g of 3-bromothiophene in 50 ml of absolute ether. The mixture was stirred for 2 h at −70°, and then at −55° was added a solution of 9.4 g of dimethyl diselenide (prepared as described in [8]) in 15 ml of absolute ether. The mixture was stirred for 1.5 h at −20° and then worked up the same as in the preceding experiment. We obtained 7.2 g (81% yield) of chromatographically pure (I); bp 95-96° (18 mm); n_D^{20} 1.6302. Found: C 33.72; 33.73; H 3.65; 3.55%. C_5H_6SSe. Calculated: C 33.90; H 3.41%.

When the experiment on the synthesis of (I) was run, where selenium and CH_3I were used instead of dimethyl diselenide, a mixture of (I) and (II) was obtained in a ratio of approximately 3 : 1 (based on the GLC analysis data).

Reaction of n-BuLi with Butyl 3-Thienyl Selenide. To a solution of 5.5 g of (II) in 25 ml of absolute ether, in a N_2 atmosphere, at room temperature, was added a solution of 1.6 g of n-BuLi in 14.5 ml of absolute ether. In this connection the temperature rose from 20 up to 30°. After stirring at room temperature for 2 h the mixture was subjected to carbonation. We obtained 5.2 g (79% yield) of a mixture of β-butylselenothiophenecarboxylic acids as a viscous oil, which crystallized on standing. Found: C 41.33; 41.43; H 4.42; 4.50%. $C_9H_{12}O_2SSe$. Calculated: C 41.07; H 4.59%.

To a solution of 4 g of the acid in 40 ml of absolute alcohol was added 1 ml of conc. H_2SO_4. The mixture was refluxed for 10 h, after which it was concentrated to half-volume, and the residue was dissolved in water and extracted twice with ether. The extract was washed with saturated Na_2CO_3 solution. The alkaline extract was acidified with 1 N HCl solution and then extracted with ether. The extract was washed with water and dried over $MgSO_4$. After distilling off the ether the residue was found to contain 0.8 g of the starting acid, the molecular weight of which, determined by titration of the acid (227.3), is quite close to the calculated value (221.14).

The ether extract after washing with Na_3CO_3 solution was dried over $MgSO_4$ and then distilled. We obtained 2.7 g of a mixture of the ethyl esters of the β-butylselenothiophenecarboxylic acids with bp 150-160° (2 mm), n_D^{20} 1.5731, which, based on the GLC analysis data, is composed of 60% of the ethyl ester of 3-butylseleno-2-thiophenecarboxylic acid and 40% of the ethyl ester of 4-butylseleno-2-thiophenecarboxylic acid. Found: C 45.33, 45.55; H 5.53, 5.72%. $C_{11}H_{16}O_2SSe$. Calculated: C 45.36; H 5.54%.

Reaction of n-BuLi with Methyl 3-Thienyl Selenide (I). The metalation of 4.42 g of (I) was run in a similar manner. After carbonation we obtained 4.12 g (75%) of the β-butylselenothiophenecarboxylic acid. mp up to 174° (melts over a range). After esterification we obtained 1.2 g of acid and 2.1 g of a mixture of the ethyl esters of the β-methylselenothiophenecarboxylic acids, bp 110-140° (2 mm), which contained, based on the GLC analysis data, 56% of the ethyl ester of 3-methylseleno-2-thiophenecarboxylic acid and 44% of the ethyl ester of 4-methylseleno-2-thiophenecarboxylic acid. The assignment of the peaks was made on the basis of the exit times of the esters in harmony with the order of exit of the peaks in the preceding experiment. Found: C 38.73, 38.82; H 4.13, 4.26%. $C_8H_{10}O_2SSe$. Calculated: C 38.56; H 4.00%.

Formylation of Butyl 3-Thienyl Selenide (II). To a mixture of 8.8 g of (II) and 5 ml of DMF, with stirring and cooling in an ice bath, was added 4 ml of $POCl_3$ (the temperature at the end of addition had risen to 15°). The mixture was heated at 60-80° for 5 h, poured over 50 g of crushed ice, and then Na_2CO_3 was added to it in small portions until the CO_2 evolution ceased. The obtained oil was separated, and the aqueous layer was extracted three times with $CHCl_3$. The chloroform extracts were combined with the oil and the whole was dried over $MgSO_4$. Distillation gave 8.2 g (83%) of 3-butylseleno-2-thiophenecarboxaldehyde (V); bp 139-140° (2 mm); n_D^{20} 1.6212. Found: C 43.78, 43.54; H 4.88, 4.92%. $C_9H_{12}OSSe$. Calculated: C 43.73; H 4.89%. Semicarbazone, mp 168.5-169° (after recrystallization from alcohol). Found: C 39.68, 39.47; H 5.00, 4.99%. $C_{10}H_{15}ON_3SSe$. Calculated: C 39.48; H 4.97%.

The oxidation of (V) with Ag_2O gave 3-butylseleno-2-thiophenecarboxylic acid (III) in 87.4% yield, mp 103.5-104.5°, after recrystallization from hexane. Found: C 40.88, 40.74; H 4.53, 4.51%. $C_9H_{12}O_2SSe$. Calculated: C 41.07; H 4.59%. Ethyl ester, bp 145° (1 mm); mp 34-35° (after recrystallization from hexane). Found: C 45.62, 45.33; H 5.54, 5.35%. $C_{11}H_{16}O_2SSe$. Calculated: C 45.36; H 5.54%.

Acetylation of Butyl 3-Thienyl Selenide (II). To a mixture of 5.5 g of (II), 1.96 g of CH_3COCl and 27 ml of C_6H_5Cl at 0° was added 1.75 ml of $SnCl_4$ in 7 ml of C_6H_5Cl. After 1 h (20°) the reaction mixture was hydrolyzed with 10% HCl solution at 10-15°. The chlorobenzene layer was extracted with C_6H_5Cl. The extracts were combined, washed in succession with water, 1% NaOH solution and water, and dried over $MgSO_4$. We obtained 5.24 g (80%) of 3-butylseleno-2-acetothienone, bp 169-170° (3 mm); mp 56-57° (after recrystallization from hexane). Found: C 45.70, 46.00; H 5.20, 5.56%. $C_{10}H_{14}O_2SSe$. Calculated: C 45.98; H 5.40%.

3-Butylseleno-2-thiophenecarboxylic acid, mp 104-105° (hexane), was obtained in 47% yield by the oxidation of 3-butylseleno-2-acetothienone with iodine in pyridine. The mixed melting point with the acid, obtained by the oxidation of 3-butylseleno-2-thiophenecarboxaldehyde, was not depressed.

3-Bromo-2-thiophenecarboxaldehyde. Obtained in 74.3% yield by the method given in [9], bp 84-85° (3 mm) (crystallizes on standing).

3-Bromo-2-thiophenecarboxaldehyde Diethyl Acetal. A mixture of 13 g of 3-bromo-2-thiophenecarboxaldehyde, 15.1 g of $HC(OC_2H_5)_3$, 60 ml of absolute ethanol and 3 drops of conc. HCl was refluxed for 20 h to give 15.1 g (80.5%) of 3-bromo-2-thiophenecarboxaldehyde diethyl acetal, bp 115-117° (5 mm); n_D^{20} 1.5259. Found: C 40.70, 40.54; H 4.84, 4.85; Br 30.49, 30.57; S 12.23, 12.2%. $C_9H_{13}BrO_2S$. Calculated: C 40.76; H 4.94; Br 30.14; S 12.09%.

3-Butylseleno-2-thiophenecarboxaldehyde (V). Similar to the synthesis of (I), from 5.35 g of 3-bromo-2-thiophenecarboxaldehyde diethyl acetal, 1.3 g of n-BuLi and 5.44 g of dibutyl diselenide (synthesized by the procedure described in [10]) was obtained 3.55 g (54.8% yield) of the diethyl acetal of compound (V), bp 142-143° (2 mm); n_D^{20} 1.5335. The saponification of the diethyl acetal with HCl in methanol gave (V) in 60% yield; bp 146-147° (2 mm); n_D^{20} 1.6187. Found: C 44.04, 43.88; H 5.23, 5.11%. $C_9H_{12}OSSe$. Calculated: C 43.73; H 4.89%. Semicarbazone, mp 168-169°. The mixed melting point with the semicarbazone of the aldehyde, synthesized by the formylation of (II), was not depressed.

The oxidation of (V) with Ag_2O gave 3-butylseleno-2-thiophenecarboxylic acid in 75.3% yield, mp 103.5-104.5° (from hexane). The mixed melting point with the acid, obtained by the oxidation of the 3-butylseleno-2-thiophenecarboxaldehyde prepared by the formylation of (II), was not depressed. Ethyl ester, mp 34-35° (from hexane). Found: C 45.17, 45.42; H 5.37, 5.54%. $C_{11}H_{16}O_2SSe$. Calculated: C 45.36; H 5.54%.

4-Bromo-2-thiophenecarboxaldehyde Diethyl Acetal. The refluxing of a mixture of 6.2 g of 4-bromo-2-thiophenecarboxaldehyde [obtained by the procedure given in [9] in 72% yield; bp 104-105° (8 mm)], 7.1 g of $HC(OC_2H_5)_3$, 30 ml of absolute alcohol and 2 drops of conc. HCl for 20 h gave 7.14 g (83% yield) of 4-bromo-2-thiophenecarboxaldehyde diethyl acetal, bp 111-113° (5 mm); n_D^{20} 1.5251. Found: C 40.78, 40.74; H 4.97, 4.92; Br 30.34, 30.46; S 12.19, 12.23%. $C_9H_{13}BrO_2S$. Calculated: C 40.76; H 4.94; Br 30.14; S 12.09%.

4-Butylseleno-2-thiophenecarboxaldehyde (VI). Analogous to the diethyl acetal of 3-butylseleno-2-thiophenecarboxaldehyde, the diethyl acetal of 4-butylseleno-2-thiophenecarboxaldehyde was synthesized in 55.4% yield, bp 131-133° (1 mm); n_D^{20} 1.5341. The saponification of the diethyl acetal in methanol in the presence of conc. HCl gave (VI) in 74% yield; bp 125-130° (1 mm); n_D^{20} 1.6030. Found: C 43.68, 43.60; H 5.01, 4.91%. $C_9H_{12}OSSe$. Calculated: C 43.73; H 4.89%.

The oxidation of (VI) with Ag_2O gave 4-butylseleno-2-thiophenecarboxylic acid (IV) in 63.3% yield, bp 145-153° (1 mm); mp 45-46° (from hexane). Found: C 41.45, 41.36; H 4.54, 4.47%. $C_9H_{12}O_2SSe$. Calculated: C 41.07; H 4.59%. Ethyl ester, bp 129-131° (2 mm); n_D^{20} 1.5619. Found: C 45.29, 45.14; H 5.65, 5.43%. $C_{11}H_{16}O_2SSe$. Calculated: C 45.36; H 5.54%.

4-Bromo-3-butylselenothiophene (VIIb). Analogous to the synthesis of (II), from 12.1 g of 3,4-dibromothiophene was obtained 5.5 g (37% yield) of (VIIb), bp 127-129° (4 mm); n_D^{20} 1.6050. Found: C 32.19, 32.39; H 3.89, 3.84%. $C_8H_{11}BrSSe$. Calculated: C 32.23; H 3.72%.

4-Bromo-3-methylselenothiophene (VIIa). Analogous to the synthesis of (I), from 36.3 g of 3,4-dibromothiophene and using dimethyl diselenide was obtained 30.3 g (78.9%) of (VIIa); bp 106-108° (3 mm); n_D^{20} 1.6692. Found: C 23.46, 23.30; H 2.12, 2.00%. C_5H_5BrSSe. Calculated: C 23.46; H 1.97%.

4-Butylseleno-3-thiophenecarboxylic Acid (VIII). To a solution of 1.49 g of 4-bromo-3-butylselenothiophene, in a N_2 atmosphere, at −70°, was added a solution of 0.32 g of n-BuLi in 3 ml of absolute ether. The mixture was stirred at −70° for 2 h and then poured over dry ice. After vaporization of the CO_2, 20 ml of water was added to the residue. After shaking, the aqueous layer was separated, washed with ether, and acidified with 1 N HCl solution. An oil was obtained, which crystallized immediately. The crystals were filtered and dried. We obtained 0.85 g (64% yield) of (VIII), mp 110-111° (from water). Found: C 40.94, 40.66; H 4.68, 4.67%. $C_9H_{12}O_2SSe$. Calculated: C 41.07; H 4.59%.

4-Methylseleno-3-thiophenecarboxaldehyde (IX). To a solution of 7.2 g of n-BuLi in 61 ml of absolute ether, in a N_2 atmosphere, at −70°, was added a solution of 28.5 g of (VIIa) in 100 ml of absolute ether, and in 15 min at the same temperature was added a solution of 21.3 g of DMF in 50 ml of absolute ether. After stirring at −70° for 2 h the mixture was poured over crushed ice, and then acidified with dilute HCl solution (1 : 5) until weakly acid. The ether layer was separated, and the aqueous layer was extracted with ether. The ether extracts were washed in succession with 10% Na_2CO_3 solution and water, and then dried over $MgSO_4$. A double distillation gave 15.6 g (69% yield) of (IX); bp 121-124° (2 mm); n_D^{20} 1.6737. Found: C 34.71, 34.71; H 2.89, 2.85%. C_6H_6OSSe. Calculated: C 35.13; H 2.95%.

Preparation of bis-Selenides and Selenido Sulfides. To a solution of 10.96 g of (II) in 50 ml of absolute ether was added a solution of 3.2 g of n-BuLi in 35 ml of absolute ether at −30 to −20°, in a N_2 atmosphere. After stirring at room temperature for 1 h the mixture was cooled to −10°, and to it was added 4 g of Se, after which the reaction mass was refluxed for 2 h, cooled to −10°, and 7.1 g of CH_3I was added. After the usual workup we obtained 10.5 g (67.3%) of substance with bp 139-141° (2 mm), n_D^{20} 1.6221, which, based on the GLC data, represented a mixture of two compounds, apparently the isomeric 2-methylseleno-3-butylselenothiophene and 2-methylseleno-4-butylselenothiophene. Found: C 35.01, 35.22; H 4.43, 4.34%. $C_9H_{14}SSe_2$. Calculated: 34.62; H 4.52%.

Under analogous conditions, but using S instead of Se, was obtained in 76.4% yield a substance, which, based on the GLC analysis data, was a mixture of two substances, evidently 2-methylmercapto-3-butylselenothiophene and 2-methylmercapto-4-butylselenothiophene, with bp 129-132° (1 mm); n_D^{20} 1.6049. Found: C 40.75, 40.78; H 5.23, 5.19%. $C_9H_{14}S_2Se$. Calculated: C 40.75; H 5.32%.

The ratio of the isomers in the mixture of bis-selenides and selenido sulfides was practically the same (approximately 70% of one and approximately 30% of the other isomer).

CONCLUSIONS

1. In contrast to the alkyl 2-thienyl selenides, the alkyl 3-thienyl selenides when reacted with n-BuLi do not suffer cleavage of the alkylseleno group, and the metal atom enters both of the α-positions of the thiophene ring.

2. The reactions of electrophilic substitution in the alkyl 3-thienyl selenides proceed in the same manner as in the case of the corresponding sulfides, namely the acyl group enters the α-position of the thiophene ring, adjacent to the alkylseleno group.

LITERATURE CITED

1. Ya. L. Gol'dfarb, V. P. Litvinov, and A. N. Sukiasyan, Izv. Akad. Nauk SSSR, Ser. Khim., 2585 (1967).
2. Ya. L. Gol'dfarb, V. P. Litvinov, and A. N. Sukiasyan, Dokl. Akad. Nauk SSSR, 182, 340 (1968).
3. A. N. Sukiasyan, V. P. Litvinov, and Ya. L. Gol'dfarb, Izv. Akad. Nauk SSSR, Ser. Khim., 1345 (1970).
4. Ya. L. Gol'dfarb, V. P. Litvinov, and S. A. Ozolin, Izv. Akad. Nauk SSSR, Ser. Khim., 1419 (1968).
5. S. Gronowitz, Arkiv Kemi, 13, 269 (1958).
6. S. Gronowitz, Arkiv Kemi, 12, 239 (1958).
7. Ya. L. Gol'dfarb, M. A. Kalik, and M. L. Kirmalova, Khim. Geterotsikl. Soedin., 62 (1967).
8. M. L. Bird and F. Challenger, J. Chem. Soc., 570 (1942).
9. S. Gronowitz, P. Moses, A. B. Hornfeldt, and R. Hakansson, Arkiv Kemi, 17, 165 (1961).
10. G. G. Stoner and R. W. Williams, J. Am. Chem. Soc., 70, 1113 (1945).