SYNTHESIS OF 1-SUBSTITUTED trans-2-THIAHYDRINDANES AND 3-SUBSTITUTED trans-2-THIADECALINS

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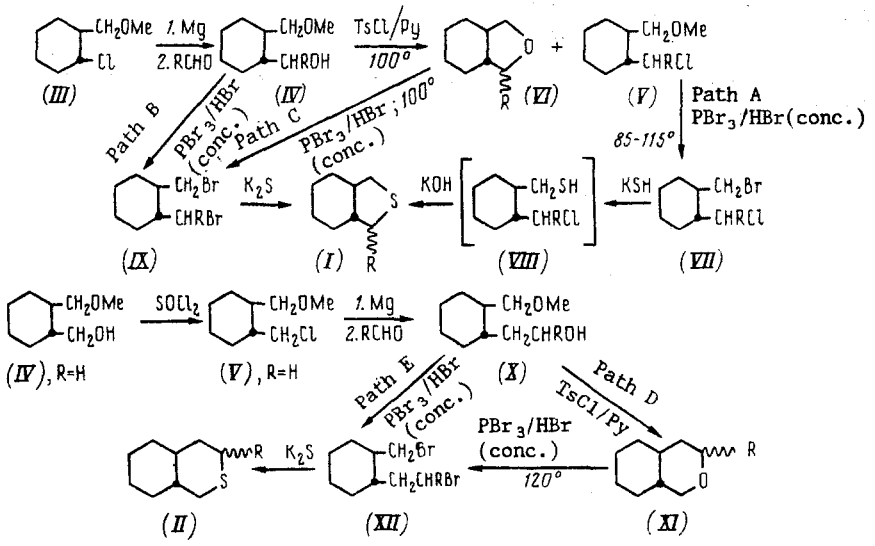
Methods of synthesis of 1-R-trans-2-thiahydrindanes and 3-R-trans-2-thiadecalins from trans-1-methoxymethyl-2-chlorocyclohexane have been developed. The order of the chromatographic elution of the isomeric sulfides formed has been found. The configurations of the compounds have been established by ^1H and ^{13}C NMR spectroscopy. The characteristics of the intermediate and final compounds are given. The splitting of 1-R-trans-2-oxahydrindanes and 3-R-trans-2-oxadecalins by the PBr_3/conc. HBr system has been effected.

In connection with the investigation of sulfurous compounds in the middle and high petroleum fractions, it was of interest to develop paths of synthesis of alkyl-substituted thiabicycloalkanes. The present work is devoted to the synthesis of 1-R-trans-2-thiahydrindanes (I) and 3-R-trans-2-thiadecalins (II), R = alkyl, aryl. These compounds have not been adequately investigated. There are reports on the unsubstituted (I), (II), R = H [1-3] and also on 1-Me-, 8-Me-, and 1-Ph-substituted (I) [4, 5], but no data are available on 3-alkyl-(aryl)-substituted (II).

A general method has been developed for the synthesis of (I) and (II) from trans-1-methoxymethyl-2-chlorocyclohexane (III), which is readily obtained from cyclohexene and methyl trichloromethyl ether [6].*

The Grignard reagent is only obtained fairly effectively from (III) by the addition of MeI and the formation of MeMgI [6]. In (IV) at R = H, it is convenient to carry out the substitution of OH by Cl by the action of $SOCl_2$. The most simple synthesis of (I) is by path B via the dibromides (IX). Similarly, in the synthesis of (II) it is not necessary that oxadecalin (XI) be generated. Compounds (IV), (X), (XII) (R = H) have been described in [6], and the properties of the new intermediate products in the synthesis of (I) and (II) are listed in Table 1.



*According to the data in [6], (III) contains ~10% of the cis isomer.

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TABLE 1. Intermediate Compounds in the Synthesis of 1-R-trans-2-Thiahydrindanes

Compound	R	Yield, %	Bp, °C (p, mm Hg)	n_D^{20}	d_4^{20}	Empirical formula	Found/Calculated, %			
							C	H	Br	Cl
(IV) *	Ph	60	–	–	–	$C_{15}H_{22}O_2$	77,63 / 76.92	10,24 / 10,16	–	–
(V)	Me	64	85(4)	1,4723	1,0174	$C_{10}H_{19}ClO$	–	–	–	18,80 / 18,59
(V)	Pr	68	104(4)	1,4711	0,9950	$C_{12}H_{23}ClO$	65,64 / 65,88	10,32 / 10,59	–	16,10 / 16,21
(VII)	Me	69	87(1,5)	1,5162	1,3587	$C_9H_{16}BrCl$	–	–	32,60 / 33,35	14,40 / 14,80
(VII)	Pr	66	111(2)	1,5090	1,2920	$C_{11}H_{20}BrCl$	–	–	29,40 / 29,86	13,00 / 13,25
(IX)	H	65	102(2,5)	1,5386	1,6158	$C_8H_{14}Br_2$	–	–	59,50 / 59,19	–
(IX)	Me	90	106(2,5)	1,5353	1,5586	$C_9H_{16}Br_2$	–	–	56,20 / 56,26	–
(IX) **	Pr	67	115(2)	1,5180	–	$C_{11}H_{20}Br_2$	–	–	48,10 / 51,21	–
(IX) *	Ph	–	–	–	–	$C_{15}H_{18}Br_2$	–	–		
(XII)	Me	80	107(1,5)	1,5275	1,4874	$C_{10}H_{18}Br_2$	40,33 / 40,30	6,13 / 6,09	53,40 / 53,62	–
(XII) **	Et	70	126(2,5)	1,5220	1,4070	$C_{11}H_{20}Br_2$	–	–	48,50 / 51,21	–
(XII) *	Pr	~85	–	–	–	$C_{12}H_{22}Br_2$	–	–	–	–
(XII) *	Ph	~70	–	–	–	$C_{15}H_{20}Br_2$	–	–	–	–

*Was not isolated in a pure state.
**Could not be isolated in a pure state.

TABLE 2. 1-R-Substituted trans-2-Thiahydrindanes (I) and 3-R-Substituted trans-2-Thiadecalins (II)

Compound	R	Order of elution during GLC	Ratio of peaks during GLC	Yield, %	Bp., °C (p, mm Hg) [mp]	n_D^{20}	d_4^{20}	Empirical formula	Found/ Calculated, %		
									C	H	S
(I)[a]	H	–	–	81	66(4) [7-8]	1,5248	1,0196	$C_8H_{14}S$	67,76 / 67,54	9,72 / 9,92	22,60 / 22,54
Mixture of (I)	trans-Me	1	1	55	77(4)	1,5182	0,9997	$C_9H_{16}S$	69,40 / 69,16	10,35 / 10,32	20,20 / 20,51
	cis-Me	2	2								
(I)	trans-Me	1	–	–	[-30]	1,5137	0,9913	"	69,38 / 69,16	10,42 / 10,32	20,30 / 20,51
(I)	cis-Me	2	–	–	(-78 glass transition)	1,5203	1,0046	"	69,23 / 69,16	10,35 / 10,32	20,20 / 20,51
(I)[b]	cis-Et	4	–	–	(-78 glass transition)	1,5160	0,9913	$C_{10}H_{18}S$	70,77 / 70,52	10,68 / 10,65	18,70 / 18,83
Mixture of (I)	trans-Pr	2	1	68	88(2)	1,5092	0,9714	$C_{11}H_{20}S$	71,52 / 71,67	10,82 / 10,94	17,40 / 17,39
(I)	cis-Pr	4	3								
(II)	cis-Et	1	2								
(II)	trans-Et	3	0,2								
(I)	cis-Pr	4	–	–	(-78 glass transition)	1,5112	0,9763	"	71,79 / 71,67	11,01 / 10,94	17,30 / 17,39
(I)[c]	cis-Ph	–	–	~70	139(2)	1,5814	1,0815	$C_{14}H_{18}S$	77,03 / 77,01	8,53 / 8,31	14,50 / 14,68
(II)[d]	H	–	–	81	86(6) [8-9]	1,5220	1,0057	$C_9H_{16}S$	69,02 / 69,16	10,33 / 10,32	20,30 / 20,51

Mixture of (II) (II) (I) (I)	cis-Me trans-Me trans-Et cis-Et	1 3 2 4	7 4 2 1	82	79,5(3)	1,5128	0,9814	$C_{10}H_{18}S$	70,41 70,52	10,52 10,65	18,70 18,83
(II)	cis-Me	1	–	–	[8-10]	1,5100	0,9755	"	70,62 70,52	10,68 10,65	18,80 18,83
(II)	trans-Me	3	–	–	[13-14]	1,5172	0,9920	"	70,53 70,52	10,64 10,65	18,70 18,83
Mixture of (II) (II) (I) (I)	cis-Et trans-Et trans-Pr cis-Pr	1 3 2 4	4,5 1 2 1,5	72	84(2)	1,5120	0,9757	$C_{11}H_{20}S$	71,66 71,67	11,07 10,94	17,30 17,39
(II) [e]	cis-Et	1	–	–	(–78 glass transition)	1,5060	0,9662	"	71,71 71,67	11,11 10,94	17,00 17,39
Mixture of [f] (II) (I)	cis-Pr trans-Bu	1 2	1 1	60	97(2)	1,5090	0,9659	$C_{12}H_{22}S$	72,69 72,66	11,22 11,18	16,10 16,16
(II) [g]	cis-Ph	–	–	50	153(2.5)	1,5730	1,0672	$C_{15}H_{20}S$	77,43 77,53	8,53 8,68	13,70 13,80

[a]Purified by the PGLC method (cf. [2]).
[b]Obtained as a by-product in the synthesis of 3-Me-trans-2-thiadecalin.
[c]Contains ~15% of a higher boiling impurity.
[d]Contains <5% of a higher boiling impurity (cf. [2, 9]).
[e]Obtained as a by-product in the synthesis of 1-Pr-trans-2-thiahydrindane.
[f]The isomers could not be separated.
[g]Contains 10% of a lower bioling impurity.

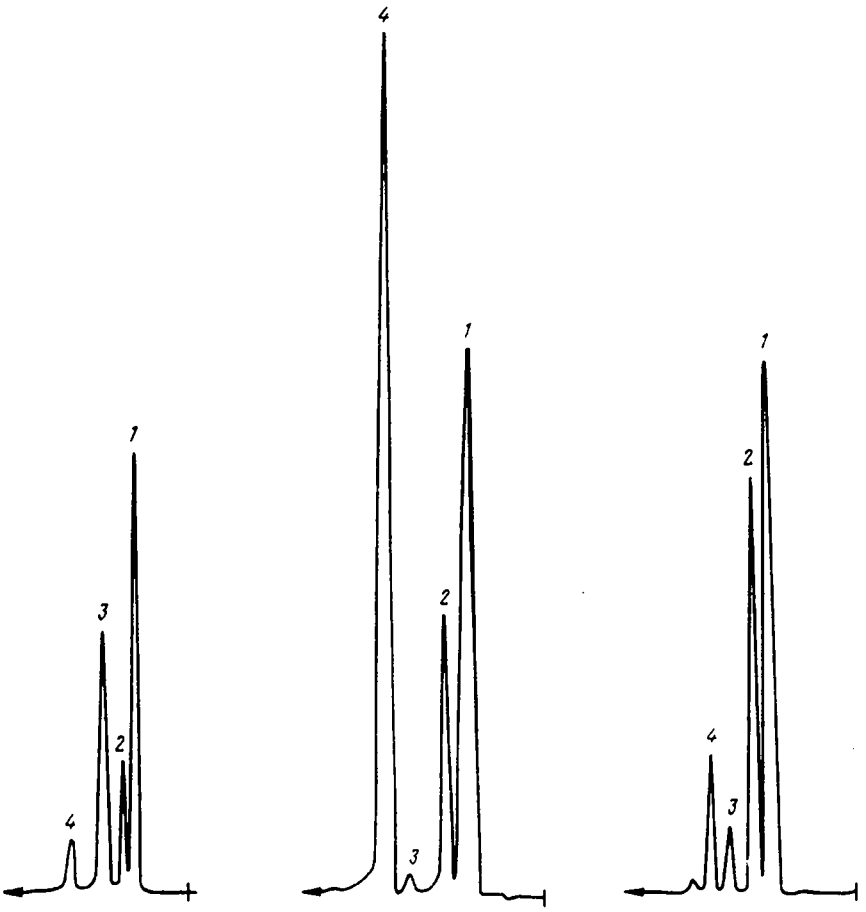

Fig. 1 Fig. 2 Fig. 3

Fig. 1. Chromatogram of a mixture obtained in the synthesis of 3-Me-trans-2-thiadecalin (II). R = Me: 1) cis-3-Me-(II); 2) trans-1-Et-(I); 3) trans-3-Me-(II); 4) cis-1-Et-(I).

Fig. 2. Chromatogram of a mixture obtained in the synthesis of 1-Pr-trans-2-thiahydrindane (I), R = Pr: 1) cis-3-Et-(II); 2) trans-1-Pr-(I); 3) trans-3-Et-(II); 4) cis-1-Pr-(1).

Fig. 3. Chromatogram of a mixture obtained in the synthesis of 3-Et-trans-2-thiadecalin (II). R = Et: 1) cis-3-Et-(II); 2) trans-1-Pr-(I); 3) trans-3-Et-(II); 4) cis-1-Pr-(I).

The cyclization of chlorobromides (VII) was carried out according to [7] in two stages, since the one-stage reaction with K_2S gives (I) in a low yield because of the preponderance of an intermolecular reaction. The synthesis of (I) by path C has no practical value because of the low availability of (VI). The synthesis of thiadecalins (II) via the chlorobromides is impossible since oxadecalins (XI) are formed during the chlorination of alcohols (X).

The chromatograms of mixtures of the end products are practically identical when obtained via oxabicycloalkanes (VI), (XI), chlorobromides (VII), or dibromides (IX), (XII). During the chromatographic separation of a mixture of isomers of (I) and (II), cis-2-R-(II) is eluted first, followed by trans-1-R-(I), trans-3-R-(II), and cis-1-R-(I). The cis- and trans-Me-(II) isomers corresponding to peaks 1 and 3 on the chromatogram (Fig. 1) could be separated by GLC and characterized. At R = H, Me for (I) or Ph for (I) and (II), the composition of the mixture of sulfides becomes considerably simplified. Compound (I) with R = H is formed with an admixture (5%) of a higher boiling product, which was identified according to GLC as a known isomer – cis-2-thiahydrindane. Compound (II) at R = H was also obtained as practically pure (content of the high-boiling impurity <5%). Compound (I) at R = Me is formed in the form of a mixture with a higher boiling isomer – cis-1-methyl-trans-2-thiahydrindane predominating in its content (1:2). Compound cis-1-Ph-(I) was obtained with an

admixture of an unidentified product (on the chromatogram there are only two peaks 7:1), possibly thiahydrindane, since the formation of thiadecalins is impossible here. Compound cis-3-Ph-(II) (the higher boiling) is formed with 10% of an unidentified impurity. In all cases, irrespective of the method of synthesis, four-component mixtures are obtained – cis- and trans-1-R-(I) and cis- and trans-3-R-(II). Some of them were isolated by PGLC and characterized (Table 2). The configuration of the individual isomers (I) and (II) was confirmed by ^1H and ^{13}C NMR [8].

Comparison of the chromatograms (Figs. 2 and 3) serves as an independent proof of the correctness of the assignment of the four peaks. The identity of the end products – a mixture of sulfides (I) and (II) obtained from alcohols (IV) at $R \geq C_2$ and (X) at $R \geq C_1$ was proved by the GLC method. Differences are observed only in the relative value of the peaks – from alcohol (IV) 2-thiahydrindanes (I) are obtained as the main product, while from alcohol (X) these are 2-thiadecalins (II). The confirmation of the fact that peaks 1 and 3 belong to 2-thiadecalins are the high melting points of compounds corresponding to these peaks (8 and 13°C, see Fig. 1, and also (II) at R = Me in Table 2) which is characteristic for thiadecalins [2, 9, 10]. Isomeric thiahydrindanes (peaks 2 and 4) have lower melting points or vitrify on cooling (see Table 2).

In the synthesis of 1-R-(I) and 3-R-(II), cis-R-isomers are preferentially formed.

The formation of a mixture of the same structural isomers (I) and (II) from alcohols (IV) and (X) even on substitution of the secondary OH group by Cl in (IV) by the action of TsCl/Py according to [11] can be attributed to the instability of secondary chlorides (V) under the conditions of the substitution of the methoxy group by bromine. It should be noted that 1-methoxy-4-chloro- and 5-chloroalkanes readily form the corresponding 1-Br-4(5)-Cl-alkanes [7].

In the present work, the splitting of 2-substituted tetrahydropyrans (THP) by the PBr_3/HBr (conc.) system has been effected for the first time [12, 13]. In fact, 3-substituted trans-2-oxadecalins (XI) can be regarded as α,β',γ-trisubstituted THP. It is known that an unsubstituted trans-2-oxadecalin (XI) at R = H is formed from methoxyalkanol (X) at R = H by the action of PBr_3/conc. HBr at 85°C [6], i.e., under the conditions of splitting of the methoxy group. To effect its splitting, as in the case of β-substituted THP [13], rigorous conditions are required (140-150°C, 2 h). α-Substituted THP, to which 3-R-trans-2-oxadecalins (XI) can be related, at $R \geq C_1$ are split relatively readily (120°C, 1 h), giving high yields (85-95%) of the corresponding dibromides (XII).

EXPERIMENTAL

The GLC analysis was carried out on a "Tsvet" chromatograph with a flame ionization detector on a 50-m long capillary column, using OU-17 as the stationary phase and H_2 as carrier gas. The preparative GLC (PGLC) was carried out on a PAKhV-05 chromatograph with a set of columns 25-6 mm in diameter and 11 m overall lengh; stationary phase – 15% PEGA on INZ-600; carrier gas He. The isomers were purified from the stationary phase impurity by refreezing in a closed system, consisting of two 5 ml vessels.

1-Pr-trans-2-Thiahydrindane (I) at R = Pr, Path A. 1. trans-1-Methoxymethyl-2-(1-chlorobutyl)cyclohexane (V) at R = Pr. A mixture of 103 g (0.52 mole) of trans-1-methoxymethyl-2-(1-hydroxybutyl)cyclohexane (IV) at R = Pr [6] with 46 ml (0.57 mole) of Py was added rapidly at 100°C to 108 g (0.57 mole) of p-toluenesulfonyl chloride [11]. The mixture was held for 1.5 h at this temperature, then was decomposed with water, the organic layer was separated and distilled under vacuum. Yield, 78 g (69%) of crude chloride (V) at R = Pr, bp 105-107°C (5 mm). After purification by heating with mixture of Py (20 ml), water (10 ml) and acetone (100 ml), the pure chloride was obtained.

2. trans-1-Bromomethyl-2-(1-chlorobutyl)cyclohexane (VII) at R = Pr. Concentrated HBr (7 ml) was added at a steady rate at 115°C in the course of 2 h to a mixture of 22.3 g (0.1 mole) of chloride (V) at R = Pr and 14 ml (0.15 mole) of PBr_3 [12]. The mixture was then cooled, treated with water and the organic layer was distilled. Yield, 22.8 g (86%) of crude chlorobromide (VII) at R = Pr, bp 112-115°C (2 mm). By repeated distillation, pure chlorobromide, bp 105°C (1.5 mm) was obtained.

3. 1-Pr-trans-2-Thiahydrindane (I) at R = Pr. A mixture of 16.6 g (0.06 mole) of chlorobromide (VII) at R = Pr with a KSH solution obtained by saturating a H_2S solution with 5.2 g

(0.09 mole) of KOH in 40 ml of EtOH at −8°C, was heated at 100°C for 2 h in a stainless steel autoclave. After cooling, a solution of 5.2 g of KOH in 40 ml of EtOH was added, and the mixture was heated for another 2 h at 125°C. Water was added, the product was extracted with pentane and distilled in vacuo. Yield, 8.4 g (73%) of crude sulfide (I) at R = Pr, bp 93°C (2.5 mm). The purification was carried out according to [14] by the action of PBr_3/conc. HBr and Na (see Table 2). GLC analysis: four peaks (see Fig. 2).

Path B. 1. trans-1-Bromomethyl-2-(1-bromobutyl)cyclohexane (IX) at R = Pr. A 16.8-g portion (0.08 mole) of alcohol (IV) at R = Pr was added rapidly with ice-cooling to 18 ml (0.19 mole) of PBr_3. The mixture was then heated to 80°C and 6 ml of conc. HBr was added at a steady rate in the course of 55 min. After cooling, the mixture was decomposed with water, the lower organic layer was separated, and dried over Na_2SO_4. Yield, 23 g (88%) of crude dibromide.

2. 1-Pr-trans-2-Thiahydrindane (I) at R = Pr. A 12-g portion (0.21 mole) of KOH was dissolved in 100 ml of EtOH, one-half of the solution was saturated with H_2S at 0°C and mixed with the remaining solution. One-half of the alcoholic K_2S solution obtained was placed in a flask, heated to boiling, and the remaining fraction of the K_2S solution and 23 g (0.075 mole) of dibromide (IX) at R = Pr were added at a steady rate, with stirring, in the course of 1 h. The solution was boiled for another 2.5 h, cooled, and water and 15 ml of heptane were added. The organic layer was separated, and the product was separated on a rectification column. Thus, 9.2 g of a fraction bp 55-130°C (3 mm) were obtained with a calculated content (% S) of 6.5 g of the sulfide. Yield, 42% based on alcohol (IV) at R = Pr used. Purification, carried out according to [14] (see above), gave 5 g of sulfide (I) at R = Pr (see Table 2). In the GLC analysis results similar to the preceding ones were obtained.

Path C. 1. trans-1-Bromomethyl-2-(1-bromobutyl)cyclohexane (IX) at R = Pr. A 6-ml portion of conc. HBr was added at a steady rate in the course of 1 h at 100°C to a mixture of 11.2 g (0.067 mole) of trans-2-oxahydrindane [6] and 9 ml (0.1 mole) of PBr_3. The mixture was cooled, treated with water, the main product was separated, and the aqueous layer was extracted with 5 ml of pentane. The combined organic solution was dried over anhydrous Na_2SO_4 and pentane was evaporated under vacuum. Yield, 22 g of a crude dibromide; 6.4 g of the product was distilled under vacuum to yield 4 g of a distillate, bp 115°C (2 mm) and 0.5 g of a phosphorus containing resin. The calculated yield of dibromide was 14 g (67%) (see Table 1).

2. 1-Pr-trans-2-Thiahydrindane (I) at R = Pr. A 20-g portion of the dibromide was introduced into a reaction with K_2S as described above. Yield, 5.8 g (49%) of crude sulfide, bp 82-85°C (2 mm). After purification according to [14], 4.3 g of sulfide (I) at R = Pr was obtained (see Table 2). In the GLC analysis results similar to the preceding ones were obtained.

3-Et-trans-2-Thiadecalin (II) at R = Et. Path D. 1. trans-1-Bromomethyl-2-(2-bromobutyl)cyclohexane (XII) at R = Et. A 24-ml portion (0.25 mole) of PBr_3 was added to 30 g (0.18 mole) of a mixture of isomeric 3-Et-trans-2-oxadecalins [6], and then 14 ml of conc. HBr was added at a steady rate at 120°C in the course of 1 h. After cooling, the mixture was decomposed with water, the organic layer was separated, and the aqueous layer was extracted with pentane (1 × 20 ml). The combined organic solution was dried over anhydrous Na_2SO_4, and pentane was evaporated under vacuum. From the residue 53 g of a crude dibromide were obtained.

2. 3-Et-trans-2-Thiadecalin (II) at R = Et. From 52 g (0.17 mole) of crude dibromide (XII) at R = Et and 28 g (0.25 mole) of K_2S in an alcoholic solution, 19.2 g (61%) of a crude sulfide, bp 80-87°C (2 ml) were obtained. The product purified according to [14] had bp 84°C (2 ml), n_D^{20} 1.5110, d_4^{20} 0.9741. GLC analysis: Four peaks (see Fig. 3).

Path E. 1. trans-1-Bromomethyl-2-(2-bromobutyl)cyclohexane (XII) at R = Et. A 35-g portion (0.17 mole) of trans-1-methoxymethyl-2-(2-hydroxybutyl)cyclohexane (X), at R = Et was added with cooling to 33 ml (0.35 mole) of PBr_3 and then 19 ml of conc. HBr was added at a steady rate at 120°C in the course of 1.5 h. After the usual treatment, 58.6 g of a crude dibromide were obtained; 9.8 g of the product were distilled under vacuum to yield 6.4 g (70%) of (XII) R = Et.

2. 3-Et-trans-2-Thiadecalin (II) at R = Et. In the reaction of the above obtained dibromide (0.12 mole) with 20 g (0.18 mole) of K_2S, 15.8 g (72%) of a crude sulfide was obtained. The physical constants of (II) at R = Et after the usual purification are given in Table 2. In the GLC analysis results similar to the preceding ones were obtained.

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