SYNTHESIS OF SUBSTITUTED THIABICYCLANES

I. A New Synthesis of cis-1-Thiahydrindan and cis-2-Thiabicyclo[3,3,1]Nonane

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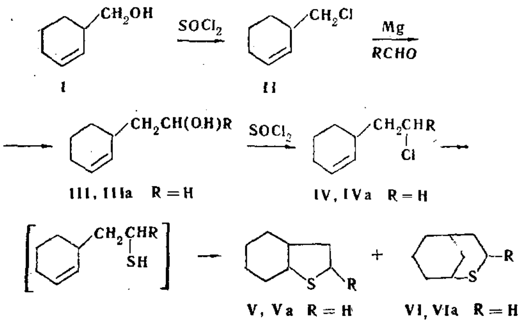
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 3, No. 6, pp. 1031–1035, 1967

UDC 547.89.07:543.544:543.422.4

A simple preparative method for the synthesis of cis-1-thiahydrindan and cis-2-thiabicyclo[3,3,1]nonane has been developed. The method can be used to obtain substituted thiabicyclanes by a general method starting from 3-chloromethylcyclohexene. In the cyclization of 3-(β-mercaptoethyl)cyclohexane both by an ionic and by a radical mechanism, a mixture of cis-1-thiahydrindan and cis-2-thiabicyclo[3,3,1]nonane in approximately equal amounts is formed.

In order to study the cyclic sulfides present in petroleum oils and to find methods for their rational utilization, the development of a general method of synthesis of substituted thiabicyclanes is of interest. Up to the present time, these compounds have been little known. Below we describe the following route for the synthesis of 3-substituted 2-thiabicyclononanes.

Scheme A



The starting material selected was 3-chloromethylcyclohexene (II), the preparation of which from the readily accessible 3-hydroxymethylcyclohexene (I) [1] can easily be carried out on the large scale. The reaction of II with Mg and the aldehyde RCHO leads to the secondary alcohol III; by the action of $SOCl_2$ III is converted into the chloride IV which, on being heated with alcoholic NaSH solution, gives a mixture of the thiabicyclanes V and VI (ionic cyclization mechanism).

By this general route, using formaldehyde as the initial aldehyde (R = H) we have obtained 1-thiahydrindan (Va) and the previously unreported 2-thiabicyclo[3,3,1]nonane (VIa). All three stages of the reaction take place with fairly high yields. The separation of the isomeric sulfides Va and VIa formed in approximately equal amounts was carried out by preparative gas-liquid chromatography.

The physicochemical characteristics and IR spectrum of the 1-thiahydrindan (Va) that we obtained agree completely with the characteristics of cis-1-thiahydrindan and differed considerably from those of the trans isomer [2]. Compound VIa is a white crystalline volatile substance with the odor of camphor, which is characteristic for 1,3-bridge systems regardless of the presence or absence of a heteroatom (S or O). The large difference in the melting points of Va and VIa enables them to be separated by freezing out.

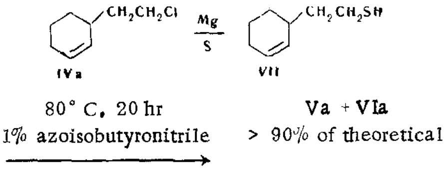
The solid product VIa must be assigned the cis-configuration for the following reasons. The formation of the two substances Va and VIa takes place by one and the same mechanism; the difference consists only in the addition of the RS ion to different C atoms between which there is a double bond. At the same time, an analytical chromatogram of the mixture of sulfides shows the presence of only two clear peaks, corresponding to Va and VIa.

The trans configuration of VIa can hardly exist because of the pronounced stresses, which can be readily seen by considering Stuart–Briegleb stereo models. It is also shown by the fact that the sulfone of cis-1-thiahydrindan is obtained in 92% yield by the cyclization of the corresponding 1,4-diene with SO_2 (with subsequent reduction of the double bond) [2].

All that has been said above shows the stereospecificity of the closure reaction of a system containing a double bond in the ring and a —SH group in the side chain, at least for the case of the formation of 1-thiahydrindan (Va) and 2-thiabicyclo[3,3,1]nonane (VIa).

We have also obtained compounds Va and VIa by scheme B:

Scheme B



In this case, also, i.e., in the radical cyclization of the thiol VII, the isomeric sulfides Va and VIa are formed in approximately equal yields, as with ionic cyclization.

The method of obtaining the thiabicyclanes by scheme A (without the isolation of the mercaptans formed as intermediates) is far simpler, and more convenient, and gives better yields. The three-stage scheme A can be recommended as a general preparative method, in spite of the fact that it leads to a mixture of two thiabicyclanes of different structures. Both groups of compounds are of interest in view of the fact that the probability of the presence of 1,3-condensed saturated systems in natural substances is not less probable than the presence of 1,2-condensed saturated systems. This is shown, in particular, by the chemistry of the terpenes and by the presence in petroleum of such compounds as adamantane and thiaadamantane and also by recent investigations on the isomerism of the conversion of pentalanes and hydrindans into derivatives of bicyclo [3, 2, 1] octane [3, 4].

The separation of the isomeric thiabicyclanes of types V and VI should not present serious difficulties since, judging from literature data [5], 1, 3- or 1, 4-bridge systems have considerably higher melting points than 1, 2-cyclized compounds.

EXPERIMENTAL

3-Chloromethylcyclohexene (II). A two-liter flask fitted with a stirrer, dropping funnel, reflux condenser, and thermometer was filled with 700 g (6.25 mole) of 3-hydroxymethylcyclohexene (I), and 580 ml (8.12 mole) of vinyl chloride was added over 1 hr with stirring. The mixture was heated in the water bath for 2 hr (reaction temperature of the mixture 80° C). Then it was cooled and poured onto ice. The lower organic layer was separated off, washed with a solution of sodium carbonate, and dried with anhydrous Na_2SO_4 (with satisfactory settling, the acidic aqueous layer need not be extracted). Vacuum distillation gave a chloride fraction with bp up to 130° C (15 mm), weight 546 g; the bulk distilled at 66°–70° C (23 mm), and the residue, 130 g, consisted of a dark brown oil, apparently 3-hydroxymethylcyclohexene sulfite*. At room temperature, a solution of 56 g of potassium hydroxide in ethanol was added in one portion to the residue, which led to a pronounced rise in temperature. The reaction mixture was cooled in the water bath, and after the vigorous reaction had ended it was boiled for 2 hr and was then cooled, neutralized with sulfuric acid (1:1 in ethanol) and subjected to vacuum distillation with no account being taken of the voluminous precipitate of potassium salts. About 120 g of the initial 3-hydroxymethylenecylohexene was obtained; this substance was treated again as described above with vinyl chloride to give an additional 85% of chloride fraction and 50 g of heavy residue. Analogously, the 50 g of heavy residue gave another 30 g of chloride fraction. The chloride fractions were combined and distilled through a column (a column with an efficiency of 10 theoretical plates was used in this work). This gave a total of 650 g (80%) of 3-chloromethylcyclohexene with bp 65°–66° C (23 mm), d_4^{20} 1.0263; n_D^{20} 1.4880. Found, %: Cl 27.57%; MR_D 36.67. Calculated for $C_7H_{11}Cl$, %: Cl 27.18; MR_D 36.46.

3-β-(Hydroxyethyl)cyclohexene (III). With stirring and cooling, formaldehyde vapor was passed into a solution of the Grignard reagent obtained in the usual way from 390 g of 3-chloromethylcyclohexene and 216 g of Mg. The top end of the condenser was connected with a Tishchenko bottle containing a 20 mm layer of mercury; the overpressure favored the absorption of the formaldehyde. The reaction was complete in approximately 1 hr. The Tishchenko bottle was disconnected and with cooling and stirring dilute (1:2) hydrochloric acid was added. The reaction mixture was decanted from the excess of Mg that had not reacted, the ethereal layer was separated off and the aqueous layer was extracted with ether. The ethereal solutions were combined and the ether was distilled off. To bring about the methanolysis of the partly formed formal, 500 ml of methanol and 1.5 ml of concentrated sulfuric acid were added to the residue and the methanol was slowly distilled off over 2-4 hr. Then the residue was neutralized by the addition of sodium methoxide and the methanol was distilled off on the boiling water bath. The resulting product (280 g) was distilled in vacuum from a Claisen flask and then through a column. This gave 210 g (55.5%) of 3-(β-hydroxyethyl) cyclohexene with bp 109°–111° C (23 mm); d_4^{20} 0.9580; n_D^{20} 1.4869. Found, %: C 76.41; H 10.99%; MR_D 37.88. Calculated for $C_8H_{14}O$, %: C 76.14; H 11.18%; MR_D 37.78. According to the literature [6], n_D^{25} 1.4722.

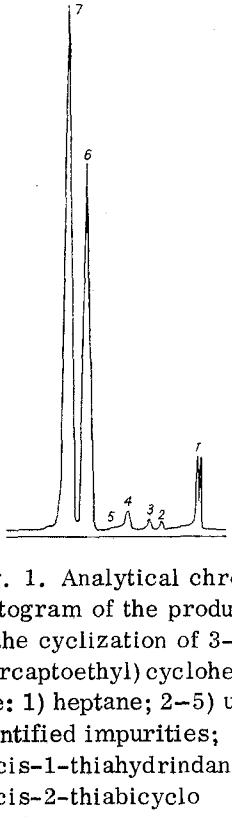


Fig. 1. Analytical chromatogram of the product of the cyclization of 3-(β-mercaptoethyl) cyclohexene: 1) heptane; 2–5) unidentified impurities; 6) cis-1-thiahydrindan; 7) cis-2-thiabicyclo [3, 3, 1] nonane.

3-(β-Chloroethyl)cyclohexene (IVa). Two hundred grams of compound (IIIa) was treated with thionyl chloride as in the synthesis of II. Distillation through a column yielded 174 g (80%) of IVa with bp 84°–87° C (23 mm); d_4^{20} 1.0055; n_D^{20} 1.4867. Found, %: Cl 24.11; MR_D 41.35. Calculated for $C_8H_{13}Cl$, %: Cl 24.51%; MR_D 41.37.

Comparative Characteristics of the Compounds

Compound	B_p, ° C (pressure, mm)	d_4^{20}	n_D^{20}	MR_D	
				Found	Calculated
BF	103 (20)	1,0391	1.5300	42.29	42.70
cis-1-Thiahydrindan	102 --102.5 (20)	1.0383	1.5308	—	—
trans-1-Thiahydrindan	102.7—103.7 (21)	1.0209	1.5248	—	—

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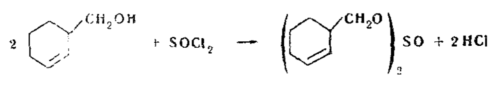
*This ester can be formed by the reaction:



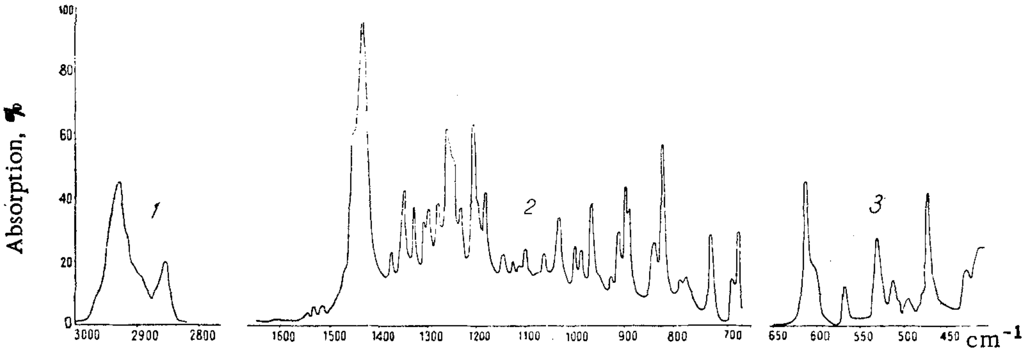


Fig. 2. IR spectrum of cis-1-thiahydrindan: 1) 3000–2800 cm^{-1} region, solution in CCl_4, c = 1.2%, d = 35 μ; 2) 1600–700 cm^{-1} region, film of liquid, d = 32 μ; 3) 650–400 cm^{-1} region, film of liquid, d = 109 μ.

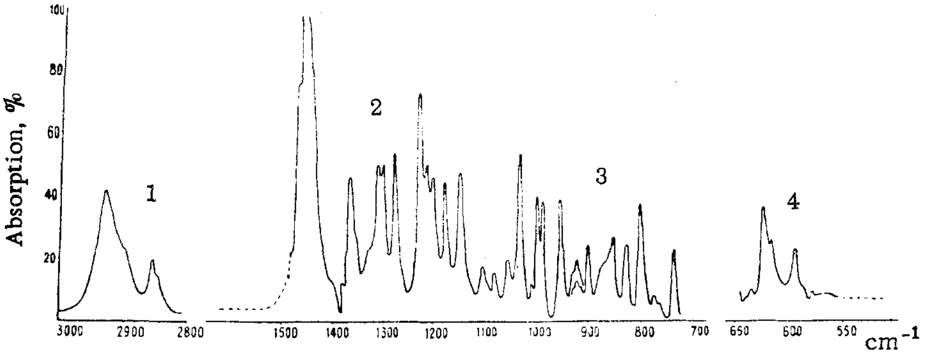


Fig. 3. IR spectrum of cis-2-thiabicyclo[3,3,1]nonane: 1) 3000–2800 cm^{-1} region, solution in CCl_4, c = 1.2%, d = 35 μ; 2) 1500–900 cm^{-1} region, solution in CCl_4, c = 18%, d = 104 μ; 3) 900–700 cm^{-1} region, solution in CS_2, c = 9%, d = 104 μ; 4) 650–550 cm^{-1} region, solution in CCl_4, c = 18%, d = 104 μ.

Cis-1-Thiahydrindan (Va) and cis-2-thiabicyclo[3, 3, 1] nonane (VIa). A solution of 8 g (0.35 g-atom) of Na in 150 ml of absolute ethanol was saturated with hydrogen sulfide at 3° C. The resulting solution of sodium hydrogen sulfide was mixed with 24.1 g (0.166 mole) of IVa and the mixture was heated in a hermetically sealed stainless vessel at 130° C for 3 hr. Then it was poured into 200 ml of 10% aqueous KOH and extracted twice with hexane. The hexane extracts were combined, dried with anhydrous Na_2SO_4, and fractionated through a column. This gave 20.5 g (86.5%) of a mixture of Va and VIa boiling between 102° and 107° C (23 mm). The distillation product began to crystallize in the refrigerator, and in the receiver it set to a colorless crystalline mass. This was treated with an equal volume of n-heptane and the mixture was boiled with 4 g of Na for 1 1/2 hr, after which it was cooled, filtered, and distilled through a column. This gave 19.5 g of a mixture of the thiabicyclanes Va and VIa with bp 103° C (20 mm). Found, %: S 22.50. Calculated for $C_8H_{14}S$, %: 22.54.

When the product was subjected to analytical chromatography, only two main peaks, of similar areas, were obtained (Fig. 1, peaks 6 and 7). (The analytical and the subsequent preparative chromatography were carried out by D. K. Zhestkov, I. V. Cherepanova, and F. V. Kozoleva.) The smallest peaks (2–5) are apparently due to contamination with a small amount (1–2%) of the unsaturated hydrocarbons that may be formed through the partial dehydrochlorination of IVa. The separation of 1.5 g of the mixture (diluted with heptane 1:1) on the preparative gas-liquid chromatograph gave 0.6 g of liquid Va and 0.7 g of crystalline VIa. A comparison of the physicochemical characteristics of Va with those reported for cis-1-thiahydrindan and trans-1-thiahydrindan [2] is given in the table.

The IR spectrum of Va (the spectra of compounds Va and VIa were obtained by L. R. Barykina on a IKS-14 spectrometer with LiF, KBr, and NaCl prisms) (Fig. 2) was identical with the spectrum of cis-1-thiahydrindan given by Birch et al. [2]: 2932, 2854, 1440, 1381, 1356, 1311, 1303, 1285, 1267, 1238, 1212, 1202, 1190, 1152, 1133, 1108, 1067, 1042, 1007, 994, 973, 919, 906, 900, 848, 833, 791, 782, 735, 694, 684, 613, 603, 568, 527, 466 cm^{-1}.

Characteristics of cis-2-thiabicyclo[3, 3, 1] nonane (VIa). The cis-2-thiabicyclo[3, 3, 1] nonane (VIa), which has not been reported in the literature, melted at 101°–103° C in a sealed capillary. It was soluble in methanol, ethanol, acetone, heptane, and benzene. Found, %: S 22.75. Calculated for $C_8H_{14}S$, %: S 22.54. IR spectrum of cis-2-thiabi-cyclo[3, 3, 1] nonane (VIa): 2932, 2862, 1445, 1363, 1306, 1297, 1275, 1223, 1210, 1200, 1178, 1147, 1104, 1080, 1056, 1032, 1001, 990, 954, 928, 922, 902, 852, 826, 806, 734, 623, 615, 595 cm^{-1} (Fig. 3).

3-(β-Mercaptoethyl) cyclohexene (VII). With cooling and stirring, 8 g (0.25 g-atom) of finely ground sulfur was added to the Grignard reagent obtained from 40 g (0.273 mole) of IVa; stirring was continued for another 30 min, after which the mixture was decomposed with dilute HCl (1:1). The ethereal solution was separated off and dried with Na_2SO_4, the ether was evaporated off, and the residue was distilled in vacuum. This gave 16.5 g (46% on the amount of sulfur taken) of the previously unreported VII, boiling at 100°–102° C (20 mm). Found, %: S 19.61. Calculated for $C_8H_{14}S$, %: S 22.54. The high-boiling residue (14 g) was not investigated. No further purification of VII was carried out.

Cyclization of VII by a radical mechanism. A solution of 4 g of VII in 4 ml of heptane was heated in a sealed tube at 80° C for 20 hr in the presence of 0.04 g of azoisobutyronitrile. Then the contents of the tube were transferred to a flask fitted with a reflux condenser, about 1 g of Na was added, and the mixture was boiled for 2 hr. After cooling it was filtered, the heptane was driven off, and the residue was distilled in vacuum. Two fractions were collected (a total of 3.5 g) with almost the same boiling point, 102° C (20 mm), which rapidly crystallized to a colorless mass.

The analytical chromatography of the two fractions showed the presence of two well-separated peaks coinciding with the peaks of the chromatograms of the products described previously. The chromatogram of the first fraction contained peaks of unidentified low-boiling impurities (~5%).

The chromatographic analysis of the products of the cyclization of 3-(β-mercaptoethyl)cyclohexene was carried out on analytical (KhTV-1) and preparative (KhTV-2) gas chromatographs designed by the Special Design Bureau of the Topchiev Institute of Petrochemical Synthesis, AS USSR. The chromatographic conditions were: steel columns 4.35 m × 4 mm (analytical) and 3 m × 14 mm (preparative). The stationary phase was poly(ethylene glycol succinate), 10% on INZ-600 with a grain size of 0.2–0.4 mm. The column temperature was 150° C. The carrier gas (helium) was passed through the analytical column at the rate of 26 ml/min and through the preparative column at the rate of 108 ml/min. Thermal conductivity detectors were used.

REFERENCES

1. N. P. Volynskii, G. D. Gal'pern, and A. B. Urin, ZhOrKh, 2, 1043, 1966.

2. S. F. Birch, R. Dean, H. Hunter, and E. Whitehead, J. Org. Chem., 20 1178, 1955.

3. A. F. Plate, N. A. Belikova, A. A. Bobyleva, N. I. Gusar, and S. V. Vitt, DAN, 163, 902, 1965.

4. N. S. Vorob'eva, Candidate's thesis [in Russian], Moscow, 1965.

5. B. V. Aivazov, S. M. Petrov, V. R. Khairullina, and V. G. Yapryntseva, Physicochemical Constants of Organosulfur Compounds [in Russian], Moscow, 122, 1964.

6. L. F. Fieser and M. T. Zeffler, J. Am. Chem. Soc., 70, 3195, 1948.

28 February 1966

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