REACTION OF 3,4-DIHYDRO-2H-THIOPYRAN WITH PHENYLHYDRAZINES. SYNTHESIS OF HOMOTHIOTRYPTOPHOLS

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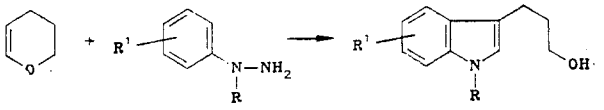
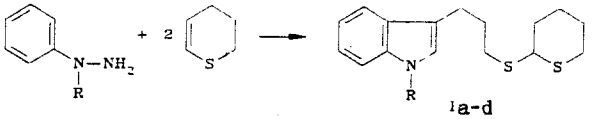
The reaction between 3,4-dihydro-2H-thiopyran and phenylhydrazines leads to S-tetrahydrothiopyranyl derivatives of 3-(3-indolyl)propanethiols (homothiotryptophols). The removal of the tetrahydrothiopyranyl protective grouping in these compounds and the production of homothiotryptophols can be realized as a result of acidic hydrolyis in the presence of phenylhydrazines.

We have previously shown that dihydropyran reacts with arylhydrazines to give 3-(3-indolyl)-propanols (homotryptophols) [1].



In the present research we attempted to extend this reaction to dihydrothiopyran to obtain homologs of thiotryptophol. The latter, inasmuch as they are sulfur analogs of homotryptophols, may be of interest as biologically active compounds. However, they have thus far remained almost uninvestigated in this respect because of the lack of convenient methods for their preparation. The known methods for the synthesis of homothiotryptophols are based on the multistep modification of the hydroxy group in the homotryptophol to a mercapto group [2].

We carried out the reactions of dihydrothiopyran with hydrochlorides of various phenylhydrazines in aqueous dioxane, i.e., under the same conditions used to obtain homotryptophols [1]. However, instead of the expected mercaptans V the only reaction products proved to be their tetrahydrothiopyranyl derivatives I.



I a R=H; b R=CH_3; c R=C_6H_5; d R=$CH_2C_6H_5$

We were unable to obtain homothiotryptophols, i.e., products of the reaction of phenylhydrazine with dihydrothiopyran in a ratio of 1:1, by any changes in the conditions under which this reaction is carried out. The use of protic (alcohols) or water-containing (aqueous dioxane) solvents invariably led to a 1:2 adduct. Even a manyfold excess of phenylhydrazine did not change the course of the reaction. Although we did, to be sure, detect the formation of a homothiotryptophol when we carried out the reaction in acetic acid in the presence of HCl, large amounts of dimer II [3], which does not react with phenylhydrazine, were obtained along with it.

It should be noted that dimerization of the dihydrothiopyran in a blank experiment proceeded to completion after 3 h.

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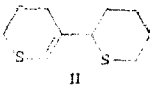
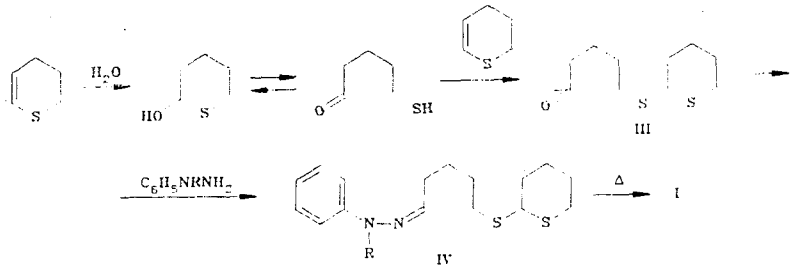


II

The reaction did not take place in absolute dioxane. This makes it possible to assume that the initial addition of water to dihydrothiopyran is necessary for the reaction to occur; the resulting 2-hydroxytetrahydrothiopyran exists in equilibrium with its open tautomeric form – 5-mercaptopentanal [4]. The latter is removed from the equilibrium by the addition of a second molecule of the starting dihydrothiopyran to give aldehyde III, which also reacts further with phenylhydrazine to give phenylhyhdrazone IV, which then participates in the Fischer reaction.



III

IV

We were able to isolate hydrazone IV (R = $CH_2C_6H_5$) by carrying out the reaction at room temperature in aqueous dioxane. When the temperature is raised, this hydrazone is converted smoothly to indole Id.

The PMR spectra are most characteristic (Table 1) for confirmation of the structures of Ia-d, even though they are quite complex in view of the fact that the molecule contains an asymmetric carbon atom and a large number of methylene groups, the protons of which are diastereotopic and may have different chemical shifts. Signals that are peculiar to the structure of a 3-substituted indole are observed in the aromatic-proton region: the 4-H doublet is shifted to weakest field, while the 2-H singlet of the indole ring is shifted to strong field. The aliphatic part of the spectrum is considerably more complicated for interpretation (Fig. 1). The signal of the proton of the dithioacetal fragment (S–CH–S), which shows up at ~4 ppm in the form of a doublet of doublets, is most characteristic here. The remaining signals are superimposed on one another. The use of the method of double resonance made it possible to isolate the signals of the trimethylene link that joins the two heterorings and determine their chemical shifts. In the case of irradiation of a sample of Ib with a second radio-frequency field ν_2, which corresponds to the center of the symmetrical multiplet at 2.01 ppm, one observes conversion of the triplet at 2.86 ppm to a singlet and of the multiplet at 2.6-2.8 ppm to two doublets of an AB system with a spin-spin coupling constant (SSCC) of 12 Hz. This high SSCC is characteristic for geminal protons. Thus taking into account that the signals that couple with the irradiated multiplet are found at weaker field, the multiplet centered at 2.01 ppm should be assigned to the signal from the protons of the β-methylene link and the triplet at 2.86 ppm and the multiplet at 2.6-2.8 ppm that couple with it should be assigned to the α- and γ-methylene groups, respectively. We assigned the signals of the α- and γ-methylene groups on the basis of their chemical shifts and on the basis of the fact that the γ-methylene protons, as the closest to the chiral center, manifest diastereotopic differences in the chemical shifts particularly strongly ($\Delta\delta$ = 0.10 ppm).

To obtain homothiotryptophols we removed the tetrahydrothiopyranyl protective group in indoles I. It is known that cleavage of dithioacetals proceeds with difficulty and does not go to completion, since the equilibrium of the reaction is shifted markedly to favor their formation [5]. Reagents that irreversibly tie up one of the compounds formed are usually introduced into the reaction mixture to shift the equilibrium to favor the formation of cleavage products. We selected ethanedithiol and phenylhydrazines as reagents of this type.

In fact, complete removal of the tetrahydrothiopyranyl protective group occurs when a solution of indole Id in ethane-dithiol is treated with boron trifluoride etherate at room temperature for 2 days. Homothiotryptophol Vd and 5-mercaptopentanal dithioacetal VI are formed as a result (tetrahydrothiopyranyl derivative VII of ethanedithiol is also possibly present in the reaction mixture).

TABLE 1. Characteristics of 1-(2-Tetrahydrothiopyranylthio)-3-(3-indolyl)propanes I and 3-(3-Indolyl)propanethiols V

Compound*	Empirical formula	R_f	UV spectrum		ν,** cm^{-1}	PMR spectrum,*** δ, ppm (J, Hz)							Yield, % (method)
			λ_{max}, nm	lg ε		α-CH_2 (t, 2H)	β-CH_2 (2H)	γ-CH_2 (2H)	R	2-H (s, 1H)	4-H (d, 1H)	other protons	
Ia	$C_{16}H_{21}NS_2$	0,11	224 277 sh. 285 292	4,48 3,65 3,69 3,64	3503 (free) NH) 3442 (assoc) NH)	2,77 (7,2)	1,92 q (7,2)	2,61 m	7,48 br.s 1H, H	6,66	7,42	3,77 dd, 1 H, S—CH—S (6,5; 3,0)	76
Ib	$C_{17}H_{23}NS_2$	0,27	227 285 sh 291	4,62 3,80 3,82		2,86 (7,2)	2,01 m	2,68 dt. (12,8; 7,5) and 2,78 dt (12,8; 7,5)	3.73 s 3H, CH_3	6,85	7,59 (9,2)	3,92 dd, 1H, S—CH—S (7,9; 3,0)	41
Ic	$C_{22}H_{25}NS_2$	0,41	220 261 302 370	4,48 4,34 4,08 2,26		2,87 (7,2)	2,00 m	2,61 dt. (12,7; 7,9) and 2,73 dt (12,7; 7,9)	C_6H_5		7,53 (7,7)	3,83 dd, 1H, S—CH—S (7,3; 3,5)	52
Id	$C_{23}H_{27}NS_2$	0,29	234 285 sh. 290	4,08 4,32 4,36		2,83 (7,5)	1,97 m	2,56 dt . (12,5; 7,0) and 2,66 dt (12,5; 7,0)	5.12 s 2H, CH_2	6,78	7,50 (8,5)	3,79 dd , 1H, S—CH—S (6,5; 3,5)	79
V b	$C_{12}H_{15}NS$	0,44	224 285 sh 291	4,63 3,88 3,90	2570 (SH)	2,82 (7,1)	1,95q (H_α, H_β, 7,1; H_β, H_γ, 7,0)	2,51 q (H_β, H_γ 7,0; H_γ, SH 7,9)	3,72 s 3H, CH_3	6,71	7,43 (7,7)	1,12 t, 1H, SH (7,9)	26 (C)
Vc	$C_{17}H_{17}NS$	0,61	221 262 302	4,54 4,31 4,07	2569 (SH)	2,90 (7,2)	2,03 q (H_α, H_β 7,2; H_β, H_γ 6,8)	2,57 q (H_β, H_γ 6,8; H_γ, SH 8,1)	C_6H_5	—	—	1,16 t, 1H, SH (8,1)	41 (C)
Vd	$C_{18}H_{19}NS$	0,48	226 276 sh. 290 297 sh.	4,53 3,73 3,76 3,73	2576 (SH)	2,80 (7,0)	1,92 q (7,0)	2,47 q (H_β, H_γ 7,0; H_γ, SH 7,7)	5,11 s 2H, CH_2	6,72	—	1,10 t 1H, SH (7,7)	45 (A) 49 (B) 39 (C)

*Compound Ia had mp 78-80°C (from hexane); Vc had mp 59-61°C.
**In solution in CCl_4 for Ia, and KBr pellets for Vc.
***At 100 MHz for Ia and Vd; in $CDCl_3$ for Ib.

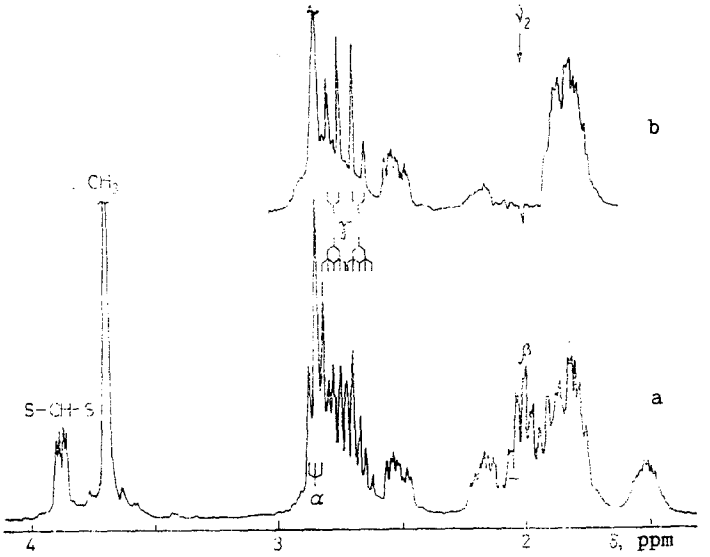
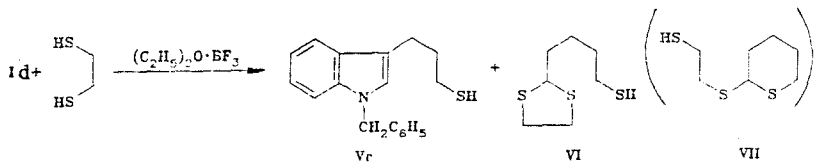
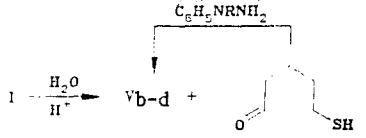


Fig. 1. PMR spectrum of 1-(2-tetrahydrothiopyranyl)-3-(1-methyl-3-indolyl)propane (Ib): a) aliphatic part; b) fragment of the spectrum in the case of irradiation of the sample with a second radio-frequency field with saturation of the multiplet centered at 2.01 ppm.



Unfortunately, the isolation of homothiotryptophol Vd from the reaction mixture proved to be a rather laborious process because of the close boiling points and close chromatographic mobilities of the resulting mercaptans Vd, VI, and VII. We therefore turned to another method – hydrolytic cleavage of dithioacetals I in the presence of the starting phenylhydrazine. The possibility of shifting the equilibrium to favor the cleavage products due to Fischer reaction of the phenylhydrazine and 5-mercaptopentanal formed in hydrolysis attracted us here. Finally, we hoped that this method should have returned a certain part of the mercapto aldehyde to the Fischer reaction, thereby increasing the yield of homothiotryptophol V.

Removal of the tetrahydrothiopyranyl protective group occurs when dithioacetals I are heated in acetic acid in the presence of hydrochloric acid and the hydrochloride of the corresponding phenylhydrazine, and N-substituted homothiotryptophols Vb-d are formed (an N-unsubstituted homothiotryptophol was not isolated).

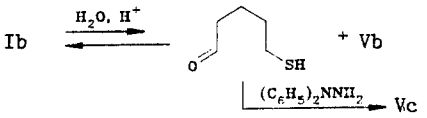


V b R=CH_3; c R=C_6H_5; d R=$CH_2C_6H_5$

It should be noted that under the same conditions but in the absence of a phenylhydrazine the hydrolysis of dithioacetals I proceeds very slowly, and their cleavage cannot be carried out completely.

Since the yields of homothiotryptophols V proved to be lower than 100%, there was no assurance that the mercapto aldehyde formed as a result of hydrolysis, by undergoing the Fischer reaction with the phenylhydrazine, gives an additional amount of the homothiotryptophol. To convince ourselves of this we carried out a cross reaction. As demonstrated by TLC, a mixture

of two homothiotryptophols Vb and Vc is formed in the cleavage of dithioacetal Ib (R = CH_3) in the presence of an "extraneous" phenylhydrazine (R = C_6H_5).



It hence follows that in the hydrolysis of dithioacetals I the resulting mercapto aldehyde is actually removed from the equilibrium reaction as a result of irreversible reaction with the phenylhydrazine to give an additional amount of homothiotryptophol V.

A low-intensity band of stretching vibrations of an S—H bond is present in the IR spectra of Vb-d at 2570 cm^{-1}. The PMR spectra also confirm the structures of indolylpropanethiols V (Table 1). A triplet of the proton of the mercapto group is observed at strongest field (1.1 ppm); a quintet of protons of a β-methylene link is observed at 2.0 ppm, a quartet of γ-methylene protons is situated at ~2.5 ppm, and a triplet of protons of a α-methylene group appears at weaker field (2.8 ppm). As in the case of indoles I, a singlet of the proton in the 2 position of the indole ring (6.7 ppm) and a doublet of the proton in the 4 position, which is found at weakest field, are most characteristic for the aromatic part of the spectrum.

Thus a study of the reaction of 3,4-dihydro-2H-thiopyran with phenylhydrazines showed that there is no complete analogy in the behavior of dihydropyran and dihydrothiopyran in this reaction. In the latter case only tetrahydrothiopyranyl derivatives I are formed. For the cleavage of the dithioacetals, to isolate the thiol component we have proposed a new method based on the use of phenylhydrazines as reagents that irreversibly tie up the carbonyl component of the cleavage (5-mercaptopentanal) as a result of the Fischer reaction. On the basis of the investigated reactions we have developed a new method for the synthesis of 3-(3-indolyl)-propanethiols (homothiotryptophols) V. Let us note that this synthesis can be carried out in one step (see method C in the experimental section), i.e., without isolation of intermediate indoles I.

EXPERIMENTAL

The IR spectra of liquid films of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in isopropyl alcohol were obtained with a Hitachi EPS-3T spectrophotometer. The PMR spectra of solutions in CCl_4 were obtained with a Varian XL-100 or a Bruker WM-250 spectrometer with tetramethylsilane (TMS) as the internal standard. The mass spectra were recorded with a Varian MAT-311A spectrometer; the peaks with intensities greater than 10% are presented. Chromatography was carried out on Silufol UV-254 plates in a hexane—benzene system (1:1) with development by iodine vapors.

3,4-Dihydro-2H-thiopyran was obtained from tetrahydrothiopyran S-oxide by the method in [6].

General Method for the Synthesis of 1-(2-Tetrahydrothiopyranylthio)-3-(3-indolyl)propanes Ia-d. A 5 mmole sample of the phenylhydrazine hydrochloride was dissolved in 25 ml of dioxane, which did not contain peroxides, and 0.5 ml of water, 10 mmole of 3,4-dihydro-2H-thiopyran was added to the resulting solution, and the mixture was refluxed for 4 h. It was then cooled, and the dioxane was evaporated in vacuo. Water and benzene (30 ml each) were added to the residue, the mixture was shaken, and the organic layer was separated and washed successively with hydrochloric acid (1:1) (two 20-ml portions) and water until the wash water was neutral. It was then dried over $MgSO_4$, and the benzene was evaporated. The residue was purified by chromatography with a column (10 by 3 cm) packed with silica gel (40-100 μm) by elution with a benzene—petroleum ether system (1:1). The constants and the spectral data for the compounds obtained are presented in Table 1. Mass spectrum of 1-(2-tetrahydrothiopyranylthio)-3-(1-benzyl-3-indolyl)propane (Id), m/z (%): 381 (M^+, 9), 280 (49), 220 (12), 149 (11), 92 (11), 91 (100), 81 (10), 69 (15), 67 (18), 65 (13).

5-(2-Tetrahydrothiopyranylthio)pentanal α-Benzylphenylhydrazone (IVd, $C_{23}H_{30}N_2S_2$). A solution of 230 mg (1 mmole) of α-benzylphenylhydrazine hydrochloride and 200 mg (2 mmole) of 3,4-dihydro-2H-thiopyran in 3.5 ml of 97% dioxane was maintained at room temperature for 24 h,

after which it was diluted with 100 ml of water, and the aqueous solution was extracted with benzene (two 15-ml portions). The benzene fraction was washed with water and dried over Na_2SO_4, and the benzene was evaporated in vacuo while not heating above 40°C. The resulting oil was purified by chromatography on a plate (18 by 24 cm) with a loose layer of silica gel (40-100 μm) by passing a benzene–hexane system (1:1) twice. This procedure gave 200 mg (50%) of a colorless oil that began to crystallize on standing to give a product with mp 55-59°C and R_f 0.20. IR spectrum (CCl_4): 1610 cm^{-1} (C=N). UV spectrum, λ_{max} (log ε): 280 nm (4.26). PMR spectrum (100 MHz): 6.55 (1H, t, J = 5 Hz, N=CH), 4.89 (2H, s, N–CH_2), 3.78 (1H, dd, J_1 = 6 Hz, J_2 = 3.5 Hz, S–CH–S). Mass spectrum, m/z (%): 398 (M^+, 10), 297 (26), 207 (16), 183 (28), 182 (43), 180 (11), 173 (12), 133 (11), 107 (19), 106 (12), 105 (21), 104 (28), 103 (14), 102 (15), 101 (100), 99 (11), 95 (10), 92 (23), 91 (96), 87 (12), 85 (15), 83 (17), 82 (11), 81 (17), 79 (14), 78 (14), 77 (86).

3,3',4,4',5,6-Hexahydro-2,5'-bi-2H-thiopyran (II). A solution of 2 g (0.02 mole) of 3,4-dihydro-2H-thiopyran in 50 ml of acetic acid and 1 ml of concentrated HCl was refluxed for 3 h, after which the acetic acid was evaporated with a rotary evaporator, and the residue was fractionated in vacuo to give 0.95 g (47.5) of a product with bp 124-130°C (1 mm), mp 13-16°C, and R_f 0.49. See [3] for the IR and UV spectra. PMR spectrum (100 MHz): 5.88 (1H, s, S–CH=C), 3.15 (1H, broad d, J = 9 Hz, S–CH). M^+ 200.

3-(1-Benzyl-3-indolyl)propanethiol (Vd). A) A 3.4 ml sample of boron trifluoride etherate was added to a solution of 3.4 g (9 mmole) of indole Id in 3.4 ml of ethanedithiol, and the mixture was allowed to stand for 48 h in a nitrogen atmosphere at room temperature. Benzene (50 ml) was added to the reaction mixture, and the benzene solution was washed with water until the wash water was neutral and dried over $MgSO_4$. The benzene and excess ethanedithiol were evaporated in vacuo, and the residue was fractionated in vacuo. The fraction boiling at 200-220°C (1 mm) was purified by chromatography on a plate (18 by 24 cm) with a loose layer of silica gel (40-100 μm) by passing a benzene–hexane system (4:5) twice.

B) A solution of 1.3 g (3.4 mmole) of indole Id and 1.3 g (5.5 mmole) of α-benzylphenylhydrazine hydrochloride in 55 ml of acetic acid and 0.7 ml of concentrated HCl was refluxed for 8 h in an inert atmosphere, after which it was cooled, and the acetic acid was evaporated in vacuo. Benzene and water (50 ml each) were added to the residue, the mixture was shaken. The organic layer was separated, washed successively with three 50-ml portions of hydrochloric acid (1:1) and water until the wash water was neutral, and dried over $MgSO_4$. The benzene was evaporated, and the residue was purified by chromatography with a column (43 by 2 cm) packed with silica gel (40-100 μm) by elution with a benzene–petroleum ether system (2:3). The constants and spectral data for Vd are presented in Table 1. Mass spectrum, m/z (%): 281 (M^+, 51), 221 (21), 220 (79), 194 (74), 192 (24), 131 (34), 111 (14), 109 (11), 105 (18), 103 (30), 102 (43), 101 (100), 100 (13), 99 (22), 97 (22), 95 (16), 92 (13), 91 (99), 87 (17), 85 (17), 83 (22), 81 (17), 73 (27).

2,4-Dinitrophenyl Thioether ($C_{24}H_{21}N_3O_4S$). This compound had mp 159°C (from acetone).

General Method for the Synthesis of Indolylpropanethiols (homothiotryptophols) Vb-d without Isolation of Indoles Ib-d. C) A 5 mmole sample of the phenylhydrazine hydrochloride was dissolved in 25 ml of dioxane (without peroxides) and 0.5 ml of water, 10 mmole of 3,4-dihydro-2H-thiopyran was added, and the mixture was refluxed for 4 h. It was then cooled, and the dioxane was evaporated in vacuo. The residue was dissolved in 60 ml of acetic acid, another 5 mmole of the phenylhydrazine hydrochloride and 0.7 ml of concentrated HCl were added, and the reaction mixture was refluxed for 11 h in an inert atmosphere. The mixture was then worked up as in method B. The constants and spectral data for the compounds obtained are presented in Table 1.

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