THIOCHROMENES AND HYDROTHIOCHROMENES (REVIEW)

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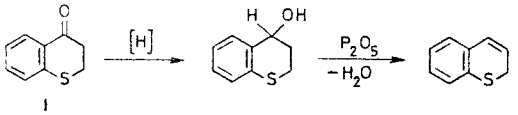
Methods for the synthesis of thiochromenes and hydrothiochromenes and their chemical properties and spectral characteristics are examined.

The chemistry of thiochromene has undergone intensive development in the last two decades, but there are no available reviews devoted to this topic. The thiochromenes and hydrothiochromenes examined in the present review are structurally related to the plant pigments flavonoids and anthocyanins, which are flavone and flavan derivatives. In many respects this explains the interest in their sulfur analogs. The search for antitumorigenic and antibacterial preparations among thiochromene derivatives has met with success [1-4]; in addition, thiochromene derivatives are accessible compounds for the synthesis of thiapyrylocyanines [5-11] and dyes for chemical fibers [7, 8]. Sulfides of the 1- and 2-thiadecalin series are used as standards in the identification of sulfur compounds present in petroleum oils.

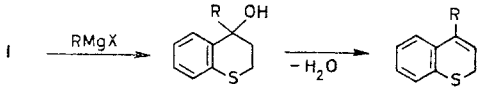
Synthesis of Thiochromenes and Hydrothiochromenes

Thiochromenes from Thiochromanones. The reduction of the carbonyl group in thio- (I) and isothiochromanones with sodium amalgam, lithium aluminum hydride, or sodium borohydride and subsequent dehydration lead to the formation of 2H-thiochromenes [5, 6, 12-18] or isothiochromenes [15, 19, 20].



I

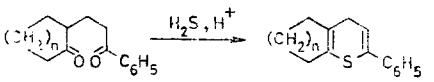
The reaction of the corresponding ketones with alkyl- and arylmagnesium halides can be used for the synthesis of 4-substituted 2H-thiochromenes [5-7, 21-24] or isothiochromenes [20]:



R = CH_3, C_2H_5, C_6H_5

Since thiochromanones are readily accessible from thiophenols, the methods presented above are valuable in a preparative respect and are suitable for the synthesis of both unsubstituted 2H-thiochromene and its homologs.

Hydrothiochromenes from 1,5-Diketones. The investigation of the reactions of "semicyclic" 1,5-diketones (II) with hydrogen sulfide and phosphorus pentasulfide has opened up the possibility of the one-step synthesis of hydrothiochromenes. Thus sulfides III with a 4H-thiopyran structure have been obtained in 48-92% yields from 1-phenyl-3-(2-oxocycloalkyl)propan-1-ones (II) (n = 1, 2) with H_2S and HCl (in ethanol at 15°C) [25].



II III

1-Methoxy-2-thiabicyclo[4.4.0]dec-3-enes are obtained from diketones when methanol is used as the solvent [26].

1,3-Diphenyl-3-(2-oxocyclohexyl)propan-1-one does not react with hydrogen sulfide under identical conditions but gives 1-methoxy-3,5-diphenyl-2-oxabicyclo[4.4.0]dec-3-ene. The five-membered analog of diketone II in methanol and in ethanol gives thiopyran III (n = 1) in high yield (85%) [26].

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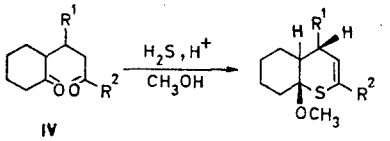
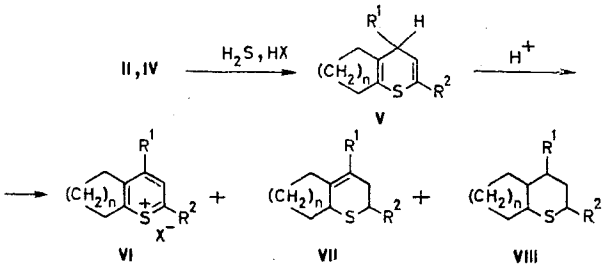


IV

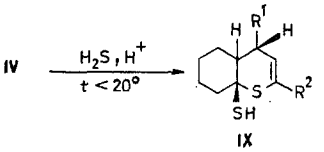
R^1 = H aryl ; R^2 = aryl

In acetic acid at temperatures above 20°C 5,6-polymethylenethiopyrans V [27], which are formed from 1,5-diketones II and IV, disproportionate to 5,6-polymethylenethiapyrylium salts VI and 1-thiabicycloalkenes VII or 1-thiabicycloalkanes VIII [28-31].

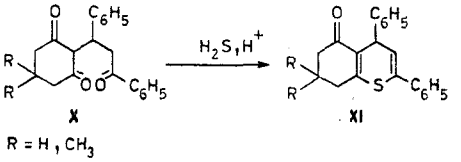


X = Cl, Br, ClO_4, BF_4

Diketones IV are converted to 1-mercapto-1,3-diaryl-2-thiabicyclo[4.4.0]dec-3-enes (IX) in acetic acid in the presence of $HClO_4$ at temperatures below 20°C or in trifluoroacetic acid with a large excess of hydrogen sulfide.



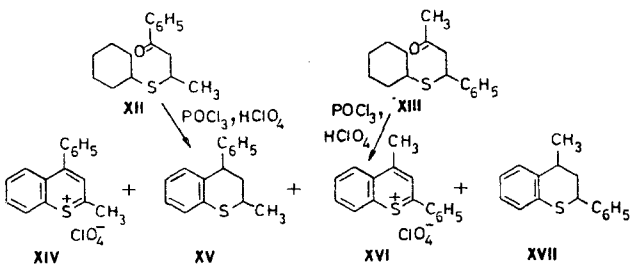
In contrast to the 1,5-diketones examined above, triketones X form 5-oxo-5,6,7,8-tetrahydro-4H-thiochromenes (XI) in 72-96% yields under the influence of hydrogen sulfide in the presence of HCl or $HClO_4$ in acetic acid, dioxane, benzene, methanol, or in trifluoroacetic acid [32].



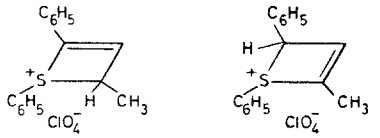
R = H, CH_3

The formation of sulfides XI is also observed when diketones X are heated with phosphorus pentasulfide in pyridine, during which the second oxo group of the alicycle does not undergo reaction with phosphorus pentasulfide [32]. When 5-oxo-2,4-diphenyl-5,6,7,8-tetrahydro-4H-chromene is refluxed with P_2S_5 in pyridine for a long time, only the oxygen atom of the heteroring undergoes exchange with sulfur to give a sulfide of the XI type [32].

Cyclization of 3-Oxoalkyl Aryl Sulfides. One might have expected the formation of 2H-thiochromenes in the cyclodehydration of 3-oxoalkyl aryl sulfides with polyphosphoric acid (PPA), $POCl_3$, or $HClO_4$; however, 2H-thiochromenes are only intermediates, since they readily undergo disproportionation to thiachromylium salts and thiochromans [5, 7, 21, 33]. The cyclodehydration of isomeric oxosulfides XII and XIII leads to mixtures of four substances (XIV-XVII) in both cases [34].



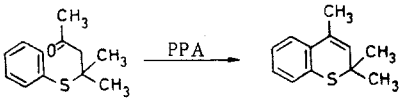
In other words, in the case of oxo sulfide XII, in addition to the usual disproportionation products (XIV and XV), one observes the formation of XVI and XVII. The rearrangement proceeds through thionium salts XVIII and XIX, which could be isolated and identified [34].



XVIII XIX

The corresponding thiochromenes were not isolated under the conditions of this reaction.

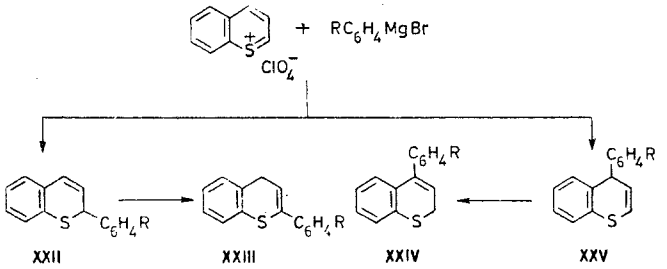
In the cyclodehydration of ketone XX with PPA the final reaction product is 2H-thiochromene XXI, which does not undergo disproportionation because of the absence of a labile hydrogen atom [5].



XX XXI

Thiochromenes and Hydrothiochromenes from Sulfonium Salts. Calculations of the electron densities in 1- or 2-thiachromylium cations make it possible to assume nucleophilic attack at $C_{(2)}$, $C_{(4)}$, or $C_{(1)}$; this is in agreement with the experimental data on the course of chemical reactions with nucleophiles (Grignard reagents, metal hydrides, and water) [35-37].

1-Thiachromylium perchlorate reacts with arylmagnesium halides to give a mixture consisting of primary products of addition to $C_{(2)}$ and $C_{(4)}$ (XXII and XXV), as well as two products of isomerization (XXIII and XXIV) of the latter [38].



XXII XXIII XXIV XXV

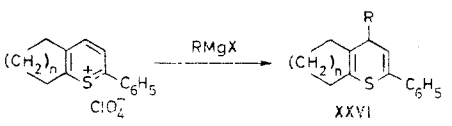
Sulfides XXII and XXV undergo isomerization spontaneously at room temperature, during which the double bond is shifted each time to a position in conjugation with the newly introduced aryl substituent.

The ratio between the 2- and 4-addition products depends on the character of the substituents in the aryl ring: 4-CH_3, 4-CH_3O, 4-CH_3S, and 3-CH_3O substituents favor the formation of products of addition to $C_{(2)}$, and 4-Br and 3-Br promote attack in the 4 position; finally, 3-CH_3S and H lead to an isomer ratio of 1:1 [38].

The direction of nucleophilic attack depends not only on the charge distribution in the cation but also on the degree of substitution of the cation, the character of the nucleophilic partner, the temperature, the absence of air oxygen, and other factors. Thus 2,4-diphenyl-1-thiachromylium perchlorate reacts with phenylmagnesium bromide to give exclusively 2,2,4-triphenyl-2H-thiochromene [39].

One's attention should be directed to the possibility of attack on the heteroatom in the 1-aryl-2-thiachromylium cation by Grignard reagents [41-43], which amended the prevailing (prior to 1974) ideas regarding the addition of Grignard reagents to 1-thiachromylium and 2-thiachromylium cations exclusively to the carbon atom [6, 38-40, 44]. Thus 1-aryl-2-thiachromylium perchlorates react with phenylmagnesium bromide in a nitrogen atmosphere to give S-aryl-thianaphthalene and S-aryl-2-thiachromenium salts [41-43].

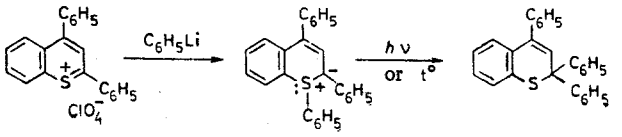
2-Phenyl-5,6-polymethylenethiapyrylium perchlorates react with Grignard reagents to give 4-substituted 2-phenyl-5,6-polymethylene-4H-thiopyrans (XXVI) (R = CH_3, C_2H_5, $CH_2C_6H_5$; n = 1, 2) in 80-90% yields [28, 45].



XXVI

The reactions with organomagnesium reagents thus give particularly good results when one of the positions (2 or 1) in the cation is occupied and attack is possible only in the free position, as in the case examined above.

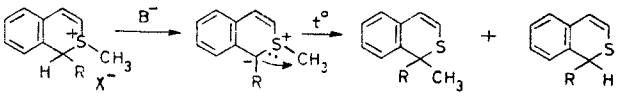
Phenyllithium attacks thiachromylium salts at the sulfur atom to give S-phenylthianaphthalenes, which undergo isomerization to the corresponding thiochromenes when they are heated or irradiated [39, 43, 46]. Thus 1-thianaphthalene XXVII is converted to 2H-thiochromene XXVIII in 83% yield when it is heated in ether solutions [39].



XXVII XXVIII

Since the stabilities of thianaphthalenes depend directly on the degree of substitution and the electronic structures of the substituents [39], products of complete destruction of the cyclic structure are sometimes formed along with oligomers; for example, 1-(p-tolyl)-2-thiochromene was isolated in only 5% yield [47]. Because of this, organolithium compounds are less frequently used for the preparation of thiochromenes.

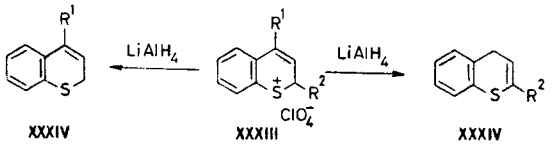
S-Methylsulfonium salts of the XXIX type are converted to 2-thiochromenes XXXI and XXXII (R = H, C_6H_5, C_6H_4Cl-4) through 2-thianaphthalenes XXX when they are deprotonated by strong bases [42, 44, 48, 49].



XXIX XXX XXXI XXXII

If R = aryl, one can isolate the corresponding 2-thianaphthalenes XXX, which undergo rearrangement to 2-thiochromenes when they are heated to 40°C [44, 48, 49]. When there is no substituent in the 1 position, the resulting thianaphthalene is converted to 2-thiochromene XXXI (R = H) even at −65°C. 1-Substituted 2-thiochromenes XXXII are the products of a side reaction [48, 49].

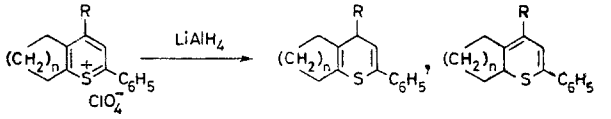
A convenient preparative method for the synthesis of 2H- and 4H-thiochromenes or hydrothiochromenes is the reduction of thiachromylium or hydrothiachromylium perchlorates with lithium aluminum hydride. 4-Aryl- and 2-aryl-1-thiachromylium perchlorates (XXXIII) react with $LiAlH_4$ in ether to give, respectively, 4-aryl-2H- (XXXIV) or 2-aryl-4H-thiochromenes (XXXV) in up to 90% yields; i.e., the hydride ion adds to the unsubstituted carbon atom [38].



XXXIV XXXIII XXXIV

XXXIII a R^1 = aryl ; R^2 = H ; b R^1 = H, R^2 = aryl

Lithium aluminum hydride reduces 4-unsubstituted 5,6-polymethylenethiapyrylium perchlorates (XXXVI) to the corresponding 4H-thiopyrans (XXXVII; R = H, n = 1, 2) in 80-90% yields [28].



XXXVI XXXVII XXXVIII

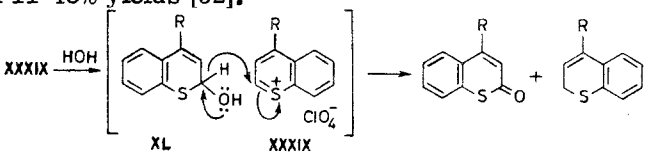
Under the same conditions 2,4-diphenyl-5,6-polymethylenethiapyrylium salts (XXXVI, n = 1, 2) form primarily 6H-thiopyrans XXXVIII in 60% yields [50]. Replacement of the 4-C_6H_5 group by a benzyl group leads to a decrease in the yield of 6H-thiopyran XXXVIII (R = $CH_2C_6H_5$, n = 1) to 25%, and the chief reaction product (44% yield) becomes 4H-thiopyran XXXVII (R = $CH_2C_6H_5$, n = 1) [50]. The introduction of a $C_6H_4OCH_3$-4 or $C_6H_3(OCH_3)_2$-3,4 group in the 4 position apparently increases the electron density on $C_{(4)}$ significantly as compared with $C_{(6)}$, as a result of which the hydride ion attacks $C_{(6)}$ to give exclusively 6H-thiopyrans XXXVIII [50].

Sodium borohydride can be successfully used in place of lithium aluminum hydride for the reduction of thiachromylium perchlorates [5, 51].

If one regards thiachromylium salts as the foundation for the synthesis of thiochromenes, one cannot fail to discuss some of the reactions with such nucleophiles as water, mercaptans, etc., although the preparative value of these reactions is limited.

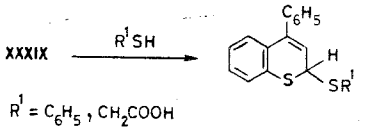
2H-Thiochromenes are formed along with thiocoumarins (in a ratio of 1 : 1) in the hydrolysis of 4-substituted thiachromylium perchlorates with a solution of sodium bicarbonate. The reaction proceeds through

the pseudobase and suggests hydride-ion transfer from the α-pseudobase XL to perchlorate XXXIX. The 2H-thiochromenes are obtained in 11-43% yields [52].



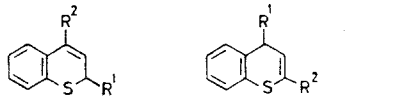
XL, XXXIX R = C_6H_5, $C_6H_4OCH_3$-4, 2-C_4H_3S

The reaction of perchlorate XXXIX (R = C_6H_5) with thiophenol or mercaptoacetic acid at room temperature gives sulfides of the 2H-thiochromene series in 83 and 39% yields, respectively [52].



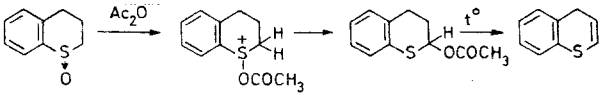
R^1 = C_6H_5, CH_2COOH

In addition, thiachromylium perchlorates are capable of adding acetylacetone [6] or dimethylaniline [6, 12] in alkaline media to give the corresponding substituted thiochromenes:



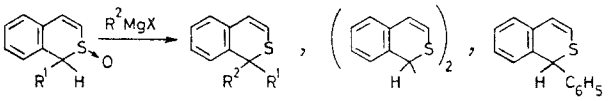
R^1 = $CH(COCH_3)_2$, $C_6H_4N(CH_3)_2$-4; R^2 = H, C_6H_5

Thiochromenes from Sulfoxides. Unsubstituted 4H-thiochromene was first obtained in 1961 from thiochroman 1-oxide under the conditions of the Pummerer reaction [13].



This reaction is apparently a general reaction for sulfoxides of thiochromans that have a hydrogen atom in the α position. Thus 2-methylthiochroman 1-oxide forms 2-methyl-4H-thiochromene when it is refluxed with acetic anhydride [53]. One should note the preparative value of the examined reaction for the preparation of 4H-thiochromenes, including unsubstituted 4H-thiochromene [13].

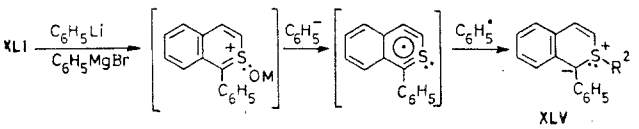
2-Thiochromene sulfoxide (XLI, R^1 = H) reacts with phenylmagnesium bromide to give 1-phenyl-2-thiochromene (XLII, R^1 = H, R^2 = C_6H_5) and dimer XLIII in 63 and 0.8% yields, respectively [43].



XLI R = H, C_6H_5

When R^1 = C_6H_5 in sulfoxide XLI, the yield of sulfide XLII (R^1 = C_6H_5, R^2 = CH_3) is reduced to 22%, and the formation of traces of sulfide XLIV (5.7%) are noted [43].

2-Thianaphthalenes XLV are formed in 34-57% yields in the reaction of sulfoxide XLI (R^1 = C_6H_5, $C_6H_4CH_3$-4) with excess organometallic reagents (phenyllithium, arylmagnesium bromides) [43]. The authors explain the formation of 2-thianaphthalenes XLV as being due to simultaneous ionic and radical reactions [43].

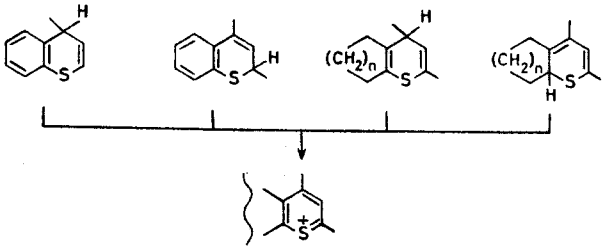


XLV

Pyrolysis of thiochroman at 500°C leads to the formation of thiochromene in small amounts (3.5%), in addition to indene (49%), benzothiophene (45%), and benzene derivatives (2.5%) [54].

Properties of Thiochromenes and Hydrothiochromenes

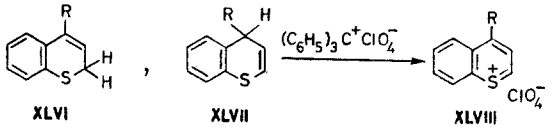
Salt Formation. As in the case of the simplest thiopyrans [55], splitting out of a hydride ion to give the corresponding cation is characteristic for condensed derivatives of thiopyrans.



However, as compared with thiopyrans, thiochromenes (benzothiopyrans) are characterized by lower lability of the hydride ion. Thus thiochromene in formed in 100% yield in the reaction of thiachromylium perchlorate with 4H-thiopyran, whereas in the reaction of dibenzothiapyrylium perchlorate with 2H-thiochromene the equilibrium is shifted to favor the thiachromylium perchlorate [17].

It has been established that in the series of benzo derivatives of pyrylium, thiapyrylium, and selenapyrylium ions the most stable ion is the thiachromylium ion, and thiochromene consequently splits out a hydride ion more readily than the corresponding O and Se derivatives [17].

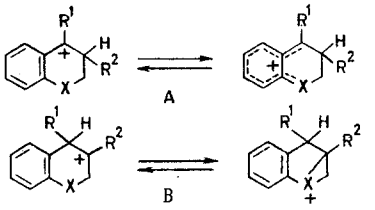
Triphenylmethyl perchlorate is often used as a hydride-ion acceptor in the preparation of 1-thiachromylium salts [7, 16, 17, 38, 56-58]. The reactions are usually accomplished in solvents such as acetonitrile, methylene chloride, or nitromethane, and the salts are obtained in 60-90% yields [7, 16, 17, 37, 57]. Mixtures of 2H and 4H isomers XLVI and XLVII give the same 4-arylthiachromylium perchlorate (XLVIII) [38].



XLVI XLVII XLVIII

Under the influence of protic acids, thiochromenes and hydrothiochromenes undergo disproportionation with intermolecular hydride-ion transfer [5, 7, 23, 25, 31, 50, 51, 58, 59]. The disproportionation of 2H-thiochromenes with PPA and perchloric acid to give thiochromenes and thiachromylium salts has been described [5, 7, 23, 51, 58]. The disproportionation is associated with hydride-ion transfer from $C_{(2)}$ of 2H-thiochromene to $C_{(4)}$ of the carbonium ion formed by protonation of the 2H-thiochromene [7].

When deuteropolyphosphoric acid was used, it was shown that protonation of the 2H-thiochromenes apparently takes place at the $C_{(3)}$ atom [7]. However, a study of the relative stabilities of $C_{(4)}$ and $C_{(3)}$ carbonium ions formed from carbinols of the thiochroman, 1,2,3,4-tetrahydroquinoline, and chroman series by electron impact showed that $C_{(4)}$ carbonium ions A are more stable by factors of two, eight, and 20, respectively, for the S, CH_3N, and O analogs owing to the delocalization of the charge in the aromatic system and on the heteroatom [50].



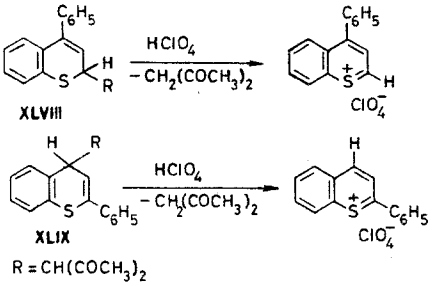
At the same time, $C_{(3)}$ carbonium ion B, which is formed from 2H-thiochromene (X = S), is stabilized by reaction through space with the d orbitals of the sulfur atom. This sort of stability is impossible for the CH_3N and O analogs. Participation of both carbonium ion A and ion B in disproportionation is conceivable, although $C_{(3)}$ carbonium ion B is less stable [50].

Hydride transfer during the disproportionation of 3,4-dimethyl-2H-thiochromene proceeds stereoselectively and leads primarily to cis-3,4-dimethylthiochroman (85% yield); the trans isomer (15%) is also present in the mixture [50]. Proceeding from the structures of carbonium ions A and B, Klimenko and co-workers [50] assumed that nonplanar ion B ensures stereospecific control in the hydride-transfer reaction. However, if one takes into account the lower relative stability (by a factor of two) of carbonium ion B as compared with ion A, it is difficult to explain the high yield (~35%) of cis-3,4-dimethylthiochromanone [51, 60].

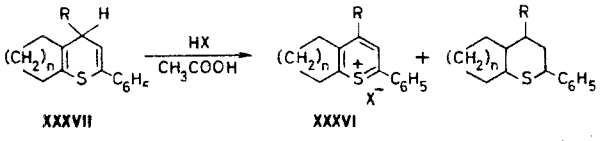
The degree of disproportionation of 4-substituted 2H-thiochromenes depends on the steric and electronic peculiarities of the substituent attached to $C_{(4)}$. Higher yields (42-43%) of thiachromylium perchlorates are noted if this substituent is phenyl or 2-thienyl. When alkyl groups (CH_3, iso-C_3H_7) are introduced in the 4 po-

sition, the yields of perchlorates decrease to 20-25%. The presence of a tert-butyl group attached to $C_{(4)}$ excludes the possibility of disproportionation, and the formation of a perchlorate is not observed. On the other hand, the presence of substituents (phenyl, 2-thienyl, or methyl) in the 2 position does not present any difficulties in the migration of a hydride ion from $C_{(2)}$ to the carbonium ion [58].

Thiochromenes XLVIII and XLIX do not undergo disproportionation, but under the influence of perchloric acid they split out acetylacetone and are converted to 4-phenyl- and 2-phenylthiachromylium perchlorates, respectively [6].

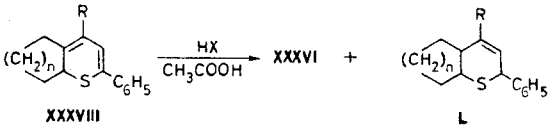


Complete or partial reduction of the double bonds of the heteroring is observed in the disproportionation of 5,6-polymethylenethiopyrans with protic acids, depending on the structure of the thiopyran, the degree of substitution, and the protonating strength of the acid [25, 31, 50, 59]. Thus 2-phenyl-4H-thiopyrans XXXVII react with 70% $HClO_4$ or hydrogen bromide in acetic acid to give perchlorates XXXVI and the corresponding thiabicycloalkanes [25, 31].



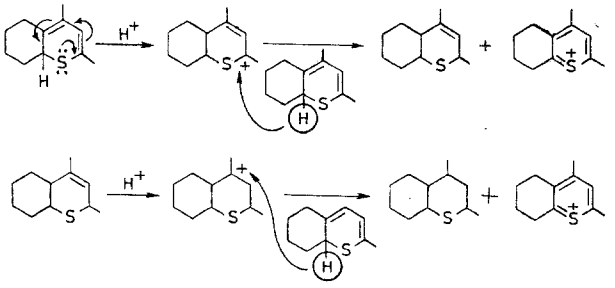
Although the reduction of the double bonds in 4H-thiopyrans XXXVII apparently proceeds in a stepwise manner, the corresponding dihydrothiopyrans cannot be isolated.

On the other hand, under similar conditions 2-phenyl-6H-thiopyrans XXXVIII give 2-thiabicycloalkenes L in addition to the corresponding salts XXXVI [R = C_6H_5, $C_6H_4OCH_3$-4, and $C_6H_3(OCH_3)_2$]; the 2-thiabicycloalkanes are detected only by chromatography in this case [25, 50].



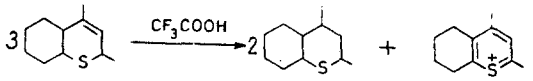
From the structure of the resulting 2-thiabicycloalkenes (L) it can be assumed [25, 50] that reduction of the diene system of double bonds of the heteroring takes place in the 1,4 position.

6H-Thiopyrans XXXVIII undergo complete disproportionation with trifluoroacetic acid, which has high solvating and ionizing properties [59]; i.e., both double bonds of the heteroring are reduced to give 2-thiabicycloalkanes and 5,6-polymethylenethiapyrylium trifluoroacetates XXXVI (X = CF_3COO) in a ratio of 1:2.

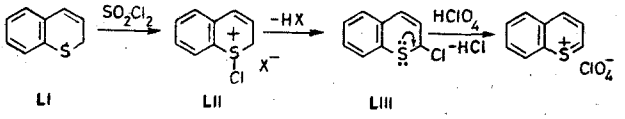


It is apparent from the scheme in [50, 59] that 2-thiabicycloalkenes are intermediates in the reaction. It has been shown that owing to the high hydride lability of the α-hydrogen atoms in the dihydrothiopyran ring, 2-thiabicycloalkenes undergo disproportionation with trifluoroacetic acid to give 5,6-polymethylenethiapyrylium trifluoroacetates and 2-thiabicycloalkanes [59]; one molecule of the salt and two molecules of the thiacyclo-

hexane are formed from three molecules of the dihydrothiopyran [59], i.e., the ratio of the yields is the reciprocal of the ratio observed in the disproportionation of 5,6-polymethylenethiopyrans [50].

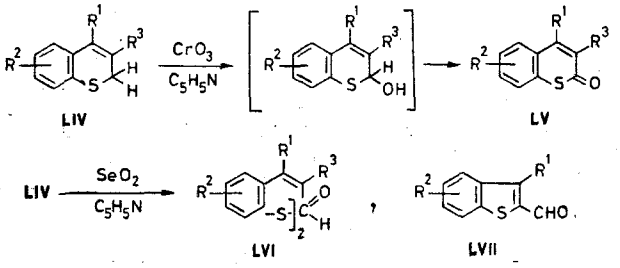


2-Substituted and 2,4-disubstituted 2H(4H)-thiochromenes are also converted to the corresponding thiachromylium perchlorates when they are treated successively with sulfuryl chloride plus o-chloranil and 70% perchloric acid [6, 14]. In this case 2H-thiochromene LI reacts with sulfuryl chloride to give S-chlorosulfonium salt LII, which is subsequently stabilized to α-chloro thioether LIII as a result of S→C transhalogenation and elimination of acid; LIII is converted to thiachromylium perchlorate when it is treated with $HClO_4$ [14].



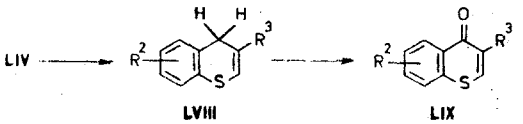
LI LII LIII

Sulfones and Sulfoxides. It is not possible to convert unsubstituted 2H- and 4H-thiochromenes [12, 13] to sulfones by direct oxidation with, for example, hydrogen peroxide [12, 13]. The use of chromic anhydride in pyridine as an agent for the oxidation of 2H-thiochromenes leads to thiocoumarins LV; i.e., the α-methylene group of the heteroring undergoes oxidation [61, 62].



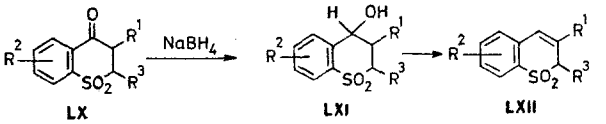
LIV LV LVI LVII

The formation of dialdehyde LVI and an aldehyde (LVII) of the benzothiophene series is noted in the oxidation of 2H-thiochromenes LIV with selenium dioxide in pyridine at 50°C [61, 62]. In addition, if R^1=H, isomerization of 2H-thiochromene LIV to 4H-thiochromene LVIII and oxidation of the latter to thiochromone LIX are possible in the case of oxidation with selenium dioxide [61].



LIV LVIII LIX

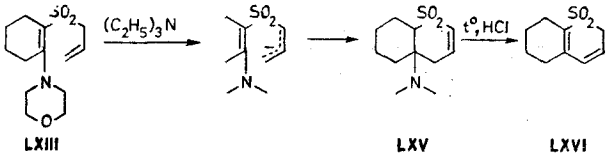
A convenient preparative method for the synthesis of sulfones of the 2H-thiochromene series is an indirect method based on the use of thiochromanone dioxides LX as the starting widely accessible sulfones. Sulfones LXII were obtained by reduction of 4-oxothiochroman 1,1-dioxides LX [62-64] with sodium borohydride and subsequent dehydration of 4-hydroxythiochroman 1,1-dioxides LXI in the presence of hot 85% phosphoric acid [65-67].



LX LXI LXII

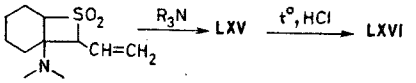
Isothiochromene 2,2-dioxide and its derivatives were similarly obtained [67, 68]. Oxidation of thiochromenes with m-chloroperbenzoic acid gives sulfoxides in up to 85% yields [43].

The simplest 5,6,7,8-tetrahydrothiochromenes are unknown, but their sulfones can be synthesized from 1-morpholino-2-allylsulfonylcyclohexene (LXIII) or 2-vinylthietane 1,1-dioxide LXIV. Thus when sulfone LXIII is heated in anhydrous dioxane with an equimolar amount of triethylamine, it is converted to 2,3-tetramethylene-3-morpholino-4H-thiopyran 1,1-dioxide (LXV), after which treatment with hydrogen chloride and heating of



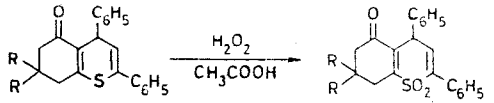
LXIII LXV LXVI

the mixture give 2,3-tetramethylene-2H-thiopyran 1,1-dioxide (LXVI) [69], which was previously [70] described as the 4H isomer. Sulfone LXVI can also be obtained by isomerization of 2-vinylthietane 1,1-dioxide LXIV [69].



LXIV

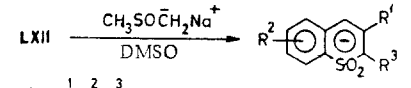
2-Phenyl-5,6-polymethylene-4H-thiopyrans (XXVI) undergo resinification during attempts to oxidize them with hydrogen peroxide. The resistance of thiopyrans to oxidation increases as the degree of substitution of the thiopyran ring increases and substituents are introduced in the alicycle, and the preparation of sulfones from them becomes possible. Thus 5-oxo-5,6,7,8-tetrahydrothiochromenes (VI, R = H, CH_3) are oxidized smoothly with hydrogen peroxide in acetic acid to dioxides LXVII [32].



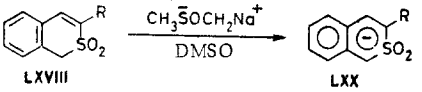
VI LXVII

The properties of 2H-thiochromene 1,1-dioxides (LXII) and 2-thiochromene 2,2-dioxides (LXVIII) have been most fully studied [66, 67, 70]. The α-methylene protons of these sulfones undergo deuterium exchange at room temperature in a mixture of d_5-pyridine and D_2O. According to PMR spectroscopic data, 2- and 3-CH_3 groups reduce the rate of exchange in the methylene group of the heteroring by one order of magnitude [67]. Lower acidities of the methyl-substituted derivatives as compared with the related compounds were also noted during an investigation of the PMR spectra of methanol solutions of the sulfones in the presence of sodium methoxide [66].

The reaction of sulfones LXII and LXVIII with methylsulfinylsodium in dimethyl sulfoxide (DMSO) in a nitrogen atmosphere at −50°C leads to the formation of the corresponding S,S-dioxide anions LXIX and LXX [67].



LXIX $R^1, R^2, R^3 = H, CH_3$ LXIX

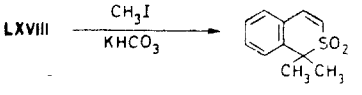


LXVIII LXX

LXVIII, LXX R = H, CH_3

The increased stability of the above anions as compared with anions with an open chain − $R^1\bar{C}HSO_2R^2$ (R^1 = H, C_2H_5, $C_6H_5CH=CH$; $R^2 = C_6H_5$, CH_3, and $C_6H_5CH_2$) − is explained by delocalization of the negative charge in both the heterocyclic and benzene rings; this is confirmed by the kinetics of deuterium exchange [67] and by a study of their PMR spectra [66].

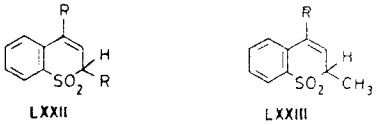
Owing to their acid properties, 1-thiochromene and 2-thiochromene S,S-dioxides undergo nucleophilic substitution reactions under conditions of medium basicity; for example, 1,1-dimethyl-2-thiochromene 2,2-dioxide (LXXI) is formed from sulfone LXVIII (R = H) on reaction with methyl iodide in acetone in the presence of potassium bicarbonate [70]:



LXXI

Sulfones LXII undergo simultaneous alkylation at $C_{(2)}$ and $C_{(4)}$ [70].

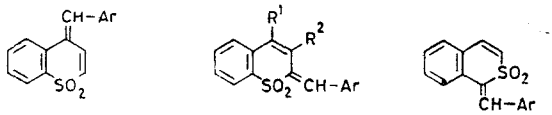
Products LXXII and LXXIII, which display strongly acidic character, were similarly obtained by reaction with 2,4-dinitrochlorobenzene [70].



LXXII LXXIII

LXXII, LXXIII $R = C_6H_4(NO_2)_2$ - 2,4

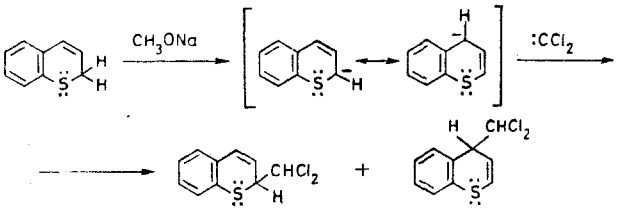
1-Thiochromene and 2-thiochromene S,S-dioxides undergo condensation with aromatic aldehydes in acetic acid in the presence of sodium acetate to give the corresponding arylidene derivatives (LXXIV-LXXVI) [70].



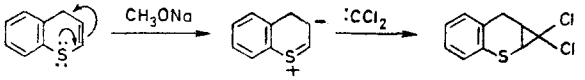
LXXIV LXXV LXXVI

Thus 1-thiochromene and 2-thiochromene S,S-dioxides behave like CH acids. The nucleophilic behavior of 1-thiochromene and 2-thiochromene S,S-dioxide anions is similar to the behavior of indenyl and fluorenyl anions [70].

Reactions of Dichlorocarbene with 2H- and 4H-Thiochromenes. 2H-Thiochromene reacts with dichlorocarbene in petroleum ether at 0-25°C to give a mixture of 2-dichloromethyl-2H-thiochromene and 2-dichloromethyl-4H-thiochromene (in a ratio of 2.4:1) [13]. In addition to these products, a diadduct, the structure of which was not established, was detected. The ratio of products of addition to $C_{(2)}$ and $C_{(4)}$ is 1:1 when the reaction is carried out in a polar solvent (dimethoxyethane).



In contrast to 2H-thiochromene, the 4H isomer reacts with dichlorocarbene to give a single adduct with a 1,1-dichlorocyclopropane structure [13].

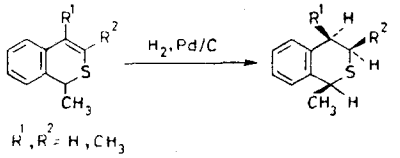


The difference in the behavior of the 2H and 4H isomers of thiochromene is explained by the fact that in the latter the 3p electrons of the sulfur atom interact with the π bond, activating it and promoting the addition of dichlorocarbene [13]. The stability of the dichlorocyclopropane derivative, which undergoes decomposition only at 210°C in quinoline with hydrogen sulfide evolution and the production of 2-chloronaphthalene, has been noted [13].

In contrast to unsubstituted 2H-thiochromene, 4-methoxy-2-methyl-2H-thiochromene gives an adduct with dichlorocarbene [71]; the reason for this is apparently polarization of the double bond due to p, π conjugation of the free electron pairs of the oxygen atom of the CH_3O group and the π bond of the heteroring.

Reduction of Thiochromenes and Hydrothiochromenes. The catalytic reduction of thiochromenes [5, 7, 23, 51], 2-thiochromenes [20], and 5,6-polymethylenethiopyrans [52, 72] is of great interest. In the case of thiochromenes [5, 7, 23, 51] and isothiochromenes [20] one double bond of the heteroring undergoes hydrogenation on Pd/C or platinum dioxide, and the corresponding 1- and 2-thiochromans are formed.

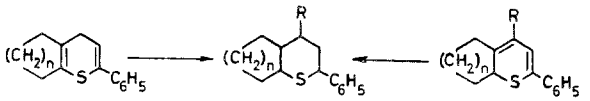
The reduction of 3,4-dimethyl-2H-thiochromene on Pd/C in ethyl acetate at 30°C proceeds stereoselectively to give the cis isomer in ~85% yield [51]. Hydrogenation of 1,3- or 1,4-dimethyl-2-thiochromenes on palladium (at 80°C and 40 atm) leads exclusively to cis-1,3- or 1,4-dimethylisothiochromenes [20].



$R^1, R^2 = H, CH_3$

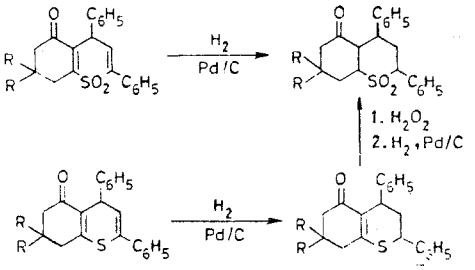
2-Thiabicycloalkanes are formed in the hydrogenation of 2-aryl- and 2,4-diaryl-5,6-polymethylene-4H(6H)-thiopyrans on 10% Pd/C at 100°C and an initial hydrogen pressure of 50 atm; i.e., both double bonds of the heteroring undergo reduction [52, 72]. The stereochemistry of the hydrogenation products has not been studied.

The double bonds of the heterorings in the sulfones undergo hydrogenation under identical conditions. Thus 2H-thiochromene 1,1-dioxide can be reduced to thiochroman 1,1-dioxide on Pd/C in methanol [64].

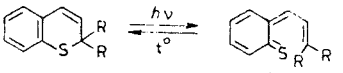


R = H, C_6H_5, $C_6H_5CH_2$, $C_6H_4OCH_3$-4, $C_6H_3(OCH_3)_2$-3,4; n = 1,2

The catalytic reduction of 5-oxo-5,6,7,8-tetrahydro-4H-thiochromene 1,1-dioxides takes place with retention of the carbonyl group, whereas the catalytic reduction of the sulfides proceeds with retention of the angular double bond in conjugation with the carbonyl group [73].



Photochromism of 2H-Thiochromenes. Like chromenes [75], selenochromenes [76], dihydroquinolines [77], and dihydronaphthalenes [78, 79], 2H-thiochromenes undergo valence isomerization when they are irradiated [74].



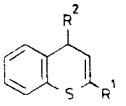
R = C_6H_5, H

Open form A can be observed spectrophotometrically at low temperatures, and it was noted that the acyclic product of the photochemical reaction has a deeper color [74].

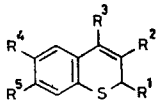
The electronic structures and spectral characteristics of the valence isomers of 2H-thiochromenes have been calculated by means of self-consistent field (SCF) MO LCAO methods within π-electron [Pariser–Parr–Pople (PPP)] and all-valence [complete neglect of differential overlap (CNDO)] approximations [80]. It was shown that in the case of $S_0 \rightarrow S_1$ excitation in open form A the sulfur atoms participate actively in conjugation; this also determines the bathochromic shift of the long-wave maximum as compared with the O and N analogs [80].

Spectral Characteristics. A large number of studies have been devoted to the UV and PMR spectra of 2H-thiochromenes [5, 13, 16, 18, 24, 38, 48, 52]. Less study has been devoted to the UV and PMR spectra of 4H-thiochromenes [13, 38], and no systematic spectral studies of them have been made. The PMR spectra of 5,6-polymethylene-4H(6H)-thiopyrans have been studied [74, 75]. Uncoordinated data on the IR spectra of thiochromenes [13, 52], and 5,6-polymethylenethiopyrans [25-31, 50] are also available in the literature.

TABLE 1. Spectral Characteristics of 4H-Thiochromenes



R^1	R^2	λ_{max}, nm (log ε) (in ethanol)	δ, ppm (in CCl_4) 2-H	3-H	4-H	Citation
H	H	224 (3,82), 236 (3,72), 242 (3,72), 274 (3,62)	6,30	5,89	3,24	13
C_6H_5	H	239 (4,21), 252 (4,15), 280 (3,65)	—	6,15	3,34	38
$C_6H_4OCH_3$-4	H	260 (4,34), 283 (3,90)	—	6,07	3,45	38
$C_6H_4OCH_3$-3	H	242 (4,16), 282 (3,76)	—	6,17	3,44	38
$C_6H_4SCH_3$-4	H	276 (4,39), 300 (4,09)	—	6,13	3,44	38
$C_6H_4SCH_3$-3	H	235 (4,37), 253 (4,35), 289 (3,68)	—	5,92	3,19	38
C_6H_4Br-4	H	254 (4,34), 285 (3,72)	—	6,15	3,47	38
C_6H_4Br-3	H	240 (4,21), 252 (4,19), 288 (4,54)	—	6,08	3,35	38
$C_6H_4CH_3$-4	H	245 (4,26), 280 (3,75)	—	6,11	3,44	38
H	C_6H_5	224 (4,17), 240 (3,86), 280 (3,67)	6,20	5,85	4,42	38
H	$C_6H_4SCH_3$-4	262 (4,28), 290 (3,79)	6,32	5,91	4,47	38
H	C_6H_4Br-4	230 (4,34), 277 (3,76)	6,38	5,94	4,54	38

TABLE 2. Spectral Characteristics of 2H-Thiochromenes 

R¹	R²	R³	R⁴	R⁵	λ_{max}, nm (log ε) (in ethanol)	δ, ppm (in CCl_4)			Citation
						2-H	3-H	4-H	
H	H	H	H	H	243 (4,29), 277 (3,35), 327 (3,00)	3,35	5,82	6,36	5,13
CH_3	H	H	H	H	242 (4,35), 280 sh (3,35), 324 (3,13)	—	—	—	5
H	CH_3	H	H	H	246 (4,06), 283 sh (3,76), 320 (3,14)	3,20	—	6,18	5,48
H	H	CH_3	H	H	244 (4,33), 272 sh (3,78), 323 (3,12)	3,64	6,11	—	5,83
CH_3	H	CH_3	H	H	244 (4,29), 275 sh (3,70), 322 (3,05)	4,04	6,19	—	5,83
C_6H_5	H	H	H	H	248 (4,38), 280 sh (3,49), 332 (3,23)	4,77	5,82	6,50	38
H	C_6H_5	H	H	H	—	3,65	—	6,7	48
$C_6H_4OCH_3$-4	H	H	H	H	244 (4,43), 280 sh (3,75), 330 (3,22)	4,79	5,87	6,54	38
$C_6H_4OCH_3$-3	H	H	H	H	248 (4,37), 280 (3,73), 327 (3,27)	4,79	5,85	6,53	38
$C_6H_4SCH_3$-4	H	H	H	H	249 (4,41), 260 sh (4,34), 322 (3,42)	4,77	5,88	6,58	38
C_6H_4Br-3	H	H	H	H	249 (4,41), 285 (3,57), 325 (3,40)	4,73	5,73	6,58	38
$C_6H_4CH_3$-4	H	H	H	H	248 (4,28), 280 (3,57), 330 (3,09)	4,73	5,80	6,43	38
H	H	C_6H_5	H	H	236 (3,40), 282 (3,49), 325 (3,70)	3,32	5,93	—	38,52
H	H	2-Thienyl	H	H	235 (3,86), 260 (3,80), 300 (4,10), 340 (3,40)	3,35	6,20	—	52
H	H	$C_6H_4OCH_3$-4	H	H	244 (4,43), 286 sh (3,67), 320 (3,30)	3,34	5,91	—	38,52
H	H	$C_6H_4OCH_3$-3	H	H	240 (4,33), 280 sh (3,80), 327 (3,22)	3,38	6,00	—	38
H	H	$C_6H_4SCH_3$-4	H	H	248 (4,35), 268 (4,30), 295 (3,85), 327 (3,30)	3,34	5,95	—	38
H	H	$C_6H_4SCH_3$-3	H	H	234 (4,43), 248 (4,40), 286 (3,55), 320 (3,25)	3,24	5,78	—	38
H	H	C_6H_4Br-4	H	H	240 (4,44), 253 (4,34), 287 (3,44), 329 (3,09)	3,35	5,96	—	38
H	H	C_6H_4Br-3	H	H	235 (4,36), 248 (4,30), 282 (3,53), 327 (3,24)	3,23	5,98	—	38
H	H	$C_6H_4CH_3$-4	H	H	241 (4,38), 286 (3,51), 324 (3,25)	3,34	5,93	—	38
H	C_6H_5	$C_6H_4OCH_3$-4	H		248 (3,95), 317 (4,36)	—	—	—	24
H	C_6H_5	C_6H_5	H	CH_3O	249 (4,27), 274 (4,30), 323 (3,40)	—	—	—	24
H	C_6H_5	H	Cl	H	—	3,67	—	6,58	18
H	H	H	CH_3	H	246 (4,35), 276 (3,38), 296 (3,19), 334 (3,14)	3,35	5,83	6,36	16
H	H	H	CH_3O	H	243 (4,25), 276 (3,50), 292 (3,23), 345 (3,14)	3,34	5,88		16
H	H	H	CH_3S	H	248 (4,34), 284 (3,73), 305 (3,47), 344 (3,07)	3,35	5,83	6,33	16
H	H	H	Cl	H	247 (4,41), 282 (3,44), 298 (3,28), 338 (3,15)	3,40	5,92	6,40	16
H	H	H	Br	H	248 (4,39), 280 (3,50), 298 (3,33), 336 (3,08)	3,35	5,83	6,31	16
H	H	H	H	CH_3	248 (4,42), 290 (3,36), 300 (3,27), 328 (3,15)	3,35	5,74	6,34	16
H	H	H	H	CH_3O	251 (4,35), 301 (3,51), 317 (3,75)	3,33	5,64	6,55	16
H	H	H	H	CH_3S	254 (4,13), 274 (4,26), 307 (3,77), 330 (3,51)	3,35	5,75	6,42	16
H	H	H	H	Cl	250 (4,44), 293 (3,38), 301 (3,28), 332 (3,19)	3,35	5,17	6,32	16
H	H	H	H	Br	250 (4,45), 293 (3,43), 302 (3,35), 332 (3,24)	3,33	5,78	6,30	16

Since the unambiguous assignment of the absorption bands in the near-UV regions of the spectra to the corresponding electron transitions is difficult for thiochromenes and 5,6-polymethylenethiopyrans, we will restrict ourselves to an examination of the electronic spectra for purposes of identification of these structures.

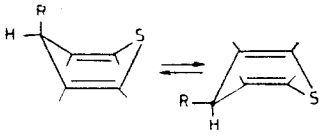
The data presented in Tables 1 and 2 illustrate the possibility of the application of the electronic spectra for the identification of 4H- and 2H-thiochromenes. The presence of a conjugated double bond in the heteroring in 2H-thiochromenes leads to a 50 nm (average value) bathochromic shift of the long-wave absorption band; this is characteristic for all of the described 2H-thiochromenes [5, 16, 38, 52]. The bathochromic shift of the long-wave band is even greater for 2,4-diaryl-5,6-polymethylene-6H-thiopyrans (λ_{max} 252-258, 353-360 nm) [50].

A comparison of the chemical shifts of the heteroring protons for the isomeric 4H- and 2H-thiochromenes (Tables 1 and 2) shows that the signals of the 2-H protons of the 2H-thiopyran system [13, 16, 18, 38, 48, 52, 81-83] are observed at weaker field than the signals of the 4-H protons of the 4H-thiopyran system [13, 38, 81, 82].

The PMR spectra of 4-substituted 2-phenyl-5,6-polymethylene-4H- and -6H-thiopyrans were examined in [81, 82].

The signals of the 6-H protons of 4-substituted 2-phenyl-5,6-polymethylene-6H-thiopyrans are observed at 3.95-4.05 ppm [81].

In conclusion, let us say a few words regarding the stereochemical peculiarities of some condensed 4H-thiopyran derivatives. The PMR spectra of 2-phenyl-5,6-polymethylene-4H-thiopyrans have been studied, and it has been shown that the differences in the 3-H and 4-H spin–spin coupling constants in different solvents (CCl_4, C_6H_6, and deuteroacetone) are associated with inversion of the heteroring [82].



The $J_{3,4}$ values and, consequently, the conformational lability of the heteroring change in different ways when a substituent is introduced in the 4 position of five-membered and six-membered analogs. The fraction of the conformer with an axial substituent is 49% for 2-phenyl-4-benzyl-5,6-trimethylene-4H-thiopyran in carbon tetrachloride solution at room temperature and increases to 80% for its six-membered analog. The introduction of a carbonyl group in the 5 position of the alicycle increases the conformational rigidity of the thiopyran fragment, and the fraction of the conformer with an axial substituent reaches 98% for 5-oxo-2,4-diphenyl-5,6,7,8-tetrahydrothiochromene [82]. The mole fraction of the conformer with an axial substituent increases, as a rule, on passing to polar solvents.

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ALKYLATION OF ANIONOID INTERMEDIATES IN THE REACTION OF BENZOFURAN WITH LITHIUM IN HEXAMETAPOL

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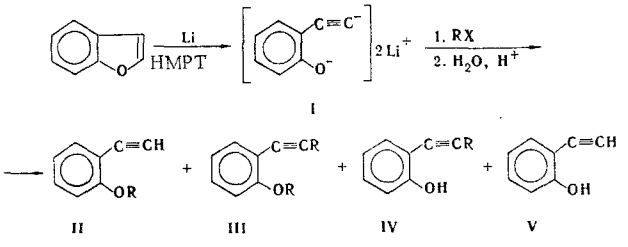
UDC 547.728.1:542.953

It is shown that the principal pathway in the reaction of benzofuran with a solution of lithium in hexametapol is opening of the furan ring of benzofuran to give a dilithium derivative. Mono- and dialkylation products are formed when the reaction mixture is treated with alkylating agents. It was established by the use of alkylating agents with different degrees of hardness that the oxygen atom is a softer polarizable center than the sp-hybridized carbanion center.

The reaction of benzofuran with a solution of sodium in liquid ammonia leads to hydrogenolysis of the furan ring of benzofuran to give o-ethylphenol [1].

We have investigated the reaction of benzofuran with a solution of lithium in hexametapol [hexamethylphosphoric triamide (HMPT)]. It is known that aryl alkyl ethers undergo cleavage in an alkali metal–hexametapol medium [2]. An investigation of the products of alkylation of the anionoid intermediates formed in the reaction of benzofuran with a solution of lithium in hexametapol shows that in our case the principal pathway is opening of the furan ring to give a dianion (I) or its dilithium derivative. Anion I is evidently formed as a result of the addition of two electrons to the benzofuran molecule, since only 50% of the benzofuran undergoes reaction with one equivalent of lithium.



Mono- and dialkylation products are formed in the case of alkylation with alkylating agents with different degrees of hardness and subsequent treatment of the reaction mixture with water (Table 1).

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