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Thioalkylation Reactions

V.I.Dronov and Yu.E.Nikitin

A systematic account is given of data on thioalkylation reactions—reactions involving the substitution of mobile hydrogen atoms by an alkylthiomethyl (or another alkylthioalkyl) group on treatment with formaldehyde (or other aldehydes) and a thiol.
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I. INTRODUCTION

The aminomethylation reaction (the Mannich reaction) is widely known and has been described in detail in reviews and monographs.[1-6] It consists of the treatment of certain compounds containing mobile protons (ketones, phenols, various heterocycles, etc.) with formaldehyde and primary or secondary amines (or ammonia) whereby it is possible to introduce the alkylaminomethyl group into such compounds:

$$RH + CH_2O + HN\!\!\left\langle \right. \rightarrow RCH_2N\!\!\left\langle \right. + H_2O .$$

In the course of the investigation of the condensation of ketones with formaldehyde and thiols, we introduced the term "thioalkylation" for this reaction by analogy with the Mannich reaction.[7] We include among thioalkylation reactions all those in which treatment of compounds having mobile protons with formaldehyde (or other aldehydes) and a thiol results in the substitution of these protons by an alkylthiomethyl (or another alkylthioalkyl) group:

$$RH + CH_2O + R'SH \rightarrow RCH_2SR' + H_2O .$$

These reactions are analogues of the Mannich reaction and constitute a special case of the more general thiomethylation reaction [sic (Ed.of Translation)].[8]

A series of such reactions have been described in the literature long before we investigated the thioalkylation of ketones. In this communication we give a systematic account of such reactions and have combined them under a common name (such combination without taking into account the reaction mechanism is to some extent rather formal).

II. THIOALKYLATION REACTIONS

1. Thioalkylation of ammonia and amines

The familiar reaction involving the aminomethylation of thiols can be formally regarded as thioalkylation in which amines or ammonia function as compounds with mobile protons:

$$R_2NH + CH_2O + R'SH \rightarrow R_2NCH_2SR' + H_2O .$$

Since this reaction has been described in the literature only very briefly,[6] we decided to carry out a more detailed survey.

Tris(arylthiomethyl)amines were obtained for the first time[9] by refluxing arenethiols and hexamethylenetetramine in anhydrous dioxan in a nitrogen atmosphere (toluene-α-thiol reacts analogously):

$$(CH_2)_6N_4 + 6RSH \rightarrow 2N(CH_2SR)_3 + 2NH_3 ;$$
R=C_6H_5, p-BrC_6H_4, p-$O_2NC_6H_4$, p-$CH_3C_6H_4$, $C_6H_5CH_2$.

The attempt to obtain tris(pentylthiomethyl)amines by this procedure was unsuccessful.

Analogous results have been obtained[10] on refluxing (for 15–30 min) arenethiol (or toluene-α-thiol), a 37% solution of formaldehyde, and aqueous ammonia (in molar proportions of 3 : 3 : 1) in alcohols. The reaction with benzenethiol was carried out for 2 h without heating:

$$NH_3 + 3CH_2O + 3RSH \rightarrow N(CH_2SR)_3 + 3H_2O ;$$
R=C_6H_5; p-t-$C_4H_9C_6H_4$; p-ClC_6H_4; m-$CH_3C_6H_4$; p-$O_2NC_6H_4$; 2, 4, 6-$(CH_3)_3C_6H_2$; 2-$C_{10}H_7$; $C_6H_5CH_2$.

The yields of tris(arylthiomethyl)amines were 21.5–80.5%.

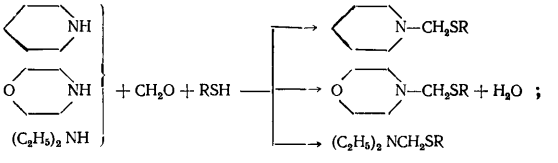
Bis(ethylthiomethyl)amine was synthesised by the reaction of ammonium chloride, a 37% aqueous solution of formaldehyde, and ethanethiol in molar proportions of 3.96 : 9.87 : 6.46 at pH < 6 and subsequent treatment of the reaction mixture with an excess of a dilute solution of sodium hydroxide.[11]

The thioalkylation of amines was first described by McLeod and Robinson.[12] The reaction of diethylamine with 35% aqueous formaldehyde solution and ethanethiol afforded diethyl(ethylthiomethyl)amine in 53% yield:

$$(C_2H_5)_2NH + CH_2O + C_2H_5SH \rightarrow (C_2H_5)_2NCH_2SC_2H_5 + H_2O .$$

Diethyl(isopropylthiomethyl)amine was obtained analogously.

A more detailed study of the thioalkylation of secondary aliphatic amines showed[13] that, in contrast to phenols, the reaction of arenethiols with formaldehyde and secondary aliphatic amines results in the formation of aryl dialkylaminomethyl sulphides and not Mannich bases. Thus a series of aryl piperidinomethyl, aryl morpholinomethyl, or aryl diethylaminomethyl sulphides have been obtained from the corresponding amines, aqueous formaldehyde, and various arenethiols:



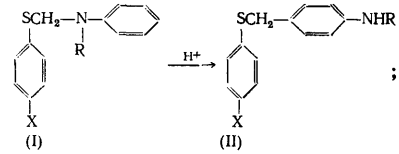
R=C_6H_5; o-$CH_3C_6H_4$; m-$CH_3C_6H_4$; 2-$C_{10}H_7$; 1-$C_{10}H_7$; p-$O_2NC_6H_4$; p-ClC_6H_4; p-BrC_6H_4; 2, 5-$Br_2C_6H_3$; p-$CH_3OC_6H_4$; 2, 4, 6-$(CH_3)_3C_6H_2$.

The secondary amine was added to an equimolar amount of the arenethiol at a temperature not exceeding 20 °C and the mixture was then treated with an equimolar amount of aqueous formaldehyde (37%), the mixture was heated to 80 °C, and was maintained at this temperature for 2 h. The yields were 22–89% of aryl piperidinomethyl sulphides, 33–96% of aryl morpholinomethyl sulphides, and 31–71% of aryl diethylaminomethyl sulphides.

The thioalkylation of secondary aliphatic amines has been investigated[14] and it has been established that, when a solution of 0.1 mole of an arenethiol, 0.1 mole of aryl methylamine, and 0.10–0.17 mole of a 35–40% aqueous solution of formaldehyde are heated in 20 ml of alcohol at 80 °C for 2 h, *N*-aryl-*N*-methylaminomethyl sulphides are obtained in 66–93% yield:

$$R'NHCH_3 + CH_2O + R^2SH \rightarrow R'(CH_3)NCH_2SR^2 + H_2O;$$
$$R' = C_6H_5;\ R^2 = C_6H_5,\ p\text{-}ClC_6H_4;\ 2,4,6\text{-}(CH_3)_3C_6H_2;\ C_6Cl_5;$$
$$R' = p\text{-}O_2NC_6H_4;\ R^2 = p\text{-}ClC_6H_4;\ R' = p\text{-}CH_3OC_6H_4;\ R^2 = p\text{-}ClC_6H_4.$$

The aryl *N*-arylthiomethyl sulphides (I), obtained by the thioalkylation of aromatic amines in the presence of strong acids, readily rearrange in high yields into the isomeric aryl *p*-aminobenzylsulphides (II):[14]

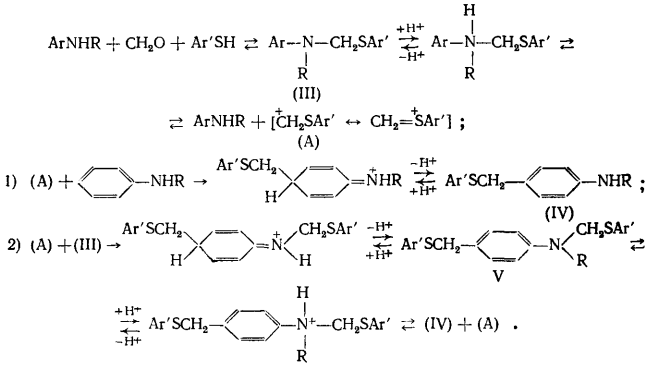


(I) (II)

X=H, Cl; R=H, CH_3.

In order to obtain compound (II), the sulphide (I) is refluxed with an equimolar amount of concentrated hydrochloric acid in 95% alcohol. Under analogous conditions, the sulphides (II) can be obtained in one stage by condensing aromatic amines and thiols with formaldehyde in the presence of strong acids (HCl, HBr, H_2SO_4). The aromatic thiols employed were C_6H_5SH, $p\text{-}ClC_6H_4SH$, $p\text{-}CH_3C_6H_4SH$, $p\text{-}O_2NC_6H_4SH$, and 2,4-$(CH_3)_3C_6H_2SH$, while the aromatic amines were $C_6H_5NH_2$, $2\text{-}C_{10}H_7NH_2$, $m\text{-}ClC_6H_4NH_2$, $p\text{-}CH_3C_6H_4NH_2$, and *N*-methylaniline. The yields of the products were 39–90%.

The mechanism of this reaction evidently involves the protonation of aryl *N*-alkyl-*N*-arylaminomethyl sulphide (III) at the nitrogen atom and subsequent decomposition into the initial amine and the resonance-stabilised carbonium-sulphonium ions (A).[16] The latter can then alkylate either the alkylarylamine or the sulphide (III); in the former case *N*-alkyl-*p*-aminobenzyl aryl sulphide(IV) is formed immediately after deprotonation while in the latter the intermediate *N*-alkyl-*N*-arylthiomethyl-*p*-aminobenzyl aryl sulphide (V) is produced and is then converted into the aryl benzyl sulphide (IV) with regeneration of the ion (A):

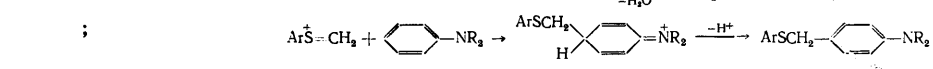


The second hypothesis is supported by the fact that the intermediate (V) can be isolated in a satisfactory yield when the reaction of *p*-chlorobenzenethiol and formaldehyde with *N*-methylamine is carried out in the presence of concentrated hydrochloric acid at 40 °C; this product is fully converted into the sulphide (IV) on raising the temperature to 80 °C. This mechanism is also confirmed by the finding that the *ortho*-product of the condensation reaction was not obtained even in those cases where the *p*-position in the aromatic amine is occupied (with the exception of the reaction with $2\text{-}C_{10}H_7NH_2$ [15]); it has been noted that the large size of the arylthiomethyl group prevents the entry of the substituent into the *ortho*-position.

Apart from the primary and secondary amines, tertiary aromatic amines also enter into the reaction described above, but the yields of products are then low (15–33%):[16]



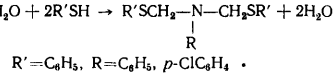
The mechanism involving the intermediate formation of arylthiomethanol, whose protonation and subsequent elimination of the water molecule yield a carbonium-sulphonium ion, has been proposed for this reaction. The ion reacts with an arylamine to form aryl *NN*-dialkyl-*p*-aminobenzyl sulphide:[16]



A study of the thioalkylation of primary aromatic amines[14] established that, in contrast to primary aliphatic amines and benzylamines, which usually give rise to a mixture of secondary and tertiary amines via the Mannich reaction, aromatic amines condense with arenethiols and formaldehyde (in molar proportions of 1 : 1 : 1) to form almost exclusively aryl *N*-arylaminomethyl sulphides:

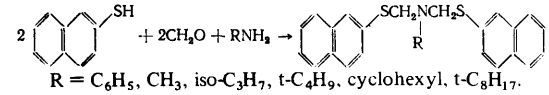
$$RNH_2 + CH_2O + R'SH \rightarrow RNHCH_2SR' + H_2O$$
$$R = C_6H_5;\ R' = C_6H_5;\ p\text{-}ClC_6H_4;\ 2,4,6\text{-}(CH_3)_3C_6H_2;\ R' = p\text{-}ClC_6H_4;$$
$$R\ m\text{-}ClC_6H_4;\ p\text{-}ClC_6H_4;\ p\text{-}CH_3OC_6H_4;\ p\text{-}O_2NC_6H_4.$$

The yields of the reaction products are 16–86%, when the thiol : amine : formaldehyde molar ratios are 2 : 1 : 2, 1,3,5-triaryl-1,5-dithia-2-azapentanes are obtained:



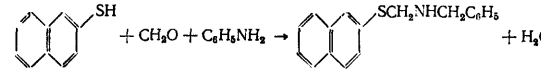
$R' = C_6H_5,\ R = C_6H_5,\ p\text{-}ClC_6H_4$.

The thioalkylation of various aliphatic amines with naphthalene-2-thiol and formaldehyde in molar proportions of 1 : 2 : 2 (in ethyl acetate at 25–28 °C for 48 h) leads to analogous results:[17,18]

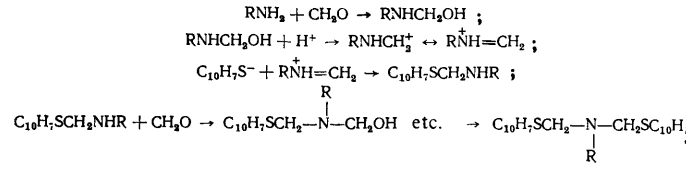


R = C_6H_5, CH_3, iso-C_3H_7, t-C_4H_9, cyclohexyl, t-C_8H_{17}.

The yields of the reaction products are 55–95%. The condensation of naphthalene-2-thiol, formaldehyde, and benzylamine also yielded benzylaminomethyl-2-naphthyl sulphide:



The following reaction mechanism has been proposed:[18]



2. Thioalkylation of Hydrogen Halides

The familiar reaction involving the chloromethylation of thiols can be regarded as a thiomethylation reaction in which hydrogen chloride behaves as a compound with a mobile proton:

$$HCl + CH_2O + RSH \rightleftarrows RSCH_2Cl + H_2O.$$

Böhme[19] obtained chloromethyl ethyl sulphide by this reaction for the first time by passing hydrogen chlorides into a mixture of ethanethiol and paraformaldehyde cooled to −15 °C:

$$n\,C_2H_5SH + (CH_2O)_n + n\,HCl \rightleftarrows n\,C_2H_5SCH_2Cl + n\,H_2O.$$

Alkyl and aryl chloromethyl sulphides $RSCH_2Cl$, where R = CH_3,[20,22] C_2H_5,[19,22,26] C_3H_7,[20,22] iso-C_3H_7,[22] n-C_4H_9, iso-C_4H_9, s-C_4H_9, t-C_4H_9, n-C_5H_{11}, s-C_5H_{11},[22,23] C_6H_{13},[22,28] 2-ethylbutyl, 1-methylheptyl,[23] C_8H_{17},[28,29] $C_{12}H_{25}$, $C_{14}H_{20}$,[28] cyclohexyl,[22] C_6H_5, *p*-ClC_6H_4, or $C_6H_5CH_2$ [20] having different structures were subsequently obtained with the aid of this procedure. The yields of alkyl chloromethyl sulphides are 43–85%.

When paraldehyde was used instead of paraformaldehyde, a series of alkyl and aryl α-chloroethyl sulphides were obtained:

$$3RSH + (CH_3CHO)_3 + 3HCl \rightleftarrows 3RSCHCl + 3H_2O;$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad CH_3$$

R = CH_3 (Refs.20, 21), C_2H_5 (Refs.20–22, 24, 26), t-C_4H_9 (Ref.27), C_6H_5 (Ref.21), iso-C_3H_7 (Refs.22, 24), alkyl (Refs.24, 25), C_4H_9, C_5H_{11} (Refs.22, 24).

The yields of the products are 30–90%.

Other aldehydes have also been used:

$$RSH + R'CHO + HCl \rightleftarrows RSCHCl + H_2O;$$
$$\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\quad R'$$

R = CH_3, R′ = C_6H_5 (Ref.20); R = R′ = C_2H_5 (Ref.21); R = C_2H_5, R′ = n-C_3H_7, iso-C_3H_7, C_6H_5 (Ref.26).

The yields of the α-chloroalkyl sulphides in these syntheses are 40–81%.

In one investigation acetone was used in the thioalkylation of hydrogen chloride instead of an aldehyde and α-chloroisopropyl ethyl sulphide was then obtained in 20% yield:

$$C_2H_5SH + CH_3COCH_3 + HCl \rightleftarrows CH_3C(Cl)SC_2H_5 + H_2O.$$
$$\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\quad CH_3$$

The thioalkylation of hydrogen chloride in a solvent (CH_2Cl_2) using anhydrous calcium or magnesium sulphate to absorb the water formed in the reaction[30] did not result in an increase of the yield of the required product. The yields were 50% of $C_2H_5SCH_2Cl$, 63% of iso-$C_3H_7SCH_2Cl$, and 45% of $CH_3SCH(Cl)CH_3$. In the syntheses by Böhme's method the yields are 43–60% of the first product,[19,20,22,26] 85% of the second product,[22] and 30–59% of the third product.[20,21]

In the thioalkylation of hydrogen chloride in benzene[28,31] the yields of alkyl chloromethyl sulphide are independent of the length of the hydrocarbon group in the thiol and depend mainly on the reaction temperature and the amount of solvent employed. The highest yields (>70%) are reached at 0–10 °C when CH_2O and RSH are employed in molar proportions of 1.2 : 1 (the benzene : thiol ratio is 4.5 : 1).

There has been one study on the thioalkylation of hydrogen bromide[20] in which bromomethyl ethyl sulphide was obtained by Böhme's method in 44% yield.

The data on the mechanism of the thioalkylation of *NN*-dialkylanilines suggest the following most probable mechanism of the thioalkylation of hydrogen halides:

$$RSH + CH_2O \rightleftarrows RSCH_2OH;$$
$$HX \rightleftarrows H^+ + X^-;$$
$$RSCH_2OH + H^+ \rightarrow RSCH_2\overset{+}{O}H_2 \xrightarrow{-H_2O} RSCH_2^+ \leftrightarrow R\overset{+}{S}{=}CH_2;$$
$$RSCH_2^+ + X^- \rightarrow RSCH_2X;$$
$$X = Cl, Br.$$

3. Thioalkylation of Ketones

The thioalkylation of ketones was investigated for the first time by the authors of the present review.[32] It was established[33] that the reaction proceeds readily in the presence of alkalis; calcium carbonate weakly catalyses the reaction, while triethylamine has no catalytic effect. When piperidine is added to a mixture of a ketone, a thiol, and formaldehyde, *N*-alkylthiomethylpiperidine is formed but does not catalyse the reaction. The reaction in the presence of alkalies is exothermic and in many cases reaches completion very rapidly at room temperature. In the remaining instances heating of the mixture to 50 °C is sufficient to complete the reaction.

Aliphatic, cyclic, and aliphatic-aromatic ketones and all thiols other than aromatic thiols enter into the thioalkylation reaction. The methylene group adjoining the carbonyl group in alkyl methyl ketone is the most reactive.

When a fivefold excess of the ketone is treated with equimolar amounts of a thiol, formaldehyde, and sodium hydroxide, mono(alkylthiomethyl)-substituted ketones are obtained:[7,33,34]

$$R^1COCH_2R^2 + CH_2O + R^3SH \rightarrow R'COCH(R^2)CH_2SR^3 + H_2O;$$
$R^1{=}R^2{=}CH_3$; $R^3{=}C_2H_5$; n-C_4H_9; t-C_4H_9; C_8H_{17}, cyclohexyl; $C_6H_5CH_2$; $R^1{=}CH_3$; $R^2{=}C_3H_7$; $R^3{=}C_4H_9$; $R'{=}C_6H_5$, $R^2{=}CH_3$, $R^3{=}C_2H_5$, n-C_4H_9, t-C_4H_9, cyclohexyl; $R^1R^2{=}(CH_2)_4$; R^3-n-C_4H_9; t-C_4H_9; cyclohexyl; $R^1{=}CH_3$; $R^2{=}H$; $R^3{=}C_4H_9$; $R'{=}C_6H_5$; $R^2{=}H$; $R^3{=}C_4H_9$, C_8H_{17}.

The yields of the reaction products are 50.2–100%.

When equimolar amounts of acetone, butanethiol, formaldehyde, and sodium hydroxide interact, 61% of bis(butylthiomethyl)acetone and only 10.5% of mono(butylthiomethyl)acetone are obtained. The reaction involving acetophenone produces analogously under these conditions 64.2% of bis(butylthiomethyl)acetophenone and 25.9% of the mono-(butylthiomethyl) derivative.[35] This can be explained by the fact that the methylene group, which is more reactive than the methyl group, appears next to the carbonyl group in the mono(butylthiomethyl) derivatives formed:

$$CH_3COCH_3 + CH_2O + C_4H_9SH \rightarrow CH_3COCH_2CH_2SC_4H_9 + H_2O;$$
$$CH_3COCH_2CH_2SC_4H_9 + CH_2O + C_4H_9SH \rightarrow CH_3COCH(CH_2SC_4H_9)_2 + H_2O.$$

When ketones were allowed to react with twice the molar amounts of a thiol, formaldehyde, and sodium hydroxide in an aqueous alcoholic medium at 20–50 °C, bis(alkylthiomethyl)-substituted ketones were obtained in 38–93% yields:[33,35]

$$R^1COCH_2R^2 + 2\,CH_2O + 2\,R^3SH \rightarrow R^1COC(R^2)(CH_2SR^3)_2 + 2\,H_2O;$$
$R^1{=}CH_3$; $R^2{=}H$; $R^3{=}C_2H_5$; C_4H_9; $R^1{=}C_6H_5$; $R^2{=}H$; $R^3{=}C_2H_5$; C_4H_9; C_6H_{13}; cyclohexyl; $C_6H_5CH_2$; $R^1R^2{=}(CH_2)_3CH$; $R^3{=}C_4H_9$.

It is noteworthy that the introduction of the first $RSCH_2$ group into the ketone molecule, with the exception of acetone and acetophenone, takes place readily, while the introduction of the second $RSCH_2$ group is difficult. This fact is manifested particularly clearly in the thioalkylation of cyclohexanone with butanethiol. The introduction of the

first $C_4H_9SCH_2$ group into the cyclohexanone molecule proceeds via an exothermic reaction and is completed in 2 h, while the introduction of the second $C_4H_9SCH_2$ group requires prolonged (10 h) heating at 50 °C.[35]

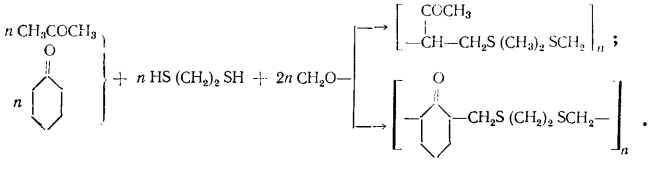
When butanone is thioalkylated with two moles of butanethiol and formaldehyde, 1,3-bis(butylthiomethyl)-2-butanone is obtained, while the reaction with three moles of ethanethiol and formaldehyde gives rise to 1,3,3-tris(ethylthiomethyl)-2-butanone. The third $C_2H_5SCH_2$ group enters the sterically more hindered 3-position rather than the 1-position.[35]

The thioalkylation of acetone by four moles of a thiol, formaldehyde, and sodium hydroxide results in the formation of 1,1,3,3-tetrakis(alkylthiomethyl)-2-propanones:[33]

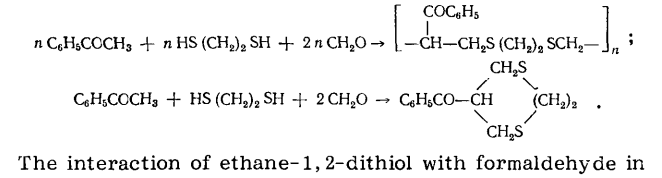
$$CH_3COCH_3 + 4\,CH_2O + 4RSH \rightarrow (RSCH_2)_2CHCOCH(CH_2SR)_2 + 4\,H_2O;$$
$$R = C_2H_5;\ C_4H_9;\ C_6H_{11};\ C_{12}H_{25};\quad t\text{-}C_{12}H_{25};\ \text{cyclohexyl},\ C_6H_5CH_2\ .$$

The yields of the required products are 77–93%.

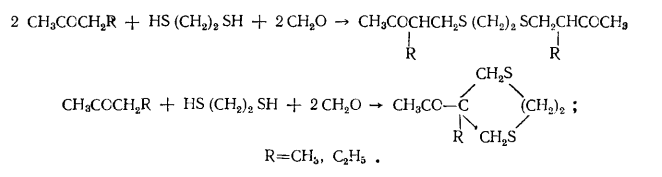
The thioalkylation of ketones by dihydric thiols, particularly by ethane-1,2-dithiol, has been investigated.[36] The condensation of acetone and cyclohexanone with formaldehyde and ethane-1,2-dithiol in molar proportions of 1 : 2 and 4 : 1 in the presence of alkali at room temperature gives rise to polymeric ketobis-sulphides in yields of 92.2 and 94% respectively:



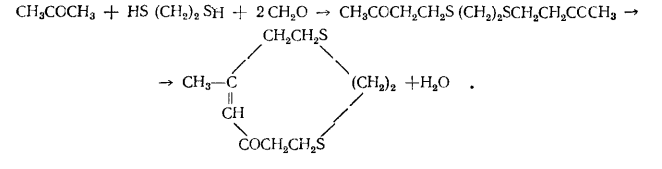
The yield of the polymeric ketobis-sulphides obtained from acetophenone under these conditions is 16.7% and the main reaction product is 6-benzoyl-1,4-dithiacycloheptane (71.4%):[36]



The interaction of ethane-1,2-dithiol with formaldehyde in molar proportions of 1 : 2.4 with a 20-fold excess of butanone or 2-pentanone at 20 °C in the presence of alkali yields 3,10-dimethyl- and 3,10-diethyl-5,8-dithiadodecane-2,11-diones respectively together with small amounts of 6-methyl- and 6-ethyl-6-acetyl-1,4-dithiacycloheptanes respectively:[36]

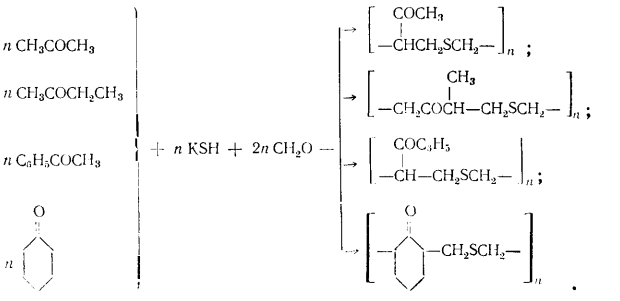


6-Benzoyl-1,4-dithiacycloheptane and 3-methyl-6,9-dithiacycloundec-2-en-1-one are obtained from acetophenone and acetone respectively under analogous conditions:[36]

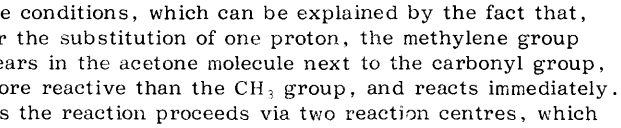


The thioalkylation reaction where hydrogen sulphide is used instead of a thiol can be compared with the Mannich reaction in which ammonia is used instead of an amine. The thioalkylation of ketones by potassium hydrogen sulphide and formaldehyde[37] is close to the thioalkylation of ketones by ethane-1,2-dithiol and formaldehyde as regards the character of the products obtained.[36]

The condensation of acetone, butanone, cyclohexanone, or acetophenone with potassium hydrogen sulphide and formaldehyde in molar proportions of 1 : 2 : 2.2 at room temperature affords polymeric ketosulphides in almost quantitative yields:

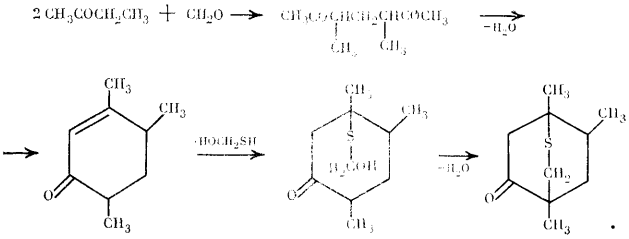


The interaction of butanone, 2-pentanone, or 2-hexanone with potassium hydrogen sulphide and formaldehyde in molar proportions of 2 : 0.5 : 1.23 at room temperature produces respectively 3,7-dimethyl-, 3,7-diethyl-, and 3,7-dipropyl-5-thianonane-2,8-diones in 15–49% yields:



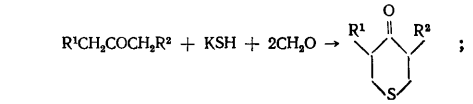
Only polymrtic products are obtained from acetone under these conditions, which can be explained by the fact that, after the substitution of one proton, the methylene group appears in the acetone molecule next to the carbonyl group, is more reactive than the CH_3 group, and reacts immediately. Thus the reaction proceeds via two reaction centres, which leads to the formation of polymeric products. For other alkyl methyl ketones, the reaction can proceed both via two reaction centres and one reaction centre (in the latter case via the most reactive methylene group with formation of 3,7-dialkyl-5-thianonane-2,8-diones).

Together with polymeric products, 1,4,5-trimethyl-7-thiabicyclo[2.2.2]octan-2-one is obtained in 20% yield on condensation of butanone with potassium hydrogen sulphide and formaldehyde in molar proportions of 1 : 0.15 : 0.36 at 50 °C:



The condensation of potassium hydrogen sulphide and formaldehyde with ketones containing two methylene groups with identical reactivities next to the carbonyl group can yield cyclic γ-ketosulphides. Thus a series of 2,6-dialkyl-4-thiacyclohexanones have been obtained in the form of mixtures of *cis*- and *trans*-isomers, with the former predominating slightly, in the course of one month at room temperature or 20–30 h at 50 °C using ketone : potassium

hydrogen sulphide : formaldehyde molar ratios of 1 : 1 : 2 in alcohol:[33]



$R^1=R^2=C_2H_5$; C_3H_7; C_4H_9; C_7H_{15}; $R^1=C_6H_5$, $R^2=CH_3$.

The yields of the cyclic γ-ketosulphides are 23–72.5%.

Amino-derivatives of ketosulphides have been obtained by the condensation of ketones with formaldehyde and aminothiols in the presence of sodium hydroxide.[33] A series of mono(dialkylaminoethylthiomethyl)-substituted ketones have been obtained from equimolar amounts of *N*-(2-mercaptoethyl)-amines, formaldehyde, and sodium hydroxide with a fivefold excess of the ketone:

$$RCOCH_2R^1 + HSCH_2CH_2NR_2^2 + CH_2O \rightarrow RCOCH(R^1)CH_2SCH_2CH_2NR_2^2 ;$$

$RR^1=(CH_2)_4$; $R_2^2=(CH_2)_5$; $R=C_6H_5$; $R^1=CH_3$; $R_2^2=(C_2H_5)_2$; $(CH_2)_5$; $(CH_2)_2O(CH_2)_2$.

The reaction of acetophenone with twice the molar amounts of *N*-(2-mercaptoethyl)amine, formaldehyde, and sodium hydroxide gave rise to a series of bis(dialkylaminoethylthiomethyl)-substituted ketones:

$$C_6H_5COCH_3 + 2HSCH_2CH_2NR_2 + 2CH_2O \rightarrow C_6H_5COCH(CH_2SCH_2CH_2NR_2)_2 ;$$

$R_2=(C_2H_5)_2$; $(CH_2)_5$; $(CH_2)_2O(CH_2)_2$.

Tetrakis(dialkylaminoethylthiomethyl)-substituted ketones have been synthesised from acetone with four molar amounts of *N*-(2-mercaptoethyl)amine, formaldehyde, and sodium hydroxide:

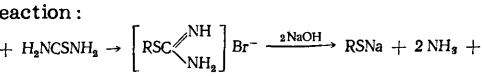
$$CH_3COCH_3 + 4HSCH_2CH_2NR_2 + 4CH_2O \rightarrow$$
$$\rightarrow (R_2NCH_2CH_2SCH_2)_2CHCOCH(CH_2SCH_2CH_2NR_2)_2 ;$$
$$R_2=(C_2H_5)_2, (CH_2)_5 .$$

3-Ethylthiomethyl-2-butanone has been obtained[38] in 80% yield by thioalkylating butanone with ethanethiol using the method which we have described:

$$CH_3COCH_2CH_3 + C_2H_5SH + CH_2O \rightarrow CH_3COCH(CH_3)CH_2SC_2H_5 + H_2O .$$

The vacuum distillation of the reaction products led to the isolation of high-molecular-weight fractions of the hydroxymethyl derivative of 3-ethylthiomethyl-2-butanone in 80% yield, but the position of the hydroxymethyl group in this compound was not established.

In the thioalkylation of ketones, Babakhanova et al.[39] used as a thiol component alkaline solution of *S*-alkylisothiuronium salts, which were obtained by the reaction of alkyl bromides with thiourea. They established that the side products resulting from the alkaline decomposition of *S*-alkylisothiuronium salts do not affect the yield of the ketosulphides, which amount to 80–90% relative to the alkyl bromides used in the reaction:



$$RSNa + CH_3COCH_2CH_3 + CH_2O \rightarrow CH_3COCH(CH_3)CH_2SR ;$$
$$R=C_2H_5, C_3H_7, C_4H_9 .$$

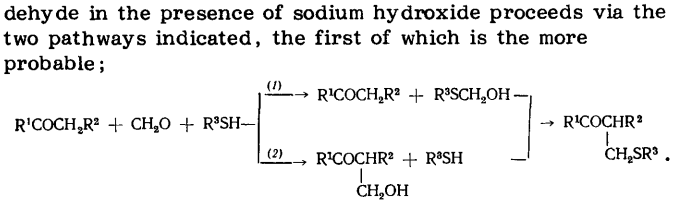
Ketosulphides have been obtained by the condensation of ketones, 1,3-diketones, or β-ketoacids esters with thiols and aldehydes in THF at 70 °C in the course of 5 h in the presence of catalytic amounts of concentrated sulphuric acid:[40]

$$RCOCH_2R^1 + R^2CHO + R^3SH \xrightarrow{H^+} RCOCH(R^1)CH(R^2)SR^3 + H_2O ;$$

$R=CH_3$; $R^1=CH_3CO$; $R^2=R^3=C_6H_5$; $RR^1=(CH_2)_4$; $R^2=H$; $R^3=C_2H_5$; C_6H_5; $RR^1=(CH_2)_2$; $(CH_2)_3$; $R^2=H$; $R^3=C_3H_5$; $R=CH_3$, $R^1=CH_3CO$; C_3H_5CO; $COOC_2H_5$; $R^2=H$; $R^3=C_3H_5$; $R=C_6H_5$; $R^1=COOC_2H_5$; $R^2=H$; $R^3=C_6H_5$.

The yields of the ketosulphides amount to 31–92%.

It has been established experimentally[33] that the reaction involving the thioalkylation of ketones by thiols and formaldehyde in the presence of sodium hydroxide proceeds via the two pathways indicated, the first of which is the more probable;



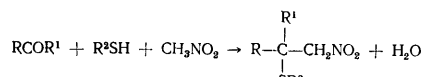
The condensation of ketones with thiols and aldehydes in the presence of strong acids[40] apparently proceeds via the formation of a carbonium-sulphonium ion as an intermediate. Thus the mechanism of this reaction is analogous to that of the Mannich reaction.[6]

4. Thioalkylation of Nitroalkanes

When a mixture of propanol, toluene-α-thiol, and nitromethane was heated at 100 °C for 30 min in the presence of catalytic amounts of piperidine, 2-(benzylthio)nitrobutane was obtained in 76% yield; 2-(benzylthio)-2-phenylnitroethane has been obtained analogously from benzaldehyde (4 h, 100 °C, yield 53%; 20 days, approximately 20 °C, yield 64%):[41]

$$RCHO + R'SH + CH_3NO_2 \rightarrow RCH(SR')CH_2NO_2 + H_2O ;$$
$$R=C_2H_5, C_6H_5, R'=C_6H_5CH_2 .$$

Ketones have also been used in this reaction instead of aldehydes, but they proved to be less reactive. On refluxing in the presence of piperidine (for 24 h), 1-(ethylthio)-1-nitromethylcyclohexane has been obtained in 50% yield from cyclohexanone, ethanethiol, and nitromethane, while 2-(butylthio)-2-methylnitropropane has been synthesised in 58% yield from acetone, butanethiol, and nitromethane:

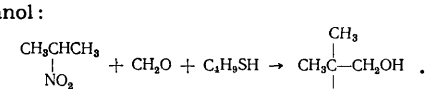


$R=R^1=CH_3$; $R^2=C_4H_9$; $RR^1=(CH_2)_5$; $R^2=C_2H_5$.

It has been suggested[41] that the condensation of nitroalkanes with aldehydes or ketones proceeds via the intermediate formation of nitro-olefins to which thiols then add:

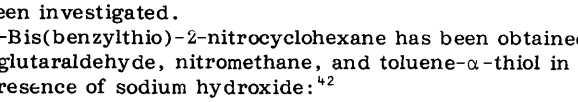
$$RCHO + CH_3NO_2 \rightarrow RCH(OH)CH_2NO_2 \xrightarrow{-H_2O} RCH{=}CHNO_2 \rightarrow$$
$$\xrightarrow{R'SH} RCH(SR')CH_2NO_2 .$$

The interaction of 2-nitropropane, formaldehyde, and butanethiol in the presence of piperidine yields 2-methyl-2-nitropropanol:

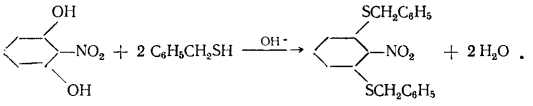


The latter is not dehydrated with formation of a nitro-olefin and the thioalkylation reaction does not take place. The behaviour of other nitroalkanes in this reaction has not so far been investigated.

1,3-Bis(benzylthio)-2-nitrocyclohexane has been obtained from glutaraldehyde, nitromethane, and toluene-α-thiol in the presence of sodium hydroxide:[42]



The same product is obtained under analogous conditions from toluene-α-thiol and 2-nitrocyclohexane-1,3-diol:



The latter is apparently an intermediate in the reaction described above.

Thus the condensation of nitromethane with thiols and aldehydes (or ketones) results in the substitution of the mobile proton of nitromethane by the thioalkyl group and the reaction can be formally classified as a thioalkylation reaction although the mechanism is different from that of other such reactions.

5. Thioalkylation of 1,3-Disulphones

The thioalkylation of sulphones was first investigated by the authors of the present review.[43] Benzyl phenyl sulphone, bis(phenylsulphonyl)methane, and bis(butylsulphonyl)-methane were used as the sulphones, whilst the thiols were butanethiol, 2-methylpropane-2-thiol, cyclohexanethiol, and benzenethiol. It was established that the above sulphones and thiols can be arranged in the following sequences in terms of their reactivity in the thioalkylation reaction:

$$(C_6H_5SO_2)_2CH_2 > (C_4H_9SO_2)_2CH_2 > C_6H_5SO_2CH_2C_6H_5 ;$$
$$t\text{-}C_4H_9SH > \text{cyclo-}C_6H_{11}SH > C_4H_9SH > C_6H_5SH .$$

The sulphone thioalkylation products have been obtained in 9–93% yields from equimolar amounts of the sulphone, the thiol, a 34% aqueous solution of formaldehyde, and sodium hydroxide in alcoholic solution with heating (to 50–55 °C; 78 °C in the case of benzyl phenyl sulphone) until the qualitative test for the thiol was negative (c.f. Houben-Weyl[44]):

$$RSO_2CH_2R^1 + R^2SH + CH_2O \rightarrow RSO_2CH(R^1)CH_2SR^2 + H_2O ;$$
$$R = C_6H_5;\ R^1 = SO_2C_6H_5;\ R^2 = C_4H_9;\ \text{cyclohexyl};\ C_6H_5;$$
$$R = C_4H_9;\ R^1 = SO_2C_4H_9;\ R^2 = C_4H_9;\ \text{cyclohexyl};$$
$$R = R^1 = C_6H_5;\ R^2 = C_4H_9;\quad t\text{-}C_4H_9;\ \text{cyclohexyl} .$$

The thioalkylation of 1,3-disulphones with formaldehyde and potassium hydrogen sulphide has also been investigated.[45] The reaction was carried out in a mixture of dioxan and methanol at room temperature using the molar ratios 1 : 3-disulphone : KSH : CH_2O = 2 : 1 : 2. 1,1,5-5-Tetrakis-(butanesulphonyl)-3-thiapentane, 1,1,5,5-tetrakis(cyclo-hexanesulphonyl)-3-thiapentane, 1,1,5,5,-tetrakis(benzene-sulphonyl)-3-thiapentane, and 1,2,6,7-tetrakis(benzene-sulphonyl)-4-thiaheptane have been obtained from bis(butanesulphonyl)methane, bis(cyclohexanesulphonyl)-methane, bis(benzenesulphonyl)methane, and 1,2-bis-(benzenesulphonyl)ethane respectively:

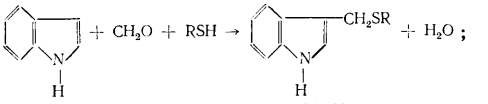
$$2(RSO_2)_2CH_2 + 2CH_2O + KSH \rightarrow (RSO_2)_2CHCH_2SCH_2CH(SO_2R)_2 ;$$
$$R = C_4H_9;\ \text{cyclohexyl};\ C_6H_5 ;$$
$$2C_6H_5SO_2CH_2CH_2SO_2C_6H_5 + 2CH_2O + KSH \rightarrow$$
$$\rightarrow C_6H_5CH_2\underset{\displaystyle SO_2C_6H_5}{\underset{|}{C}}HCH_2SCH_2\underset{\displaystyle SO_2C_6H_5}{\underset{|}{C}}HCH_2SO_2C_6H_5 .$$

The yields of the reaction products are 30–50%.

6. Thioalkylation of Other Compounds

It has been established[46] that the thioalkylation of indole, antipyrine, and 2-naphthol proceeds satisfactorily under conditions very similar to those necessary for the optimum yields of Mannich bases. The weak bases, namely indole and antipyrine, are thioalkylated in weakly acid media, while the weakly acidic 2-naphthol is thioalkylated only in a basic medium.

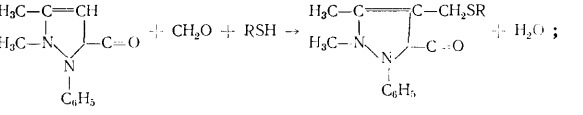
Thus the condensation of indole, a 40% aqueous solution of formaldehyde, and alkanethiols (or toluene-α-thiol) in aqueous acetic acid in the course of six days at room temperature gives rise to the corresponding 3-(alkylthiomethyl)indoles:



R = C_2H_5; C_3H_7; C_4H_9; $C_6H_5CH_2$.

The yields of the products of the reactions of alkane thiols are approximately 25%, while the reaction of toluene-α-thiol gives rise to 14% of the product; under these conditions, benzenethiol does not react.

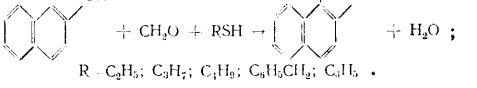
The thiolalkylation of antipyrine with paraformaldehyde and thiols in aqueous acetic acid takes place at 100 °C in the course of 23–47 h, the corresponding 4-(alkylthiomethyl)-antipyrines being obtained:



R C_2H_5; C_3H_7; C_4H_9; $C_6H_5CH_2$; C_6H_5 .

In the reactions involving benzenethiol and toluene-α-thiol the yields of products are approximately 80%, while in the reactions of propane- and butane-thiols they are 42 and 62% respectively. Owing to its low boiling point, ethanethiol does not react satisfactorily under these conditions. 4-(Ethyl-thiomethyl)antipyrine has been obtained in 17% yield on condensing ethanediol, a 40% aqueous solution of formalde-hyde, and antipyrine in aqueous acetic acid at room tempera-ture for 14 days.

The corresponding 1-alkylthiomethyl-2-naphthols have been obtained from 2-naphthol, a 40% aqueous solution of formaldehyde, and thiols in alcohol in the presence of tri-ethylamine (6 days at room temperature):



R = C_2H_5; C_3H_7; C_4H_9; $C_6H_5CH_2$; C_6H_5 .

The yields of the condensation products are 76–79%. On decrease of the reaction time to three days, the yields are halved.

It is believed[46] that the first stage of the reaction which they investigated involves the addition of the thiols to formaldehyde with formation of alkylthiomethanols, which then react with indole, antipyrine, or 2-naphthol. This has been demonstrated by the fact that the reactions of phenyl-thiomethanol with antipyrine give rise to 4-(phenylthio-methyl)antipyrine, while the reaction of ethylthiomethanol and 2-naphthol gives rise to 1-ethylthiomethyl-2-naphthol in approximately the same yield as in the reactions of anti-pyrine or 2-naphthol with a thiol and formaldehyde. The authors do not rule out the possibility of an alternative mechanism involving the addition of indole, antipyrine, or 2-naphthol to formaldehyde with subsequent interaction of the resulting hydroxymethyl derivatives with the thiols, but they do not state that this mechanism has been confirmed experimentally.

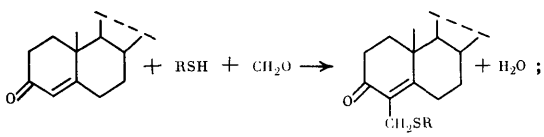
Certain compounds containing in the molecule a double bond conjugated with the carbon group, namely CO–CH=X (X = C or N), undergo the thioalkylation reaction. Thus it has been established[47] that treatment of α-ketoaldehyde ω-monoarylhydrazones with thiols and formaldehyde in acetic acid in an atmosphere of nitrogen results in the substitution of the proton in the α-position relative to the carbonyl group:

$$RCOCH{=}N{-}NHAr + R'SH + CH_2O \rightarrow RCOC(CH_2SR'){=}N{-}NHAr + H_2O;$$

R=R'=C_6H_5; Ar=C_6H_5; *p*-ClC_6H_4; *m*-ClC_6H_4; *m*-$O_2NC_6H_4$; R=CH_3; R'=CH_2CO_2H; Ar=C_6H_5.

The yields of the reaction products are 20–50%. It is believed[47] that the reaction proceeds via the intermediate formation of hemimercaptals.

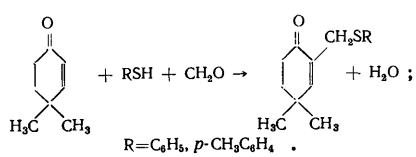
When a mixture of a 3-oxo-Δ^4-steroid, a thiol, aqueous formaldehyde (40%), triethylamine, and alcohol in proportions of 5 : 4 : 3 : 3 : 10–30 by weight (depending on the solubility of the steroid) is heated (60 °C, 30–50 h), 4-alkylthiomethyl-3-oxo-Δ^4-steroids are obtained in a satisfactory yield:[48,49]



R=C_2H_5; C_4H_9; C_6H_{11}; $C_6H_5CH_2$; C_6H_5, *p*-$CH_3C_6H_4$, furfuryl, CH_2CH_2OH; $(CH_2)_2CO_2CH_3$.

When triethanolamine is used as the catalyst and solvent and the mixture is heated to 110–150 °C, the reaction time is reduced to 8–16 h. Paraformaldehyde can be used in this reaction instead of aqueous formaldehyde and triethylamine can be replaced by other tertiary amines: trimethylamine, tri(n-propyl)amine, and *N*-methylpiperidine.

The corresponding 2-(alkylthiomethyl)substituted products are obtained in 70–72% yields by an analogous method on heating in alcohol a mixture of 4,4-dimethylcyclohex-2-en-1-one, a thiol, a 37% aqueous formaldehyde solution, and triethylamine in molar proportions of 1 : 1.5 : 1.6 : 1.4:[50]



R=C_6H_5, *p*-$CH_3C_6H_4$.

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It follows from the foregoing that the thioalkylation reactions have been little investigated. The thioalkylation of amines, hydrogen chloride, and ketones has been most thoroughly investigated hitherto, but only isolated studies have been made of the thioalkylation of other compounds.

With the exception of the thioalkylation of amines, the mechanisms of other reactions have also been little studied. All the reactions described in this review, apart from the thioalkylation of nitroalkanes, apparently proceed via a similar mechanism. The thioalkylation of nitroalkanes takes place via the intermediate formation of nitroalkenes with subsequent addition of thiols to the latter. The thioalkylation of primary and secondary amines proceeds via the mechanism of the Mannich reaction:[6] via the intermediate formation of aminomethanols $>N{-}CH_2OH$ in alkaline media or carbonium-immonium ions $>N{-}CH_2^+ \leftrightarrow >\overset{+}{N}{=}CH_2$ in acid media.

The mechanism of the thioalkylation of *NN*-dialkylanilines, ketones, indole, antipyrine, 2-naphthol, α-ketoaldehyde ω-monoarylhydrazones, and hydrogen halides is apparently analogous to the mechanism of the Mannich reaction (it involves the intermediate formation of the thiomethanols $RSCH_2OH$ in alkaline media and the carbonium-sulphonium ions $RSCH_2^+ \leftrightarrow R\overset{+}{S}{=}CH_2$ in acid media). However, one should not assume that all the compounds undergoing the Mannich reaction undergo thioalkylation or conversely. These reactions have their own specific features. For example, phenol readily undergoes the Mannich reaction but does not undergo the thioalkylation reaction. Conversely, bis(benzenesulphonyl)methane readily undergoes thioalkylation but does not produce Mannich bases.[51]

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Institute of Chemistry,
The Bashkir Branch of the
USSR Academy of Sciences,
Ufa