PART - III

TITANIUM TETRACHLORIDE, AN EFFICIENT AND CONVENIENT REAGENT FOR THIOACETALIZATION

THIOACETALIZATION

Abstract

$TiCl_4$ and anhy. $FeCl_3$ were used as reagents for thioacetalization of carbonyl compounds. $TiCl_4$ was shown to be an efficient reagent for this purpose, whereas anhy. $FeCl_3$ was found to be inferior to $TiCl_4$.

INTRODUCTION

The stability exhibited by dithioacetals and 1,3-dithiolanes (1,3-dithianes) under usual acid or basic conditions[1] has led to their wide synthetic utility as carbonyl protecting groups[1,2] and as synthons in a variety of synthetic operations,[3] in addition these carbonyl derivatives have served as intermediates in the conversion of a carbonyl function to a hydrocarbon derivative.[4] In general, these thioacetals are obtained by acid catalysed condensations of thiols with carbonyl compounds[2,3] or by reaction of carbonyl compounds with orthothio-boric esters[5] or thiosilanes[6] (and a Lewis acid) or by exchange reaction of derived acetals with thiols.[7] A brief survey of methods for preparation of thioacetals are described below.

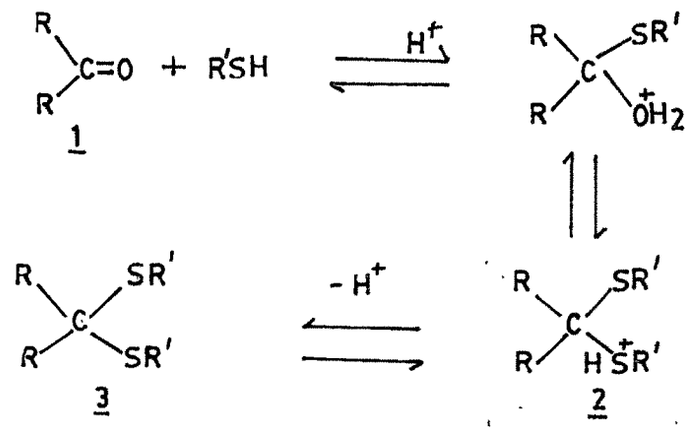
General methods of preparation of thioacetals from carbonyl compounds and thiols.

1) Protic acid catalysed thioacetalization

$$RR'C{=}O + R''SH \xrightarrow{H^+} RR'C(SR'')_2$$

For condensation of carbonyl compounds with thiols or dithiols, acid catalysts used are concd. HCl aqs.[1,2,8], and p-toluene sulfonic acid.[9] Dry HCl gas has also been used.[1,2,8] Concd. hydrochloric acid has been invariably used in carbohydrate thio-acetal preparations.[10]

The thioacetalization of organic carbonyl compounds is considered[11] to proceed by way of electrophylic addition of one thiol molecule, followed by bimolecular displacement of water from the protonated monothiohemiacetal intermediate, and finally deprotonation of the dithioacetal thus formed; each step is presumed to be reversible.

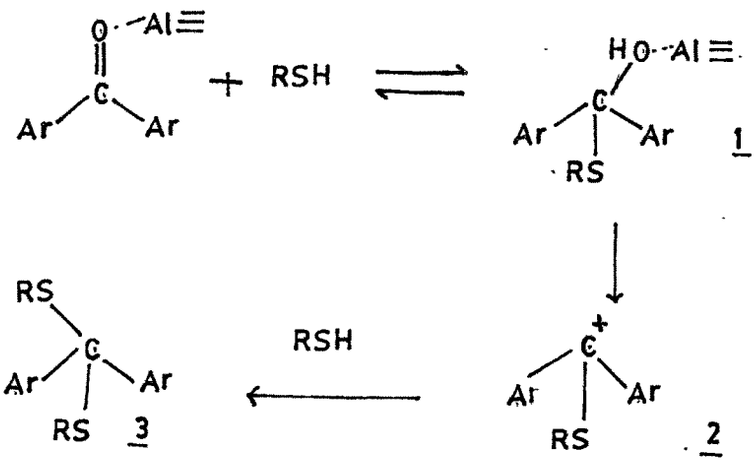


The reaction between a carbonyl compound and a thiol in acidic medium generally leads to the formation of a thioacetal, although some scattered reports in the literature indicate that certain carbonyl compounds yield unsaturated sulfides (enol thioethers) rather than the expected thioacetals. Thus 1,3-cyclohexane diones[12] form 3-alkylthio-2-cyclohexenones when treated with a thiols in presence of hydrogen chloride.

2) Lewis acid catalysed thioacetalization. For the thioacetalization of carbonyl compounds with thiols, more frequently used lewis acids are $ZnCl_2$[1,2], ZnI_2[2], BF_3: etherate[1,2] and $AlCl_3$[14].

A number of thioacetals are orepared by Lewis acid catalysed thioacetalizations. In thiscase yields are generally good.

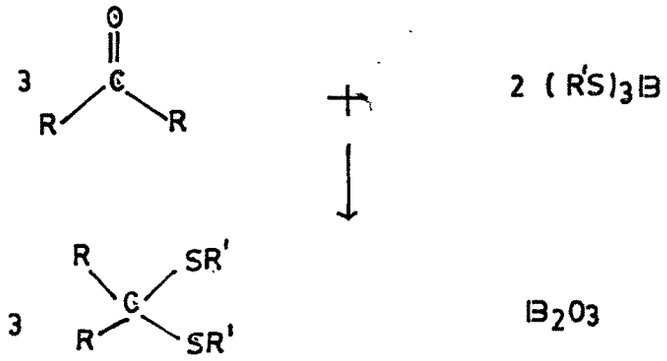
Recently anhydrous $AlCl_3$[14] has been successfully employed as a convenient reagent, and has been shown to be superior, especially for thioacetalization of less reactive aromatic carbonyl compounds. The efficiency of $AlCl_3$ was attributed to the strong affinity of $AlCl_3$ for oxygen, thereby facilitating the breakdown of the sterically hindered tetrahedral hemiketal intermediate (1) to the more accessible trivalent carbonium ion intermediate (2); the latter afforded the thioacetal (3), when reacted with second mole of the thiol.



In general, carbonyl compounds having an α-proton reacted with monothiols to give only moderate yields of the desired thioacetals, and in case of highly enolizable carbonyl

compounds, only the elimination products, i.e., vinylsulfides were formed. However, this competing reaction could be effectively subdued by emoloying a dithiol instead of a monothiol. Under these conditions, the desired thioacetal was observed to predominate to the virtual exclusion of the elimination reaction.

3) Thioacetals from ortho-thioboric esters. Ortho-thioboric esters $(RS)_3B$, can be orepared by the action of mercaptans on boron sulfide. These esters react with aldehydes or ketones to give the corresponding thioacetals[5] and boric anhydride.

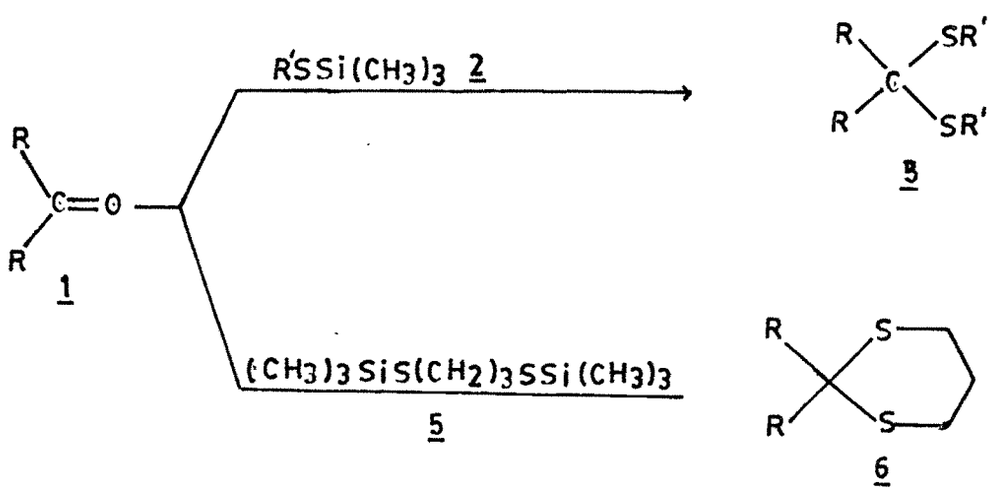


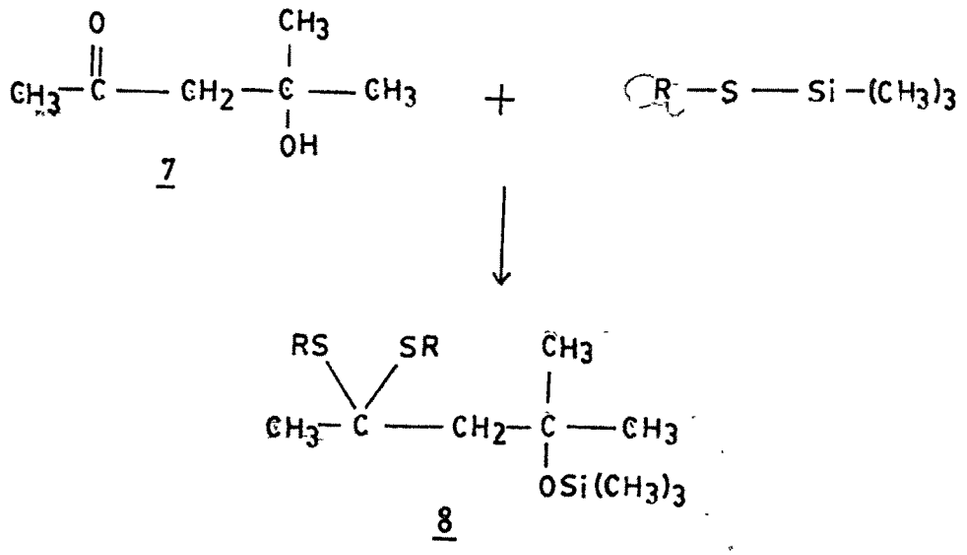
This reaction seems to be general for aliphatic and aromatic carbonyl comoounds. Yields are good and it oroceeds without the undesirable side-reactions at room temperature in neutral medium. This reaction shows some analogy with the interchange of oxygen for sulfur on the boron atoms of B_2S_3;

when this sulfide is allowed to react with a carbonyl compound.

The exchange is much favoured, thermodynamically, by the difference in the heats of formation of B-S and B-O bonds. This should be, in fact, the driving factor of the reaction. The reaction proceeds in neutral medium and shows an inductive period, the initiation of the process being indicated by the precipitation of boronoxide. These results were interpreted as indication of a free-radical mechanism for this reaction. However, in some cases[15] only moderate yields of thioacetals were obtained by this method.

4) Zinc iodide catalysed carbonyl thioacetalizations with thiosilanes. Monothiosilanes (2) or dithiosilanes (5) react smoothly with both aldehydes and ketones in presence of zinc iodide to give thioacetals 3 and 6 respectively.[6]





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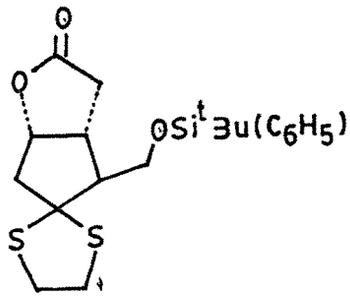
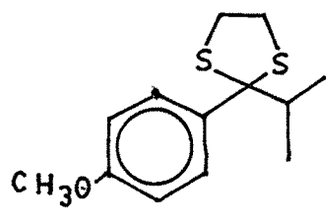
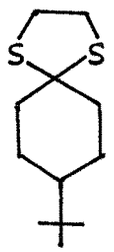
Since thiosilanes are effective silylating agents, 3 equiv. of thiosilane must be employed in such cases as shown by the reaction of diacetone alcohol (7) with ethylthiotrimethylsilane, which oroceeds without any evidence of dehydration, thus illustrating the mildly acidic nature of these reactions. Furthermore, when anhydrous zinc iodide was employed as an acid catalyst, the formation of vinyl sulfides, which frequently arises from subsequent acid catalysed elimination of the thioacetal adducts of the monothiosilanes has not been observed. In the selective monothioacetalization of 4-androstene-3,17-dione and presterone with ethylenedithio-bis(trimethyl silane), the appropriate 3-ethylenethioacetals have been obtained in good yields.

The use of thiosilanes in these processes holds a great deal of promise as an exceptionally mild procedure for effecting carbonyl derivatization.

5) Magnesium and zinc-catalysed thioacetalization. More recently[16] magnesium and zinc triflates have been used for the thioacetalization of acid sensitive compounds. The thio acetals prepared by this method are:







The α-β-unsaturated ketone Δ^4-cholesten-3-one was thio-acetalized in 98% yield to give a 4:1 mixture of Δ^4 and Δ^5-cholestenone thioacetals. However, with zinc triflate as catalyst the thioacetalization of piperitone with 1,2-ethanedithiol

gave mainly the Michael adduct of the thioacetal; Carvone also showed similar tendency.

PRESENT WORK

Our interest in this area led us to investigate the catalytic activity of two other Lewis acids, $FeCl_3$ and $TiCl_4$. While $FeCl_3$ proved to be inferior, the latter has shown excellent activity and gave the thioacetals from carbonyl-compounds in almost quantitative yields.

Ferric chloride catalysed thioacetalization

Ferric chloride is a typical Lewis acid, used in a variety of organic reactions[17a-g]. It is a powerful dehydrating reagent, and has been used for the dehydration of alcohols[17g]. Recently, it has been used for O-isopropylidenation of sugars.[18]

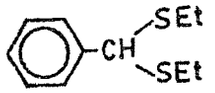
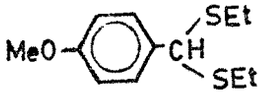
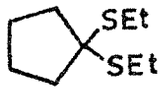
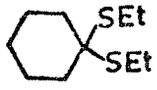
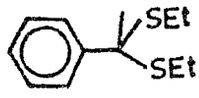
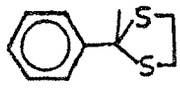
In view of its dehydrating ability, $FeCl_3$ appeared to be a promising reagent for thioacetalization of carbonyl compounds.

When organic carbonyl compounds were treated with thiol in presence of ferric chloride in dry chloroform at 25°, they reacted with thiol to yield thioacetals in good yields (Table 1, entries 1,3,4,5,6,7).

Aromatic and aliphatic aldehydes when treated with ethanethiol in presence of ferric chloride in dry chloroform furnished thioacetals in excellent yields within 4 hr (Table 1, entries, 1,3,4). In case of ketones (Table 1, entries 5,6,7), even though yields were good, the reaction was very slow (24 hr). In all the cases there was no side reaction, and products were clean and purified by simple distillation.

Although chloroform was used in the thioacetalization reactions, acetonitrile was also found to be a good solvent for this reaction. Various concentrations of reagents were tried, and 30% of ferric chloride with respect to the carbonyl compound was found to be most suitable. Sluggish reaction rates were observed when the quantity of the ferric chloride used was less than 30% by weight of the carbonyl compounds. The rate of the reaction was not much influenced by using excess of ferric chloride.

Table 1. Thioacetals by $FeCl_3$ and $TiCl_4$ methods

No	Product	Yield(%)		Reaction time* (hr)	
		$FeCl_3$	$TiCl_4$	$FeCl_3$	$TiCl_4$
1	$Me(CH_2)_5CH(SEt)_2$	95	95	4.0	1.0
2	$Me(CH_2)_5CH$<S,S>	—	95	—	0.5
3		95	95	5.0	1.0
4		95	99	4.0	1.0
5	$Me(CH_2)_4C(SEt)_2Me$	95	98	20.0	6.0
6		98	98	20.0	6.0
7		95	98	24.0	6.0
8		—	90	—	12.0
9		—	96	—	3.0
10		—	90	—	12.0
11	$Me\text{-}C(SEt)_2\text{-}CH_2.COOEt$	—	98	—	6.0

*Monitoring of the reaction was done by Glc and the reaction duration represent near 100% conversion of the carbonyl compound.

Even though the yields of the thioacetals were good, the rate of the reaction was rather slow with ferric chloride as a catalyst for thioacetalization of carbonyl compounds.

Titanium tetrachloride catalysed thioacetalization of carbonyl comoounds.

The thioacetalization with $FeCl_3$ was time consuming, hence we turned our attention to titanium tetrachloride for this purpose.

Titanium tetrachloride is known to have a strong affinity for oxygenated organic compounds, and also possesses powerful dehydrating action.[19] It has been used as a dehydrating reagent in the formation of carboxamates[19] and in the transformation of primary amides into nitriles.[20] In view of these characteristics, titanium tetrachloride seems to be a promising reagent for the purpose on hand.[21]

Indeed, when carbonyl compounds were treated with $TiCl_4$ for a brief time, usual work up and isolation gave an excellent yield of the thioacetals (Table 1). Aldehydes (Table 1, entries 1,3,4) reacted with thiols in the presence of $TiCl_4$, at room temp. in dry chloroform to yield thioacetals in excellent yields. The reaction was fast (1 hr) and the products were devoid of any side-products. Ketones, when subjected to this catalysis, furnished thioacetals in attractive yields (Table 1, entries, 5 to 8, 10, 11).

Cyclic ethylene thioacetals were formed when a carbonyl compound was allowed to react with ethylene dithiol in presence of titanium tetrachloride. As expected, the reaction rate was very fast (Table 1, entries 2, 9).

It is interesting to note that, carbonyl compounds having an α-proton gave excellent yields of thio-acetals with ethanethiol in presence of $TiCl_4$ (Table 1, entries 1,5,6,7), in contrast to the performance of $AlCl_3$ catalysis,[14] which gave only moderate yields.

It may be mentioned that, enolizable carbonyl compounds have been noted[14] to furnish only vinyl sulfides with thiols under $AlCl_3$ catalysis. In contrast, with $TiCl_4$ even highly enolizable ethyl acetoacetate gave a near quantitative yield of the thioacetal with ethanethiol.

In all the cases, the product were clean and purified by simple distillation.

This thioacetalization is presumed to proceed through the initial co-ordination of $TiCl_4$ to the carbonyl oxygen (Fig. 1). This is followed by the nucleophilic attack of the thiol which gives the intermediate (2), which either go to thioacetal (4) *via* direct nucleophilic displacement by another molecule of thiol or can proceed *via* carbonium ion intermediate (3), followed by its capture by another molecule of thiol.

In all the cases $TiCl_4$ was shown to be an excellent catalyst for thioacetalization of carbonyl compounds with thiols. Compared to this, $FeCl_3$ was inferior, which gave the same results with carbonyl compounds but the reaction rates were slow. (Table 1).

Conclusion: This reaction therefore, represents a simple, yet efficient method for thioacetalization of carbonyl compounds under very mild reaction conditions. It is general in scope and does not require any specific reagent and therefore be regarded as standard thioacetalization prodedure.

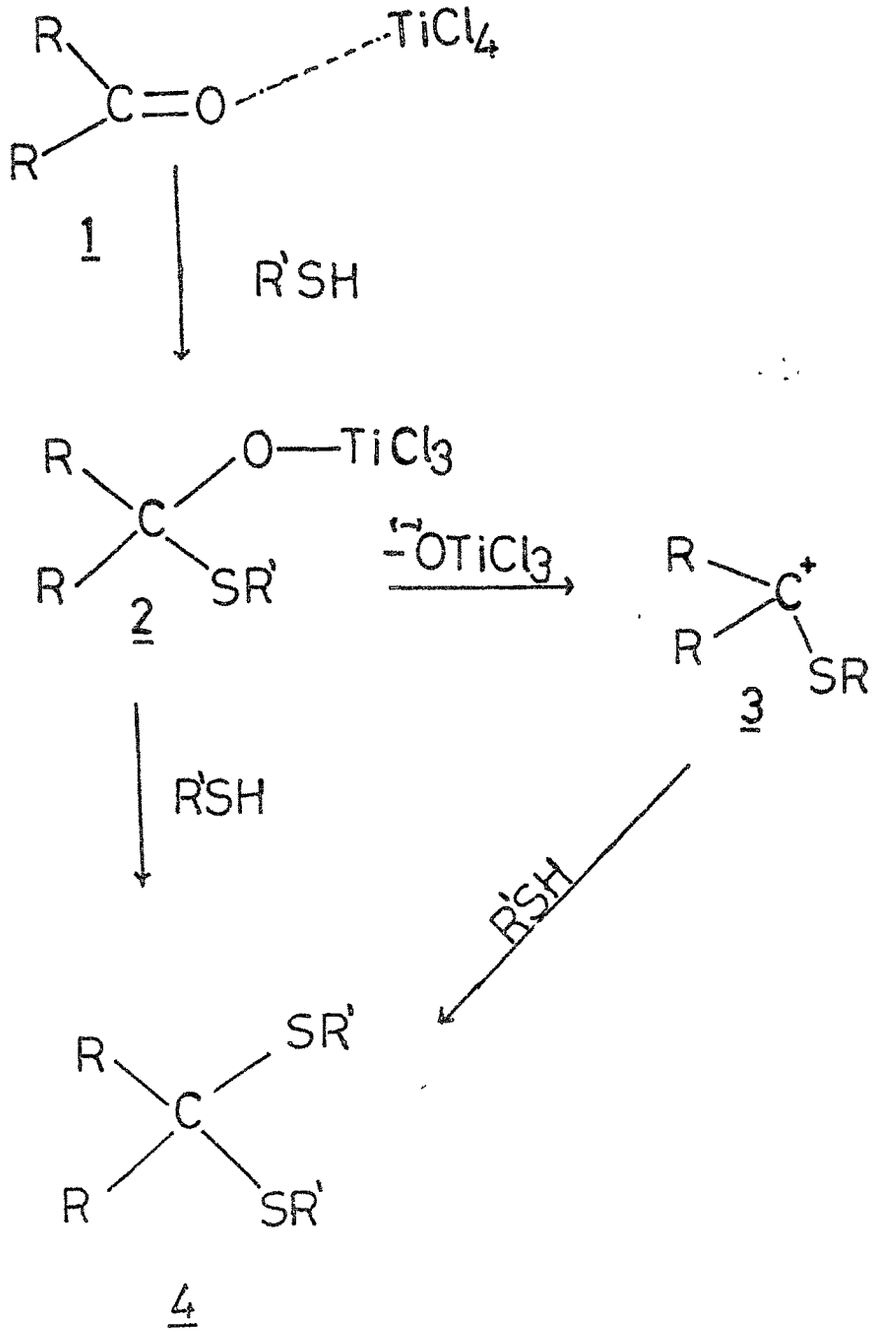

R
C=O
R
TiCl4
1
R'SH
R
O—TiCl3
C
R
SR'
2
⁻OTiCl3
R
C+
R
SR
3
R'SH
R'SH
R
SR'
C
R
SR'
4

Fig.1

EXPERIMENTAL

For general remarks, see Chapter-II, Part-I. Reactions were monitered by Glc.

Procedure A (Ferric chloride method)

To a stirred soln of the carbonyl compound (10 mmole) and ethanethiol (25 mmole) in dry chloroform (5 ml) at -10 to -15°C, anhydrous ferric chloride (0.3 g, 1.8 mmole) was added and the reaction temp was allowed to attain room temo.(28-30°) during next few minutes. After stirring at this temo. for 3-4 hr (in case of aldehydes) or 20-24 hr (for ketones), aq. potassium carbonate soln (10%, 5 ml) was added and the chloroform layer separated. The aq. phase was extracted with chloroform (5 ml x 3), washed with water, brine and dried (Na_2SO_4). After removal of the solvent, the product was distilled.

Procedure B (Titanium tetrachloride method)

A soln of the carbonyl compound (10 mmole) and the desired monothiol (25 mmole) or dithiol (12.5 mmole) in dry chloroform was cooled to -10° to -15°, and $TiCl_4$ (0.25 g; 1.3 mmole) was introduced with stirring and the reaction temperature was allowed to attain room temperature (28-30°) during the next few minutes. After stirring at this temp. for an hour (in case of aldehydes) or 6-12 hr (for ketones) in the case of monothiols or half these times for the dithiol, water (5 ml),

was introduced and the chloroform layer separated. The aq. phase was extracted with chloroform (5 ml x 3) and the combined extracts washed with water (5 ml x 3), brine and dried (Na_2SO_4). After removal of the solvent, product was distilled.

Heptaldehyde diethyldithioacetal[6] 1

Heptaldehyde diethyldithioacetal (1) was prepared in 95% yield by both the methods A and B (98% purity by glc 10% SE-30, 170°, Rt 8.0 min), b.p. 120-23°/5 mm (lit.[8], b.p. 90°/0.02 mm).

PMR: C-C-C$\underline{H}_3$, (3H, bt, 0.92 ppm), C$\underline{H}_2$ S-CH_2-C$\underline{H}_3$, (16H, m, 1.35 ppm), -S-C$\underline{H}_2$, (4H, m, 2.62 ppm), S-C$\underline{H}$, (1H, t, 3.72 ppm, J = 7Hz).

Heptaldenyde ethylenedithioacetal[22] 2

Heptaldehyde ethylene-dithioacetal (2) was prepared in 95% yield by method A (98% purity by glc, 10% SE-30, 170°, Rt 7 min), b.p. 115-118°/4mm (lit.[22], b.p. 100.5-101/1.1 mm).

PMR: C-C-C$\underline{H}_3$ (3H, bt, 0.89 ppm), C$\underline{H}_2$ (10H, 2b, 1.32 and 1.75 ppm), S-C$\underline{H}_2$ (4H, s, 3.18 ppm), S-C$\underline{H}$ (1H, t, 4.4 ppm, J = 7 Hz).

Benzaldehyde diethyldithioacetal[14] 3

Benzaldehyde diethyldithioacetal (3) was prepared in 95% yield by both the methods A and B. (99% purity by glc, 10% SE-30, 170°, Rt 10 min.), b.p. 125-30°/5 mm (lit.[14], b.p. 144-6/8 mm).

PMR: $C\underline{H}_3$ (6H, t, 1.22 ppm J = 7.5 Hz), $S\text{-}C\underline{H}_2$ (4H, m, 2.5 ppm), $-S\text{-}C\underline{H}$ (1H, s, 4.89 ppm); aromatic-$\underline{H}$ (5H, m, 7.28 ppm).

Anisaldehyde diethyldithioacetal;[15] 4

Anisaldehyde diethyldithioacetal (4) was prepared in 95 and 99% yield by the methods A and B respectively. (97% purity by Glc, 10% SE-30, 200° Rt 9 min.), b.p. 150-51°/6 mm.

PMR: $C\text{-}C\underline{H}_3$ (6H, t, 1.25 ppm; J = 7.5 Hz), $O\text{-}C\underline{H}_3$ (3H, s, 3.81 ppm), $S\text{-}C\underline{H}$ (1H, s, 4.9 ppm), aromatic-$\underline{H}$ (4H, 2d 6.85 and 7.36 ppm, J = 8Hz).

Methylamyl ketone diethyldithioacetal[13] 5

Methylamylketone diethyldithioacetal (5) was prepared in 95 and 98% yield by the methods A and B respectively. (95% purity by Glc, 10% SE-30, 200°, Rt 5 min), b.p. 135-36°/7 mm.

PMR: $C\text{-}C\text{-}C\underline{H}_3$ (3H, bt, 0.96 ppm), $C\underline{H}_2$, $S\text{-}C\text{-}C\underline{H}_3$ (17H, m, 1.35 ppm), $S\text{-}C\underline{H}_2$ (4H, q, 2.6 ppm, J = 7.5Hz).

Cyclopentanone diethyldithioacetal[8] 6

Cyclopentanone diethyldithioacetal (6) was prepared in 98% yield by methods A and B. (95% purity by Glc, 10% SE-30, 100° Rt 3 min), b.p. 110-111°/6 mm.

PMR: CH_3, (6H, t, 1.25 ppm J = 7.5 Hz), -S-CH_2 (4H, q, 2.6 ppm, J = 7.5 Hz), CH_2 (8H, m, 1.85 ppm).

Cyclohexanonediethyldithioacetal[6] 7

Cyclohexanonediethyldithioacetal (7) was prepared in 95 and 98% by methods A and B respectively (98% purity by Glc, 10% SE-30, 170°, Rt 7 min), b.p. 125-30°/6 mm (lit.[8], 35°/2mm).

PMR: CH_3 (3H, t, 1.20 ppm, J = 7.5 Hz), S-CH_2 (4H, q, 2.67 ppm J = 7.5 Hz), CH_2 (10H, m, 1.6 ppm).

Acetophenone diethyldithioacetal,[13] 8

Acetophenone diethyldithioacetal (8) was prepared in 90% yield by method B (91% purity by Glc, 10% SE-30, 200°, Rt 5 min.), b.p. 145-50°/6 mm.

PMR: CH_3 (6H, t, 1.3 ppm, J = 7.5 Hz), S-CH_2 (4H, q, 2.60, J = 7.5 Hz), S-C-CH_3 (3H, s, 2.10 ppm), aromatic-H (5H, 2m, 7.28, 7.69 ppm).

Acetophenone ethylenedithioacetal[8] 9

Acetophenone ethylenedithioacetal (9) was prepared by

method B in 96% yield (purity 98% by Glc, 10% SE-30, 170°, Rt 7 min.), b.p. 140-42°/5 mm, (lit.[8] 131°/3 mm).

PMR: CH_3 (3H, s, 2.13 ppm), CH_2 (4H, m, 3.32 ppm), aromatic-H (5H, 2m, 7.25 and 7.75 ppm).

Benzophenone diethyldithioacetal[5], 10

Benzophenone diethyldithioacetal (10) was prepared in 90% yield by method B. (98% purity by glc, 10% SE-30, 200° Rt 4 min), b.p., 185-90°/1 mm (lit.[5], b.p. 165-70/0.7 mm).

PMR: CH_3 (6H, t, 1.5 ppm; J = 7.5 Hz), CH_2 (4H, q, 2.3 ppm, J = 7.5 Hz), aromatic-H (5H, 2m, 7.22 and 7.49 ppm).

Ethylacetoacetate diethyldithioacetal (11)

Ethylacetoacetate diethyldithioacetal (11) was prepared by method B in 98%, (98% purity by Glc, 10% SE-30, 200°C, Rt, 3 min.). b.p. 130-35°/10 mm.

PMR: $-CH_3$ (9H, m, 1.22 ppm), $S-C-CH_3$ (3H, s, 1.7 ppm), $-\overset{O}{\overset{\|}{C}}-CH_2$, $S-CH_2$ (6H, m, 2.62 ppm), $O-CH_2$ (2H, q, 4.1 ppm, J = 7Hz).

IR : 3420, 2970, 1230, 1440, 1365, 1320, 1260, 1185 and 1062 cm^{-1}.

(Found: C, 50.42; H, 8.52; S, 26.30. $C_{10}H_{20}O_2S_2$ requires: 50.79; H 8.53; 27.08%).

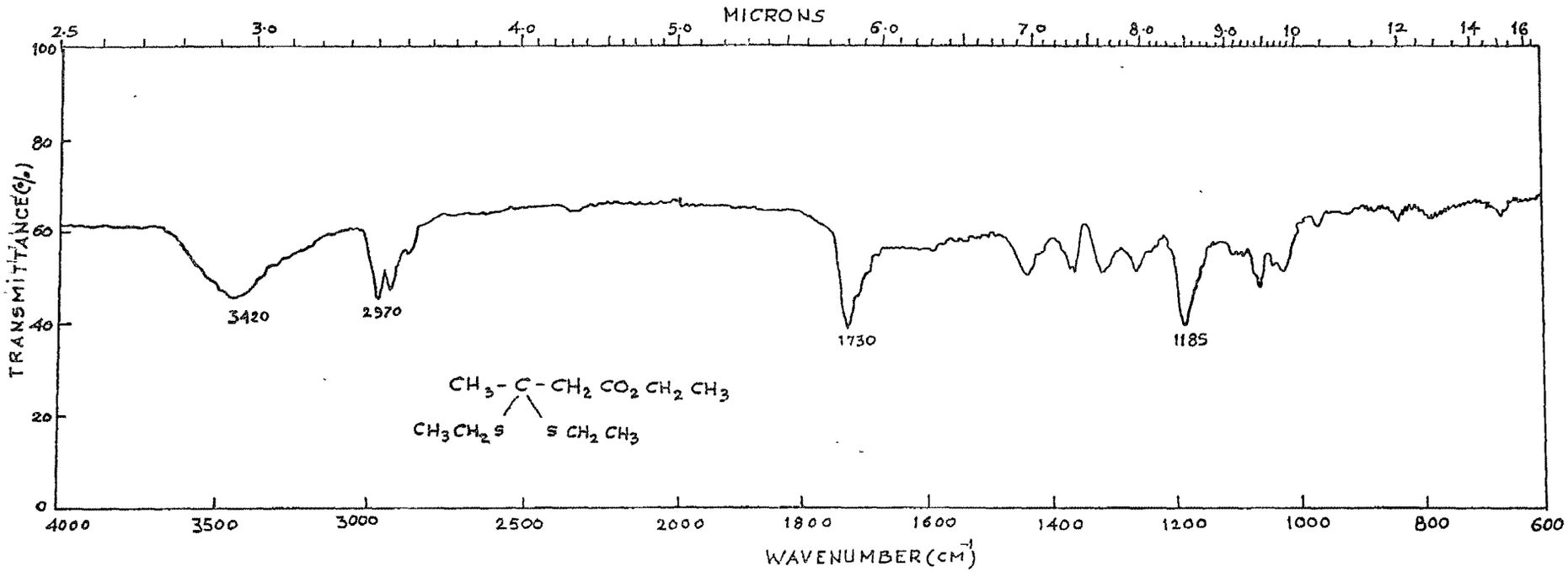


Fig. 2 - IR Spectrum of ethylacetoacetate diethyldithioacetal (11)

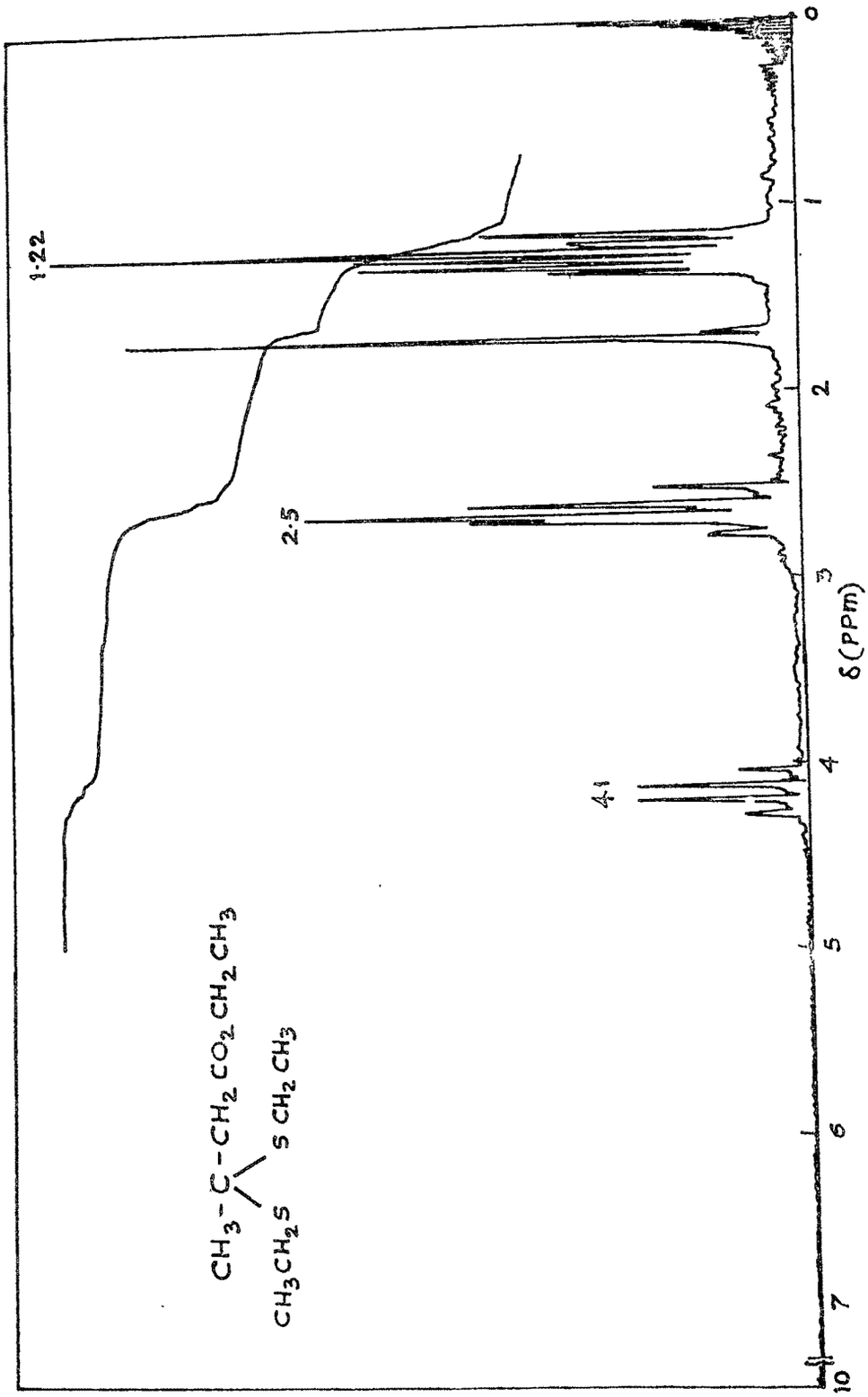


Fig. 3 - PMR Spectrum of ethylacetoacetatediethyldithioacetal (11)

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