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Studies of Acetothiolacetate

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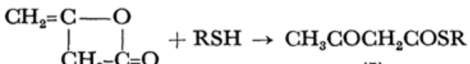
Ketene dimer reacted with mercaptan to give acetothiolacetate (I) in the presence of triethylamine. The ester I underwent a thermal condensation to give dehydroacetic acid (III), with the liberation of mercaptan, merely upon heating, and the reaction was effectively promoted in the presence of triethylamine. The ester I reacted with alkyl halide and acyl halide in dioxane to give α-alkyl and α-acylacetothiolacetate (II) respectively. Ethyl acetothiolacetate, ethyl α-methylacetothiolacetate, and ethyl α-acetylacetothiolacetate reacted with mercuric oxide at a low temperature to give diacetylacetone (VI), methyl ethyl ketone, and dehydroacetic acid (III) respectively.

Although there have been some indications of the differences between esters and thiolesters, acetothiolacetate (I) has been investigated extensively by only a few workers, including Cronyn[1] and Reid.[2]

The present work was undertaken in order to establish an effective way of preparing the ester I and in order to study the chemical properties of I and the related compounds.

In the present study, mercaptans were allowed to react with ketene dimer in the presence of triethylamine; acetothiolacetates (I) were thus conveniently prepared in 30—56% yields.[*1]

The synthesis of I was unsuccessful when sulfuric acid or *p*-toluenesulfonic acid was used as the catalyst because of contamination by persistent impurities.[*2]



$$CH_2{=}C{-}O,\ CH_2{-}C{=}O + RSH \rightarrow CH_3COCH_2COSR$$

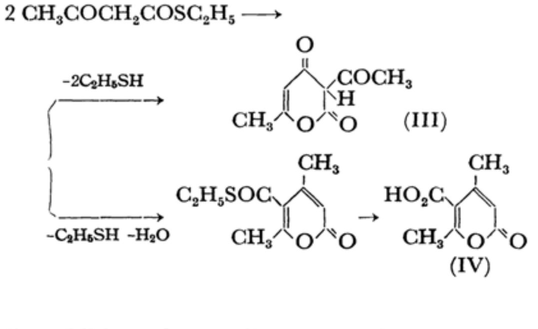
(I)

Ia) $R = C_2H_5$ Ib) $R = (CH_3)_2CH$
Ic) $R = C_2H_5(CH_3)CH$ Id) $R = (CH_3)_3C$

TABLE 1. PREPARATION OF ACETOTHIOLACETATE (CH_3COCH_2COSR)

R	Bp °C/mmHg	Yield %	Anal S% Calcd	Found
C_2H_5	110/30	56	21.93	21.65
$(CH_3)_2CH$	94—95/10	34	20.01	20.11
$C_2H_5(CH_3)CH$	103—104/10	30	18.40	18.71
$(CH_3)_3C$	85—86/6	31	18.40	18.31

It has been known that 2 mol of ethyl acetoacetate lose 2 mol of ethanol when heated at about 200°C; giving dehydroacetic acid (III) in a 53% yield.[3] Similarly, it has been found that a considerable amount of Ia can be converted into III even at 100—120°C with the liberation of mercaptan. Since the anion stability of the ethylmercapto group is greater than that of the alkoxyl group, mercaptan is more readily eliminated than alcohol from the corresponding esters.



(III)

(IV)

The addition of a small amount of triethylamine caused a marked increase in the yield of III, whereas the reaction was not accerelated by sodium acetate. On the other hand, acetic acid rather hindered the reaction and cold concentrated sulfuric acid caused it to give isomeric isodehydroacetic acid (IV).

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[1] M. W. Cronyn, M. P. Chang and R. A. Wall, *J. Am. Chem. Soc.*, **77**, 3031 (1955).

[2] R. B. Baker and E. E. Reid, *ibid.*, **51**, 1567 (1927); *ibid.*, **59**, 1089 (1937).

[*1] For the preparation of I, two methods have already been established, namely, by the Claisen condensation of thiolacetate with sodium (15% yield)[2] or isopropylmagnesium bromide (25—70% yield).[1]

$$2\,CH_3COSC_2H_5 \xrightarrow{\text{Na or } i\text{-PrMgBr}} CH_3COCH_2COSC_2H_5$$

[*2] Alkyl acetoacetate was prepared from ketene dimer and alcohols in the presence of acids (A. B. Boese, U. S. Pat. 2167168).

[3] F. Arndt, "Organic Syntheses," Coll. Vol. III, p. 231 (1955).

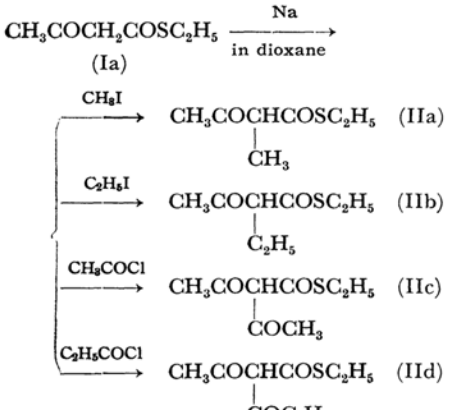
TABLE 2. THERMAL CONDENSATION OF Ia

Catalyst	g	Product	Yield %	Recovered ester %
none	—	dehydroacetic acid	38	60
$(C_2H_5)_3N$	0.2		75	20
$NaHCO_3$	0.2		58	35
CH_3CO_2Na	0.2		35	40
CH_3CO_2H	0.2		8	80
H_2SO_4	—	isodehydroacetic acid	23	—

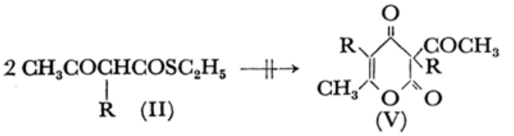
This thermal condensation was also extended to α-alkyl and α-acylacetothiolacetate. The alkylation and acylation of Ia were carried out by ordinary methods with the aid of sodium in dioxane, in which the sodium salt of Ia was readily dissolved. The NMR spectra of the products showed that the *C*-alkylated and *C*-acylated compounds were exclusively obtained. However, since these substituted acetothiolacetates were stable at higher temperatures even in the presence of triethylamine, the expected compounds V were not obtained.

TABLE 3. PREPARATION OF α-SUBSTITUTED ETHYL ACETOTHIOLACETATE $(\mathrm{CH_3CO\underset{R}{C}HCOSC_2H_5})$

R	Bp °C/mmHg	Yield %	Anal S% Calcd	Anal S% Found
CH_3	114—115/30	93	20.01	19.81
C_2H_5	120—121/29	47	18.40	18.63
CH_3CO	124—125/29	58	17.04	17.27
C_2H_5CO	128—129/29	52	15.86	15.68



$$\underset{\text{(Ia)}}{\mathrm{CH_3COCH_2COSC_2H_5}} \xrightarrow[\text{in dioxane}]{\text{Na}} \begin{cases} \xrightarrow{\mathrm{CH_3I}} \mathrm{CH_3CO\underset{CH_3}{C}HCOSC_2H_5} \quad \text{(IIa)} \\ \xrightarrow{\mathrm{C_2H_5I}} \mathrm{CH_3CO\underset{C_2H_5}{C}HCOSC_2H_5} \quad \text{(IIb)} \\ \xrightarrow{\mathrm{CH_3COCl}} \mathrm{CH_3CO\underset{COCH_3}{C}HCOSC_2H_5} \quad \text{(IIc)} \\ \xrightarrow{\mathrm{C_2H_5COCl}} \mathrm{CH_3CO\underset{COC_2H_5}{C}HCOSC_2H_5} \quad \text{(IId)} \end{cases}$$



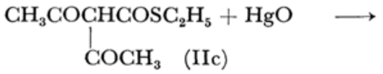
R=CH_3, C_2H_5, CH_3CO, C_2H_5CO

On the other hand, when yellow mercuric oxide was added to Ia at room temperature, a vigorous reaction took place and mercury ethylmercaptide was formed, along with carbon dioxide. At lower temperatures, the reaction proceeded slowly to give a substance melting at 44—46°C. It was not the expected dehydroacetic acid, but was identfied as diacetylacetone (VI) by elementary analysis and by conversion into its bisphenylhydrazone.

Similarly, the reaction of ethyl α-methylacetothiolacetate (IIa) with mercuric oxide gave a small amount of methyl ethyl ketone, whereas ethyl α-acetylacetothiolacetate (IIc) yielded acetylacetone and III.

$$\underset{\text{(Ia)}}{\mathrm{CH_3COCH_2COSC_2H_5}} + \mathrm{HgO} \longrightarrow$$

$$\underset{\text{(VI)}}{\mathrm{CH_3COCH_2COCH_2COCH_3}} + \mathrm{Hg(SC_2H_5)_2} + \mathrm{CO_2}$$



$$\mathrm{CH_3CO\underset{COCH_3}{C}HCOSC_2H_5} \text{ (IIc)} + \mathrm{HgO} \longrightarrow$$

$$\mathrm{CH_3COCH_2COCH_3} + \mathrm{III} + \mathrm{Hg(SC_2H_5)_2} + \mathrm{CO_2}$$

Experimental

Acetothiolacetic Acid Esters (I). To 0.35 mol of mercaptan containing 0.2 m*l* of triethylamine, 0.35 mol of the ketene dimer was added, drop by drop, over a 1-hr period at the boiling point of the mercaptan. After 1 hr, the reaction mixture was distilled and the corresponding acetothiolacetate was obtained.

In the case of the ethyl ester, the procedure had to be modified slightly to prevent the evaporation of ethylmercaptan. To 0.35 mol of ethylmercaptan containing 0.2 m*l* of triethylamine, 0.35 mol of the ketene dimer was added, drop by drop, over a 1-hr period at 0—5°C. The mixture was then stirred at room temperature until the odor of the ketene dimer was lost. Then the mixture was distilled. These results are shown in Table 1.

Ethyl α-Alkyl and α-Acylacetothiolacetate (II). To a suspension of 0.17 g atom of sodium in 60 m*l* of dioxane, 0.18 mol of Ia was added, drop by drop, at room temperature. After the sodium had dissolved, 0.18 mol of alkyl halide or acyl halide was stirred in at such a rate that the temperature did not exceed 50°C. The mixture was then stirred at the same temperature for 4 hr. After cooling, the sodium halide was filtered off and the filtrate was concentrated under reduced pressure. The residue was distilled to give ethyl α-alkyl and α-acylacetothiolacetate (II).

Dehydroacetic Acid (III). (Thermal Condensation of Ia). Ten grams of Ia containing 0.2 g of a catalyst were heated in an oil bath at 100—120°C. The evolution of ethylmercaptan was observed. After 2 hrs' heating, the reaction mixture was distilled to give III and recovered Ia. The results are summarised in Table 2.

Isodehydroacetic Acid (IV). The procedure of the reaction of Ia with sulfuric acid was similar to that described in the preparation of IV from ethyl acetoacetate.[4] The product was recrystallised from benzene; yield, 22.5%; mp 153°C, undepressed upon admixture with an authentic sample of IV.

The Reaction of Ia with Mercuric Oxide. Ia (29 g, 0.2 mol) was added to a suspension of yellow mercuric oxide (21 g, 0.1 mol) in 60 m*l* of ether over a one-hour period between −20°C and −30°C. After the mixture had then been stirred a further 35 hr at the same temperature, mercury mercaptide (mp 85°C recrystallised from ethanol) was filtered off and the ether was evaporated. The residue was distilled to give fractions boiling at 105—118°C/8 mmHg. The distillate solidified on cooling and was recrystallised from petroleum ether to give pure diacetylacetone (VI), mp 44—46°C; yield, 5 g, and bisphenylhydrazone, mp 140—142°C, undepressed by admixture with an authentic sample.*3

Found; C, 58.99; H, 7.12%; mol wt (Cryoscopy in benzene), 140.3. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09%; mol wt, 142.2.

The Reaction of IIc with Mercuric Oxide. IIc (38 g, 0.2 mol) was added, drop by drop, to a suspension of yellow mercuric oxide (21 g, 0.1 mol) in 60 m*l* of ether over a 1-hr period at 0—5°C. After the mixture had then been stirred for 48 hr at the same temperature, the mercaptide thus precipitated was filtered off and the filtrate was distilled. Two fractions, boiling at 120—140°C and at 120—135°C/5 mmHg, were collected. The first fraction was redistilled to give 6 g of acetylacetone, bp 135—138°C. It was identified by the formation of the semicarbazone, mp 108—110°C, undepressed on admixture with a sample prepared from commercial acetylacetone. The second fraction immediately solidified and was recrystallised from ethanol to give 3 g of III, mp 109°C.

The authors wish to thank Professor Yojiro Tsuzuki for his helpful advice and encouragement.

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[4] N. R. Smith and R. H. Wiley, "Organic Syntheses," Coll. Vol. IV, p. 549 (1963).

*3 The authentic bisphenylhydrazone was obtained by the reaction of phenylhydrazine with diacetylacetone prepared from dehydroacetic acid (F. Feist, *Ann.*, **257**, 276 (1890)).