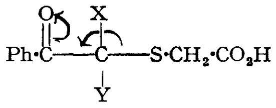
454. *The Carbon–Sulphur Fission in Thio-ethers. Part I. The Retarding Influence of α-Methyl Groups and of the Length of the Acid Chain on the Alkaline Hydrolysis of (2-Ketoalkylthio)- and (*p*-Nitrotriphenylmethylthio)-acetic Acids.*

By Youssef Iskander and Rasmy Tewfik.

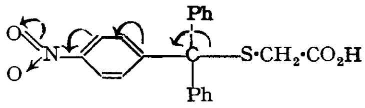
The action of alkalis on thio-ethers of the structure Ph•CO•CXY•SZ ($Z = CH_2{\cdot}CO_2H$, $CH_2{\cdot}CH_2{\cdot}CO_2H$, $CHMe{\cdot}CO_2H$, or $CMe_2{\cdot}CO_2H$) was found to take any of the following four courses : (*a*) a C–SZ fission, (*b*) a CO–C fission, (*c*) a combination of (*a*) and (*b*), or (*d*) no fission whatever. The fission (*a*) was gradually retarded by introduction of one or two methyl groups in the α-position ($Z = CHMe{\cdot}CO_2H$ or $CMe_2{\cdot}CO_2H$) or by increase in the length of the acid chain ($Z = CH_2{\cdot}CH_2{\cdot}CO_2H$). Where X = Y = Ph, and less readily where X = H and Y = Ph, the retardation of the C–SZ fission was accompanied by a CO–C fission, but where X = Y = H and where the retardation of the C–SZ fission was complete ($Z = CMe_2{\cdot}CO_2H$) no CO–C fission occurred.

In the compounds $p\text{-}NO_2{\cdot}C_6H_4{\cdot}CPh_2{\cdot}SZ$ it was also found that when $Z = CHMe{\cdot}CO_2H$ the C–SZ fission was slower than when $Z = CH_2{\cdot}CO_2H$ and was completely absent when $Z = CH_2{\cdot}CH_2{\cdot}CO_2H$ or $CMe_2{\cdot}CO_2H$. The significance of these results is discussed.

The alkaline hydrolysis of thio-ethers of the general formula R•SZ was discussed by Iskander (*J.*, 1948, 1549) and shown to depend on the electron deficiency at the sulphur atom caused by electron-attractive groups in R such as the carbonyl or the nitro-group in the β- or a β-conjugated position :



and



The attachment of phenyl groups to the α-position in R caused retardation of the hydrolysis with a consequent attack of the alkali on the carbonyl group, while in Z the length of the chain of the acid was found also to be a retarding factor. In order to clarify these views, experiments were designed to amplify the last two factors and to introduce a third one, namely, the attachment of methyl groups at the α-position in Z. The following table combines the results now described with some previously recorded (standard time of the hydrolysis experiments was 30 minutes except as otherwise stated) :

R.	(1) SZ = $S{\cdot}CH_2{\cdot}CO_2H$.	(2) SZ= $S{\cdot}CHMe{\cdot}CO_2H$.	(3) SZ = $S{\cdot}CMe_2{\cdot}CO_2H$.	(4) SZ = $S{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$.
$Ph{\cdot}CO{\cdot}CH_2$	CO—C—↓S[1]	CO—C—↓S	CO—C—↓S trace	CO—C—↓S 40%
$Ph{\cdot}CO{\cdot}CHPh$	CO—C—↓S[2] 3·5 min.[3]	CO↓—C—↓S 20% 80%	CO↓—C—S	CO—C—↓S[3] 15% (20 min.)
$Ph{\cdot}CO{\cdot}CPh_2$	CO↓—C—↓S[3] 20% 80%	CO↓—C—S	CO↓—C—S	CO↓—C—S[3]
$NO_2{\cdot}C_6H_4{\cdot}CPh_2$	C—↓S[3] 5 min.	C—↓S 15 min.	unchanged	unchanged

[1] Holmberg, *Chem. Zentr.*, 1936, I, 4564. [2] Behaghel and Schneider, *Ber.*, 1935, **68**, 1588.
[3] Schönberg and Iskander, *J.*, 1942, 90.

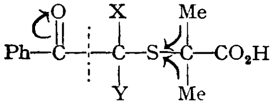
It is seen that all the α-thio-*iso*butyric acids (col. 3) have resisted hydrolysis completely except for a trace in the phenacyl compound, and the α-thio-propionic acids (col. 2) occupied intermediate position between these acids and the thio-acetic acids (col. 1). Similarly, the β-thio-propionic acids (col. 4) occupy an intermediate position between the α-thio-propionic acids and *iso*butyric acids.

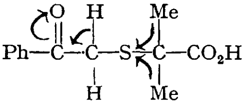
In the phenacyl series of compounds, where no phenyl groups hinder the C–S fission, one methyl group attached to the α-position in Z was not sufficient to retard the hydrolysis, while two methyl groups could stop it completely; on the other hand, increase in the length of the acid chain could lead to a C–S fission only of 40% after ½ hour's boiling with alkali. Furthermore, in all the compounds of this series no elimination of the benzoyl group occurs even in the case of α-(phenacylthio)*iso*butyric acid where the C–S fission was completely hindered, while in the cases of α-(α-benzoylbenzylthio)- and α-(benzoydiphenylmethylthio)-*iso*butyric acids complete elimination of the benzoyl group readily occurs. This is clearly due to the increased possibility in the phenacyl compounds for enol formation by the action of the alkali :

$$Ph{\cdot}CO{\cdot}CH_2{\cdot}S{\cdot}CMe_2{\cdot}CO_2H + 2NaOH \longrightarrow Ph{\cdot}C(ONa){:}CH{\cdot}S{\cdot}CMe_2{\cdot}CO_2Na + 2H_2O$$

and accordingly no seat for the nucleophilic reagent will be available (cf. Beckham, *J. Amer. Chem. Soc.*, 1934, **56**, 1122, who found that cleavage of diketones of the general formula R·CO·CHR′·COR″ occurs on the unenolised side of the diketone).

It appears from the above results that the factors decreasing the strengths of the acids under discussion, *i.e.*, the length of the acid chain or the substitution of the α-hydrogen atoms by methyl groups, were the same factors that retarded the C–S fission of these thio-ethers, enriching the sulphur atom with electrons in the same way as they must have transmitted a +*I* effect towards the carboxyl group :





and accordingly the alkali attacks and eliminates the carbonyl group in the α-benzoylbenzyl and the α-benzoyldiphenylmethyl compounds, or forms the enolate compound with the phenacyl compounds, while the *p*-nitrotriphenylmethylthio-acids containing these retarding factors are recovered unchanged.

EXPERIMENTAL.

Microanalyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected.

α-(Phenacylthio)propionic Acid.—Phenacyl chloride (3·1 g.) in alcohol (40 c.c.) was treated with a solution of α-mercaptopropionic acid (2·1 g.) and sodium hydrogen carbonate (4·3 g.) in water (20 c.c.), and the mixture boiled on the water-bath for 15 minutes. (Continued boiling caused gradual formation and deepening of a yellow colour.) Cooling, dilution with water, extraction with ether to remove any turbidity, and finally acidification gave the *acid* (4·1 g.) which separated from carbon tetrachloride in prisms, m. p. 90—92° (Found : C, 58·6; H, 5·5; S, 14·1. $C_{11}H_{12}O_3S$ requires C, 58·9; H, 5·4; S, 14·3%).

Alkaline hydrolysis. The acid (4 g.) in 5% sodium hydroxide solution (100 c.c.) was boiled for 0·5 hour, the colour of the solution changing from yellow through orange to light red, while oily drops collected on the surface of the solution. The oil, extracted with ether, proved to be acetophenone (1·6 g.), and the alkaline solution on acidification gave only hydrogen sulphide and colloidal sulphur.

β-(Phenacylthio)propionic Acid.—Prepared from phenacyl chloride (3·1 g.) and β-mercaptopropionic acid (2·1 g.) and isolated by the method described above, the *acid* (4·2 g.) crystallised from dilute alcohol in colourless needles, m. p. 63—65° (Found : C, 54·5; H, 6·1; S, 13·5. $C_{11}H_{12}O_3S,H_2O$ requires C, 54·5; H, 5·8; S, 13·2%).

Alkaline hydrolysis. The acid (2 g.) was hydrolysed as above. The oil (few drops), extracted with ether, was identified as acetophenone, and the yellow alkaline solution, on acidification, gave hydrogen sulphide and a yellow precipitate (1·2 g.) which separated from dilute alcohol as yellow crystals, m. p. 63—65° alone or mixed with the original acid. Repeated crystallisation from carbon tetrachloride gave the colourless form of the acid.

*α-(Phenacylthio)*iso*butyric Acid.*—Prepared from phenacyl chloride (3·1 g.) and α-mercapto*iso*butyric acid (2·4 g.) as above, the *acid* (4·6 g.) separated from carbon tetrachloride in fine needles, m. p. 107—108° (Found : C, 60·5; H, 5·9; S, 13·3. $C_{12}H_{14}O_3S$ requires C, 60·5; H, 5·9; S, 13·4%).

Alkaline hydrolysis. The acid (1 g.) was boiled with 5% sodium hydroxide solution (25 c.c.) for 1 hour. Only a trace of acetophenone was extracted with ether, and the yellow alkaline solution, on acidification, gave an orange precipitate (0·9 g.) which separated from alcohol or from carbon tetrachloride (after several crystallisations) in fine needles, m. p. 107—108° alone or mixed with the original acid.

α-(Benzylthio)propionic Acid (Suter, *Z. physiol. Chem.*, 1895, **20**, 278).—Prepared from benzyl chloride (2·5 g.) and α-mercaptopropionic acid (2·1 g.) as above (but with 1 hour's boiling), the acid (3 g.) crystallised from dilute alcohol in needles, m. p. 77—78° (Suter, *loc. cit.*, gives m. p. 73—74°) (Found : C, 61·6; H, 6·0; S, 16·1. Calc. for $C_{10}H_{12}O_2S$: C, 61·2; H, 6·1; S, 16·3%). The acid was recovered almost unchanged after 1 hour's boiling with 5% sodium hydroxide solution.

α-(α-Benzoylbenzylthio)propionic Acid.—Prepared from α-benzoylbenzyl chloride (4·6 g.) and α-mercaptopropionic acid (2·1 g.) with 1 hour's boiling, the *acid* (5·8 g.), by fractional crystallisation from benzene–light petroleum, yielded two types of crystals : (*a*) needles, m. p. 110—111° (1·8 g.) (Found : C, 67·9; H, 5·5; S, 10·8. $C_{17}H_{16}O_3S$ requires C, 68·0; H, 5·3; S, 10·7%), and (*b*) prisms, m. p. 152—155° (0·8 g.) (Found : C, 67·9; H, 5·4; S, 10·8%). The remainder of the acid remained in the mother-liquors. One form is probably the mixture (DD′ and LL′), and the other the racemic form (DL′ + LD′).

Alkaline hydrolysis. The acid (either form) (2 g.) was hydrolysed as above. The solution became turbid after 3 minutes (cf. comparative experiment on the hydrolysis of the α-thioacetic and β-thiopropionic acids, Schönberg and Iskander, *J.*, 1942, 94), but after 0·5 hour's boiling the cooled turbid solution deposited deoxybenzoin (1·05 g.). The alkaline filtrate, on acidification, gave hydrogen sulphide and a colourless precipitate (0·13 g.) which separated from dilute alcohol in fine needles, m. p. 76—78° alone or mixed with α-(benzylthio)propionic acid (*ca.* 80% C–S fission and *ca.* 20% CO–C fission).

*α-(Benzylthio)*iso*butyric Acid.*—Prepared from benzyl chloride (2·5 g.) and α-mercapto*iso*butyric acid (2·4 g.) as above, the acid (4 g.) separated from dilute alcohol in needles, m. p. 96—97° (the m. p. 131° recorded by Larsson and Monies, *Trans. Chalmers Univ. Technol.*, 1945, **47**, 9, has been disproved) (Found : C, 62·6; H, 6·7; S, 15·1. Calc. for $C_{11}H_{14}O_2S$: C, 62·9; H, 6·7; S, 15·2%).

*α-(α-Benzoylbenzylthio)*iso*butyric Acid.*—Prepared from the chloride (4·6 g.) and α-mercapto*iso*butyric acid (2·4 g.), the *acid* (6·2 g.) separated from dilute alcohol in needles, m. p. 129—130° (Found : C, 68·6; H, 5·8; S, 10·4. $C_{18}H_{18}O_3S$ requires C, 68·8; H, 5·7; S, 10·2%).

Alkaline hydrolysis. The acid was hydrolysed as above for 0·5 hour. The clear solution finally obtained gave, on acidification, a colourless precipitate which separated from dilute alcohol in needles, m. p. 96—97° alone or mixed with α-(benzylthio)*iso*butyric acid.

α-(Diphenylmethylthio)propionic acid.—Diphenylmethyl bromide (2·5 g.) reacted vigorously with α-mercaptopropionic acid (1·1 g.) with evolution of hydrogen bromide; when the reaction subsided, the mixture was heated at 100° until no more hydrogen bromide was evolved. After cooling, the solid reaction mixture was extracted with sodium hydrogen carbonate solution which on acidification gave the acid (2·6 g.), separating from dilute alcohol in needles, m. p. 144—145° (Found : C, 70·4; H, 6·3; S, 11·9. $C_{16}H_{16}O_2S$ requires C, 70·6; H, 5·9; S, 11·8%).

*α-(Diphenylmethylthio)*iso*butyric Acid.*—Prepared from the bromide (2·5 g.) and α-mercapto*iso*butyric acid (1·2 g.), the *acid* (2·7 g.) separated from dilute alcohol in fine needles, m. p. 119—120° (Found : C, 71·6; H, 6·3; S, 10·9. $C_{17}H_{18}O_2S$ requires C, 71·2; H, 6·3; S, 11·2%).

β-(Diphenylmethylthio)propionic Acid.—[Cf. its formation by alkaline hydrolysis of β-(α-benzoyldiphenylmethylthio)propionic acid, Schönberg and Iskander, *loc. cit.*]. Prepared from the bromide (2·5 g.) and β-mercaptopropionic acid (1·1 g.), the acid (2·5 g.) separated from dilute alcohol in fine needles, m. p. 89—90° (Found : C, 71·0; H, 6·0; S, 11·5. Calc. for $C_{16}H_{16}O_2S$: C, 70·6; H, 5·9; S, 11·8%).

This acid, like the two preceding, was recovered almost unchanged after 0·5 hour's boiling with 5% sodium hydroxide solution.

α-(α-Benzoyldiphenylmethylthio)propionic Acid.—α-Benzoyldiphenylmethyl chloride (3·1 g.) and α-mercaptopropionic acid (1·1 g.) in dry toluene (30 c.c.) were boiled for 4 hours until no more hydrogen chloride was evolved. The solution was then treated with ether and the acid extracted with cold sodium hydroxide solution (2·5%). (The acid is so weak that it could not be extracted with sodium hydrogen carbonate solution.) Acidification gave the acid (3·5 g.) as a viscous mass which could not be solidified or crystallised.

Alkaline hydrolysis. The acid was dissolved in 5% sodium hydroxide solution and boiled for 0·5 hour. Acidification of the resulting clear solution gave a white solid which separated from dilute alcohol in needles, m. p. 144—145° alone or mixed with the α-(diphenylmethylthio)propionic acid.

α-(*α-Benzoyldiphenylmethylthio*)iso*butyric Acid.*—Prepared from α-benzoyldiphenylmethyl chloride (3·1 g.) and α-mercapto*iso*butyric acid (1·2 g.), the acid (2·9 g.) was obtained as a viscous mass which could not be solidified or crystallised.

Alkaline hydrolysis. Hydrolysis by 5% sodium hydroxide solution for 0·5 hour gave a white solid which separated from dilute alcohol in needles, m. p. 119—120° alone or mixed with α-(diphenylmethylthio)*iso*butyric acid.

α-(*Triphenylmethylthio*)iso*butyric Acid.*—Triphenylmethyl chloride (2·8 g.) and α-mercapto*iso*butyric acid (1·2 g.) in dry toluene (30 c.c.) were boiled for 2 hours. The *acid* (2·1 g.), isolated as usual, separated from dilute alcohol in small plates, m. p. 155—156° (Found: C, 75·8; H, 6·2; S, 8·8. $C_{23}H_{22}O_2S$ requires C, 76·2; H, 6·1; S, 8·8%).

This acid and α-(triphenylmethylthio)propionic acid (Billmann and Due, *Bull. Soc. chim.*, 1924, **35**, 387) were recovered almost unchanged after 0·5 hour's boiling with 5% sodium hydroxide solution.

α-(p-*Nitrophenyldiphenylmethylthio*)*propionic Acid.*—Prepared from the chloride (3·2 g.) and α-mercaptopropionic acid (1·1 g.) in boiling dry toluene (30 c.c.) (3 hours) and isolated as above, the *acid* (0·5 g.) separated from carbon tetrachloride in very pale yellow needles, m. p. 173—174° (Found: C, 67·2; H, 5·1; N, 4·0; S, 8·6. $C_{22}H_{19}O_4NS$ requires C, 67·2; H, 4·8; N, 3·6; S, 8·1%).

Alkaline hydrolysis. The acid (0·1 g.) was hydrolysed as described above. Turbidity began to appear after the first 5 minutes, and after 15 minutes the liberated oil was extracted from the red liquid with ether and crystallised from light petroleum (b. p. 50—60°) from which it separated in crystals, m. p. 90—94° alone or mixed with an authentic specimen of *p*-nitrotriphenylmethane. Acidification of the alkaline solution gave much hydrogen sulphide.

β-(p-*Nitrotriphenylmethylthio*)*propionic Acid.*—Prepared as above from the chloride (3·2 g.) and β-mercaptopropionic acid (1·1 g.) and isolated in the usual way, the *acid* (0·5 g.) separated from dilute alcohol in pale yellow needles, m. p. 125—126° (Found: N, 3·5; S, 8·2. $C_{22}H_{19}O_4NS$ requires N, 3·6; S, 8·1%).

α-(p-*Nitrotriphenylmethylthio*)iso*butyric Acid.*—Prepared from the chloride (3·2 g.) and α-mercapto*iso*butyric acid (1·2 g.), the *acid* (0·3 g.) separated from carbon tetrachloride in pale yellow prisms, m. p. 155—156° (decomp.) (Found: N, 3·1. $C_{23}H_{21}O_4NS$ requires N, 3·4%).

The last two acids were recovered almost unchanged after being boiled with 5% sodium hydroxide solution for half an hour. The sodium salts of these two acids are slightly soluble in cold water, and their solutions acquire in sunlight a yellow colour which fades again in the dark.

Neutral Hydrolysis of Tetraphenyldithiodiacetic Acid.—The acid (Becker and Bistrzycki, *Ber.*, 1914, **47**, 3154) was boiled in dry acetone or ethyl methyl ketone for 6 hours; no blue colour was formed and the substance was recovered unchanged; but when it was boiled with acetone or ethyl methyl ketone containing a few drops of distilled water a blue colour was formed. After 6 hours' boiling, the acetone or ethyl methyl ketone was distilled off and the blue residue (thiobenzophenone) extracted with boiling light petroleum (b. p. 60—70°). Remaining in the hydrolysis flask was a solid which after extraction with ether and crystallisation from acetic acid separated as colourless crystals, m. p. 150—152° alone or mixed with authentic thiobenzilic acid (cf. Schöberl, *Ber.*, 1937, **70**, 1188). The ethyl ester of this acid (Becker and Bistrzycki, *loc. cit.*) was recovered almost unchanged after 6 hour's boiling in moist acetone or ethyl methyl ketone and no blue colour was formed. Although the acid dissolves in cold pyridine giving an immediate dark blue colour, the ethyl ester dissolves without producing any colour.

The authors express their gratitude to Professor J. Kenyon, F.R.S., for advice.

FAROUK I UNIVERSITY, FACULTY OF SCIENCE, ALEXANDRIA. [*Received, January 22nd*, 1951.]