

456. *The Carbon-Sulphur Fission in Thio-ethers. Part III.* The Retarding Influence of the Length of the Radical Chain and of a Second α -Thio-acetic Acid Group on the Alkaline Hydrolysis of (Nitrobenzylthio)- and (Nitrodiphenylmethylthio)-acetic Acids.*

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The action of alkalis on (*p*-nitrodiphenylmethylthio)acetic acid (cf. I) and (*p*-nitrodiphenylmethylenedithio)diacetic acid (cf. II) gives *p*-azoxybenzophenone, whereas that on (*p*-nitrobenzylidenedithio)diacetic (III) and (*2-p*-nitrophenylethylthio)acetic acid effected, not a C-S fission, but the formation of *aci*-structures leading to secondary products which are brownish-red acids still containing nitrogen and sulphur. Further, while (*m*-nitrobenzylthio)acetic acid (see Part II) is completely unchanged by alkalis, the *m*-nitro-compounds of the present series of acids, although they likewise do not suffer a C-S fission, nevertheless undergo secondary changes leading to the formation of brownish-red acids again still containing nitrogen and sulphur, thus showing the influence of the additional phenyl and α -thioacetic acid groups in this respect. The significance of these results is discussed.

THE retarding influences on the alkaline hydrolyses of thio-ethers which are discussed in this paper, namely, (*a*) the substitution of α -hydrogen atoms of the nitrobenzyl radical in (*p*- and *m*-nitrobenzylthio)acetic acids by a phenyl group or a second thioacetic acid group or by both

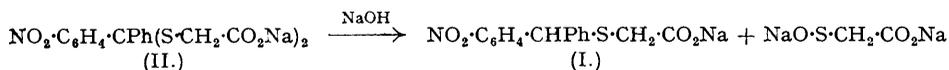


and (*b*) the interruption of conjugation of the nitro-group with the sulphur atom by a CH_2 group ($\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{SZ}$), were applied so as to throw further light on the mechanism of the C-SZ fission in these and similar structures, and to decide whether the presence of one or of the two α -hydrogen atoms in the nitrobenzyl group is necessary for the formation of the azoxy-carbonyl system finally obtained.

Hydrolysis of (*p*-nitrobenzylthio)acetic acid (see Part II) and (*p*-nitrodiphenylmethylthio)acetic acid (cf. I), which differ only by a phenyl group in the α -position, led to *p*-azoxybenzaldehyde and *p*-azoxybenzophenone, respectively. This result shows that the presence of only one hydrogen atom in the α -position sufficed for the formation of the azoxy-carbonyl system, and accordingly, in the case of (*p*-nitrobenzylthio)acetic acid, one of the two α -hydrogen atoms cannot have been involved in the mechanism of the formation of *p*-azoxybenzaldehyde. The formation of *p*-azoxybenzophenone, on the lines suggested for the formation of *p*-azoxybenzaldehyde through an intermediate stage of *p*-hydroxylaminobenzaldehyde

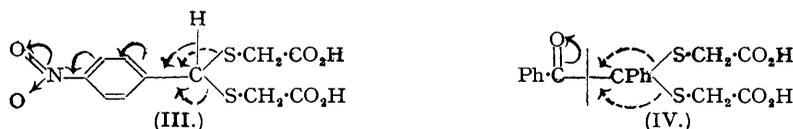
* Part II, preceding paper.

(Part II), might have taken place also *via* the formation of *p*-hydroxylaminobenzophenone (an unknown compound), and whether the C-SZ fission or the *aci*-formation preceded the other on the first attack of the alkali could not be proved; but in the sodium salt of (*p*-nitrodiphenylmethylenedithio)diacetic acid (cf. II), where no α -hydrogen atom is present, the only possibility for the relay of the electromeric displacements towards the powerful electron-attractive nitro-group under the influence of the alkali was one C-SZ fission resulting in the formation of (I) :



which, in turn, was converted into *p*-azoxybenzophenone as before. The sulphide ion (after the decomposition of the liberated sulphenoacetic acid molecule) did not convert *p*-azoxy- into *p*-azo-benzophenone (contrast the case of *p*-azoxybenzaldehyde).

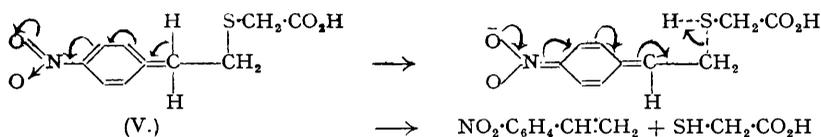
The C-SZ fission, however, was completely prevented in the case of *p*-nitrobenzylidenedithio)diacetic acid (III). The product, although different from the starting material and still unidentified, was again a brownish-red acid containing nitrogen and sulphur. Had the C-S fission occurred first in this compound, the final product could have been *p*-azobenzaldehyde through the prior formation of (*p*-nitrobenzylthio)acetic acid (cf. Part II). *aci*-Formation must therefore have been the quicker process occurring in this compound. Both sulphur atoms must have contributed equally in the electromeric displacements towards the nitro-group, so that neither atom becomes sufficiently deficient in electrons to allow C-S cleavage to be faster than the *aci*-formation. The same explanation is applicable to the case of the acid (IV), where the C-S fission is also prevented by elimination of the benzoyl group (Behaghel and Schneider, *Ber.*, 1935, 68, 1588) :



The non-nitro-compounds corresponding to the above series of thio-ethers, as well as the corresponding *m*-nitro-compounds, did not suffer a C-S fission, although the latter compounds were converted into nitrogen- and sulphur-containing unidentified acids. That from (*m*-nitrodiphenylmethylthio)acetic acid differed from the starting material only in being red, both being viscous liquids giving the same analytical data; on the other hand, the resinous acids from *m*-nitrobenzylidenedithiodiacetic acid and *m*-nitrodiphenylmethylenedithiodiacetic acid differed from their starting materials in their analytical data. Since (*m*-nitrobenzylthio)acetic acid did not suffer such a change (cf. Part II), it seems that the additional phenyl or α -thioacetic acid group was responsible for unexplained changes.

The interruption of conjugation of the nitro-group with the sulphur atom by a CH_2 group in α -(2-*p*-nitrophenylethylthio)acetic acid (V) has also prevented the C-S fission, and again *aci*-formation must have occurred, as indicated by the formation of a brownish-red acid containing both nitrogen and sulphur. A side reaction in the hydrolysis of (V) is the formation of a very small amount of *p*-nitrostyrene, a reaction which occurs *only* in neutral medium, most of the acid being recovered unchanged. This side reaction is similar to the main decomposition reaction of $\text{Ph} \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CHPh} \cdot \text{S} \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$, which gives benzoylstyrene and thioglycollic acid (Behaghel and Ratz, *Ber.*, 1939, 72, 1257).

The corresponding (2-*m*-nitrophenylethylthio)acetic acid, prepared from *m*-nitrostyrene and mercaptoacetic acid in presence of ascaridole (cf. the general method of preparation of similar compounds, Kharasch and Mayo, *Chem. and Ind.*, 1938, 752), although only obtained as an impure viscous oil, was recovered unchanged from the alkaline medium after 15 minutes' boiling, thus pointing to the influence of the *p*-nitro-group in initiating the partial decomposition of (V) into *p*-nitrostyrene, a reaction which does not occur either with the non-nitro- or the *m*-nitro-compound :



EXPERIMENTAL.

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

(*p*-Nitrodiphenylmethylthio)acetic Acid.—*p*-Nitrodiphenylmethanol (Lund., *Ber.*, 1937, **70**, 1520) (5 g.) and mercaptoacetic acid (3 g.) were heated together at 110° while dry hydrogen chloride was passed into the molten mixture for 1 hour. Cooling, treatment with sodium hydrogen carbonate solution, filtration to remove unchanged alcohol (0.3 g.), and finally acidification gave an oil which solidified in the ice-chest to a pale yellow acid (6.3 g.) which separated from benzene in prisms (6.1 g.), m. p. 127—128° (Found: C, 59.9; H, 4.4; N, 4.7; S, 10.4. $C_{15}H_{13}O_4NS$ requires C, 59.3; H, 4.4; N, 4.6; S, 10.5%).

Alkaline hydrolysis. The acid (2 g.) dissolved in cold 5% sodium hydroxide solution (20 c.c.) with the formation of a clear yellow colour which gradually changed to deep orange-red. After 15 minutes at room temperature turbidity began to appear, and after 24 hours a solid cake was formed in the dark solution. Dilution with water, filtration, and washing with water gave a deep orange, solid *p*-azoxybenzophenone (1.4 g.) which crystallised from acetic acid as golden yellow shining plates, m. p. 200° (Found: C, 76.8; H, 4.6; N, 7.2%; M, 410. $C_{26}H_{18}O_3N_2$ requires C, 76.8; H, 4.5; N, 6.9%; M, 406). *p*-Azoxybenzophenone is recorded as being formed, together with *p*-azobenzophenone, by the alkaline reduction of *p*-nitrobenzophenone but could not be isolated from the mixture which was reduced as a whole by alcoholic ammonium sulphide to *p*-hydrazobenzophenone which, in turn, could be oxidised by mercuric oxide to pure azobenzophenone, m. p. 219° (Carré, *Compt. rend.*, 1907, **144**, 34; *Bull. Soc. chim.*, 1909, **5**, 277). The pure *p*-azoxybenzophenone obtained on hydrolysis of our acid could be similarly changed through the same steps into *p*-azobenzophenone, m. p. 219° (Found: C, 79.5; H, 4.7; N, 7.6%; M, 393. Calc. for $C_{26}H_{18}O_2N_2$: C, 79.9; H, 4.6; N, 7.2%; M, 390).

Acidification of the deep-red alkaline filtrate after the hydrolysis caused decolourisation, with the evolution of hydrogen sulphide and a little sulphur dioxide and the precipitation of colloidal sulphur.

The same hydrolysis products were obtained by 5 minutes' boiling with 5% sodium hydroxide solution.

(*m*-Nitrodiphenylmethylthio)acetic Acid.—*m*-Nitrodiphenylmethanol, prepared by Meerwein-Ponndorf reduction (Lund, *loc. cit.*) of *m*-nitrobenzophenone in almost theoretical yield, crystallises from light petroleum (b. p. 60—80°) in clusters of needles, m. p. 68—70° (Found: C, 67.9; H, 5.0; N, 6.3. Calc. for $C_{15}H_{11}O_3N$: C, 68.3; H, 4.8; N, 6.1%) (cf. its preparation by Newman and Smith, *J. Org. Chem.*, 1948, **13**, 592, by Grignard reagents at -70°).

The alcohol (8 g.) and mercaptoacetic acid (3.2 g.) were heated together at 80—90° while dry hydrogen chloride was passed into the molten mixture for 1½ hours. Treatment as for the *p*-isomer gave an oil (9 g.) which did not solidify in the ice-chest and could neither be distilled under reduced pressure nor crystallised. After repeated liberation from sodium hydrogen carbonate solution, extraction with ether, and boiling of the ethereal solutions with charcoal, the acid was obtained as a viscous colourless liquid (Found: C, 59.3; H, 4.7; N, 4.3; S, 9.7. $C_{15}H_{13}O_4NS$ requires C, 59.3; H, 4.4; N, 4.6; S, 10.5%).

Alkaline hydrolysis. The clear yellow solution of the acid (2 g.) in 5% sodium hydroxide solution (20 c.c.) acquired a brownish-red colour after 5 minutes' boiling, but no precipitate was formed. On acidification a trace of hydrogen sulphide was detected while the liberated brownish-red oily acid, after liberation from sodium hydrogen carbonate solution and boiling of the ethereal extracts with charcoal several times, was obtained as a red viscous oil (1.7 g.), analysis of which (Found: C, 59.7; H, 4.5; N, 4.6; S, 10.5%) still agrees closely with that of the original acid.

(Diphenylmethylthio)acetic acid, m. p. 128—130° (Holmberg, *J. pr. Chem.*, 1934, **141**, 93; Behaghel and Ratz, *Ber.*, 1939, **72**, 1275), was recovered almost unchanged after 0.5 hour's boiling with 5% sodium hydroxide solution.

(*p*-Nitrodiphenylmethylenedithio)diacetic Acid.—(a) *p*-Nitrobenzophenone (10 g.) and mercaptoacetic acid (10 g.) were heated together on the water-bath with passage of dry hydrogen chloride for 5 hours. The usual treatment afforded unchanged *p*-nitrobenzophenone (6 g.) and a viscous substance (12 g.) from which, after extraction with ether and crystallisation from benzene-alcohol, the acid separated in aggregates of needles (6.5 g.), m. p. 169—170° (Found: C, 51.7; H, 3.9; N, 3.7; S, 16.4. $C_{17}H_{15}O_6NS_2$ requires C, 51.9; H, 3.8; N, 3.6; S, 16.3%). Passage of dry hydrogen chloride for 1 hour only gave a 33% yield.

(b) Heating a mixture of *p*-nitrobenzophenone dichloride (6.5 g.) and mercaptoacetic acid (4.1 g.) on the water-bath until no more hydrogen chloride was evolved and then isolation of the products as described above gave only 2.3 g. (27.2%) of the acid.

(c) Heating a mixture of *p*-nitrobenzophenone (10 g.) and mercaptoacetic acid (8 g.) in presence of freshly fused and powdered zinc chloride (2.5 g.) for 2 hours (cf. Bongartz, *Ber.*, 1888, **21**, 478) gave only 2 g. (12%) of the pure acid.

Alkaline hydrolysis. The acid (2 g.) dissolved in 5% sodium hydroxide solution (20 c.c.) with the formation of a clear yellow colour which changed after a few seconds to deep yellow and then to brown; during 10 minutes a yellow flocculent sticky precipitate separated. After 24 hours in the cold the precipitate obtained (0.8 g.) crystallised from acetic acid in golden-yellow shining plates, m. p. 200° alone or mixed with the azoxybenzophenone (Found: C, 76.9; H, 4.5; N, 6.9%). The alkaline filtrate, on acidification, liberated hydrogen sulphide and a little sulphur dioxide with the precipitation of colloidal sulphur.

The same products of hydrolysis were obtained by 5 minutes' boiling with 5% sodium hydroxide solution.

(*m*-Nitrodiphenylmethylenedithio)diacetic acid.—Dry hydrogen chloride was passed into a molten mixture of *m*-nitrobenzophenone (10 g.) and mercaptoacetic acid (8 g.) on the water-bath for 1 hour. This afforded unchanged *m*-nitrobenzophenone (3.5 g.) and a very viscous dark sticky material (9.3 g.) from which the acid was obtained, after crystallisation from benzene-alcohol, as clusters of needles (5 g.), m. p. 159—160° (Found: C, 52.0; H, 3.8; N, 3.7; S, 16.5. $C_{17}H_{15}O_4NS_2$ requires C, 51.9; H, 3.8; N, 3.6; S, 16.3%).

Alkaline hydrolysis. A solution of the acid (4 g.) in 5% aqueous sodium hydroxide (50 c.c.) at room temperature gave, after 26 hours, no precipitate, whilst acidification of the resulting deep red solution liberated very little sulphur dioxide with the precipitation of a dark brown sticky material (3 g.). Boiling this with benzene removed unchanged acid, and repeated precipitation from sodium hydrogen carbonate solutions then yielded a dark brown solid, m. p. 185—190° (decomp.) (Found: C, 61.7; H, 3.7; N, 3.6; S, 12.4%), very soluble in pyridine or aniline, hardly soluble in alcohol or ether.

(*Diphenylmethylenedithio*)diacetic Acid. Bongartz's method (*loc. cit.*) gave a very poor yield of this acid. This author reports failure with the following method which we found to give the best yield: Dry hydrogen chloride was passed into a mixture of benzophenone (2 g.) and mercaptoacetic acid (2 g.) at 110° for 2 hours. Isolated as described above, the acid (3 g.) crystallised from dilute acetic acid in shiny plates, m. p. 162—163° [m. p.s recorded are 163—164° (*Ber.*, 1886, **19**, 1931) and 175—176° (*Ber.*, 1888, **21**, 478)].

The acid (1 g.) was recovered almost unchanged (m. p. 166°; 0.8 g.) after 0.5 hour's boiling with 5% sodium hydroxide solution.

(*p*-Nitrobenzylidenedithio)diacetic Acid.—The foregoing method was superior to that of Bongartz (*loc. cit.*). Prepared from *p*-nitrobenzaldehyde (10 g.) and mercaptoacetic acid (12 g.) on the water-bath with passage of dry hydrogen chloride for 1 hour, the pure acid (12.5 g.), formed glistening needles (from water), m. p. 161—162°.

Alkaline hydrolysis. The acid (5 g.) dissolved in cold 5% sodium hydroxide solution (50 c.c.) with the formation of a deep red solution in the course of few seconds, but after 5 minutes' boiling no precipitate was produced. Acidification gave a little hydrogen sulphide and a dark brown solid. Boiling water removed from this any unchanged acid, and repeated precipitation from sodium hydrogen carbonate solution yielded an acid as a dark brown-red powder which did not melt but decomposed above 350° (Found: C, 54.8; H, 3.9; N, 8.4; S, 18.8%), insoluble in most of the organic solvents, freely soluble in cold pyridine or aniline.

The same result was obtained by carrying out the reaction at room temperature for 24 hours.

(*m*-Nitrobenzylidenedithio)diacetic Acid.—This was obtained in good yield and quality by Bongartz's method (*loc. cit.*) or by using hydrogen chloride as the condensing agent as described above. The crude acid (19.4 g.) obtained from *m*-nitrobenzaldehyde (10 g.) and mercaptoacetic acid (12 g.) separated from chloroform in colourless needles, m. p. 130—131°.

Alkaline hydrolysis. The acid (3 g.) dissolved in cold 5% sodium hydroxide solution (30 c.c.) with the formation of a clear brownish-red solution, which, after 5 minutes' boiling, gave no precipitate. Acidification gave very little hydrogen sulphide and a very dark brown tarry substance which did not solidify in the ice-chest but after repeated precipitation from sodium hydrogen carbonate solution and storage in a desiccator for 24 hours gave an acid as a dark brown-red powder (2.2 g.), m. p. 85—90° (decomp.) (Found: C, 46.8; H, 3.7; N, 4.7; S, 19.7%), partly soluble in hot alcohol or hot acetic acid, freely soluble in cold pyridine or aniline.

(Benzylidenedithio)diacetic acid (Bongartz, *loc. cit.*) was recovered almost unchanged after 0.5 hour's boiling with 5% sodium hydroxide solution.

(2-*p*-Nitrophenylethylthio)acetic Acid.—2-*p*-Nitrophenylethyl chloride (10 g.) (Barger, *J.*, 1909, **95**, 2194) in alcohol (50 c.c.) was treated with a solution of mercaptoacetic acid (5 g.) and sodium hydrogen carbonate (9.2 g.) in water (40 c.c.), and the mixture boiled on the water-bath for 1 hour. Cooling, dilution with water, filtration, and acidification gave a yellow oil which solidified (11.2 g.) in the ice-chest. Crystallisation from carbon tetrachloride gave colourless scales of the acid, m. p. 85° (Found: C, 49.7; H, 4.7; N, 5.8; S, 13.3. $C_{10}H_{11}O_4NS$ requires C, 49.7; H, 4.6; N, 5.8; S, 13.3%).

Alkaline hydrolysis. The acid (8 g.) in 5% sodium hydroxide solution (200 c.c.) was boiled under reflux for 5 minutes. The deep red solution was steam-distilled until no further turbidity appeared in the distillate. The volatile *p*-nitrostyrene solidified in the ice-chest as crystals of m. p. 21° (Basler, *Ber.*, 1883, **16**, 3007, reported m. p. 29°; Strassburg, Gregg, and Walling, *J. Amer. Chem. Soc.*, 1947, **69**, 2141, reported m. p. 21.4°) which on treatment with bromine in ether gave the pale yellow dibromide (Basler, *loc. cit.*), m. p. 72° [from light petroleum (b. p. 50—60°)] (Found: C, 31.3; H, 2.6; N, 5.1; Br, 51.5. Calc. for $C_8H_7O_2NBr_2$: C, 31.1; H, 2.3; N, 4.5; Br, 51.7%). The alkaline steam-distillation residue, on acidification, gave hydrogen sulphide and a brown gelatinous precipitate; boiling this with carbon tetrachloride to remove any unchanged acid, and repeated precipitation from sodium hydrogen carbonate solution, gave a brownish-red powder (6.9 g.) which did not melt but decomposed above 350° (Found: C, 56.8; H, 4.5; N, 6.2; S, 9.9%). The same products were obtained by hydrolysis at ordinary temperature during 24 hours.

Hydrolysis in neutral medium. A solution of the sodium salt of the acid, prepared by neutralisation of the acid with sodium hydrogen carbonate, was boiled under reflux for 1 hour. No darkening took place, but again a little *p*-nitrostyrene could be isolated by steam-distillation after which most of the original acid was recovered unchanged.

(2-*m*-Nitrophenylethylthio)acetic Acid.—*m*-Nitrostyrene (Frausnitz, *Ber.*, 1884, **17**, 596) (3 g.) was treated with 100% mercaptoacetic acid (2 g.) and ascaridole (0.5 c.c.), and the mixture left at room

temperature for 36 hours [cf. preparation of (2-phenylethylthio)acetic acid by Kharasch, Read, and Mayo, *Chem. and Ind.*, 1938, 752]. By treatment with ether and extraction with sodium hydrogen carbonate solution, the acid was obtained as a yellow viscous oil which could neither be solidified nor distilled in a vacuum. After repeated liberation from sodium hydrogen carbonate solution and extraction with ether, it remained as an impure viscous oil (1.5 g.) (Found : N, 5.9; S, 11.1. Calc. for $C_{10}H_{11}O_4NS$: N, 5.8; S, 13.3%).

Alkaline hydrolysis. The acid was recovered as a viscous oil after being boiled with 5% aqueous sodium hydroxide for 15 minutes (Found : N, 5.1; S, 10.8%).

(2-Phenylethylthio)acetic Acid.—This acid (Holmberg, *J. pr. Chem.*, 1934, 141, 93) was recovered completely unchanged after 0.5 hour's boiling with 5% alkali solution.

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