455. *The Carbon–Sulphur Fission in Thio-ethers. Part II.* The Retarding Influence of α-Methyl Groups and of the Length of the Acid Chain on the Alkaline Hydrolysis of (Nitrobenzylthio)acetic Acids.*

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The retarding influences of the α-methyl groups and the length of the acid chain on the C–S fission of thio-ethers (Part I) is unable to prevent the alkaline hydrolysis of the corresponding *o*- and *p*-nitrobenzylthio-acids where the *aci*-formation, which is a completed electromeric displacement, has led to the inevitable fission of these thio-ethers. The differences due to the presence of the various retarding factors could not be detected with the *p*-nitro-compounds because of the final transformation of the *p*-nitrobenzyl system into the same substance, *p*-azoxybenzaldehyde, in all the cases examined; but in the cases of the *o*-nitro-compounds the transformation of the *o*-nitrobenzyl system into anthranil, thioanthranil, or *o*-aminobenzaldehyde points to the influence of the retarding factors.

The *m*-nitrobenzylthio-acids were recovered completely unchanged from the alkaline solutions after 15 minutes' boiling, and the *o*- and the *p*-nitro-compounds were rapidly and completely hydrolysed even in the cold. The significance of these results is discussed.

In the preceding paper, the retarding influences of α-methyl groups and the length of the acid chain on the hydrolysis of (2-ketoalkylthio)- and (*p*-nitrotriphenylmethylthio)-acetic acids were clearly traced, and in this research these same retarding structures were attached to the (nitrobenzylthio)acetic acids to ascertain whether they were able to retard the C–S fission to any extent. In the preceding paper it was found that, although (*p*-nitrotriphenylmethylthio)-acetic acid was quickly hydrolysed by alkalis, and the corresponding α-thio-propionic acid required a longer time for its complete hydrolysis, yet the corresponding β-thio-propionic and α-thio-*iso*butyric acid resisted hydrolysis completely. Now it is found that all the corresponding *o*- and *p*-nitrobenzyl compounds can be easily hydrolysed irrespective of all the retarding influences present in the acid chain. The tendency for *aci*-formation in the present case must have led to successive mobilities in the molecule resulting in the inevitable fission of the compound with the transformation of the nitrobenzyl system into an azo-benzoyl system:

$$NO_2{\cdot}C_6H_4{\cdot}CH_2{\cdot} \xrightarrow{-H_2O} [{:}N{\cdot}C_6H_4{\cdot}CO{\cdot}]$$

the final state of which depends upon the mechanism of the reaction and the nature of the medium.

The products of hydrolysis of (*p*-nitrobenzylthio)acetic acid (I; $Z = CH_2{\cdot}CO_2H$) and β-(*p*-nitrobenzylthio)propionic acid (I; $Z = CHMe{\cdot}CO_2H$) by 5 minutes' boiling with 5% alkali (Schönberg and Iskander, *J.*, 1942, 90) were *p*-azobenzaldehyde and *p*-azoxybenzaldehyde, respectively, and the explanation suggested at that time for the production of these two products was simply that the β-sulphenopropionic acid which has oxidising properties could oxidise *p*-azobenzaldehyde (supposed to be initially formed in both cases) to the azoxy-aldehyde in the second case, while in the first case the sulphenoacetic acid, which has no oxidising properties, leaves *p*-azobenzaldehyde unchanged. Now, conversely, it has been shown that the initial product in both reactions is the azoxy-compound and that its formation is independent of the presence of an oxidising agent, since the product of hydrolysis of (*p*-nitrobenzylthio)-acetic acid after only one minute in the hot (or 10 minutes in the cold) was found to be exclusively *p*-azoxybenzaldehyde, and similarly the hydrolysis of α-(*p*-nitrobenzylthio)propionic acid, where the second hydrolysis product "α-sulphenopropionic acid" has no oxidising properties, was found also after 5 minutes' boiling with alkali to be *p*-azoxybenzaldehyde, which on longer boiling (15 minutes) was changed mostly into *p*-azobenzaldehyde. The reduction of the former to the latter aldehyde is therefore due to the sodium sulphide liberated in solution after the decomposition of the sulphenoacetic or α-sulphenopropionic acid, while with β-(*p*-nitrobenzylthio)propionic acid further boiling did not affect the azoxy-

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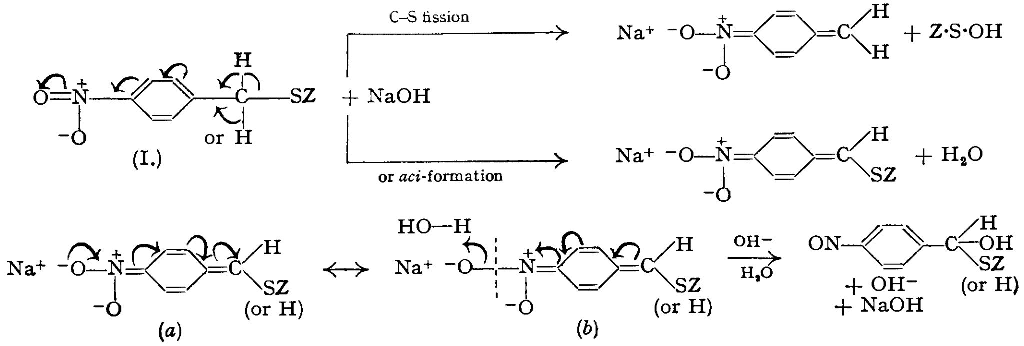
* Part I, preceding paper.

aldehyde because the second product " β-sulphenopropionic acid " did not decompose in solution to give a sulphide ion but changed into the corresponding disulphide, " β-dithiodipropionic acid." In presence of as little sodium sulphide as could be liberated from the decomposition of an equivalent amount of sulphenoacetic acid, the hydrolysis of the propionic acid both in the hot (5 minutes) and in the cold (24 hours) gave *p*-azobenzaldehyde.

The hydrolysis of α-(*p*-nitrobenzylthio)*iso*butyric acid, like that of β-(*p*-nitrobenzylthio)-propionic acid, gave *p*-azoxybenzaldehyde and α-dithiodi*iso*butyric acid.

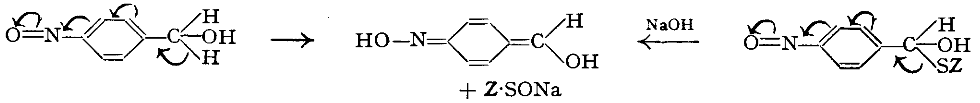
The rearrangement of the *p*-nitrobenzyl system into the azoxy-aldehyde seems to have occurred *via* a *p*-nitroso-alcohol according to scheme A (*o*-nitrotoluene is known to be changed into *o*-nitrosobenzyl alcohol under the influence of alkalis; Kalle & Co., D.R.-P. 194,811; *Chem. Zentr.*, 1908, I, 1345) :



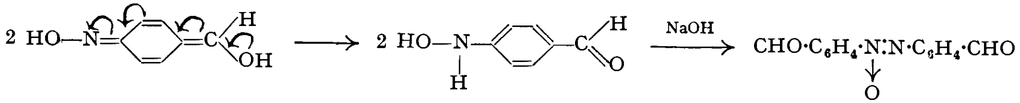
(Scheme A.)

(Z = $CH_2{\cdot}CO_2H$, $CH_2{\cdot}CH_2{\cdot}CO_2H$, $CHMe{\cdot}CO_2H$, or $CMe_2{\cdot}CO_2H$.)

The electronic displacements (*b*) are the results of the attack of the nucleophilic reagent on the α-carbon atom, while those shown in (*a*) are only favoured in acid medium to give the original nitro-compound. The *p*-nitroso-alcohol, being considered as a secondary nitroso-compound, must have rearranged to the more stable oxime (scheme B) ; this, in turn, can be considered as the imidol type of *p*-hydroxyaminobenzaldehyde which is known to be changed by the action of alkalis into *p*-azoxybenzaldehyde (Alway, *Ber.*, 1903, **36**, 2306) (scheme C) :



(Scheme B.)



(Scheme C.)

In parallel with the mechanism suggested above, the final stage in the rearrangement of the *o*-nitrobenzyl system is expected to be anthranil, which is the decomposition product of *o*-nitrosobenzyl alcohol (Bamberger, *ibid.*, p. 839) or of *o*-hydroxyaminobenzaldehyde, which is only known in solution (Bamberger and Elger, *ibid.*, p. 3653). Actually, the alkaline hydrolysis of α-(*o*-nitrobenzylthio)acetic acid gave thioanthranil, while the acidic mother-liquor after being diazotised and boiled with water, gave 5-nitrosalicylic acid, the expected product of the action of excess of nitrous acid on anthranilic acid (cf. Deninger, *J. pr. Chem.*, 1890, **42**, 551) which, in turn, must have been formed after the action of alkalis on the initially expected product of the hydrolysis, *viz.*, anthranil.

The hydrolysis of α-(*o*-nitrobenzylthio)propionic acid gave a steam-volatile liquid which was neither thioanthranil nor *o*-aminobenzaldehyde ; this was also obtained in a very pure state from β-(*o*-nitrobenzylthio)propionic acid, while again the hydrolysis of α-(*o*-nitrobenzylthio)*iso*butyric acid gave a trace of a steam-volatile oil not containing sulphur. The different results obtained from the alkaline hydrolyses of the last four acids point to the influence of the length of the acid chain or of the presence of α-methyl groups, in that it confers on these compounds different susceptibilities to the attack by the alkali.

Some brownish-red acids, containing nitrogen and sulphur, were isolated from the reaction mixtures after the hydrolyses of all the *o*- and the *p*-nitrobenzylthio-acids investigated, and their structures are still to be investigated.

The *m*-nitrobenzylthio-acids corresponding to the above series of compounds were recovered completely unchanged from the boiling alkaline solutions after 15 minutes, showing that hydrolysis requires to be initiated by electromeric displacements through a conjugated system starting from the influencing group (nitro- or keto-group) and ending at the sulphur atom, a condition which is not satisfied in these *m*-nitro-compounds.

EXPERIMENTAL.

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

α-(p-*Nitrobenzylthio*)*propionic Acid*.—*p*-Nitrobenzyl chloride (4·3 g.), dissolved in alcohol (70 c.c.), was treated with a solution of α-mercaptopropionic acid (2·7 g.) and sodium hydrogen carbonate (5 g.) in water (20 c.c.), and the mixture heated on the water-bath for 1 hour. Cooling, dilution with water, removal of turbidity with ether, and finally acidification gave an *acid* (4·5 g.) which separated from dilute alcohol in creamy white needles, m. p. 92° (Found : C, 50·3 ; H, 4·7 ; N, 5·8 ; S, 13·7. $C_{10}H_{11}O_4NS$ requires C, 49·8 ; H, 4·6 ; N, 5·8 ; S, 13·3%).

Alkaline hydrolysis. The acid (5 g.) was dissolved in 5% sodium hydroxide solution (125 c.c.) and gradually warmed on the water-bath for 3 minutes. The solid obtained (1·6 g.) crystallised from benzene in yellow needles, m. p. 190° alone or mixed with an authentic specimen of *p*-azoxybenzaldehyde. On acidification of the alkaline filtrate, hydrogen sulphide was evolved and a red acid (1·5 g.) was precipitated. This acid could only be purified by repeated precipitation from sodium hydrogen carbonate solution ; it formed a brownish-red powder which did not melt below 350° (Found : C, 54·0 ; H, 4·3 ; N, 5·0 ; S, 10·4%), and was very soluble in cold alcohol and hot acetic acid, insoluble in ether or benzene ; its constitution is still unknown. The acidic mother-liquor on diazotisation and coupling with β-naphthol gave a red dye, and when diazotised and boiled with water gave a hydroxy-acid (0·1 g.) which crystallised from dilute alcohol in creamy white needles, m. p. 245—247° (Found : N, 7·7%) ; its constitution is unknown. The hydrolysis was repeated with 15 minutes' boiling; the solid obtained was extracted with hot benzene which gave a small amount of *p*-azoxybenzaldehyde, while the residue crystallised from acetic acid in orange-red crystals, m. p. 230—235° alone or mixed with an authentic specimen of *p*-azobenzaldehyde.

α-(p-*Nitrobenzylthio*)iso*butyric Acid*.—Prepared from *p*-nitrobenzyl chloride (4·3 g.) and α-mercapto-*iso*butyric acid (3 g.) and isolated as described above, the *acid* (4·5 g.) crystallised from dilute alcohol in pale yellow needles, m. p. 145—146° (Found : C, 52·1; H, 5·2; N, 5·4; S, 12·2. $C_{11}H_{13}O_4NS$ requires C, 51·8 ; H, 5·1 ; N, 5·5 ; S, 12·5%).

Alkaline hydrolysis. The acid (5 g.) was hydrolysed as described above. The solid obtained (1·2 g.) was *p*-azoxybenzaldehyde. Acidification of the alkaline filtrate gave little hydrogen sulphide with the gradual precipitation of a dark solid (1·5 g.). This was extracted with boiling water which, on cooling, gave leaflets, m. p. 197° alone or mixed with an authentic specimen of α-dithiodi*iso*butyric acid ; the residue (0·2 g.) was a red acid which after repeated precipitation from sodium hydrogen carbonate solution was obtained as a red powder, m. p. 127—130° (decomp.) (Found : C, 54·9; H, 4·9; N, 7·6; S, 9·6%) ; its constitution is unknown. The acidic mother-liquor on diazotisation and coupling with β-naphthol gave a red dye, and on being diazotised and boiled with water gave a hydroxy-acid (0·1 g.) which crystallised from boiling water in needles, m. p. 207—213° (Found : N, 7·7%) ; its constitution is unknown.

Alkaline Hydrolysis of (p-*Nitrobenzylthio*)*acetic Acid*.—(*a*) Hydrolysis (cf. Schönberg and Iskander, *J.*, 1942, 90) for 1 minute in boiling alkali gave only *p*-azoxybenzaldehyde. (*b*) Hydrolysis in the cold for 1 minute or for 10 minutes also gave *p*-azoxybenzaldehyde. Repetition of (*a*) and (*b*) in an atmosphere of nitrogen gave the same results.

Alkaline Hydrolysis of β-(p-*Nitrobenzylthio*)*propionic Acid in the Presence of Sodium Sulphide* (cf. Schönberg and Iskander, *loc. cit.*).—The acid (2 g.) was dissolved in 5% sodium hydroxide solution (50 c.c.) containing sodium sulphide (0·65 g.), and the mixture (*a*) boiled for 5 minutes, or (*b*) left for 24 hours in the cold. The product in both cases was *p*-azobenzaldehyde.

A suspension of *p*-azoxybenzaldehyde (1·1 g.) in 5% sodium hydroxide solution (50 c.c.) containing sodium sulphide (0·65 g.) was boiled for 5 minutes; reduction to *p*-azobenzaldehyde was complete.

(m-*Nitrobenzylthio*)*acetic Acid*.—Prepared from *m*-nitrobenzyl chloride (4·3 g.) and mercaptoacetic acid (2·5 g.) and isolated as above, the *acid* (4·5 g.) crystallised from dilute alcohol in creamy white needles, m. p. 81—82° (Found : C, 47·4; H, 4·2; N, 6·6; S, 14·5. $C_9H_9O_4NS$ requires C, 47·6; H, 4·0; N, 6·2; S, 14·1%).

β-(m-*Nitrobenzylthio*)*propionic Acid*.—Prepared from the chloride (4·3 g.) and mercapto-acid (2·7 g.) as above, the *acid* (5 g.) crystallised from dilute alcohol in creamy white needles, m. p. 99° (Found : C, 50·2; H, 4·7; N, 6·0; S, 13·6. $C_{10}H_{11}O_4NS$ requires C, 49·8; H, 4·6; N, 5·8; S, 13·3%).

α-(m-*Nitrobenzylthio*)*propionic Acid*.—Prepared from the chloride (4·3 g.) and mercapto-acid (2·7 g.) as above, the *acid* (4·6 g.) crystallised from dilute alcohol in creamy white needles, m. p. 82° (Found : C, 50·0; H, 4·7; N, 5·9; S, 13·8. $C_{10}H_{11}O_4NS$ requires C, 49·8; H, 4·6; N, 5·8; S, 13·3%).

α-(m-*Nitrobenzylthio*)iso*butyric Acid*.—Prepared from the chloride (4·3 g.) and mercapto-acid (3 g.) as above, the *acid* (4·6 g.) crystallised from dilute alcohol in creamy white needles, m. p. 93° (Found: C, 51·7; H, 5·2; N, 5·3; S, 11·7. $C_{11}H_{13}O_4NS$ requires C, 51·8; H, 5·1; N, 5·5; S, 12·5%).

The four *m*-nitrobenzylthio-acids were recovered unchanged after 15 minutes' boiling with 5% sodium hydroxide solution.

(o-*Nitrobenzylthio*)*acetic acid*.—Prepared from the chloride (Holleman, *Rec. Trav. chim.*, 1914, **33**, 15; b. p. 118°/1·5 mm., 125°/4·0 mm.) (4·3 g.) and mercaptoacetic acid (2·5 g.) as above, the *acid* (4·5 g.) crystallised from dilute alcohol in creamy white scales, m. p. 98—99° (Found: C, 47·7; H, 3·9; N, 5·8; S, 13·5. $C_9H_9O_4NS$ requires C, 47·6; H, 4·0; N, 6·2; S, 14·1%).

Alkaline hydrolysis. A solution of the acid (5 g.) in 5% sodium hydroxide solution (125 c.c.) was distilled until the distillate was no longer turbid. Extraction of the distillate with ether gave a pale yellow oil (0·25 g.) which contained nitrogen and sulphur and gave with an alcoholic solution of mercuric chloride a double compound, m. p. 210° alone or mixed with that from authentic thioanthranil (Bamberger, *Ber.*, 1909, **42**, 1667). Other experiments to prove the identity of the oil as thioanthranil were all positive (cf. Gabriel and Leupold, *Ber.*, 1898, **31**, 2186).

Acidification of the alkaline solution remaining from the hydrolysis gave hydrogen sulphide and a small amount of sulphur dioxide with gradual precipitation of a red sticky mass which when shaken with sodium hydrogen carbonate solution and ether dissolved partly among the two layers, leaving a very small amount of a neutral substance containing nitrogen and sulphur. Evaporation of the ethereal layer left free sulphur; the hydrogen carbonate layer after acidification gave a brownish-red acid (0·5 g.) which after repeated precipitation from carbonate solution was further purified by precipitation from an alcoholic solution by the addition of excess of ether as a brownish-red powder, m. p. 193—197° (decomp.) (Found: C, 52·1; H, 4·1; N, 6·3; S, 7·1%); its constitution is unknown. The acidic mother-liquor, after the isolation of the red sticky mass, on diazotisation and coupling with β-naphthol gave a red dye and on being diazotised and boiled with water gave a hydroxy-acid (0·9 g.) which crystallised from hot water in needles, m. p. 226—227° alone or mixed with authentic 5-nitrosalicylic acid (Deninger, *J. pr. Chem.*, 1890, **42**, 551).

α-(o-*Nitrobenzylthio*)*propionic Acid*.—Prepared from the chloride (4·3 g.) and mercapto-acid (2·7 g.) as above, the *acid* (5 g.) crystallised from dilute alcohol in pale yellow prisms, m. p. 124—125° (Found: C, 49·8; H, 4·7; N, 5·8; S, 13·1. $C_{10}H_{11}O_4NS$ requires C, 49·8; H, 4·6; N, 5·8; S, 13·3%).

Alkaline hydrolysis. The acid (5 g.) was hydrolysed as described above. The volatile oil (0·15 g.) did not contain sulphur but had an odour of anthranil. It gave a picrate, m. p. 233—237°, and a mercuric chloride compound, m. p. (rapid heating) 180—185° (no melting on slow heating). On being diazotised and boiled with water it gave a phenol which crystallised from dilute alcohol in pale yellow needles (Found: C, 50·3; H, 3·0; N, 7·8. Calc. for $C_7H_5O_4N$: C, 50·3; H, 3·0; N, 8·4%), m. p. 121—122° alone or mixed with authentic 5-nitrosalicylaldehyde, m. p. 126° (Miller, *Ber.*, 1887, **20**, 1929). The oil has not yet been identified.

Acidification of the alkaline solution remaining after hydrolysis gave hydrogen sulphide and a little sulphur dioxide with the gradual precipitation of a brownish-red sticky mass (0·7 g.) which, on treatment as previously, left in the ethereal layer a small amount of sulphur, while the hydrogen carbonate layer, on acidification, gave a dark brownish-red acid (0·5 g.), soluble in cold alcohol or hot glacial acetic acid, insoluble in ether or benzene. It was obtained after repeated precipitation from carbonate solution as a brown powder, m. p. 104—105° (decomp.) (Found: C, 59·6; H, 4·2; N, 8·1; S, 6·2%); its constitution is unknown. The acidic mother-liquor, after isolation of the red sticky mass, on diazotisation and coupling with β-naphthol gave a red dye, and when diazotised and boiled with water gave a hydroxy-acid (1·1 g.) which crystallised from dilute alcohol in needles, m. p. 235° which gave a deep violet with ferric chloride (Found: N, 7·3%); its structure is unknown.

β-(o-*Nitrobenzylthio*)*propionic Acid*.—Prepared from the chloride (4·3 g.) and mercapto-acid (2·7 g.) as above, the *acid* (5 g.) crystallised from dilute alcohol in pale yellow needles, m. p. 77—78° (Found: C, 49·4; H, 4·7; N, 6·0; S, 13·2. $C_{10}H_{11}O_4NS$ requires C, 49·8; H, 4·6; N, 5·8; S, 13·3%).

Alkaline hydrolysis. The acid (5 g.) was hydrolysed as described above. The volatile substance (0·6 g.) solidified immediately in silvery scales, m. p. 39—40° alone or mixed with authentic *o*-aminobenzaldehyde (*Helv. Chim. Acta*, 1935, **18**, 1235). Its mercuric chloride compound (Friedländer. *Ber.*, 1882, **15**, 2572) crystallised from dilute alcohol in needles, m. p. (rapid heating) 135—140° or (slow heating) 209—210°. On diazotisation of *o*-aminobenzaldehyde in hydrochloric acid solution and boiling with water, the solution, after cooling, precipitated a phenol which crystallised from dilute alcohol in yellow needles, m. p. 118—120° (Found: C, 50·2; H, 3·2; N, 8·5. Calc. for $C_7H_5O_4N$: C, 50·3; H, 3·0; N, 8·5%). The mixed m. p. with authentic 5-nitrosalicylaldehyde of m. p. 126° gave no depression.

Acidification of the alkaline solution remaining from the hydrolysis liberated small amounts of hydrogen sulphide and sulphur dioxide, with the gradual precipitation of a brown sticky mass (0·4 g.) which on treatment as above gave a brown acid (0·3 g.), soluble in cold alcohol or hot acetic acid, insoluble in ether or benzene. It was obtained after repeated precipitation from carbonate solution as a black powder, m. p. 165° (decomp.) (Found: C, 56·3; H, 4·0; N, 7·9; S, 12·3%); its constitution is unknown.

The acidic mother-liquor, after separation of the brown sticky mass, on diazotisation and coupling with β-naphthol gave a red dye, and on diazotisation and boiling with water gave a hydroxy-acid (0·8 g.) which crystallised from dilute alcohol in fine needles, m. p. 200—208°, and gave a deep violet-red colour with ferric chloride (Found: N, 7·1%); its constitution is still unknown.

α-(o-*Nitrobenzylthio*)iso*butyric Acid*.—Prepared from the chloride (4·3 g.) and mercapto-acid (3 g.) as above, the *acid* (5 g.) crystallised from dilute alcohol in pale yellow needles, m. p. 90—91° (Found: C, 52·0; H, 5·2; N, 5·4; S, 12·7. $C_{11}H_{13}O_4NS$ requires C, 51·8; H, 5·1; N, 5·5; S, 12·5%).

Alkaline hydrolysis. The acid (5 g.) was hydrolysed as described earlier. The volatile substance consisted of a slight trace of an oil containing no sulphur, with an odour of anthranil. It gave a picrate and a mercuric chloride compound. Acidification of the residual alkaline solution liberated a small amount of hydrogen sulphide with the gradual precipitation of a red sticky mass (0·6 g.) which on similar treatment as before gave a brown acid (0·5 g.), insoluble in ether or benzene, soluble in cold alcohol or hot glacial acetic acid. Repeated precipitation from carbonate solutions gave a dark brown powder, m. p. 85—100° (decomp.); its constitution is unknown. The acid chloride, prepared from the acid and thionyl chloride as a dark red viscous mass was treated with absolute alcohol, and the resulting ethyl ester separated from carbon tetrachloride–light petroleum as a brown powder, m. p. 180—185° (Found: C, 57·6; H, 4·2; N, 7·5; S, 5·6%).

The acidic mother-liquor on diazotisation and coupling with β-naphthol gave a red dye, and on diazotisation and boiling gave a hydroxy-acid (0·6 g.) which crystallised from dilute alcohol in needles, m. p. 186—205°, and gave a deep violet-red colour with ferric chloride (Found: N, 7·8%); its constitution is unknown.

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