313. *Synthetic Applications of Activated Metal Catalysts. Part III.* Desulphurisation of Thiazoles with Raney Nickel.*

By G. M. Badger and N. Kowanko.

Benzothiazoles are desulphurised, in excellent yield, to the expected secondary amines by treatment with very active Raney nickel (W6 or W7) in boiling methanol. Neutral, less active catalysts (W5) are relatively ineffective; but in the presence of alkali, ring fission followed by desulphurisation occurs to yield mixtures of aniline, methylaniline, and *o*-aminothiophenol.

Simple substituted thiazoles are more labile and desulphurisation apparently occurs by two competing mechanisms. In the first (favoured by alkaline conditions) ring fission evidently occurs before desulphurisation. In the second (favoured by the use of the neutral W6 catalyst) the initial desulphurisation is followed by fission of a C–N bond and formation of carbonyl derivatives by hydrolysis.

Desulphurisation of thiophen derivatives with Raney nickel has been extensively investigated in recent years, and has been used for the preparation of a wide variety of fatty acids.[1,2] However, relatively few attempts to desulphurise thiazoles have been recorded, and indeed the literature is discouraging. Thus Cook, Heilbron, and Levy[3] removed only the mercapto-group by treatment of 5-amino-2-mercapto-4-phenylthiazole with Raney nickel. Similarly 2-mercaptobenzothiazole has been converted into benzothiazole[4] with catalyst prepared by the Mozingo method;[5] but under alkaline conditions a mixture of aniline and methylaniline was reported.[4] Hurd and Rudner[6] obtained *o*-aminothiophenol, *o*-aminodiphenyl disulphide, and aniline on desulphurisation of benzothiazole in the presence of ammonia. A systematic examination of the desulphurisation of thiazoles and benzothiazoles is now reported.

The mechanism of the desulphurisation is still obscure, but it is reasonable to assume that the initial step involves chemisorption of the sulphur on the catalyst by means of the sulphur's lone-pair of electrons. No complicating factors exist with simple thiophen derivatives, but with thiazoles the lone pair of the hetero-nitrogen atom will compete for the active centres in much the same way that pyridine and other similar heteroaromatic compounds act as catalyst "poisons" in hydrogenations.[7,8] That is presumably why thiazoles are more difficult to desulphurise than thiophen derivatives. So most of the present work was carried out with the very active (neutral) W6 and the similarly active

* Part II, *J.*, 1956, 616.

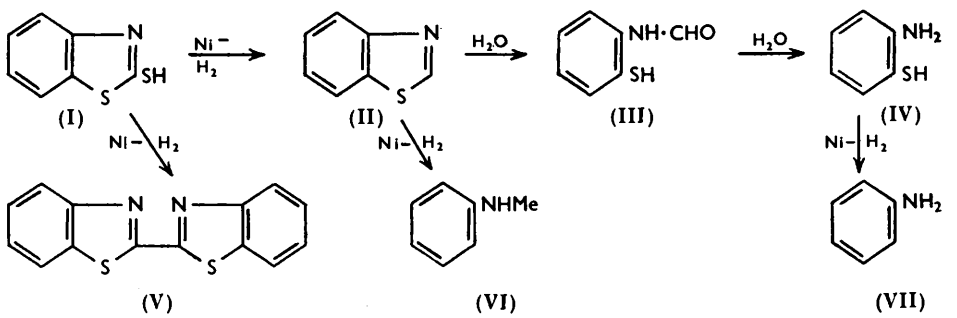
[1] Badger, Rodda, and Sasse, *J.*, 1954, 4162.
[2] Sy, Buu-Hoï, and Dat Xuong, *Compt. rend.*, 1954, **239**, 1224, 1813; 1955, **240**, 442, 785; *Bull. Soc. chim. France*, 1955, 1583; Sy, *ibid.*, p. 1175.
[3] Cook, Heilbron, and Levy, *J.*, 1947, 1598.
[4] Ivanoff and Ivanoff, *Compt. rend. Acad. bulgare Sci.*, 1952, **5**, No. 1, 13.
[5] Mozingo, Wolf, Harris, and Folkers, *J. Amer. Chem. Soc.*, 1943, **65**, 1013; Mozingo, *Org. Synth.*, 1941, **21**, 15.
[6] Hurd and Rudner, *J. Amer. Chem. Soc.*, 1951, **73**, 5157.
[7] Lindlar, *Helv. Chim. Acta*, 1952, **35**, 456; Elsner and Paul, *J.*, 1953, 3156.
[8] Badger and Sasse, *J.*, 1956, 616.

(alkaline) W7 catalysts.[9] The solvent is also important in desulphurisations and for non-acidic sulphur compounds ethanol has been most commonly used. However, as primary amines had been reported among the products of some thiazole desulphurisations,[4,6] and as ethanol is known to ethylate such bases in the presence of Raney nickel,[10] this solvent seemed contraindicated. Methanol was therefore used for most of the experiments as this alcohol does not alkylate amines in the presence of Raney nickel.

When treated with either W6 or W7 catalyst in boiling methanol both benzothiazole (II) and 2-methylbenzothiazole were smoothly desulphurised in excellent yield to the expected methylaniline and ethylaniline respectively. W5 catalyst was less effective, however, for with 2-mercaptobenzothiazole (I) it gave only benzothiazole (II) and a trace of 2 : 2′-dibenzothiazolyl (V). The latter was presumably formed by dimerisation of two free radicals resulting after removal of the thiol groups.

With W5 in methanol to which sodium hydroxide had been added, 2-mercaptobenzothiazole gave a mixture of aniline, methylaniline, *o*-aminodiphenyl disulphide, and dibenzothiazolyl. In a related experiment in which benzothiazole was refluxed with alkaline methanol before addition of W5 catalyst, the proportion of aniline to methylaniline was greatly increased. Similarly, reaction of 2-mercaptobenzothiazole with a W7 catalyst which had been heated *in vacuo* to remove some of the hydrogen (" dehydro-W7 ") gave aniline, methylaniline, benzothiazole, and dibenzothiazolyl.

The thiazole ring is known to be subject to ring fission in the presence of alkali. With the very active (alkaline) W7 catalyst it seems that desulphurisation occurs before ring fission, and the secondary amine is the only product. With the less active W5 and dehydro-W7 catalyst, however, it seems that ring fission occurs to some extent before



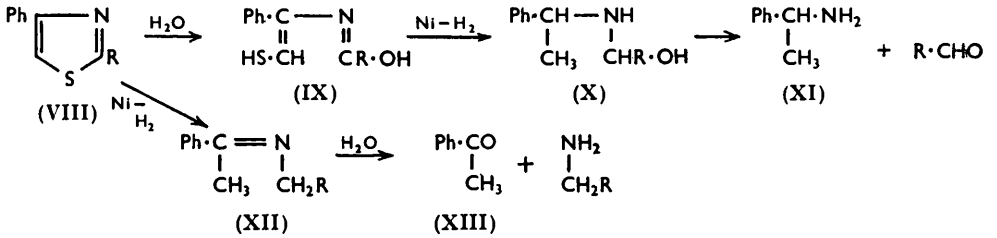
desulphurisation. The intermediate formyl derivative (III) would then give *o*-aminothiophenol (IV) and this was isolated in its oxidised form, 2 : 2′-diaminodiphenyl disulphide. The isolation of this product was only made possible by the use of less than the optimum amount of nickel catalyst; but desulphurisation did occur to some extent, giving aniline (VII).

Desulphurisation of several 4-phenylthiazoles and of 2-amino-4-methyl-5-phenylthiazole with either W6 or W7 catalyst has been found to be more complex. All the 4-phenylthiazoles (VIII) gave α-methylbenzylamine (XI) with either catalyst, and 2-amino-4-methyl-5-phenylthiazole gave the analogous product, α-methylphenethylamine, showing that cleavage of the $C_{(2)}$–N bond had taken place as well as hydrogenolysis of the C–S bonds. The 2-aminothiazoles all evolved ammonia vigorously. With W6 catalyst 4-phenylthiazole and 2-amino-4-phenylthiazole both gave some acetophenone (XIII); but this

[9] Billica and Adkins, *Org. Synth.*, 1949, **29**, 24; Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 695.

[10] Rise and Kohn, *ibid.*, 1955, **77**, 4052; Kao, Tilak, and Venkataraman, *J. Sci. Ind. Res., India*, 1955, **14**, *B*, 624.

compound was not detected when W7 was used. However, 2-amino-4-methyl-5-phenylthiazole gave the analogous phenylacetone with both W6 and W7, and 2-α-naphthyl-4-phenylthiazole also gave some acetophenone with W7. No ketone was isolated after reaction of 2 : 4-diphenylthiazole with either catalyst, and on distillation of the basic fraction disproportionation took place to give α-methylbenzylamine (XI) and benzaldehyde. A similar disproportionation occurred when the basic fraction from the desulphurisation of 2-α-naphthyl-4-phenylthiazole was heated, and α-methylbenzylamine and 1-naphthaldehyde were isolated. Some 1-methylnaphthalene was also detected after desulphurisation of this thiazole.



The most reasonable explanation for these results is that two competing mechanisms are operating, the extent of each depending on the experimental conditions and particularly on the alkalinity of the mixture. W7 catalyst contains a considerable amount of caustic alkali and this may well lead to ring fission of the thiazole system before desulphurisation : however, the mixture is alkaline even when W6 is used on account of the presence of the thiazole itself and (as the reaction proceeds) of the basic products.

It is suggested that an initial ring fission to the intermediate thiol (IX) would be followed by desulphurisation to the base (X), and that this disproportionates during subsequent distillation to give the α-methylbenzylamine observed experimentally, and an aldehyde. Benzaldehyde and 1-naphthaldehyde were identified after the desulphurisation of 2 : 4-diphenylthiazole and 2-α-naphthyl-4-phenylthiazole respectively. Some disproportionation of the base (X) may also occur during the reaction. If this does take place the aldehyde concerned would be reduced to the hydrocarbon : it is significant that 1-methylnaphthalene was also isolated after desulphurisation of 2-α-naphthyl-4-phenylthiazole. No toluene was detected in similar experiments with 2 : 4-diphenylthiazole, but this could well be due to the experimental difficulties.

For the second and competing mechanism, it is suggested that the initial step is desulphurisation and partial hydrogenation of the thiazole to the unsaturated intermediate (XII). Fission of this with acid, during working-up, would give acetophenone (XIII), and this product has been isolated in nearly all experiments involving desulphurisation with W6 catalyst. Similarly, desulphurisation of 2-amino-4-methyl-5-phenylthiazole with either W6 or W7 gave some of the analogous phenylacetone. Moreover, Hurd and Rudner [6] also isolated acetophenone on desulphurisation of both 2-mercapto- and 2-amino-4-phenylthiazole. Such a mechanism implies the formation of a primary amine ($R{\cdot}CH_2{\cdot}NH_2$) as the second fragment. No methylamine could be detected during the actual desulphurisation of 4-phenylthiazole; but methylamine was evolved and identified on treatment of the reaction mixture with hydrochloric acid. It seems therefore that hydrogenolysis stops at the intermediate (XII), and that fission to the ketone (XIII) and the primary amine is a hydrolytic process catalysed by hydrochloric acid.

Experimental

Preparation of Catalysts.—The Raney nickel catalysts designated W5, W6, and W7 were prepared by the methods of Billica and Adkins [9] except that for the final washings methanol was used in place of ethanol, and the centrifugation was omitted. The catalyst was freshly

prepared for each experiment. " Dehydro-W7 " catalyst was prepared as described by Badger and Sasse.[8]

Desulphurisation of 2-Mercaptobenzothiazole.—(i) A mixture of 2-mercaptobenzothiazole (10 g.), W5 Raney nickel (from 65 g. of alloy), and methanol (250 c.c.) was refluxed for 8 hr. The hot mixture was filtered, the catalyst was washed with boiling methanol, and the combined filtrates were evaporated. An additional small amount of product was obtained on dissolution of the catalyst in dilute hydrochloric acid, basification, steam-distillation, and extraction of the distillate with ether. The combined oil was distilled, to give benzothiazole, b. p. 230° (4·41 g., 54·5%). The picrate formed yellow needles, m. p. and mixed m. p. 169·5—170° (Found : C, 43·2; H, 2·5; N, 15·5. Calc. for $C_{13}H_8O_7N_4S$: C, 42·9; H, 2·2; N, 15·4%). The residue from the distillation was recrystallised from xylene. 2 : 2′-Dibenzothiazolyl (10 mg.) formed plates, m. p. 297·5—298° alone or mixed with a specimen prepared by the method of Zubarowski[11], who, however, gives m. p. 306—308°.

(ii) In a similar experiment, sodium hydroxide (2 g.) was added to the reaction mixture. Evaporation of the methanol gave a tarry residue which was dissolved in ether and extracted with dilute sodium hydroxide. When kept in air the alkaline extract deposited 2 : 2′-diaminodiphenyl disulphide (0·75 g., 10·1%) as yellow plates, m. p. and mixed m. p. 93—94° (Found : C, 58·0; H, 4·7; N, 11·4; S, 26·4. Calc. for $C_{12}H_{12}N_2S_2$: C, 58·1; H, 4·8; N, 11·3; S, 25·8%). The dihydrochloride of this base crystallised from concentrated hydrochloric acid as needles, m. p. 210—211° (Found : C, 40·3; H, 5·2. Calc. for $C_{12}H_{16}O_2N_2S_2Cl_2$: C, 40·5; H, 5·1%). The recorded m. p.[12] for this salt (112—114°) seems to be in error.

The oil obtained by evaporation of the ether was subjected to a Hinsberg separation with toluene-*p*-sulphonyl chloride (9 g.) and 10% aqueous sodium hydroxide. This gave 2 : 2′-dibenzothiazolyl (0·55 g., 6·9%), *N*-methyltoluene-*p*-sulphonanilide (4·1 g., 47·5%), and toluene-*p*-sulphonanilide (1·5 g., 16·5%), all identified by comparison with authentic specimens.

(iii) 2-Mercaptobenzothiazole (12 g.) in methanol (150 c.c.) was refluxed with dehydro-W7 nickel (from 125 g. of alloy) for 29 hr. Extraction of the catalyst with methanol and xylene and concentration to small volume gave 2 : 2′-dibenzothiazolyl (0·52 g., 5·6%), m. p. and mixed m. p. 295—298°. The residual oil, on treatment with toluene-*p*-sulphonyl chloride and aqueous sodium hydroxide, gave benzothiazole, b. p. 230° (3·44 g., 35·1%) (picrate, m. p. 169°), *N*-methyltoluene-*p*-sulphonanilide (3·60 g., 22%), and toluene-*p*-sulphonanilide (1·23 g., 7·2%), identified as above.

Desulphurisation of Benzothiazole.—(i) Benzothiazole (6 g.), W7 Raney nickel (from 65 g. of alloy), and methanol (250 c.c.) were refluxed for 3 hr. Treatment of the product with toluene-*p*-sulphonyl chloride and sodium hydroxide gave *N*-methyltoluene-*p*-sulphonanilide (8·4 g., 84%) as sole product.

(ii) Similar desulphurisation with W6 Raney nickel, etc., gave the same amide in 87% yield.

(iii) A mixture of benzothiazole (10 g.) and sodium hydroxide (15 g.) in methanol (150 c.c.) was refluxed for 2½ hr., and W5 Raney nickel (from 65 g. of alloy) then added. After a further 8 hours' refluxing the product was treated with toluene-*p*-sulphonyl chloride to give *N*-methyltoluene-*p*-sulphonanilide (1·23 g., 7·25%) and toluene-*p*-sulphonanilide (4·69 g., 29·5%).

(iv) Benzothiazole (10 g.) and dehydro-W7 Raney nickel (from 65 g. of alloy) in sulphur-free xylene (35 c.c.) were refluxed for 12 hr. (cf. ref. 8). Distillation of the product gave unchanged benzothiazole (8·4 g.) and the residue, after recrystallisation from xylene, was identified as 2 : 2′-dibenzothiazolyl (0·02 g.) as usual.

Desulphurisation of 2-Methylbenzothiazole.—(i) 2-Methylbenzothiazole (5 g.), W6 Raney nickel (from 65 g. of alloy), and methanol (250 c.c.) were refluxed for 3 hr. The product gave *N*-ethyltoluene-*p*-sulphonanilide (8·35 g., 82%) as needles, m. p. and mixed m. p. 86°.

(ii) Similar desulphurisation with W7 Raney nickel gave the amide in 80% yield. No by-products could be detected in either case.

Preparation of Thiazoles.—4-Phenylthiazole[13] was prepared from phenacyl bromide and thioformamide; 2 : 4-diphenylthiazole[14] from phenacyl bromide and thiobenzamide; and 2-amino-4-phenylthiazole[15] from phenacyl bromide and thiourea.

[11] Zubarowski, *Zhur. obshchei Khim.*, 1951, **21**, 2055.
[12] Cymerman-Craig, Rogers, and Warwick, *Austral. J. Chem.*, 1955, **8**, 252.
[13] Wiley, England, and Behr, " Organic Reactions," 1951, Vol. VI, 367.
[14] Hubacher, *Annalen*, 1890, **259**, 237.
[15] Traumann, *ibid.*, 1888, **249**, 35.

2-α-Naphthyl-4-phenylthiazole. A solution of α-naphthonitrile (30 g.) and dimethylamine (2 c.c.) in ethanol (200 c.c.) was cooled to −10° and saturated with hydrogen sulphide, quickly transferred to an autoclave, and heated at 80—90° for 4 hr. After evaporation the residue was extracted with ether, and the extract washed with dilute hydrochloric acid and water, dried, and evaporated. The resulting crude α-thionaphthamide (9 g.) was heated with phenacyl bromide (9·6 g.), sodium acetate (3·85 g.), and ethanol (45 c.c.) on the steam-bath until the solvent had evaporated. Water was added, the mixture extracted with ether, and the ether dried and evaporated. After chromatography in light petroleum, on alumina, and crystallisation from light petroleum, *2-α-naphthyl-4-phenylthiazole* (11·0 g., 19·5%) formed plates, m. p. 88° (Found: C, 79·5; H, 4·5; N, 4·5. $C_{19}H_{13}NS$ requires C, 79·4; H, 4·5; N, 4·9%).

2-Amino-4-methyl-5-phenylthiazole. Benzyl methyl ketone [16] (70 g.), thiourea (78 g.), and iodine (133 g.) were heated on the steam-bath for 8 hr.[17] The mixture was then extracted with ether, and the residue dissolved in boiling water and treated with charcoal. The filtrate was basified with potassium carbonate, and the product purified by recrystallisation from ethanol and then benzene. *2-Amino-4-methyl-5-phenylthiazole* (21 g., 21%) was obtained as plates, m. p. 165° (Found: C, 63·4; H, 5·2. $C_{10}H_{10}N_2S$ requires C, 63·2; H, 5·3%). The *picrate* crystallised from ethanol in yellow needles, m. p. 248° (Found: C, 45·9; H, 3·2; N, 16·5. $C_{16}H_{13}O_7N_5S$ requires C, 45·8; H, 3·1; N, 16·7%).

Desulphurisation of 4-Phenylthiazole.—(i) 4-Phenylthiazole (10 g.), W7 Raney nickel (from 65 g. of alloy), and methanol (250 c.c.) were refluxed for 3 hr. The combined filtrate and methanol washings were acidified with dilute hydrochloric acid (100 c.c.), and the solvent was evaporated on the steam-bath. Basification of the dark red residue with 20% aqueous sodium hydroxide, followed by ether-extraction and distillation of the dried extracts, gave α-methylbenzylamine, b. p. 190—195° (2·3 g.), characterised as the oxalate, m. p. 235—236° (lit., m. p. 238°) (Found: C, 65·0; H, 7·2; N, 8·2. Calc. for $C_{18}H_{24}O_4N_2$: C, 65·1; H, 7·2; N, 8·4%). A higher-boiling fraction (1·3 g.) was identified as unchanged 4-phenylthiazole (m. p. 44°) (picrate, m. p. and mixed m. p. 163°).

(ii) Similar desulphurisation with W6 Raney nickel and evaporation of the acidified solvent gave a dark red residue. Extraction with ether and water, and subsequent evaporation of the dried ethereal solution, gave acetophenone (0·75 g.), identified as the 2 : 4-dinitrophenylhydrazone. The aqueous extract was basified and warmed, the liberated methylamine being identified by passing the gas into a solution of 1-chloro-2 : 4-dinitrobenzene. The cooled alkaline solution was then extracted with ether and evaporation of the dried solution gave the basic products. Distillation gave α-methylbenzylamine, b. p. 195° (1·95 g.) (oxalate, m. p. and mixed m. p. 235°), and 4-phenylthiazole (1·55 g.), identified as the picrate.

Desulphurisation of 2-Amino-4-phenylthiazole.—(i) Desulphurisation of 2-amino-4-phenylthiazole (10 g.) with W7 catalyst as described for 4-phenylthiazole gave α-methylbenzylamine (4·03 g.) {oxalate, m. p. and mixed m. p. 235°; chloroplatinate, m. p. 215—216° (decomp.) [lit., m. p. 213—214° (decomp.)]}. Ammonia was liberated during the reaction, and a very little methylamine was also detected by using 1-chloro-2 : 4-dinitrobenzene.

(ii) Similar desulphurisation by means of the W6 catalyst and subsequent evaporation of the acidified methanol gave a partly solid mass, which was filtered off and washed with ether. Recrystallisation of the solid from dilute hydrochloric acid gave 2-amino-4-phenylthiazole hydrochloride (4 g.), m. p. and mixed m. p. 204°. The ethereal solution, which was separated into neutral and basic fractions, gave acetophenone (1·50 g.), identified as the 2 : 4-dinitrophenylhydrazone, and α-methylbenzylamine (2·15 g.; b. p. 190°) identified as the oxalate, m. p. and mixed m. p. 235°.

Desulphurisation of 2 : 4-Diphenylthiazole.—(i) Desulphurisation of 2 : 4-diphenylthiazole (10 g.) with W7 Raney nickel as described for 4-phenylthiazole gave benzaldehyde (1·65 g., 28%), identified as the 2 : 4-dinitrophenylhydrazone, and α-methylbenzylamine (1·05 g., 18·6%), identified as the oxalate, m. p. 235°.

(ii) Similar desulphurisation by means of W6 Raney nickel gave a product which was separated into basic and non-basic fractions. Recrystallisation of the " non-basic " fraction from benzene–hexane gave unchanged 2 : 4-diphenylthiazole (2·35 g.), identified by comparison with an authentic specimen. The basic fraction was distilled, to give α-methylbenzylamine (b. p. 195°; 0·95 g.) identified as the oxalate, m. p. 235°, and another fraction which

[16] *Org. Synth.*, Coll. Vol. II, p. 391.
[17] Cf. King and Hlavecek, *J. Amer. Chem. Soc.*, 1950, **72**, 3722.

decomposed at *ca.* 250° with evolution of ammonia. From this fraction benzaldehyde (2·53 g.) was obtained as the 2 : 4-dinitrophenylhydrazone.

Desulphurisation of 2-Amino-4-methyl-5-phenylthiazole.—(i) Desulphurisation of this thiazole (8 g.) was effected as usual with W7 catalyst, and the residue, after evaporation of the acidified solvent, separated into neutral and basic fractions. The neutral fraction (0·25 g.) was identified as phenylacetone, giving a 2 : 4-dinitrophenylhydrazone, orange needles, m. p. 155° (lit., m. p. 155—156°), and a semicarbazone, needles, m. p. 195° (lit., m. p. 195—198°). Distillation of the basic fraction gave α-methylphenethylamine (1·175 g.; b. p. 200—202°) (lit., b. p. 203°) (Found : C, 80·25; H, 9·95; N, 10·2. Calc. for $C_9H_{13}N$: C, 80·0; H, 9·6; N, 10·4%). The chloroplatinate crystallised from dilute hydrochloric acid in golden-yellow needles, decomp. *ca.* 220°. The analytical specimen was dried *in vacuo* over sodium hydroxide and phosphoric oxide (Found : C, 31·9; H, 4·4; N, 4·05; Cl, 30·7; Residue, 27·9. Calc. for $C_{18}H_{28}N_2Cl_6Pt$: C, 31·8; H, 4·1; N, 4·1; Cl, 31·3; Pt, 28·7%). Distillation of the high-boiling fraction gave unchanged 2-amino-4-methyl-5-phenylthiazole (0·85 g.) identified as the picrate, m. p. and mixed m. p. 248°.

(ii) Similar desulphurisation over W6 catalyst gave a partly solid product. Separation of the crystals, followed by basification, gave unchanged 2-amino-4-methyl-5-phenylthiazole (2·77 g.), identified as the picrate. The liquid product was separated into neutral and basic fractions. The neutral fraction (0·75 g.) was identified as phenylacetone, giving a 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 155°. Distillation of the basic fraction gave α-methylphenethylamine (b. p. 200—203°; 1·80 g.), identified as the chloroplatinate. Recrystallistion of the residue gave unchanged base (2·55 g.), identified as the picrate.

Desulphurisation of 2-α-Naphthyl-4-phenylthiazole.—Desulphurisation of the thiazole (10 g.) was effected by 3 hours' refluxing with W7 Raney nickel (from 65 g. of alloy) in methanol (250 c.c.). The combined filtrate and washings was acidified with dilute hydrochloric acid (100 c.c.) and evaporated. Addition of excess of picric acid to the distillate, followed by concentration, gave 1-methylnaphthalene picrate (1·8 g.). After recrystallisation from ethanol this had m. p. and mixed m. p. 142°. The residue from the desulphurisation was separated into basic and non-basic fractions in the usual way. The latter, on removal of the ether, deposited unchanged base (2·15 g.), identified by comparison with an authentic specimen. Distillation of the remainder of the neutral fraction gave acetophenone (0·38 g.), identified as the dinitrophenylhydrazone. The basic fraction gave α-methylbenzylamine (0·85 g.; identified as the oxalate, m. p. 235°), and distillation of the high-boiling fraction (b. p. 260—280°) gave a yellow oil (2·05 g.). The major portion (2·0 g.) was shown to be 1-naphthaldehyde by conversion into its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 255°.

Microanalyses were carried out by the C.S.I.R.O. Microanalytical Laboratory, Melbourne. We are also grateful to Dr. W. H. F. Sasse for helpful discussions.

UNIVERSITY OF ADELAIDE, SOUTH AUSTRALIA. [*Received, November 13th*, 1956.]