Reaction of Phenylacetonitrile Anion with Sulphites: a Novel Isothiazole Synthesis

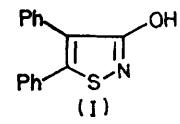
By M. D. Scott, Chemical Development, G. D. Searle & Co. Ltd., Lane End Road, High Wycombe, Bucks

4,5-Diphenylisothiazol-3-ol has been prepared by reaction of phenylacetonitrile anion with sulphites. A tentative mechanism is proposed for the reaction. α-Cyano-α-(4,5-diphenylisothiazol-3-yl)benzyl phenyl thione (IV) and 4-imino-2,3,5-triphenylhex-2-enedinitrile (V) were also isolated from the reaction mixtures.

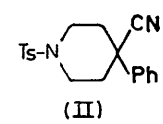
ALTHOUGH many isothiazoles have been prepared since the original synthesis of the parent system,[1] preparations of mononuclear 3-hydroxyisothiazoles have been limited to two reports.[2,3] Thus it was of interest when the hitherto unknown 3-hydroxy-4,5-diphenylisothiazole (I) was obtained during the preparation of the piperidine (II) from the anion of phenylacetonitrile, prepared in toluene by reaction of phenylacetonitrile with sodamide, and *NN*-bis-2-chloroethyltoluene-*p*-sulphonamide.

Two possible sources for the sulphur atom required for the formation of the isothiazole ring were considered: the tosyl group and the thionyl chloride used to prepare the *NN*-bis-2-chloroethyltoluene-*p*-sulphonamide *in situ* from *NN*-bis-2-hydroxyethyltoluene-*p*-sulphonamide. Since the thionyl chloride appeared to be the most likely source of the sulphur, thionyl chloride or a solution of sulphur dioxide in toluene was added to sodiophenylacetonitrile. This gave only phenylacetonitrile and tar. Examination of the reaction of *NN*-bis-2-hydroxyethyltoluene-*p*-sulphonamide with thionyl chloride showed that under certain conditions a crystalline product was obtained instead of the oily dichloride. This was shown to be the sulphite (III) which when treated with sodiophenylacetonitrile gave 3-hydroxy-4,5-diphenylisothiazole. Since diethyl sulphite reacted in a similar way the non-intervention of the tosyl-amino-moiety was proved. Analytical and n.m.r. and mass spectral evidence supported formulation of the compound as (I). In particular the presence of the fluorene cation, *m/e* 165, characteristic of the spectra of many heterocycles containing phenyl groups on adjacent carbon atoms was observed.[4] Desulphurisation of the compound with Raney nickel in ethanol yielded 2,3-diphenylpropionamide thus providing final proof of its structure.

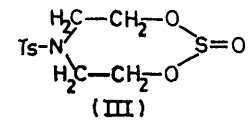
The compound appears to exist almost entirely as the isothiazolol rather than the isothiazolone tautomer. Thus the compound forms a sodium salt with aqueous sodium hydroxide, gives a purple colour with ferric chloride, and its i.r. spectrum shows no significant absorption above 1630 cm^{-1}; these properties are in accord with those reported for other hydroxy(phenyl)isothiazoles;[2,5]



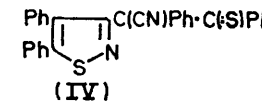
(I)



(II)



(III)



(IV)

TABLE

Sulphite	Base	Yield pure isothiazole (%)	M.p.	Recovered * $PhCH_2CN$ (%)	Compound (IV) * (%)
Dimethyl	$NaNH_2$	27	245—247°	22	14
Diethyl	$NaNH_2$	38	245—250	10	15
Diethyl	NaH	2	230—240	38	60
Di-n-butyl	$NaNH_2$	22	243—248		16
Dibenzyl	$NaNH_2$	10	240—247		9
Diphenyl	$NaNH_2$	5	244—247	36	18
N-Tosyldiethylamino	$NaNH_2$	18	245		

* Total yields estimated by quantitative i.r. spectroscopy.

The parent isothiazol-3-ol exists, in part as the isothiazolone.[6,7]

Methylation of (I) with dimethyl sulphate in the presence of aqueous alkali gave a methyl derivative, the i.r. spectrum of which showed strong absorption at 1650 cm^{-1}; this was consistent with the compound being 2-methyl-4,5-diphenylisothiazol-3-one. The absence of a methoxy-group was confirmed by a methoxy-assay.

The 3-hydroxy-compound when heated with phosphorus pentachloride in toluene gave a chlorine-containing product which on reaction with methanol yielded dimethyl 4,5-diphenylisothiazol-3-yl phosphate. The reaction was shown to be general for a number of sulphites (see Table).

[1] A. Adams and R. Slack, *Chem. and Ind.*, 1956, 1232.
[2] J. Goerdeler and W. Mittler, *Chem. Ber.*, 1963, **96**, 944.
[3] W. D. Crow and N. J. Leonard, *J. Org. Chem.*, 1965, **30**, 2660.
[4] J. H. Bowie, B. K. Simons, and S. O. Lawesson, *Rev. Pure and Appl. Chem.*, 1969, **19**, 61.
[5] T. Naito, S. Nakagawa, J. Okumura, K. Kakahashi, and K. Kasai, *Bull. Chem. Soc. Japan*, 1968, **41**, 959.
[6] J. R. Christie and B. Selinger, *Austral. J. Chem.*, 1968, **21**, 1113.
[7] W. D. Crow and I. Gosney, *Austral. J. Chem.*, 1967, **20**, 2729.

After isolation of the isothiazole (I) from the reaction mixture by dilution with water three other products were detected: phenylacetonitrile, a pale yellow compound (m.p. *ca.* 205°), and a bright yellow solid [m.p. 265° (decomp.)]. On the basis of the elemental analysis and i.r. and n.m.r. spectroscopy the lower-melting compound was assigned structure (IV). Further evidence in support of this structure was obtained from the mass spectrum which, in addition to the molecular ion *m/e* 472 ($C_{30}H_{20}N_2S_2$) showed fragments at *m/e* 440, ($C_{30}H_{20}N_2S$), 235 [$C_{15}H_9NS$—derived from either the Ph–C(CN)–C(:S)Ph fragment or the 4,5-diphenylisothiazole ring], 178 (Ph–Ċ=Ċ–Ph), and 121 (Ph–C̈=S).

Treatment of this compound with Raney nickel yielded an oil which, by t.l.c. was shown to contain one major component, and a number of minor ones. The compound formed a picrate the elemental analysis of which yielded a molecular formula of $C_{20}H_{27}N$ for the major component of the desulphurisation mixture. Although n.m.r. and mass spectral data indicated that the compound contained two phenyl groups and a diethyl amino-group, there was insufficient evidence to establish the structure of the compound. The presence of only two phenyl groups can be explained in terms of an initial desulphurisation, followed by further reductive cleavage of the molecule. The ethyl groups are believed to result from reductive alkylation of the amino-group.[8]

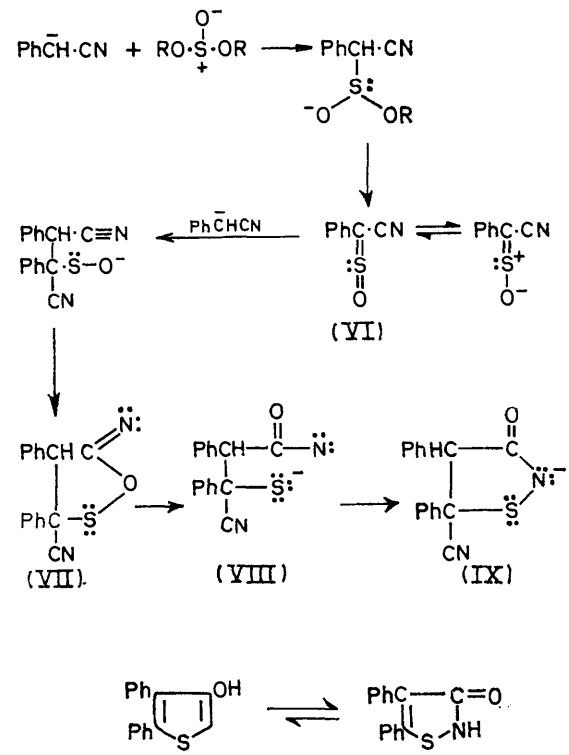
Desulphurisation using deactivated Raney nickel yielded starting material and an intractable tar.

The higher-melting compound contained no sulphur, and was assigned structure (V) on the basis of the i.r., n.m.r., and mass spectral evidence; the last named showed in addition to the molecular ion, *m/e* 346 ($C_{24}H_{16}N_3$), fragments at *m/e* 321 ($C_{23}H_{17}N_2$), 270 ($C_{18}H_{12}N_3$), and 204 ($C_{15}H_{10}N$).

PhC(CN)=C(Ph)–C(:NH)–CH(CN)Ph
(V)

A reaction with diethyl sulphite in which sodamide was replaced by a 50% dispersion of sodium hydride gave only 1·7% of the isothiazole (I), the main product being compound (IV). I.r. analysis of the crude reaction product indicated that the yield was over 60%, but only 16% was isolated as a crystalline solid.

We propose * the sequence shown in the Scheme for the reaction. Initially there is displacement of an alkoxide ion by the phenylacetonitrile anion followed by elimination of the corresponding alcohol to give the sulphine intermediate (VI). Addition of a further phenylacetonitrile anion to this followed by attack of the resulting anionic oxygen on the carbon of the nitrile group would yield the anion (VII). The fate of this compound is uncertain, but could involve the formation of the nitrene (VIII) the nitrogen atom of which would probably have a lifetime long enough to permit rotation around the carbon–carbon bond holding the nitrene group and attack of the nitrogen atom on the sulphide anion to give the cyanoisothiazolone (IX), but not long enough for the known reactions of acyl nitrenes (rearrangement to isocyanate, *etc.*) to occur. Elimination of



hydrogen cyanide would yield the tautomer of the observed product.

Reaction sequences involving an initial condensation of two phenylacetonitrile molecules were eliminated by an experiment in which work-up prior to addition of sulphite gave only starting material.

EXPERIMENTAL

Mass spectra and n.m.r. spectra were run by the Physico-Chemical Measurements Unit at the U.K. Atomic Energy Establishment, Harwell, Didcot, Berks. Interpretation of mass spectral data was also carried out by P.C.M.U. staff. I.r. spectra were run on a Unicam SP-200 spectrophotometer. The toluene used for the reactions was dried by distillation shortly before the beginning of an experiment. Sodamide used was B.D.H. reagent grade. Phenylacetonitrile was B.D.H. reagent grade and was used without purification. The sulphites used were prepared by two general methods. Alkyl sulphites were prepared using the method of Suter and Gerhat [9] and the benzyl and phenyl sulphites by the method of Richter.[10] The procedure used for all the experiments using sodamide as the base was the same, and is illustrated by the following example:

4,5-Diphenylisothiazol-3-ol (I).—A solution of phenyl

* Proposed by Dr. H. L. Dryden of the Company's Chicago laboratories.

[8] G. R. Pettit and E. E. van Tamelen, *Org. Reactions*, Vol. 12, p. 360.

[9] C. M. Suter and H. L. Gerhart, *Org. Synth.*, Coll. Vol. II, p. 112.

[10] M. M. Richter, *Ber.*, 1916, **49**, 2339, 2342.

acetonitrile (32 g) in toluene (370 ml) was cooled in ice to 5 °C under nitrogen. The ice-bath was removed and powdered sodamide (25 g) was added rapidly. The solution turned light brown and the temperature rose to *ca.* 15 °C; it was raised to 30 °C. The mixture was stirred for a short time at this temperature and then cooled again to 5 °C. Diethyl sulphite (19·1 g) was added during *ca.* 5 min. The temperature rose rapidly to *ca.* 30 °C and, initially, a brownish precipitate formed; this dissolved to give a deep orange solution which later precipitated an orange solid. Stirring was continued at room temperature for *ca.* 1 h. The mixture was then cooled initially to 5 °C and decomposed by the addition of methanol (8 ml) followed by glacial acetic acid (34 ml) at such a rate that the temperature could be maintained at *ca.* 10 °C. After the addition of the acetic acid was complete, the colour of the precipitate had changed from orange to yellow. Water (136 ml) was cautiously added, and the mixture was stirred for 0·5 h. The precipitated solid was collected and dried (16·3 g, 47%). Recrystallisation of the crude product from chloroform gave *4,5-diphenylisothiazol-3-ol* (13 g, 38%) as fine white needles, m.p. 245—247° (Found: C, 71·3; H, 4·25; N, 5·55; S, 12·4. $C_{15}H_{11}NOS$ requires C, 71·4; H, 4·35; N, 5·5; S, 12·6%), *M*, 253 (mass spec.), τ [$(CD_3)_2SO$] 2·75 (10 ArH) and 1·85 (1H, exchangeable OH).

After collection of the insoluble product, the toluene mother liquor was separated from the aqueous layer, washed with water, and evaporated on a rotary evaporator to give a brown oil (14·7 g) which solidified to a pasty material with time. Trituration of this with a little alcohol yielded *α-cyano-α-(4,5-diphenylisothiazol-3-yl)benzyl phenyl thione* (IV) (1·4 g, 4·4%), m.p. 205—207° (from ethanol) (Found: C, 76·5; H, 4·20; N, 5·95; S, 13·8. $C_{30}H_{20}N_2S_2$ requires C, 76·8; H, 4·26; N, 5·94; S, 13·60%) *M*, 472 (mass spec.), $\nu_{max.}$ ($CHCl_3$) 2260 cm^{-1} (CN), τ ($CDCl_3$) 2·6 (5 ArH), and 2·9 (15 ArH). A further quantity of compound (IV) (0·5 g, 1·5%, total yield 4·9 g, 15·1%) was obtained by acidification, and extraction of the original aqueous solution with chloroform.

In a separate experiment carried out under the same conditions except that the crude product obtained by evaporation of the toluene solution was triturated with chloroform and the crude solid dissolved in tetrahydrofuran and filtered to remove some suspended inorganic solid. Evaporation of the solvent gave an orange solid (7·71 g) which was again triturated with chloroform to give crude 4,5-diphenylisothiazol-3-ol (3·7 g) and, after evaporation of the chloroform, crude compound (IV) (3·1 g). During the recrystallisation of (IV) from alcohol, an alcohol-insoluble, bright yellow compound was collected on the filter. Recrystallisation of this material from chloroform gave what is believed to be 4-imino-2,3,5-triphenylhex-2-enedinitrile (V) (0·8 g), m.p. 265° (decomp.) (Found: C, 83·4; H, 5·35; N, 11·6, 11·7. $C_{24}H_{17}N_3$ requires C, 82·9; H, 4·9; N, 12·1%), *M*, 347 (mass spec.), $\nu_{max.}$ ($CHCl_3$) 2250 cm^{-1} (−C≡N), τ [$(CD_3)_2SO$] 1·9 (2H) and 2·7 (15ArH).

Raney Nickel Desulphurisation of 4,5-Diphenylisothiazol-3-ol.—A solution of 4,5-diphenylisothiazol-3-ol (0·5 g) in methanol (150 ml) was refluxed for 22 h in the presence of W-7 grade Raney nickel [11] prepared immediately before use from nickel–aluminium alloy (12·5 g). The solution was cooled and filtered and the methanol evaporated. The crude product (0·38 g) was dissolved in chloroform and again filtered. On evaporation 2,3-diphenylpropionamide (0·25 g) was obtained; it was crystallised from benzene–light petroleum and had m.p. and mixed m.p. with authentic material 131—134° (lit.,[12] m.p. 133—134°).

2-Methyl-4,5-diphenylisothiazol-3-one.— 4,5-Diphenylisothiazol-3-ol (2·4 g) was suspended in a solution of sodium hydroxide (0·4 g) in water (50 ml). Dimethyl sulphate (2·4 g) was added to the mixture which was then heated on a water-bath at 100° for 30 min. The mixture was cooled and extracted with dichloromethane. The extract was dried and evaporated. The crude product (1·3 g) was recrystallised from chloroform giving starting material (0·3 g). The filtrate was evaporated giving an oil (1·0 g) which on trituration with ether yielded a crystalline solid which crystallised from light petroleum to give *2-methyl-4,5-diphenylisothiazol-3-one*, m.p. 134—135° (Found: C, 71·5; H, 4·85; N, 5·25; S, 11·75. $C_{16}H_{13}NOS$ requires C, 72·0; H, 4·9; N, 5·25; S, 12·0%), $\nu_{max.}$ ($CHCl_3$) 1650 cm^{-1}, τ ($CDCl_3$) 2·7 (10ArH) and 6·58 (3H, NCH_3).

Dimethyl 4,5-Diphenylisothiazol-3-yl Phosphate.—A suspension of 4,5-diphenylisothiazol-3-ol (2 g) in dry toluene (100 ml) was treated with phosphorous pentachloride (6 g) at 25°. The mixture was stirred for 1 h during which time a white precipitate formed after which methanol (25 ml) was added. The precipitate redissolved, and the resulting solution was refluxed for 1 h. The cooled solution was then washed with sodium hydrogen carbonate solution and then with water. The solvent was evaporated, and the crude product (1·5 g) was triturated with chloroform to give unchanged starting material (0·1 g). The chloroform solution was evaporated giving a light brown oil (0·97 g) which solidified on cooling. Recrystallisation from hexane gave *dimethyl 4,5-diphenylisothiazol-3-yl phosphate* (0·6 g), m.p. 92—93° (Found: C, 56·7; H, 4·1; N, 3·9. $C_{17}H_{16}NO_4PS$ requires C, 56·6; H, 4·45; N, 3·9%), τ ($CDCl_3$) 2·7 (10H, ArH), 3·75 (3H, OMe), and 3·87 (3H, OMe).

Hydrolysis with dilute hydrochloric acid yielded 4,5-diphenylisothiazol-3-ol, m.p. 240—246°.

Raney Nickel Desulphurisation of Compound (IV).—A solution of (IV) (0·5 g) in absolute alcohol (50 ml) was treated with Raney nickel (5 g; W-4 grade) and the mixture was heated under reflux for 1 h. The catalyst was filtered off and washed with a small quantity of alcohol. The filtrate was evaporated under reduced pressure to give a straw coloured oil (0·35 g). The picrate had m.p. 141—143° (Found: C, 60·8; H, 5·75; N, 11·05. $C_{26}H_{30}N_4O_7$ requires C, 61·2; H, 5·95; N, 11·0%), τ ($CDCl_3$) 1·2 ($2H^+$-picric acid), 2·8—3·1 (11H, 10-ArH + $1NH^+$?), 6·3—7·3 (11H, >CH−, $-CH_2-$), and 8·7—9·1 (6H, Me).

The author thanks Dr. H. L. Dryden and Dr. R. Bible of the Company's Chicago research laboratories for helpful discussions, and the management of G. D. Searle & Co. for permission to publish this paper.

[1/1724 *Received*, 20*th September*, 1971]

[11] H. R. Billica and H. Adkins, *Org. Synth.*, Coll. Vol. III, p. 179.

[12] Dictionary of Organic Compounds, London, Eyre, Spottiswoode & Spon, 4th edn., 1965, vol. 3, p. 1293.