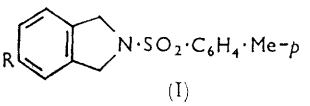
76. *The Removal of Toluene-*p*-sulphonyl Groups from Sulphonamides. Part I. Synthesis of Schiff Bases.*

By W. Paterson and G. R. Proctor.

The base-catalysed extrusion of toluene-*p*-sulphinyl anions from certain sulphonamides has been examined. Formation of Schiff bases by this process has been studied.

The toluene-*p*-sulphonyl group has been frequently employed to protect oxygen atoms in hydroxy-compounds and nitrogen atoms in amines by converting them into sulphonic esters and sulphonamides, respectively. Removal of the protecting group from the former poses few problems, indeed solvolyses of such esters have been widely studied and in some cases [1,2] have yielded synthetically useful processes for the formation of new carbon–carbon single bonds.

Sulphonamides, on the other hand, are cleaved with some difficulty.[3] Early work in the field led to the use of strong acids; for acid-sensitive molecules other methods, such as metal–ammonia cleavage [4] and lithium aluminium hydride treatment,[5] have been developed. In most of these examples amines are obtained from sulphonamides. The effect of bases on sulphonamides was studied by Ingold and his co-workers.[6,7] They concluded that bases might abstract a proton (if present) from the carbon atom adjacent to the nitrogen atom and that the carbanion thus formed might then extrude a toluene-*p*-sulphinyl anion yielding a Schiff base, but the drastic conditions employed generally made it impossible to isolate these compounds: the sulphonamide (I; R = H) gave, for



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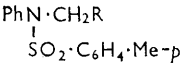

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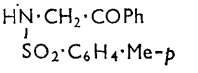
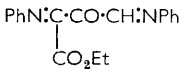


(III)

example, isoindoline and not 1*H*-isoindole. In an earlier Communication [8] we gave a preliminary account of our efforts to find suitable mild basic conditions that would cause the elimination of toluene-*p*-sulphinyl anions from suitably designed sulphonamides. We now report our conclusions regarding the type of sulphonamides that can be used and some attempts to apply the reaction usefully in synthetic work.

Alkoxides in toluene at room temperature had no effect upon the sulphonamides (II; R = H or Ph) but converted the compounds (II; R = COPh,[8,9] $C_6H_4{\cdot}NO_2$-*p*) [8] into the corresponding Schiff bases in good yield. As one would expect, the ethoxycarbonyl group in compound (II; R = CO_2Et) also activated the molecule for elimination, however several oily products were obtained, the only one that could be distilled was an imino-keto-ester $C_{18}H_{19}N_2O_3$, possibly (IV).

The sulphonamides, *e.g.*, (III), from primary amines do not undergo the elimination reaction, presumably because the proton attached to nitrogen is the most acidic in the molecule.



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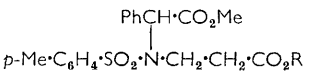

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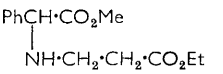
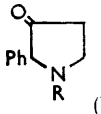


(VI)

[1] Barner, Dreiding, and Schmid, *Chem. and Ind.*, 1958, 1437.
[2] Winstein and Baird, *J. Amer. Chem. Soc.*, 1957, **79**, 756.
[3] Burwell, *Chem. Rev.*, 1954, **54**, 615.
[4] Swan and du Vigneaud, *J. Amer. Chem. Soc.*, 1954, **76**, 3111.
[5] Stetter, Schafer, and Dieminger, *Ber.*, 1958, **91**, 598.
[6] Holmes and Ingold, *J.*, 1926, 1305.
[7] Fenton and Ingold, *J.*, 1928, 3295.
[8] Paterson and Proctor, *Proc. Chem. Soc.*, 1961, 248.
[9] Fraser, Paterson, and Proctor, *J.*, 1963, 5107.

In most of the examples studied, toluene-*p*-sulphinic acid can be isolated by acidification of the aqueous alkaline layer but it seems that, on occasion, the toluene-*p*-sulphinyl anion can attack other molecules present. For example, in an attempt [10] to synthesise the diester (V; R = Et) by refluxing the ester (VIII) with ethyl β-bromopropionate and acetone in presence of anhydrous potassium carbonate, one of the products was the sulphone ester (IX) formed presumably when the expected product (V; R = Et) underwent the elimination reaction and the toluene-*p*-sulphinyl anion was trapped by reaction with ethyl β-bromopropionate. In this case the rest of the product was probably not an anil (cf. ref. 7) but was the ester (VI) since it was cyclised (without purification) to the pyrrolidin-3-one (VII; R = H), characterised as the sulphonamide (VII; R = $SO_2 \cdot C_6H_4 \cdot Me$-*p*)



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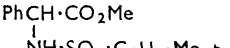
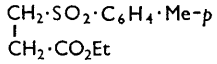


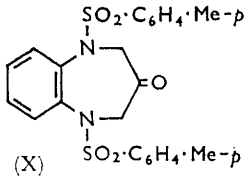
(VIII)



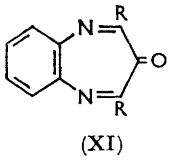
(IX)

Additionally the diester (V; R = Me), made by another route, did not give ketonic material when submitted to the Dieckmann reaction; it can now be understood that the elimination reaction would be expected to intervene and that the anil formed initially might be sterically indisposed for cyclisation. The complications encountered in the simple ester (II; R = CO_2Et) make ketone syntheses based on β-*N*-toluene-*p*-sulphonylamino-esters quite unattractive.

We have previously [11,12] described the application of the elimination reaction in the synthesis of an azadibenzotropone; the ketone (X) seemed from the foregoing experiments to be a suitable starting material for the diazabenzotropone (XI; R = H). However, bases converted (X) into a deep red substance, $C_{16}H_{14}N_2O_3S$ (m. p. 242°), unaffected by refluxing concentrated hydrochloric acid or by potassium t-butoxide in dimethyl sulphoxide. The infrared spectrum revealed hydroxyl but not carbonyl absorption. The nuclear magnetic resonance (n.m.r.) spectrum showed 10 aromatic-vinylic protons (1·5 to 3·6 τ) and 3 methyl protons (singlet, 7·65 τ): the hydroxyl proton was not recognisable. It was then discovered that the well-known diazepine [13,14] (XIII) with toluene-*p*-sulphonyl chloride formed a similar deep red compound (containing no hydroxyl group). The evidence is in favour of structures (XII) and (XIV) for these molecules.



(X)



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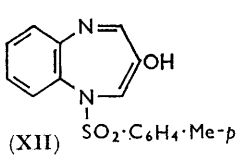

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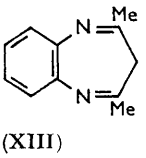

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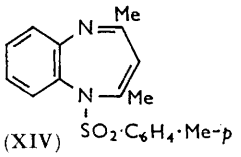

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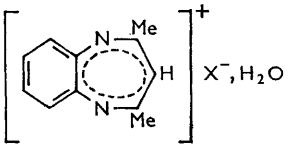

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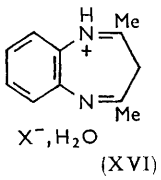

(XVI)

The unusual polarity of these sulphonamides suggests that they are diazatropylium salts [*e.g.*, (XVI; X = $SO_2 \cdot C_6H_4 \cdot Me$-*p*)] but none of these are known and in an attempt to make

[10] Proctor and Thomson, unpublished data.
[11] Paterson and Proctor, *J.*, 1962, 3468.
[12] Proctor, *Chem. and Ind.*, 1960, 408.
[13] Thiele and Steimmig, *Ber.*, 1907, **40**, 956.
[14] Barltrop, Richards, Russell, and Rybach, *J.*, 1959, 1132, 1423.

one by reacting the diazepine (XIII) with trityl perchlorate, the product isolated was the same perchlorate as that from the diazepine (XIII) and perchloric acid alone. This perchlorate was shown to be (XVI; X = ClO_4) by elemental analyses and n.m.r. spectroscopy (in SO_2); there being two protons at 5·75 (H_2O), seven protons between 2·3 and 3·7 and six protons (singlet) at 8·1 τ. The somewhat unusual chemical shift of the methine ring protons may be due to the solvent or to the molecular environment. A decision between these possibilities was not possible since the n.m.r. spectrum of the parent diazepine (XIII) can only be obtained in neutral organic solvents (see ref. 14); in sulphur dioxide the diazepine turned purple.

2*H*-Pseudoisoindoles and 1*H*-isoindoles have aroused some interest of late.[15-17] We had hoped that the sulphonamide (I; R = NO_2) might undergo base-catalysed elimination giving a 1*H*-isoindole as envisaged by Fenton and Ingold.[7] However, although compound (I; R = NO_2) reacted with alkoxides at room temperature readily compared with (I; R = H), the product was an insoluble deep blue non-crystalline material containing sulphur.

Experimental

Reactions of N-*Toluene*-p-*sulphonyl*-N-*methylaniline* (II; R = H).—The above compound was recovered quantitatively after treatment with sodium methoxide in toluene at 20° for 24 hr., potassium t-butoxide in dry dimethyl sulphoxide at 20° for 24 hr., sodium ethoxide in refluxing toluene, or potassium hydroxide in refluxing ethylene glycol.

The *N*-benzyl analogue (II; R = Ph) was similarly unaffected by these four reagents.

N-p-*Nitrobenzylaniline*.—*p*-Nitrobenzylbromide (4·75 g.), aniline, (5 ml.), and ethanol (100 ml.) were refluxed together for 3 hr., cooled, diluted, and extracted with chloroform which was washed with dilute hydrochloric acid and water, dried, and evaporated leaving the crude product (3·6 g.) as a red oil, $\nu_{max.}$ 3333 (NH) and 1625 cm.$^{-1}$ (NO_2). The N-*toluene*-p-*sulphonyl derivative* (II; R = C_6H_4·NO_2-*p*), obtained by reaction with toluene-*p*-sulphonyl chloride in dry pyridine, crystallised from methanol as cubes, m. p. 122° (Found: C, 62·9; H, 4·95; N, 7·3. $C_{20}H_{18}N_2O_4S$ requires C, 62·8; H, 4·7; N, 7·35%).

N-p-*Nitrobenzylideneaniline*.—(*a*) A nitrogen-saturated solution of the foregoing sulphonamide (1·66 g.) in dry toluene (150 ml.) was added to a nitrogen-saturated suspension of sodium methoxide (4 g.) in dry toluene (50 ml.). After 24 hr. at 20°, the mixture was poured into water and allowed to separate. The aqueous layer was extracted with chloroform and both organic extracts were washed with water. After removal of solvents, the anil crystallised from methanol as yellow plates (84%), m. p. 92° (Found: C, 69·0; H, 4·5; N, 12·55. Calc. for $C_{13}H_{10}N_2O_2$: C, 69·0; H, 4·1; N, 12·4%), $\nu_{max.}$ (Nujol) 1575 cm.$^{-1}$ (C=N). The aqueous extracts gave toluene-*p*-sulphinic acid, cubes (93 mg.), m. p. and mixed m. p. 84° (from methanol).

(*b*) *p*-Nitrobenzaldehyde (349 mg.), aniline (200 mg.), and anhydrous sodium sulphate (210 mg.) were heated together at 100° for 5 min. The crude product (450 mg.) was extracted and crystallised from ethanol as yellow plates, m. p. 92° mixed with those made by (*a*). Treatment of the anil with 2,4-dinitrophenylhydrazine hydrochloride in ethanol gave *p*-nitrobenzaldehyde 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 312°.

Reaction of Ethyl N-*Phenyl*-N-*toluene*-p-*sulphonylaminoacetate* (II; R = CO_2Et).—When the sulphonamide (2·4 g.) was treated with sodium methoxide (4·25 g.) as described previously, from the products was distilled a yellow oil, b. p. 150°/3 mm. [Found: C, 70·0; H, 5·6; N, 9·2%; *M* (cryoscopic), 323. Calc. for $C_{18}H_{16}N_2O_3$: C, 70·1; H, 5·2; N, 9·1%; *M*, 308], $\lambda_{max.}$ 1730 (ester), 1669 (αβ-unsaturated ketone) and 1620 cm.$^{-1}$ (C=N?). From the aqueous extracts was obtained toluene-*p*-sulphinic acid (120 mg.) as before.

Methyl α-*Amino*-α-*toluate*.—α-Amino-α-toluic acid (55 g.) [18] was suspended in dry methanol (250 ml.) while a stream of dry hydrogen chloride was bubbled through it until homogeneity was obtained. After being refluxed for 4 hr., the mixture was concentrated *in vacuo* and the residual solid was extracted with benzene and washed with aqueous ammonia (*d* 0·88). The

[15] Wittig and Ludwig, *Annalen*, 1954, **589**, 55.
[16] Veber and Lwowski, *J. Amer. Chem. Soc.*, 1963, **85**, 646.
[17] Thesing, Schafer, and Melchior, *Annalen*, 1964, **671**, 119.
[18] Marvel and Noyes, *J. Amer. Chem. Soc.*, 1920, **42**, 2265.

solvent was removed and the residual oil distilled at 72—74°/0·03 mm., when it set to a solid mass (12·5 g., 21%), m. p. 29°.

The N-*toluene*-p-*sulphonyl derivative* (VIII) crystallised from ethyl acetate–light petroleum (b. p. 80—90°) as needles, m. p. 111—112° (Found: C, 60·5; H, 5·3; N, 4·75; S, 9·95. $C_{16}H_{17}NO_4S$ requires C, 60·15; H, 5·4; N, 4·4; S, 10·0%).

Reaction with Ethyl β-*Bromopropionate*.—The above ester (3·33 g.) and ethyl β-bromopropionate (1·87 g.) were refluxed with anhydrous potassium carbonate (5 g.) and dry acetone (80 ml.) for 24 hr. and poured into water (500 ml.). The extract obtained with chloroform was washed with cold sodium hydroxide solution (5%) and water, dried, and evaporated leaving the crude product (3·5 g.). Distillation at 170—190°/0·04 mm. and crystallisation from light petroleum (b. p. 80—90°) gave *ethyl* β-*toluene*-p-*sulphonylpropionate* (IX) as long white needles, m. p. 42° (0·49) (Found: C, 56·4; H, 5·9; S, 12·45. $C_{12}H_{16}O_4S$ requires C, 56·25; H, 6·3; S, 12·5%).

2-*Phenyl*-N-*toluene*-p-*sulphonylpyrrolidin*-3-*one* (VII; $R_2SO_2{\cdot}C_6H_4{\cdot}$Me-*p*).—Potassium (0·31 g.) was dispersed with mechanical stirring in refluxing dry xylene (120 ml.) under dry nitrogen. t-Butyl alcohol (0·58 g.) was added, followed by a solution of the crude diester (VI) (3 g.) from the previous experiment in dry xylene (80 ml.), added dropwise during 4¼ hr. Stirring and refluxing were continued for 19 hr., after which the mixture was cooled, dilute hydrochloric acid (250 ml.) was added, and the organic layer separated. The aqueous solution was made alkaline and extracted with chloroform, the extract was evaporated, and the residue refluxed with ethanol (20 ml.) and concentrated hydrochloric acid (10 ml.) for 20 min. The cooled mixture was diluted with water and extracted with chloroform; the extract yielded an oil (0·5 g.) which formed a dark red 2,4-dinitrophenylhydrazone. The *toluene*-p-*sulphonate* crystallised from methanol as needles, m. p. 140—141° (Found: C, 64·5; H, 5·05; N, 4·1; S, 10·6. $C_{17}H_{17}NO_3S$ requires C, 64·7; H, 5·45; N, 4·45; S, 10·15%), $\lambda_{max.}$ (Nujol) 1690 cm.$^{-1}$. This formed a 2,4-*dinitrophenylhydrazone*, prisms, m. p. 226° (from acetic acid) (Found: C, 55·4; H, 4·15; N, 13·9; S, 6·8. $C_{23}H_{21}H_5O_6S$ requires C, 55·7; H, 4·25; N, 14·15; S, 6·5%).

N-(2-*Cyanoethyl*)-α-*amino*-α-*toluic Acid*.—α-Amino-α-toluic acid (10 g.), acrylonitrile (3·5 g.), aqueous potassium hydroxide, and methylated spirit (100 ml.) were refluxed together with vigorous stirring for 24 hr., cooled, and filtered. The *product* was washed with cold methanol and recrystallised from water as colourless needles (6 g.), m. p. 238° (giving a red melt) (Found: C, 64·3; H, 5·65; N, 13·55. $C_{11}H_{12}N_2O_2$ requires C, 64·7; H, 5·9; N, 13·75%).

N-(2-*Carboxyethyl*)-α-*amino*-α-*toluic Acid*.—The previous material (6 g.) was refluxed with concentrated hydrochloric acid (60 ml.) and water (60 ml.) for 7 hr.; the reaction mixture was neutralised with ammonia, evaporated *in vacuo*, and extracted with boiling water. The *diacid* crystallised as needles (2 g.), m. p. 229·5° (with effervescence) (Found: C, 58·9; H, 5·7; N, 6·1. $C_{11}H_{13}NO_4$ requires C, 59·2; H, 5·85; N, 6·3%).

The diacid was esterified with methanolic hydrogen chloride in the usual way and the product was converted into the *toluene*-p-*sulphonyl derivative* (V; R = Me) which crystallised from light petroleum (b. p. 100—120°) as prisms, m. p. 93° (Found: C, 59·2; H, 5·5; N, 3·7; S, 7·45. $C_{20}H_{23}NO_6S$ requires C, 59·25; H, 5·7; N, 3·45; S, 7·9%).

When this ester was subjected to the Dieckmann reaction using potassium t-butoxide, the product contained no ketone.

Dipotassium Salt of NN′-*Ditoluene*-p-*sulphonyl*-o-*phenylenediamine*.—A solution of potassium hydroxide (2·1 g.) in aqueous ethanol (5 ml.; 10%) was added to a hot solution of *NN′*-ditoluene-*p*-sulphonyl-*o*-phenylenediamine (7·04 g.) in ethanol (200 ml.) and the mixture cooled to 20°. Addition of acetone gave the *product* (4·8 g.), m. p. >300° (Found: C, 47·35; H, 3·8. $C_{20}H_{18}K_2N_2O_4S_2$ requires C, 48·7; H, 3·7%).

2,3,4,5-*Tetrahydro*-3-*oxo*-1,5-*ditoluene*-p-*sulphonyl*-1H-1,5-*benzodiazepine* (X).—(*a*) A mixture of the foregoing potassium salt (1·75 g.), 1,3-dibromoacetone [19] (700 mg.), and dry benzene (50 ml.), was refluxed for 2 hr. and filtered. Evaporation of the filtrate gave a gum (1·5 g.) which was chromatographed on neutral alumina. Elution with benzene gave the *product* (250 mg.) which crystallised from methanol as cubes, m. p. 182° [Found: C, 57·95; H, 4·8; N, 6·5%; *M* (isothermal distillation), 446. $C_{23}H_{22}N_2O_5S$ requires C, 57·6; H, 4·8; N, 6·1%; *M*, 458], $\lambda_{max.}$ (Nujol) 1762 cm.$^{-1}$ (C=O). The 2,4-*dinitrophenylhydrazone* crystallised from nitrobenzene as yellow needles, m. p. 208° (Found: C, 53·95; H, 4·0; N, 12·75. $C_{29}H_{26}N_6O_8S_2$ requires

[19] Weygand and Schmied-Kowarzik, *Ber.*, 1949, **82**, 333.

C, 53·55; H, 4·0; N, 12·9%), $\nu_{max.}$ (Nujol) **3333** (NH) and **1626** cm.$^{-1}$ (C=N). Elution of the column with chloroform afforded *NN'*-ditoluene-*p*-sulphonyl-*o*-phenylenediamine (865 mg.).

(*b*) *NN'*-Ditoluene-*p*-sulphonyl-*o*-phenylenediamine (6·9 g.), 1,3-dibromoacetone (3·75 g.), anhydrous sodium carbonate (20 g.), and dry toluene (1 l.) were refluxed together for 24 hr. After filtration and washing with chloroform, evaporation of the solvents gave a gum (8·05 g.). Chromatography on neutral alumina as before gave the product (2·4 g.) and the starting sulphonamide (4·3 g.). Elution with chloroform–methanol (99 : 1) gave a red solid (200 mg.) crystallising from ethanol as plates, m. p. 242° (*vide infra*).

Reaction of the Diazepinone (X) *with Bases.*—A nitrogen-saturated solution of the diazepinone (1 g.) in dry toluene (180 ml.) was added to a nitrogen-saturated suspension of sodium methoxide (2 g.) in dry toluene (50 ml.) and set aside for 48 hr. at 20°. The mixture was diluted with water and the toluene separated and evaporated, leaving the product (550 mg.) which crystallised from ethanol as plates, m. p. 242° [Found: C, 61·5; H, 4·2; N, 8·4; S, 9·1%; *M* (isothermal distillation), 350. Calc. for $C_{16}H_{14}N_2O_3S$: C, 61·15; H, 4·45; N, 8·9; S, 10·2%; *M*, 314], $\nu_{max.}$ (KCl) **3390** (OH) cm.$^{-1}$ n.m.r. signals 1·5—3·6 and 7·65 τ (singlet); area ratios **10 : 3.**

This product was identical to the one obtained in the previous section. It was also obtained from the same starting material with (i) potassium t-butoxide in ethanol (70%), (ii) potassium t-butoxide in dimethyl sulphoxide (78%), (iii) anhydrous sodium carbonate and refluxing toluene for 48 hr. (50%). It was quantitatively recovered after refluxing for 5 hr. with ethanolic potassium hydroxide and in 45% yield after being refluxed for 5 hr. with acetic acid and concentrated hydrochloric acid.

2,4-*Dimethyl*-3H-1,5-*benzodiazepine* (XIII).[13,14]—This was obtained in the usual way and was purified by sublimation at 90°/0·5 mm. and by crystallisation from benzene as colourless cubes, m. p. 130° (Found: C, 76·75; H, 6·9. Calc. for $C_{11}H_{11}N_2$: C, 77·2; H, 6·45%).

The *toluene*-p-*sulphonyl derivative* was obtained by treatment with toluene-*p*-sulphonyl chloride in pyridine and was purified by chromatography on neutralised alumina, elution by chloroform–methanol (99 : 1), and crystallisation from methanol–methylene chloride as a deep red amorphous material, m. p. >360° [Found: C, 66·6; H, 5·75; N, 8·5; S, 9·1%; *M* (isothermal distillation), 346. $C_{18}H_{18}N_2O_2S$ requires C, 66·25; H, 5·5; N, 8·6; S, 9·8%; *M*, 328]. This product was unaffected by refluxing with acids and alkalis. The *perchlorate* (XV; X = ClO_4) was obtained from the diazepine (XIII) with either perchloric acid or trityl perchlorate, and crystallised from water as purple needles, m. p. 185° (Found: C, 45·05; H, 4·95; N, 9·65. $C_{11}H_{13}ClN_2O_4,H_2O$ requires C, 45·45; H, 5·2; N, 9·65%).

5-*Nitro*-2-*toluene*-p-*sulphonylisoindoline.*—Prepared by reaction of toluene-*p*-sulphonyl chloride and 5-nitroisoindoline [20] in dry pyridine, the *product* crystallised from methanol as plates, m. p. 165° (Found: C, 56·3; H, 4·0; N, 8·6. $C_{15}H_{14}N_2O_4S$ requires C, 56·65; H, 4·4; N, 8·8%).

Reaction with Base.—The above sulphonamide (1·1 g.) in dry toluene (50 ml.) was treated with sodium methoxide (1·5 g.) in toluene (50 ml.) under nitrogen. After 48 hr. at 20°, the mixture was poured into water and filtered; the residue (450 mg., m. p. >360°) was a deep blue amorphous powder which was chromatographed on alumina. Elution with chloroform–methanol (99 : 1) gave a solid (95 mg.) which crystallised from acetone–methanol as purple needles, m. p. >300° (Found: C, 58·6; H, 4·25; N, 6·15%), $\nu_{max.}$ (Nujol) **3390**, **1600**, and **1527** cm.$^{-1}$. Tests showed that this material contained sulphur. It had poor solubility in most solvents; in perchloric acid it gave an inky blue solution.

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[20] Frankel, *Ber.*, 1900, **33**, 2810.