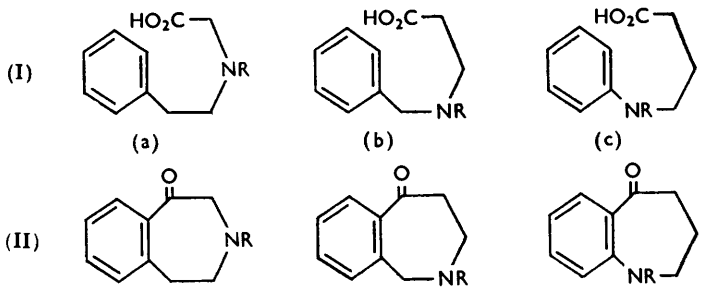
443. *Azabenzo*cyclo*heptenones. Part I. The Friedel–Crafts Reaction with Aryl-amino-acids.*

By G. R. Proctor and R. H. Thomson.

For various reasons the aryl-amino-acids (Ia, b, and c) do not, in general, cyclise to azabenzo*cyclo*heptenones although the ketone (IIa; R = *p*-$C_6H_4Me{\cdot}SO_2$) can be detected after treatment of the chloride of (Ia; R = *p*-$C_6H_4Me{\cdot}SO_2$) with aluminium chloride in carbon disulphide at a low temperature. The glycine (Ia; R = *p*-$C_6H_4Me{\cdot}SO_2$) loses carbon monoxide when heated in polyphosphoric acid and cyclises to a tetrahydro-*iso*quinoline. β-Benzylaminopropionic acids (Ib) are readily debenzylated and a variety of products is formed under Friedel–Crafts conditions. β-(3 : 4-Dimethoxybenzylamino)propionic acid readily undergoes β-elimination of the amine under acid conditions. Attempts to cyclise the γ-anilinobutyric acid (Ic; R = *p*-$C_6H_4Me{\cdot}SO_2$) or to form its acid chloride gave a lactam, with displacement of the toluene-*p*-sulphonyl group, and if the benzene ring was activated by methoxyl groups toluene-*p*-sulphonation occurred in that ring when the reaction was conducted in polyphosphoric acid. Other examples of $N \longrightarrow C$ migration of a toluene-*p*-sulphonyl group have been found. Anisole is acylated by toluene-*p*-sulphonic acid in polyphosphoric acid.

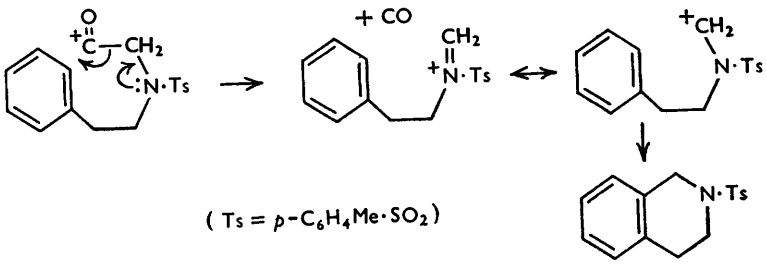
All three azabenzo*cyclo*heptenes containing nitrogen in the seven-membered ring have been known for many years but none of the simple azabenzo*cyclo*heptenones (apart from

lactams) had been obtained when this work began (one has since been prepared [1]). The cyclisation of the aryl-amino-acids (Ia, b, and c) appears to be an obvious route to them. We have found, however, that in general, but for different reasons, these three types of



acid do not cyclise to the ketones (II). In studying these reactions the toluene-*p*-sulphonyl group was selected for protection of the amino-group as this has been found satisfactory [2] (in contrast to other acyl groups [3]) in analogous quinolone syntheses; the use of *N*-alkyl groups was avoided as these would be more difficult to remove subsequently.

N-2′-*Arylethylglycines* (Ia).—Cyclisation of this type of acid has been studied by von Braun and his co-workers: by heating the acid (Ia; R = Ph·SO_2) with phosphoric oxide [4] in boiling xylene, or by treating its chloride with aluminium chloride [5] in nitrobenzene in the cold, they obtained *N*-benzenesulphonyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline with the loss of carbon monoxide. Tetrahydro-*N*-methyl*iso*quinoline was obtained likewise from the chloride of (Ia; R = Me).[6] No ketones (IIa) were detected but an azabenzo*cyclo*heptene was obtained by extending the reaction to the cyclisation of the homologous *N*-benzenesulphonyl-*N*-3′-phenylpropylglycine.[4,6] We found, similarly, that heating the acid (Ia; R = *p*-$C_6H_4Me{\cdot}SO_2$) in polyphosphoric acid yielded 1 : 2 : 3 : 4-tetrahydro-*N*-toluene-*p*-sulphonyl*iso*quinoline; no reaction occurred in the cold. Tertiary acid



chlorides frequently undergo decarbonylation when treated with aluminium chloride: RR′R″C·CO^+ ⟶ RR′R″C^+ + CO. Rothstein and Saville [7] have shown that elimination of carbon monoxide from the intermediate carbonium ion is assisted by electron-release from the alkyl groups to which it is attached, and a parallel mechanism can be envisaged for the amino-acid reactions, decarbonylation being initiated by electron release from the adjacent nitrogen atom. This apparently occurs even when the group Ar·SO_2

[1] Astill and Bockelheide, *J. Amer. Chem. Soc.*, 1955, **77**, 4080; cf. Braunholz and Mann, *Chem. and Ind.*, 1957, 266.
[2] Clemo and Perkin, *J.*, 1924, **125**, 1608; Johnson, Woroch, and Buell, *J. Amer. Chem. Soc.*, 1949, **71**, 1901; Elderfield and Maggiolo, *ibid.*, 1949, **71**, 1906.
[3] Elderfield, Gensler, Bembry, Kremer, Brody, Hageman, and Head, *ibid.*, 1946, **68**, 1259.
[4] von Braun and Bayer, *Ber.*, 1927, **60**, 1262.
[5] von Braun, Blessing, and Cahn, *Ber.*, 1924, **57**, 910.
[6] von Braun and Wirz, *ibid.*, 1927, **60**, 102.
[7] Rothstein and Saville, *J.*, 1949, pp. 1946, 1950, 1954, 1959, 1961.

is attached to it. To some extent it is possible to influence the competition between the acylation and decarbonylation by temperature control and we found that by treating the acid chloride of (Ia; R = *p*-$C_6H_4Me{\cdot}SO_2$) with aluminium chloride in carbon disulphide at 0°, or lower, some ketone (IIa; R = *p*-$C_6H_4Me{\cdot}SO_2$) was formed (along with the tetrahydro*iso*quinoline derivative) and it was isolated as its 2 : 4-dinitrophenylhydrazone. However the yield was very small. It should be possible to improve this reaction by using an acid with a more reactive benzene nucleus, but a preliminary trial with *N*-3′ : 4′-dimethoxyphenethyl-*N*-toluene-*p*-sulphonylglycine in polyphosphoric acid gave an intractable product.

β-*Benzylaminopropionic Acids* (Ib).—As benzyl groups are easily detached from nitrogen it was not expected that these acids would be of much value in the synthesis of the azabenzo*cyclo*heptenones (IIb) and we found that *N*-benzyl-amides and -sulphonamides (with the exception of *N*-4′-nitrobenzylbenzenesulphonamide) were readily split in hot benzene by aluminium chloride, the products being the free amide and diphenylmethane :

$$Ph{\cdot}CH_2{\cdot}\ddot{N}R{\cdot}SO_2{\cdot}Ar \longrightarrow Ph{\cdot}CH_2{-}\overset{+}{N}R{\cdot}SO_2{\cdot}Ar \longrightarrow Ph{\cdot}CH_2{\cdot}Ph + HNR{\cdot}SO_2{\cdot}Ar$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad {}^{-}AlCl_3$$

Various attempts to cyclise the acid (Ib; R = *p*-$C_6H_4Me{\cdot}SO_2$) or its chloride were unsuccessful but signs of fragmentation were plentiful, *e.g.*, treatment with phosphoric oxide in benzene yielded some diphenylmethane. Only when the acid chloride (III) was treated with aluminium chloride in benzene was ketonic material (IV) isolated. The other products of the reaction are as shown.

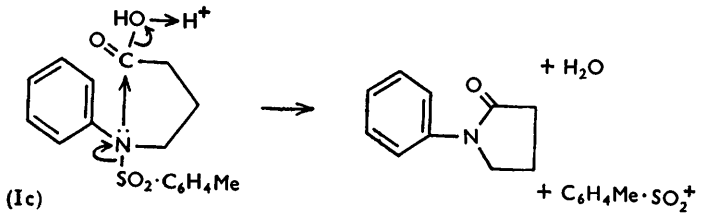
$$\underset{\text{(III)}}{Ph{\cdot}CH_2{\cdot}NTs{\cdot}CH_2{\cdot}CH_2{\cdot}COCl} \longrightarrow Ph{\cdot}CH_2{\cdot}Ph + \underset{\text{(IV)}}{NHTs{\cdot}CH_2{\cdot}CH_2{\cdot}COPh} + H_2N{\cdot}Ts$$
$$+$$
$$[Ph{\cdot}CH_2{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}NHTs] \quad \text{(V)}$$

Like a number of *N*-monoalkylsulphonamides,[8,9] the amide (IV) is insoluble in alkali but in hot dilute aqueous sodium hydroxide it was degraded to toluene-*p*-sulphonamide, a trace of benzaldehyde being also detected. The toluene-*p*-sulphonamide formed on treatment of the acid chloride (III) with aluminium chloride is probably a secondary product also derived from the sulphonamide (IV) by a β-elimination. Oxidation of the pure sulphonamide (IV) with alkaline permanganate yielded benzoic acid and toluene-*p*-sulphonamide, but a crude sample gave in addition a little *p*-benzoylbenzoic acid, presumably from a product such as (V) formed by acylation of the diphenylmethane.

Reaction of the chloride hydrochloride of the acid (Ib; R = H) with aluminium chloride in benzene gave the ketone $Ph{\cdot}CH_2{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}COPh$, previously obtained by a Mannich reaction,[10] but intramolecular acylation could not be achieved in inert solvents; β-elimination of benzylamine usually occurred and again traces of benzaldehyde were formed. Easy β-elimination also defeated attempts to utilise β-(3 : 4-dimethoxybenzylamino)propionic acid; on treatment in polyphosphoric acid this liberates veratrylamine even in the cold. In one experiment a minute yield of oil was isolated which formed a 2 : 4-dinitrophenylhydrazone. According to its analysis (C and H) it could be the azabenzo*cyclo*heptenone (IIb) but the results could not be repeated. During the toluene-*p*-sulphonylation of β-3 : 4-dimethoxybenzylpropionic acid some *N*-3 : 4-dimethoxybenzyltoluene-*p*-sulphonamide was formed and the latter also arose when the toluene-*p*-sulphonamido-acid was treated with polyphosphoric acid.

[8] Briscoe, Challenger, and Duckworth, *J.*, **1956**, 1755.
[9] Carothers, Bickford, and Hurwitz, *J. Amer. Chem. Soc.*, 1927, **49**, 2913.
[10] Mannich and Hieronimus, *Ber.*, **1942**, **75**, 61.

γ-Arylaminobutyric Acids (Ic).—The parent acid (Ic; R = H) is unknown and attempts to prepare it led to the corresponding lactam, 1-phenyl-2-pyrrolidone. The *N*-toluene-*p*-sulphonyl derivative was obtained by interaction of *N*-toluene-*p*-sulphonylaniline and ethyl γ-bromobutyrate, followed by cold alkaline hydrolysis. Attempted cyclisation of the toluene-*p*-sulphonamido-acid (Ic) in polyphosphoric acid yielded only 1-phenylpyrrolid-2-one and reaction with thionyl chloride, phosphorus pentachloride, or phosphorus oxychloride yielded, not the expected acid chloride, but a mixture of the pyrrolidone



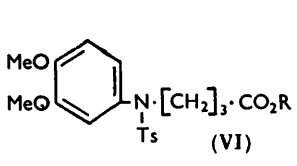
(Ic)

and toluene-*p*-sulphonyl chloride. When these experiments were complete Astill and Bockelheide [1] published essentially the same results but they inferred that reaction of the acid (Ic; R = *p*-$C_6H_4Me{\cdot}SO_2$) with phosphorus pentachloride gave the corresponding acid chloride. However we found that hydrolysis of the product obtained by treatment of the acid with thionyl chloride gave only pyrrolidone and none of the starting acid was recovered. The existence of the chloride of (Ic; *p*-$C_6H_4Me{\cdot}SO_2$) is highly improbable. This appears to be generally true of γ-amino-acids, even those containing tertiary amino-groups (cf. Wilson [11]), and is reminiscent of the alleged acid chlorides of α-acylamino-acids which are in fact oxazolone hydrochlorides.[12]

Finally the acid (VI; R = H) was examined in the hope that the methoxyl groups would promote acylation of the benzene ring. This proved to be the case, but not as expected, for heating in polyphosphoric acid gave a neutral product which we regard as the pyrrolidone (VII; R = *p*-$C_6H_4Me{\cdot}SO_2$) rather than the azabenzo*cyclo*heptenone (VIII), the toluene-*p*-sulphonyl group having migrated to an *ortho*-position (2 or 6) in the benzene ring. This compound is devoid of ketonic properties and its infrared spectrum shows a carbonyl band at 1705 cm.$^{-1}$ (in CCl_4) [cf. ν'_{CO} for 1-phenylpyrrolidone, its dimethoxy-derivative (VII; R = H), and the ketone (VIII; H in place of OMe) (see following paper) which lie at 1708, 1700, and 1688 cm.$^{-1}$ respectively in CCl_4]. On the other hand, the pyrrolidone (VII; R = H) was obtained when the acid (VI; R = H) was treated with cold hydrogen fluoride or with hot phosphoric oxide or, along with toluene-*p*-sulphonyl chloride, on reaction with thionyl chloride. We have shown that an activated benzene ring (anisole) is acylated by toluene-*p*-sulphonic acid in hot polyphosphoric acid although we have not succeeded in acylating the pyrrolidone (VIII; R = H) under these conditions. This is possibly accounted for by a steric factor which does not operate during the conversion of the acid (VI; R = H) into the pyrrolidone (VII; R = *p*-$C_6H_4Me{\cdot}SO_2$) when the approaching carbonyl group simultaneously displaces the toluene-*p*-sulphonyl group from the rear of the nitrogen atom whence it can migrate to an *ortho*-position unimpeded. Conversely, once this group is attached to the benzene ring formation of a lactam is difficult. Heating the ester (VI; R = Et) for 10 minutes in polyphosphoric acid gave the isomer (IX; R = Et), showing infrared bands at 3406 (NH) and 1729 cm.$^{-1}$ (ester C:O). Alkaline hydrolysis afforded the acid (IX; R = H) which was also obtained by heating the acid (VI; R = H) in stannic chloride. The acid (IX; R = H) did not form a lactam in hot polyphosphoric acid.

[11] Wilson, *J.*, 1952, 3524.
[12] Cornforth, " The Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 731.

Similar $N \longrightarrow C$ migrations have been noted by Mustafa and Ali [13] who found that the toluene-*p*-sulphonyl group in the naphthasultam (X), and one of the groups in *NN*-di-toluene-*p*-sulphonylaniline, migrated to the *para*-position in the presence of aluminium chloride. Johnson, Woroch, and Buell [2] noted the formation of phenyl *p*-tolyl sulphone during cyclisation of the chloride of (XI; R = H, R′ = Cl) with aluminium chloride in



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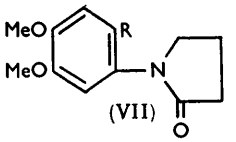

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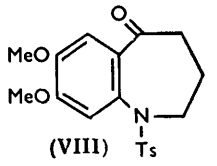
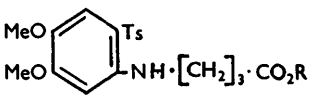


(VIII)



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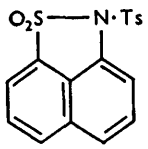
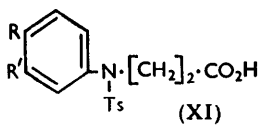
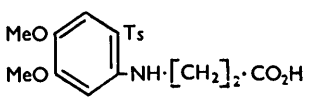


(X)



(XI)

(Ts = *p*-$C_6H_4Me \cdot SO_2$)



(XII)

benzene and in one experiment it was the main product. We have also found that the acid (XI; R = R′ = OMe) rearranges to (XII) (or the 2-acyl isomer) in hot polyphosphoric acid whereas its chloride undergoes cyclisation (without migration) to a quinolone when treated with stannic chloride in benzene.

Experimental

Microanalysis of a number of sulphonamides in this, and the following paper, gave very erratic results and the figures quoted are, in some cases, the best of several determinations.

N-(2′-*Cyanoethyl*)*benzylamine* (cf. ref. 14).—Benzylamine (214 g.) and 40% aqueous potassium hydroxide (5 ml.) were stirred in a cold-water bath while acrylonitrile (106 g.) was added during ½ hr. The solutions was stirred for 5½ hr., poured into water (500 ml.), and extracted with chloroform. The extract was dried an evaporated, and the residue distilled at 174—175°/14 mm. (85%).

N-*Benzyl*-β-*toluene*-p-*sulphonamidopropionic Acid*.—The above amine (270 g.) and 10% aqueous sodium hydroxide (1 l.) were refluxed together for 3 hr. and then cooled. The homogeneous solution was shaken with toluene-*p*-sulphonyl chloride (340 g.) in ether (1300 ml.) for 6 hr. The aqueous layer was acidified with concentrated hydrochloric acid, kept for 12 hr. at 0°, and filtered. The product was washed with cold water and crystallised from aqueous ethanol in needles, m. p. 130—133° (45%). The m. p. was raised to 136° by crystallisation from ethyl acetate–light petroleum (b. p. 80—90°). The *acid chloride* crystallised from light petroleum (b. p. 80—90°) in needles, m. p. 78° (Found: C, 58·3; H, 5·35; N, 4·0. $C_{17}H_{18}O_3NSCl$ requires C, 58·0; H, 5·1; N, 4·0%). The *amide* (from aqueous ethanol) had m. p. 125° (Found: C, 61·45; H, 6·0; N, 8·2. $C_{17}H_{20}O_3N_2S$ requires C, 61·45; H, 6·0; N, 8·45%). The *anilide* crystallised from the same solvent in needles, m. p. 146° (Found: C, 67·4; H, 5·75; N, 7·0. $C_{23}H_{24}O_3N_2S$ requires C, 67·65; H, 5·9; N, 6·85%). During the preparation of the acid chloride much acidic material was found, insoluble in light petroleum; crystallised from a small volume of water it had m. p. 180—181°; analyses indicate that it is a *monohydrate* of the starting acid (Found: C, 58·15; H, 6·0; N, 3·9; S, 9·1. $C_{17}H_{19}O_4NS,H_2O$ requires C, 58·1; H, 6·0; N, 4·0; S, 9·1%). Acidification of its alkaline solution gave *N*-benzyl-β-toluene-*p*-sulphonamidopropionic acid, m. p. 136°.

[13] Mustafa and Ali, *J. Amer. Chem. Soc.*, 1955, **77**, 4593.
[14] King and McMillan, *ibid.*, 1946, **68**, 1468.

N-*Toluene*-p-*sulphonyl*-β-*alanine* crystallised from aqueous methanol or ethyl acetate–light petroleum (b. p. 80—90°) in prisms, m. p. 123—124° (Found: C, 49·5; H, 5·25; N, 5·95; S, 13·5. $C_{10}H_{13}O_4NS$ requires C, 49·4; H, 5·4; N, 5·75; S, 13·2%).

ω-*Toluene*-p-*sulphonamidopropiophenone*.—(*a*) β-Toluene-*p*-sulphonamidopropionyl chloride (from 2 g. of the acid) was dissolved in dry benzene (25 ml.), anhydrous aluminium chloride (2 g.) was added, and the mixture refluxed for ½ hr. and left at room temperature for 2 hr. Working up gave the *ketone* as needles, m. p. 110° (74%) (from ethyl acetate–light petroleum) (Found: C, 63·1; H, 5·65; N, 4·75; S, 10·7. $C_{16}H_{17}O_3NS$ requires C, 63·35; H, 5·65; N, 4·6; S, 10·6%). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid–ethanol as orange needles, m. p. 215° (Found: C, 54·4; H, 4·2; N, 14·4; S, 6·8. $C_{22}H_{21}O_6N_5S$ requires C, 54·65; H, 4·4; N, 14·5; S, 6·6%). The *oxime* crystallised from ethyl acetate–light petroleum (b. p. 80—90°) having m. p. 131—132° (Found: C, 60·65; H, 5·4; N, 8·6; S, 10·0. $C_{16}H_{18}O_3N_2S$ requires C, 60·35; H, 5·7; N, 8·8; S, 10·1%). (*b*) *N*-Benzyl-β-toluene-*p*-sulphonamidopropionyl chloride (2·9 g.) in dry benzene (25 ml.) was treated with anhydrous aluminium chloride (3 g.) in portions with shaking, refluxed for 1½ hr., cooled, and treated with crushed ice. The benzene layer was washed successively with dilute hydrochloric acid, dilute aqueous sodium hydroxide, and water, dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil was washed with light petroleum (b. p. 80—90°) and crystallised from the same solvent (charcoal) as needles, m. p. 106° (1 g.). Admixture of this material with authentic ω-toluene-*p*-sulphonamidopropiophenone raised the m. p. to 109—110° (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 215°). From the alkaline washings toluene-*p*-sulphonamide (m. p. and mixed m. p. 137°) was obtained on acidification, and the light petroleum washings contained diphenylmethane, identified as its 4 : 4′-dinitro-derivative, m. p. and mixed m. p. 169°. If the starting material was not pure the yield of ketone was much lower and phenyl *p*-tolyl sulphone (m. p. and mixed m. p. 127°) was obtained in addition to the above.

Oxidation of the pure ketone with alkaline potassium permanganate gave only benzoic acid and toluene-*p*-sulphonamide, but a crude sample gave, in addition, an acid which crystallised from water and had m. p. 196°, alone and mixed with *p*-benzoylbenzoic acid [Found: C, 74·6; H, 4·7%; equiv. (by titration), 210. Calc. for $C_{14}H_{10}O_3$: C, 74·3; H, 4·45%; equiv., 226].

Hydrolysis. The ketone (0·75 g.) was stirred vigorously in a creased flask * with water (200 ml.) and 10% aqueous sodium hydroxide (40 ml.) at 80° for 4 hr. The cooled solution was extracted with chloroform from which a trace of benzaldehyde was isolated (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 235°). Acidification and ether extraction of the alkaline solution afforded toluene-*p*-sulphonamide, m. p. and mixed m. p. 139°.

Debenzylation Experiments.—The general method is illustrated by the following example: *N*-benzyltoluene-*p*-sulphonamide (10 g.) was dissolved in dry benzene (25 ml.), anhydrous aluminium chloride (7 g.) was added, and the mixture heated on the steam-bath for 1 hr. Ice and hydrochloric acid were then added and the mixture was set aside for 2 hr. Toluene-*p*-sulphonamide (4·2 g.), m. p. and mixed m. p. 137°, was collected by filtration and the benzene layer yielded diphenylmethane, b. p. 60—70°/0·05 mm. (3 g.) (4 : 4′-dinitro-derivative, m. p. and mixed m. p. 169°).

Similarly *N*-benzyl-*N*-methyltoluene-*p*-sulphonamide (10 g.) gave diphenylmethane (5 g.) and *N*-methyltoluene-*p*-sulphonamide (3·2 g.); *N*-benzenesulphonylbenzylamine (10 g.) gave diphenylmethane (4·5 g.) and benzenesulphonamide (2·5 g.); *N*-benzoylbenzylamine (10 g.) gave diphenylmethane (5 g.) and benzamide (3 g.); *N*-acetylbenzylamine (20 g.) gave diphenylmethane (3·5 g.) and starting material (8 g.) was recovered (reaction time 3 hr.); *N*-benzenesulphonyl-*p*-nitrobenzylamine was unaffected.

ω-*Benzylaminopropiophenone*.—β-Benzylaminopropionyl chloride hydrochloride [15] (4·5 g.) was suspended in dry benzene (25 ml.), and anhydrous aluminium chloride (3 g.) was added with shaking. The suspension was heated on the steam-bath overnight, cooled, poured on crushed ice and concentrated hydrochloric acid, and left for 2 days. The benzene layer was removed and the aqueous suspension of the amino-ketone hydrochloride filtered. It crystallised from acetone–ethanol in needles, m. p. 165° (13%) (Found: C, 69·3; H, 6·5; N, 5·45; Cl, 13·15. Calc. for $C_{16}H_{18}ONCl$: C, 69·7; H, 6·5; N, 5·1; Cl, 12·9%). The free base separated from

* *I.e.*, a flask in which indentations were made whilst hot.

[15] Fischer, *Ber.*, 1905, **38**, 2917.

light petroleum (b. p. 80—90°) in prisms, m. p. 70° (lit.,[14] 67°) (Found : N, 5·95. Calc. for $C_{16}H_{17}ON$: N, 5·85%). The *picrate*, m. p. 135°, crystallised from aqueous alcohol (Found : C, 56·65; H, 4·4; N, 11·9. $C_{22}H_{20}O_8N_4$ requires C, 56·4; H, 4·3; N, 11·95%). The 2 : 4-*dinitrophenylhydrazone* separated from ethanol in orange needles, m. p. 196° (Found : N, 15·2. $C_{23}H_{22}O_4ClN_5$ requires N, 15·35%). The *toluene*-p-*sulphonyl derivative* crystallised from light petroleum (b. p. 80—90°) in needles, m. p. 102° (Found : C, 70·1; H, 5·9; N, 3·95; S, 8·2. $C_{23}H_{23}O_3NS$ requires C, 70·2; H, 5·85; N, 3·55; S, 8·15%). The last compound formed a 2 : 4-dinitrophenylhydrazone, orange needles (from acetic acid–ethanol), m. p. 179° (Found : N, 11·7; S, 5·35. $C_{29}H_{21}O_6N_5S$ requires N, 12·2; S, 5·6%).

β-(3 : 4-*Dimethoxybenzylamino*)*propionic Acid.*—A mixture of 3 : 4-dimethoxybenzylamine (62 g.) and 40% aqueous potassium hydroxide (2·5 ml.) was treated with acrylonitrile (20 g.) as before. *N*-2′-Cyanoethyl-3 : 4-dimethoxybenzylamine distilled at 171°/0·05 mm. (52 g., 64%). This nitrile (52 g.) and 10% aqueous sodium hydroxide (350 ml.) were refluxed for 3 hr., cooled, neutralised with hydrochloric acid, and evaporated to dryness in a vacuum on the steam-bath. The solid residue was repeatedly extracted with absolute ethanol from which the colourless acid separated (after several days at 0°), having m. p. 150° (44 g., 78%) (Found : C, 59·85; H, 7·15; N, 5·85. $C_{12}H_{17}O_4N$ requires C, 60·25; H, 7·1; N, 5·85%).

The *toluene*-p-*sulphonyl derivative* had m. p. 103° (from aqueous ethanol) (Found : C, 57·75; H, 5·6; N, 3·6; S, 8·35. $C_{19}H_{23}O_6NS$ requires C, 58·0; H, 5·85; N, 3·55; S, 8·15%). With this compound was a contaminant, insoluble in dilute sodium carbonate solution, crystallising from aqueous ethanol as needles, m. p. 122° alone and with authentic N-3 : 4-*dimethoxybenzyltoluene*-p-*sulphonamide* (Found : C, 59·65; H, 5·9; N, 4·0. $C_{16}H_{19}O_4NS$ requires C, 59·8; H, 5·9; N, 4·3%).

Action of Polyphosphoric Acid on β-(3 : 4-*Dimethoxybenzylamino*)*propionic Acid.*—The acid (8 g.) in polyphosphoric acid (50 g.) was stirred and heated at 65—75° for 10 min. The red mixture was then diluted with ice and water, made alkaline with sodium carbonate, and extracted with chloroform. The residue, after removal of the solvent, formed a hydrochloride which crystallised from absolute ethanol in plates, m. p. 246—248° alone and mixed with 3 : 4-dimethoxybenzylamine hydrochloride (Found : C, 53·2; H, 6·9; Cl, 17·1. Calc. for $C_9H_{14}O_2NCl$: C, 53·1; H, 6·9; Cl, 17·4%).

Action of Polyphosphoric Acid on N-(3 : 4-*Dimethoxybenzyl*)-β-*toluene*-p-*sulphonamidopropionic Acid.*—The acid (100 mg.) was stirred at 18° with polyphosphoric acid (5 g.) for 10 min., becoming dark violet. The mixture was heated to 100° for 15 min., cooled, triturated with ice, and extracted with chloroform. The extract was dried and evaporated, and the residue crystallised from aqueous methanol in needles, m. p. 120—121° (25 mg.). The m. p. was raised to 121·5° on admixture with *N*-3 : 4-dimethoxybenzyltoluene-*p*-sulphonamide.

Ethyl γ-Bromobutyrate (cf. ref. 16).—A solution of butyrolactone (64·5 g.) in ethanol (250 ml.) was cooled to 0°, and a stream of dry hydrogen bromide was passed in (2 bubbles per second for 6 hr.). After 16 hr. at 0° the mixture was poured into cold water (1200 ml.). The oil which separated was removed; the aqueous layer was extracted with ethyl bromide (2 × 100 ml.) and the extracts were combined with the oil, washed with ice-cold 5% aqueous potassium hydroxide and water, and evaporated under reduced pressure. The residue distilled at 101—102°/26 mm. (135 g., 92%).

Ethyl γ-Toluene-p-*sulphonanilidobutyrate.*—*N*-Toluene-*p*-sulphonylaniline (49·4 g., m. p. 102°), ethyl γ-bromobutyrate (39 g.), anhydrous potassium carbonate (18 g.), and dry acetone (200 ml.) were refluxed for 22 hr. After cooling, the suspension was poured into cold water (1500 ml.) and extracted with chloroform, and the extract washed with aqueous sodium hydroxide and water, dried, and evaporated. The solid residue crystallised from light petroleum (b. p. 80—90°) in needles, m. p. 94—95° (62 g., 86%) (Found : C, 63·1; H, 6·25; N, 3·9. $C_{19}H_{23}O_4NS$ requires C, 63·15; H, 6·35; N, 3·9%). Starting material (3·4 g.) was recovered from the alkaline washings.

γ-Toluene-p-*sulphonanilidobutyric Acid.*—The above ester (7·25 g.) was dissolved in 1 : 4 v/v aqueous methanol (100 ml.) with slight warming, 10% aqueous potassium hydroxide (15 ml.) was added, and the mixture left for 16 hr. at 18—20°. The filtered solution was diluted with water (100 ml.), poured with stirring into an excess of dilute hydrochloric acid, and left for 1½ hr. The precipitate was collected, washed with water, dried, and crystallised from benzene in prisms, m. p. 165·5° (5·1 g., 76%). The yield on a 0·2-molar scale was *ca.* 100%

[14] Linstead and Meade, *J.*, 1934, 943.

(Found : C, 61·4; H, 5·6; N, 4·1; S, 9·45. $C_{17}H_{19}O_4NS$ requires C, 61·25; H, 5·7; N, 4·2; S, 9·6%).

*Reactions of γ-Toluene-*p*-sulphonanilidobutyric Acid.*—(1) *With polyphosphoric acid.* The acid (2·5 g.) was heated with polyphosphoric acid (30 g.) at 100° for 4 hr. with intermittent stirring and then poured on crushed ice. Chloroform-extraction afforded 1-phenyl-2-pyrrolidone which separated from light petroleum (b. p. 100—120°) in plates, m. p. 68—69° (0·5 g.) (Found : C, 74·25; H, 6·95; N, 9·0. Calc. for $C_{10}H_{11}ON$: C, 74·5; H, 6·9; N, 8·7%).

(2) *With thionyl chloride.* The acid (6 g.) was allowed to react with thionyl chloride (40 ml.) at room temperature for 15 min., then heated on the steam-bath for 15 min. and distilled. The product had b. p. 105—120°/0·05 mm. (6 g.) and on being boiled with aqueous sodium hydroxide for 5 min. deposited 1-phenyl-2-pyrrolidone. Vacuum-sublimation of the crude product (before distillation) gave toluene-*p*-sulphonyl chloride, m. p. and mixed m. p. 70°, whilst treatment of the distillate with aluminium chloride in benzene gave 1-phenyl-2-pyrrolidone and phenyl *p*-tolyl sulphone, m. p. and mixed m. p. 126°.

(3) The acid was recovered (95%) after treatment with hydrogen fluoride at 20° for 4 hr.

*4-Toluene-*p*-sulphonamidoveratrole.*—This *amide* was prepared in pyridine and crystallised from methanol in plates, m. p. 139° (Found : C, 58·45; H, 5·75; N, 4·5; S, 10·6. $C_{15}H_{17}O_4NS$ requires C, 58·65; H, 5·55; N, 4·55; S, 10·4%).

*Ethyl γ-*N*-(3 : 4-Dimethoxyphenyl)toluene-*p*-sulphonamidobutyrate.*—4-Toluene-*p*-sulphonamidoveratrole (61 g.), ethyl γ-bromobutyrate (39 g.), anhydrous potassium carbonate (40 g.), and dry acetone (120 ml.) were refluxed together for 15 hr., and worked up as before leaving a residue which distilled at 265—275°/0·04 mm. (75 g., 84%). After crystallisation from methanol this *ester* had m. p. 63° (Found : C, 60·0; H, 6·2; N, 3·35; S, 7·25. $C_{21}H_{27}O_6NS$ requires C, 59·8; H, 6·45; N, 3·3; S, 7·6%). Starting material (9 g.) was recovered from the alkaline washings.

The ester (75 g.) in methanol (400 ml.) was hydrolysed on a steam-bath for 40 min. with 15% aqueous sodium hydroxide (200 ml.). The product crystallised from aqueous ethanol as the *monohydrate*, prisms, m. p. 89° (68 g., 93%) (Found : C, 55·55; H, 6·25; N, 3·4; S, 8·1. $C_{19}H_{23}O_6NS,H_2O$ requires C, 55·45; H, 6·15; N, 3·4; S, 7·8%). The anhydrous *acid* was obtained by repeated crystallisation from ethyl acetate–light petroleum (b. p. 80—90°), forming needles, m. p. 127° (Found : C, 57·65; H, 5·75; N, 4·8; S, 8·1. $C_{19}H_{23}O_6NS$ requires C, 58·0; H, 5·9; N, 3·55; S, 8·15%).

*1-[3 : 4-Dimethoxy-2(or 6)-toluene-*p*-sulphonylphenyl]-2-pyrrolidone.*—The above anhydrous acid (1·3 g.) was heated at 100° for 1½ hr. with polyphosphoric acid (10 g.), cooled, diluted with water, and extracted with chloroform. The extract was washed with dilute aqueous sodium carbonate and water, dried, and evaporated. The residue crystallised from methanol in prisms, m. p. 198° (0·45 g., 36%) (Found : C, 60·7; H, 5·8; N, 3·8; S, 8·6. $C_{19}H_{21}O_5NS$ requires C, 60·75; H, 5·65; N, 3·75; S, 8·55%). The same *product* was obtained from the hydrated acid (m. p. 89°) at 50° but there was no reaction at 20°. It failed to form an oxime, semicarbazone, or 2 : 4-dinitrophenylhydrazone and could not be hydrogenated at room temperature and pressure in glacial acetic acid over a platinum catalyst.

*Ethyl γ-[3 : 4-Dimethoxy-2(or 6)-toluene-*p*-sulphonanilido]butyrate.*—Ethyl *γ-N-*(3 : 4-dimethoxyphenyl)toluene-*p*-sulphonamidobutyrate (2 g.) was heated with polyphosphoric acid (25 g.) for 10 min. at 95—100° with stirring. The dark mixture was cooled, diluted with water, and extracted with chloroform. The extract was washed with dilute aqueous sodium hydroxide, dilute hydrochloric acid, and water, dried, and evaporated. The *product* crystallised from light petroleum (b. p. 100—120°) (charcoal) in prisms, m. p. 127° (0·95 g., 48%) (Found : C, 60·2; H, 6·5; N, 3·3; S, 7·45. $C_{21}H_{27}O_6NS$ requires C, 59·8; H, 6·45; H, 3·3; S, 7·6%). Its infrared spectrum (in $CHCl_3$) showed bands at 1729 (ester C:O) and 3406 $cm.^{-1}$ (NH). It failed to form an oxime or a 2 : 4-dinitrophenylhydrazone.

This ester (0·4 g.) was refluxed for 1 hr. with 8% aqueous sodium hydroxide (20 ml.) and alcohol (5 ml.). The solution was cooled, filtered, and acidified to pH 5 and the *acid* extracted with chloroform. This crystallised from aqueous methanol as prisms, m. p. 173° (0·3 g., 80%) (Found : C, 57·65; H, 6·05; N, 3·6; S, 8·35. $C_{19}H_{23}O_6NS$ requires C, 58·0; H, 5·9; N, 3·55; S, 8·15%).

γ-N-(3 : 4-Dimethoxyphenyl)toluene-*p*-sulphonamidobutyric acid (0·5 g.) was heated with anhydrous stannic chloride (1·8 ml.) at 120° for 2 hr., cooled, treated with ice and concentrated hydrochloric acid, warmed on the steam-bath, and extracted, after cooling, with benzene and

chloroform. The combined organic extracts were dried and evaporated, and the residual acid crystallised from benzene, and then from methanol, in prisms, m. p. 169—171°, raised to 172—173° on admixture with material prepared as above.

1-(3 : 4-*Dimethoxyphenyl*)-2-*pyrrolidone*.—(*a*) γ-*N*-(3 : 4-Dimethoxyphenyl)toluene-*p*-sulphonamidobutyric acid (5 g.) was stirred for 7 hr. with phosphoric oxide (10 g.), kieselguhr (5 g.), and sodium-dried benzene (100 ml.) under reflux. After the solvent had been evaporated, the residue was made alkaline with 30% aqueous sodium carbonate and extracted with ether. The extract was dried and evaporated, leaving a residue which distilled at 200—220°/0·04 mm. The distillate of *pyrrolidone* was repeatedly crystallised from light petroleum (b. p. 80—90°), to give needles, m. p. 83—84° (1 g.) (Found : C, 65·35; H, 6·8; N, 6·3. $C_{12}H_{15}O_3N$ requires C, 65·15; H, 6·85; N, 6·35%).

(*b*) The same acid (2 g.) was dissolved in anhydrous hydrogen fluoride (25 ml.), and the orange solution left at 20° for 24 hr. After treatment with excess of aqueous sodium carbonate the pyrrolidone was extracted with chloroform, distilled *in vacuo*, and crystallised from light petroleum in needles, m. p. 82°.

(*c*) The same acid (3 g.) was refluxed with thionyl chloride (25 ml.) for 10 min., then evaporated to dryness in a vacuum. When the residue was heated *in vacuo* a sublimate appeared which crystallised from light petroleum (b. p. 50—60°) in needles, m. p. 70°, undepressed on admixture with toluene-*p*-sulphonyl chloride. The material which failed to sublime was distilled at 220°/0·05 mm. and crystallised from light petroleum in needles, m. p. 82°, raised to 83° when mixed with the pyrrolidone prepared as in (*a*).

β-N-(3 : 4-*Dimethoxyphenyl*)*toluene*-p-*sulphonamidopropionic Acid*.—(*a*) Solutions of 4-toluene-*p*-sulphonamidoveratrole (20 g.) in 8% aqueous sodium hydroxide (33 ml.) and of β-chloropropionic acid (7·1 g.) in the same alkali (33 ml.) were mixed and refluxed for 16 hr. The mixture was then stirred in ice for 45 min., next filtered, and the residue washed with 5% aqueous sodium hydrogen carbonate. In this way starting material (12 g.; m. p. 139°) was recovered. The filtrate and washings were acidified, kept at 0° for 2 hr. with stirring, and filtered. The finely ground precipitate of *acid* was washed with cold water, dried, and crystallised from benzene in prisms, m. p. 130° (8 g., 81% based on sulphonamide consumed) (Found : C, 56·85; H, 5·75; N, 3·7; S, 8·4. $C_{18}H_{21}O_6NS$ requires C, 57·0; H, 5·6; N, 3·7; S, 8·45%).

(*b*) Propiolactone (0·75 ml.) was added dropwise to a stirred solution of 4-toluene-*p*-sulphonamidoveratrole (3·1 g.) in water (20 ml.) and 10% aqueous sodium hydroxide (4 ml.). Stirring was continued for 2 hr. and the solution then left overnight at 18°. The precipitate was collected and the alkaline filtrate acidified and extracted with chloroform. The extract was washed with aqueous sodium hydrogen carbonate which was then acidified and extracted, to yield a white solid which separated from benzene in prisms, m. p. 130° (0·1 g.). Starting material recovered from the original precipitate and chloroform solution amounted to 2·7 g.

1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-*toluene*-p-*sulphonyl*-4-*quinolone*.—The above acid (4·5 g.), phosphorus pentachloride (2·5 g.), and sodium-dried benzene (300 ml.) were refluxed for ½ hr. and cooled in ice. An ice-cold solution of anhydrous stannic chloride (3·5 ml.) in benzene (15 ml.) was added and the mixture was allowed to warm to 18° during 2½ hr. To the suspension was added ice, concentrated hydrochloric acid, and ether (15 ml.) : after 1 hr., the mixture was shaken, and the organic layer removed, washed with water, aqueous sodium hydroxide, and water, dried, and evaporated. The residual *quinolone* crystallised from methanol in prisms, m. p. 176·5° (2·5 g.) (Found : C, 60·05; H, 5·6; N, 4·1. $C_{18}H_{19}O_3NS$ requires C, 59·8; H, 5·3; N, 3·9%). The 2 : 4-*dinitrophenylhydrazone* was obtained from xylene as dark red needles, m. p. 240° (Found : C, 53·4; H, 4·45; N, 12·5. $C_{24}H_{23}O_8N_5S$ requires C, 53·2; H, 4·3; N, 12·95%).

1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-1-*toluene*-p-*sulphonylquinoline*.—The above quinolone (0·5 g.), hydrazine hydrate (0·25 ml., 90%), potassium hydroxide (0·25 g.), and diethylene glycol (5 ml.) were heated to 120° under reflux for 40 min., and the condenser was removed and dried while the reaction mixture was heated to 195—200°. The condenser was placed and the temperature kept at 200° for 1 hr., after which the mixture was cooled, poured into water, and left overnight. The *product* was collected and crystallised from methanol in prisms, m. p. 169° (50 mg.) (Found : C, 62·1; H, 6·1; N, 4·05; S, 9·1. $C_{18}H_{21}O_4NS$ requires C, 62·25; H, 6·1; N, 4·05; S, 9·25%).

β-[3 : 4-*Dimethoxy*-2(or 6)-*toluene*-p-*sulphonanilido*]*propionic Acid*.—β-*N*-(3 : 4-Dimethoxyphenyl)toluene-*p*-sulphonamidopropionic acid (1 g.) and polyphosphoric acid (10 g.) were

heated together (½ hr.) at 85°, left at 18° for 16 hr., then diluted with water, and the product was extracted with chloroform. It formed crystals, m. p. 191·5° (250 mg.) (from aqueous methanol). The *compound* was readily soluble in aqueous sodium carbonate (Found: C, 56·8; H, 5·6; N, 3·85. $C_{15}H_{21}O_6NS$ requires C, 57·0; H, 5·9; N, 3·7%).

N-*Toluene*-p-*sulphonphenethylamide*.—This *amide* crystallised from light petroleum (b. p. 80—90°) in needles, m. p. 66° (26·5 g., 97%) (Found: N, 5·35; S, 11·45. $C_{15}H_{17}O_2NS$ requires N, 5·1; S, 11·65%).

N-*Phenethyl*-N-*toluene*-p-*sulphonylglycine*.—The above sulphonamide (13·75 g.), ethyl chloroacetate (6·2 g.), anhydrous potassium carbonate (13 g.), and dry acetone (150 ml.) were refluxed together (24 hr.), cooled, poured into water, and extracted with chloroform. The residual oil was refluxed with aqueous sodium hydroxide (125 ml., 10%), and methylated spirit (125 ml.) for 1 hr. to give the *acid* which crystallised from ethyl acetate–light petroleum (b. p. 80—90°) in needles, m. p. 148—149° (7 g., 42%) (Found: C, 61·6; H, 5·7; N, 3·9; S, 9·25. $C_{17}H_{19}O_4NS$ requires C, 61·3; H, 5·7; N, 4·2; S, 9·6%). Some starting material was recovered from the sodium hydroxide washings.

1 : 2 : 3 : 4-*Tetrahydro*-2-*toluene*-p-*sulphonyl*isoquinoline.—(*a*) Toluene-*p*-sulphonyl chloride and tetrahydro*iso*quinoline were heated together in dry pyridine. The *sulphonamide* crystallised from methanol in needles, m. p. 145° (Found: C, 67·2; H, 5·9; N, 4·65. $C_{16}H_{17}O_2NS$ C, 66·9; H, 5·9; N, 4·9%).

(*b*) The preceding amino-acid (1 g.) was heated with polyphosphoric acid (10 g.) at 100° for 7½ hr., cooled, and diluted with water. The chloroform extract of this mixture was washed with aqueous sodium carbonate and water, dried, and evaporated. The residue crystallised from methanol as needles, m. p. 143° (0·5 g., 59%), raised to 144° on admixture with the preceding *iso*quinoline derivative.

5-*Toluene*-p-*sulphonyl*-5-*azabenzo*cyclo*hepten*-3-*one*.—*N*-Phenethyl-*N*-toluene-*p*-sulphonylglycine (2·5 g.) was refluxed with thionyl chloride (12 ml.) for 20 min. After removal of excess of thionyl chloride under reduced pressure, the residue was dissolved in dry carbon disulphide (50 ml.) and cooled in ice and concentrated hydrochloric acid. Anhydrous aluminium chloride (2 g.) was added with swirling and the suspension was left at 0° for 2 hr. with occasional agitation; after a further 2 hr. at 18°, the solvent was removed, ice-water added and the suspension left for 12 hr., then extracted with chloroform. The extract was washed with aqueous sodium carbonate, and water, dried, and evaporated. The residue crystallised from methanol or light petroleum (b. p. 100—120°) in needles, m. p. 121° (0·6 g.). Analysis indicated that this product was a mixture of the desired azabenzo*cyclo*heptenone and the *iso*quinoline already described, and the infrared spectrum showed only a weak band at 1684 cm.$^{-1}$ (Ar·C:O). It formed a 2 : 4-*dinitrophenylhydrazone* which separated from glacial acetic acid–methanol as orange crystals, m. p. 213° (Found: C, 55·5; H, 4·4; N, 14·4. $C_{23}H_{21}O_6N_5S$ requires C, 55·75; H, 4·25; N, 14·15%).

3 : 4-*Dimethoxy*-N-*toluene*-p-*sulphonphenethylamide*.—The *sulphonamide* crystallised from methanol in needles, m. p. 136° (13·5 g.) (Found: C, 60·75; H, 6·05; N, 3·9. $C_{17}H_{21}O_4NS$ requires C, 60·9; H, 6·3; N, 4·2%), insoluble in aqueous sodium hydroxide.

N-3 : 4-*Dimethoxyphenethyl*-N-*toluene*-p-*sulphonylglycine*.—The above sulphonamide (10·1 g.), ethyl chloroacetate (3·25 ml.), anhydrous potassium carbonate (10 g.) and dry acetone (100 ml.) were refluxed for 24 hr. The crude product was hydrolysed by refluxing 8% aqueous sodium hydroxide (50 ml.) and alcohol (75 ml.) for 1½ hr. The *acid* crystallised from ethyl acetate–light petroleum (b. p. 80—90°) in needles, m. p. 145° (6·8 g., 58%) (Found: C, 58·05; H, 6·1; N, 3·4. $C_{19}H_{23}O_6NS$ requires C, 58·0; H, 5·9; N, 3·55%). Some of the starting sulphonamide was recovered from the chloroform extract. When this acid was heated with polyphosphoric acid at 80—90° a dark red colour appeared within 5 min.; the product isolated was insoluble in aqueous sodium hydroxide but failed to form a 2 : 4-dinitrophenylhydrazone; it could not be purified.

4-*Methoxy*-4′-*methyldiphenyl Sulphone*.—Anisole (0·7 g.) and toluene-*p*-sulphonic acid monohydrate (1·2 g.) (or equiv. amount of the anhydrous sodium salt) were heated in polyphosphoric acid (30 g.) for 3½ hr. at 95°. Dilution of the red mixture with ice-water precipitated the sulphone. It crystallised from aqueous methanol in needles, m. p. 103° (65%).

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