# 169. *Chemotherapeutic Agents of the Sulphone Type. Part I. Sulphones containing a* p-*Aminophenyl Group.*

By James Walker.

A number of sulphones containing the *p*-aminophenyl group have been synthesised by (*a*) reaction between sodium *p*-acetamidobenzenesulphinate and aliphatic halogen compounds, and (*b*) addition of *p*-acetamidobenzenesulphinic acid to quinones, followed, in each case, by deacetylation. The products derived from quinones showed high *in vitro* activity against a variety of pathogenic bacteria, and, *in vivo*, local application in mice disclosed marked activity against infection with an organism of the gas gangrene group.

In the development of antibacterial chemotherapy during the past decade much effort has been directed towards the study of substituted sulphanilamides, and only sporadic attempts have been made to develop drugs of the sulphone type, although it was early shown by Buttle *et al.* (*Lancet*, **1937**, i, **1331**) that 4 : 4′-diaminodiphenylsulphone (I) was highly active but too toxic for practical application. With few exceptions (*e.g.*, Buttle *et al.*, *Biochem. J.*, **1938**, **32**, 1101; Fourneau *et al.*, *Compt. rend. Soc. Biol.*, **1938**, **127**, **393**; Roblin *et al.*, *J. Amer. Chem. Soc.*, **1941**, **63**, 1930; Henkel, *Z. Immunitätsforsch.*, **1943**, **104**, 403; Burton and Hoggarth, this vol., p. 14; Bambas, *J. Amer. Chem. Soc.*, **1945**, **67**, 668, 671) most of the work on sulphones has been directed towards rendering (I) less toxic by suitable masking of the amino-groups as in promin, tibatin, and diasone. The present work started from an orientating experiment carried out to compare the *in vitro* antibacterial activity of *p*-aminophenylsulphonylmethane (II) * with sulphanilamide, the former standing in the same relationship to methane as does the latter to ammonia. Subsequently, compounds were examined which, except (VII) and (VIII), were derived from (II) by introduction of electronegative substituents into the methyl group with the object of increasing acidity, or which owed acidic properties to a phenolic hydroxyl group in close proximity to the sulphone group.

Condensation between sodium *p*-acetamidobenzenesulphinate and chloroacetic acid, chloroacetone, chloroacetonitrile, and β-diethylaminoethyl chloride hydrochloride furnished, respectively, p-*acetamidophenylsulphonyl-acetic acid*, *-acetone*, and -acetonitrile, and β-*diethylamino*-α-p-*acetamidophenylsulphonylethane*, from which, on acid hydrolysis, *p*-aminophenylsulphonylacetic acid (III), p-*aminophenylsulphonyl-acetone* (IV), *-acetonitrile* (V), and β-*diethylamino*-α-p-*aminophenylsulphonylethane hydrochloride* (VII) were obtained, respectively. Condensation with γ-diethylaminopropyl chloride hydrochloride and subsequent hydrolysis afforded γ-*diethylamino*-α-p-*aminophenylsulphonylpropane sulphate* (VIII). p-*Aminophenylsulphonylacetamidine hydrochloride* (VI) was prepared from the nitrile (V) *via* the imino-ether hydrochloride. The Hinsberg addition of sulphinic acids to quinones was applied with *p*-acetamidobenzenesulphinic acid to benzo-, tolu-, chloro-, and *p*-xylo-quinone, with the production of 2-*p*′-acetamidophenylsulphonylquinol, 4(?)-p′-*acetamidophenylsulphonyltoluquinol*, 5-*chloro*-2(?)-p′-*acetamidophenylsulphonylquinol*, and 3-p′-*acetamidophenylsulphonyl-p-xyloquinol*, respectively. With each of the two unsymmetrical quinones the orientation of the product is ambiguous and the constitutions assigned are tentative, but the considerations applicable to the Thiele

Table I.

*Antibacterial Activity* in vitro. (Dr. A. T. Fuller.)

Minimal inhibiting concentrations in mg. of drug per 100 c.c. of nutrient broth.

| Compound. | | Organism. Gram + ve. | | | Gram − ve. | | | | |
|---|---|---|---|---|---|---|---|---|---|
| $NH_2$⟨⟩$SO_2R$. | | *Strep. hæmolyt.* | *Staph. aureus.* | *Cl. welchii.* | *Bact. proteus.* | *Ps. pyocyanea.* | *Bact. coli.* | *P. murisseptica.* | *P. pestis.** |
| | R. | | | | | | | | |
| (II) | $-CH_3$ | 25 | 750 | — | 70 | 80 | 75 | — | — |
| (III) | $-CH_2\cdot CO_2H$ | 50 | >1000 | — | >1000 | >1000 | >1000 | — | — |
| (IV) | $-CH_2\cdot COMe$ | 50 | >1000 | — | 250 | 700 | 350 | — | — |
| (V) | $-CH_2\cdot CN$ | 200 | 500 | 100 | 500 | 500 | 100 | — | — |
| (VI) | $-CH_2\cdot C(NH_2){:}NH_2\}Cl$ | 20 | 250 | 70 | 1500 | 1500 | 500 | — | — |
| (VII) | $-CH_2\cdot CH_2\cdot NEt_2H\}Cl$ | 400 | >1000 | — | 800 | >1000 | 800 | — | — |
| †(IX) | $-C_6H_3(OH)_2$ (2 : 5) | 0·5 | 10 | 3 | 7 | 30 | 5 | 2 | 1—3 |
| †(X) | $-C_6H_2Me(OH)_2$ (4 : 2 : 5) | 15 | — | 7 | — | — | — | 0·5 | 1·5 |
| †(XI) | $-C_6H_2Cl(OH)_2$ (4 : 2 : 5) | 20 | — | 5 | — | — | <5 | 5 | 3 |
| | Reference compounds. | | | | | | | | |
| | Sulphanilamide | 100 | >750 | 50 | 100 | 75 | 75 | — | >100 |
| | Sulphathiazole | 15 | >100 | 5 | 10 | 5 | 5 | 2 | 1·5 |
| (XIII) | $Ph\cdot SO_2\cdot C_6H_3(OH)_2$ (1 : 2 : 5) | 5 | 10 | >20 | — | — | 100 | — | — |
| (XIV) | $C_6H_4Me\cdot SO_2\cdot C_6H_3(OH)_2$ (1 : 2 : 5) | 5 | 15 | >20 | — | — | 40 | — | — |

* Tests in this column were kindly carried out by Dr. H. Schütze (Lister Institute).

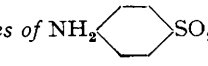
† In these compounds, for tabulation purposes only, the point of attachment of the arylsulphonyl group is regarded as position 1.

* Apart from (I), (VIII), and (XII), formulæ are given in the tables.

acetylation of quinones (Erdtman, *Proc. Roy. Soc.*, 1934, **143**, *A*, 177) are valid in the present reaction. Deacetylation afforded 2-*p'*-aminophenylsulphonylquinol (IX), 4(?)-p'-*aminophenylsulphonyltoluquinol* (X), 5-*chloro*-2(?)-p'-*aminophenylsulphonylquinol* (XI), and 3-p'-*aminophenylsulphonyl*-p-*xyloquinol* (XII). With increasing substitution in the quinol nucleus the solubility in water of the free amino-compounds rapidly diminished.

With the exception of (VIII), which was not tested against bacteria, and (XII), which was extremely insoluble in culture media, the *in vitro* antibacterial activities of the compounds are recorded in Table I. The activity of (II) was comparable with that of sulphanilamide, and none of the compounds (III), (IV), (V), (VI), and (VII) showed greater activity, although four of these six were somewhat more active than sulphanilamide against hæmolytic streptococci. It had been hoped that the behaviour of (IV) and (V) in particular would be of theoretical interest in relation to experiments by Cowles (*Yale J. Biol. Med.*, 1941—2, **14**, 599), Brueckner (*ibid.*, 1943, **15**, 813) and Bell and Roblin (*J. Amer. Chem. Soc.*, 1942, **64**, 2905), which have shown that among sulphonamides activity increases as the p$K_a$ values approach the pH of the culture media used.

TABLE II.

p$K_a$ *Values of* 

| | R. | p$K_a$. | | R. | p$K_a$. |
|---|---|---|---|---|---|
| (XV) | $-NH_2$ | 10·4 * | (II) | $-Me$ | — |
| (XVI) | $-NH\cdot COMe$ | 5·4 * | (IV) | $-CH_2\cdot COMe$ | 10·2 † |
| (XVII) | $-NH\cdot CN$ | 2·9 * | (V) | $-CH_2\cdot CN$ | 10·6 † |

* From Bell and Roblin (*loc. cit.*). † Present paper.

In sulphanilamide (XV) the introduction of the $N^1$-acetyl substituent in sulphanilylacetamide (XVI) reduced the p$K_a$ from 10·4 to 5·4, and similar introduction of the cyano-group (XVII) reduced the p$K_a$ from 10·4 to 2·9 (Table II). Introduction of the acetyl group into (II) afforded a product (IV) whose p$K_a$ was measurable in aqueous solution; the corresponding introduction of the cyano-group, however, did not give a still stronger acid but a slightly weaker one (V). Since cyano- is more electronegative than acetyl, the explanation for the order of the acid strengths of (IV) and (V) lies in the stabilisation of the anion of (IV) by resonance, $-SO_2\cdot\bar{C}H-\overset{\overset{O}{\|}}{C}-CH_3 \rightleftharpoons -SO_2\cdot CH=\overset{\overset{\bar{O}}{|}}{C}-CH_3$, whereas similar stabilisation is absent from the anion of (V), while the anions of the analogous nitrogen compounds, (XVI) and (XVII), are both capable of resonance leading to the greater separation of the p$K_a$ values. In *p*-tolylsulphonylacetone, which is analogous to (IV), Arndt and Martius (*Annalen*, 1932, **499**, 280) found no evidence for the presence of the enol form with bromine or ferric chloride, although diazomethane gave the enol ether fairly readily. The broader significance of the above comparison of ammonia and methane derivatives becomes clear when one considers that *one* strongly electronegative group introduced into ammonia will give a weak acid with p$K_a$ about 10 (*e.g.*, cyanamide, p$K_a$ 9·7; sulphanilamide, p$K_a$ 10·4), whereas *two* such negative groups must be introduced into methane to give a weak acid of comparable strength [*e.g.*, malononitrile, p$K_a$ *ca.* 10; (V) (above), p$K_a$ 10·6], while a second strongly negative group introduced into ammonia gives very strong acids with p$K_a$'s of the order of 1—3 [*e.g.*, dicyanamide; sulphanilylcyanamide (XVII), p$K_a$ 2·9; $N^1$-sulphanilylsulphanilamide, p$K_a$ 2·9; $N^1$-ethanesulphonylsulphanilamide, p$K_a$ 3·1], and a third negative group must be introduced into methane to produce very strong acids (Madelung and Kern, *Annalen*, 1922, **427**, 1). As a result, it can be seen that conditions are favourable with sulphanilamide in that a wide selection of negative groups of varying strengths is available to give acids whose p$K_a$ values are spread over the significant range between 10 and 2, and that a study comparable in scope to that of Bell and Roblin (*loc. cit.*) in the sulphanilamide series is impracticable among methane types.

High antibacterial activity was encountered among the quinol derivatives (IX), (X), and (XI) (Table I). These substances would be expected to show some of the properties of phenolic antiseptics as well as those of the " sulphonamide " type of drug, and, to assess the contribution of the former type of action to the total activity observed *in vitro*, 2-phenyl- (XIII) (Hinsberg, *Ber.*, 1894, **27**, 3259) and 2-*p*-tolylsulphonylquinol (XIV) were prepared as reference compounds. Comparing (IX) with (XIII) and (XIV), we note that the *p'*-amino-group has produced a 10-fold increase in activity against hæmolytic streptococci and a rather greater increase in activity against *B. coli*. Since Caius *et al.* (*Indian J. Med. Res.*, 1927—8, **15**, 117) have shown quinol to be the most active of a large number of phenolic compounds against plague bacilli *in vitro*, Table I records the results of tests against mouse plague and a virulent human strain, (X) being the most active of the substances tested. Buttle *et al.* (*Biochem. J.*, 1938, **32**, 1106) found (IX) to have less that 1/1000th of the activity of (I) in streptococcal infection in mice but gave no indication of its toxicity. Dr. M. van den Ende and the late Miss Dora Lush found (IX) to have a very low chronic toxicity for mice when administered in the food. Dr. F. Hawking kindly reported that the compound had a marked effect, but less than that of sulphathiazole, when administered locally to mice infected with *Cl. septicum*, and also that the solubility of the compound was too low for a single intraperitoneal dose to cause toxic symptoms in mice. Dr. Ann Bishop kindly tested (VII), (VIII), and (IX) in *P. relictum* infection of canaries but no activity was detected.

## Experimental.

Sodium *p*-acetamidobenzenesulphinate was prepared by neutralising the free acid (*Org. Synth.*, Coll. Vol. I, 7) to pH 7 with sodium hydroxide. The granular solid obtained on evaporation to dryness under reduced pressure on the water-bath was finely ground, and dried over concentrated sulphuric acid in a vacuum. The water content of the *hydrate* (Found, on different batches: loss at 110° in a vacuum, 10·7, 13·1. $C_8H_8O_3NSNa,1\frac{1}{2}H_2O$ requires $H_2O$, 10·9%. $C_8H_8O_3NSNa,2H_2O$ requires $H_2O$, 14·3%) was allowed for in the following experiments.

p-*Aminophenylsulphonylmethane* (II).—See following paper for preparation.

p-*Acetamidophenylsulphonylacetic Acid.*—Chloroacetic acid (14·2 g.) was neutralised with N-sodium hydroxide, and the solution evaporated to dryness on the water-bath with sodium *p*-acetamidobenzenesulphinate (37·2 g.). The *acid* (32 g.), liberated by hydrochloric acid, separated from water in colourless plates, m. p. 216—217° (Found: C, 46·5; H, 4·1. $C_{10}H_{11}O_5NS$ requires C, 46·7; H, 4·3%). Since this work was completed more than 3 years ago this compound has been mentioned in B.P. 563,558; no analysis is given, and the m. p.'s recorded (196—200° and 202—204°) are much lower than that now found.

p-*Aminophenylsulphonylacetic Acid* (III).—The acetyl derivative (3·55 g.) was hydrolysed by refluxing with 12% aqueous hydrochloric acid (30 c.c.) for ½ hour. The product (2·3 g.), precipitated at about pH 3, separated from water in colourless plates, m. p. 164—165° (efferv.) (Found: C, 45·0; H, 4·2. Calc. for $C_8H_9O_4NS$: C, 44·7; H, 4·2%). B.P. 563,558 records m. p. 162—164°.

p-*Acetamidophenylsulphonylacetone.*—Sodium *p*-acetamidobenzenesulphinate (15·4 g.) and freshly distilled chloroacetone (4·8 c.c.) were refluxed in 90% alcohol (100 c.c.) for 7 hours. The alcohol was then distilled off and replaced by water, the syrupy product (11·4 g.) then rapidly crystallising. The *substance* separated from 30% aqueous alcohol in colourless leaflets, m. p. 91—92° (Found: C, 50·6; H, 5·2; loss at 100° in a vacuum, 2·5. Found, on anhydrous material: C, 51·9; H, 5·0. $C_{11}H_{13}O_4NS,\frac{1}{3}H_2O$ requires C, 50·6; H, 5·2; $H_2O$, 2·3%. $C_{11}H_{13}O_4NS$ requires C, 51·8; H, 5·1%).

p-*Aminophenylsulphonylacetone* (IV).—The acetyl derivative (11·3 g.) was hydrolysed in the usual way, and the *product* (7·2 g.) separated from water in colourless rectangular prisms, m. p. 131—132° (Found: C, 50·9; H, 5·2. $C_9H_{11}O_3NS$ requires C, 50·7; H, 5·1%).

p-*Acetamidophenylsulphonylacetonitrile.*—A solution of chloroacetonitrile (13·3 g.) and sodium *p*-acetamidobenzenesulphinate (35 g.) in 75% aqueous alcohol (70 c.c.) was refluxed for 17 hours (a shorter time would have sufficed). The product (31 g.) was collected after addition of water, and separated from 20% aqueous pyridine in fine colourless needles, which were very sparingly soluble in water and the lower alcohols; m. p. 263—264° (Found: C, 50·9; H, 4·3; N, 11·7. Calc. for $C_{10}H_{10}O_3N_2S$: C, 50·4; H, 4·2; N, 11·8%). B.P. 563,558 records m. p. 260—262°, a correct analysis for sulphur, and an erroneous molecular formula.

p-*Aminophenylsulphonylacetonitrile* (V).—The acetyl derivative (23·8 g.) was refluxed with 3N-hydrochloric acid (250 c.c.) and spirit (50 c.c.) until solution took place (40 minutes). The solution was diluted with water and neutralised to about pH 6 with ammonia, a crystalline precipitate (17 g.) then separating. The *substance* crystallised from 20% aqueous alcohol in colourless hexagonal plates, m. p. 122—123° (Found: C, 49·2; H, 4·1. $C_8H_8O_2N_2S$ requires C, 49·0; H, 4·1%).

p-*Aminophenylsulphonylacetamidine Hydrochloride* (VI).—A solution of the preceding nitrile (8 g.) in dioxan (40 c.c.) and alcohol (10 c.c.) was saturated with dry hydrogen chloride at 0°, and the mixture kept in the refrigerator for 14 days. Solvent and excess of hydrogen chloride were thoroughly removed in a vacuum at room temperature, and the residue was set aside at 37° with 10% alcoholic ammonia solution (100 c.c.) for 5 days. The solution was filtered from ammonium chloride and evaporated to dryness. The residue (8·9 g.) was dissolved in water with the addition of a few drops of 2N-hydrochloric acid to give an incipient acid reaction to Congo-red, decolorised with norit, and recovered by evaporation to dryness. The *hydrochloride* separated from about 7 parts of water in colourless, flattened bipyramids, which darkened and decomposed at about 265° (Found: C, 38·7; H, 4·8; N, 16·8. $C_8H_{11}O_2N_3S,HCl$ requires C, 38·5; H, 4·8; N, 16·8%).

β-*Diethylamino*-α-p-*acetamidophenylsulphonylethane.*—Sodium *p*-acetamidobenzenesulphinate (10·28 g.) and β-diethylaminoethyl chloride hydrochloride (6·9 g.) were refluxed in aqueous solution (60 c.c.) for 5 hours. The reaction mixture was cooled, rendered strongly alkaline with sodium hydroxide, and shaken with a small volume of ether. The solid (5·6 g.) which separated at the interface was collected. The *base* separated from 25% aqueous alcohol in colourless prisms, m. p. 94—96° (Found: loss at 100° in a high vacuum, 6·1. Found, on anhydrous material: C, 56·1; H, 6·9. $C_{14}H_{22}O_3N_2S,H_2O$ requires $H_2O$, 5·7%. $C_{14}H_{22}O_3N_2S$ requires C, 56·4; H, 7·4%). The water of crystallisation was also lost in a vacuum desiccator over concentrated sulphuric acid, and the anhydrous substance was hygroscopic. This compound is mentioned in F.P. 800,535 but not characterised in any way.

β-*Diethylamino*-α-p-*aminophenylsulphonylethane Hydrocholride* (VII).—The acetyl derivative (4·45 g.) was hydrolysed in the usual way and the product was extracted with benzene from the reaction mixture after it had been rendered strongly alkaline with sodium hydroxide. The benzene solution was dried, concentrated to 50 c.c., and treated with dry hydrogen chloride. The precipitated *hydrochloride* separated from *iso*propyl alcohol in colourless, rectangular plates, m. p. 186° (Found: C, 49·3; H, 7·0; Cl, 12·2. $C_{12}H_{20}O_2N_2S,HCl$ requires C, 49·2; H, 7·2; Cl, 12·1%).

γ-*Diethylaminopropyl Alcohol.*—The following preparations of the alcohol and the corresponding chloride are substantial improvements over those of Magidson and Strukow (*Arch. Pharm.*, 1933, **271**, 572). Trimethylene chlorohydrin (43·6 g., 1 mol.), diethylamine (95 c.c., 2 mols.), and methyl alcohol (3 c.c.) were mixed, kept at room temperature for 48 hours, and then heated under reflux for 16 hours on the water-bath. The product was then isolated as described by Magidson and Strukow. The crude product (54·7 g.) was fractionated, and the fraction (48·3 g.), b. p. 85—88°/28 mm., collected.

γ-*Diethylaminopropyl Chloride.*—The conditions used previously (Walker, J., 1940, 690) were employed. The crude chloride hydrochloride was dissolved in water and strongly basified with sodium hydroxide. The crude chloride, extracted with ether, was fractionated, and the fraction (47·8 g.), b. p. 65—70°/15 mm., collected (Found: Cl, 23·1. Calc. for $C_7H_{16}NCl$: Cl, 23·7%). The free base may be preserved without appreciable change in the ice-chest for several months.

γ-*Diethylamino*-α-p-*aminophenylsulphonylpropane Sulphate* (VIII).—γ-Diethylaminopropyl chloride (10 g.) was neutralised to bromocresol-purple with N-hydrochloric acid, and the solution refluxed with sodium *p*-acetamidobenzenesulphinate (18 g.) for 12 hours. The product, liberated by addition of excess of sodium hydroxide and extracted with benzene, was recovered as a syrup (16 g.); it was immediately hydrolysed with 12% hydrochloric acid in the usual way, and the deacetylated base (11·6 g.) recovered with ether. The hydrochloride could not be crystallised, but the *sulphate*, obtained by neutralising the base in aqueous alcohol to pH 6 with sulphuric acid and evaporation, separated from spirit in colourless plates, m. p. 200° [Found: C, 49·2; H, 7·4. $(C_{13}H_{22}O_2N_2S)_2,H_2SO_4$ requires C, 48·9; H, 7·2%].

2-p′-*Acetamidophenylsulphonylquinol.*—Benzoquinone (4·32 g.) was dissolved in hot water (100 c.c.) and treated with a warm solution of sodium *p*-acetamidobenzenesulphinate (10·3 g.) in water (70 c.c.) containing N-hydrochloric acid

(41 c.c.). The colour of the quinone was rapidly discharged, and the product was precipitated as a pink granular solid. After about 15 minutes on the water-bath the mixture was cooled, and the product (12·1 g.) collected and dried. Recrystallisation from 40% aqueous alcohol in the presence of a trace of sodium hyposulphite ($Na_2S_2O_4$) afforded colourless prisms, m. p. 273° (Found : C, 54·3; H, 4·4. Calc. for $C_{14}H_{13}O_5NS$ : C, 54·7; H, 4·2%). Buttle *et al.* (*Biochem. J.*, 1938, **32**, 1108) record m. p. 282° (corr.).

2-p′-*Aminophenylsulphonylquinol* (IX).—The acetyl derivative (10 g.) was hydrolysed by refluxing with 16% hydrochloric acid (140 c.c.) for ¾ hour. The product (8·1 g.), precipitated on neutralisation with sodium bicarbonate, separated from 30% aqueous alcohol containing traces of sodium hyposulphite in colourless prisms, m. p. 176—177° (Found : C, 54·3; H, 4·3. Calc. for $C_{12}H_{11}O_4NS$ : C, 54·3; H, 4·2%). Buttle *et al.* (*loc. cit.*) record m. p. 180°.

4(?)-p′-*Acetamidophenylsulphonyltoluquinol*.—Toluquinone (4·1 g.) and *p*-acetamidobenzenesulphinic acid (from 8·6 g. of sodium salt and 35 c.c. of N-hydrochloric acid) were condensed in aqueous solution in the manner described above for benzoquinone. The *product* (9·74 g.) separated from 30% aqueous alcohol (hyposulphite) in colourless, rectangular plates, m. p. 237—239° (Found : C, 56·2; H, 4·9. $C_{15}H_{15}O_5NS$ requires C, 56·1; H, 4·7%).

4(?)-p′-*Aminophenylsulphonyltoluquinol* (X).—The acetyl derivative (7 g.), hydrolysed in the usual way, afforded the *amino*-compound (5·8 g.), which separated from 40% aqueous alcohol (hyposulphite) in short, stout, colourless prisms, m. p. 187—188° (Found : C, 56·0; H, 4·9. $C_{13}H_{13}O_4NS$ requires C, 55·9; H, 4·7%).

5-*Chloro*-2(?)-p′-*acetamidophenylsulphonylquinol*.—Chloroquinone was obtained in good yield from chloroquinol (Levy and Schultz, *Annalen*, 1881, **210**, 138) by oxidation with sodium chlorate (cf. benzoquinone, *Org. Synth.*, **16**, 73), and purified by vacuum sublimation and recrystallisation from aqueous alcohol. Chloroquinone (4·3 g.) was condensed with *p*-acetamidobenzenesulphinic acid under the conditions used for *p*-xyloquinone (below), and the *quinol* (9·2 g.) separated from aqueous alcohol in colourless microscopic prisms, m. p. 258—261° (decomp.) (Found : C, 49·4; H, 3·4. $C_{14}H_{12}O_5NSCl$ requires C, 49·2; H, 3·5%).

5-*Chloro*-2(?)-p′-*aminophenylsulphonylquinol* (XI).—The acetyl derivative (5·14 g.) was hydrolysed with 16% hydrochloric acid, and the *amino-quinol* (3·76 g.), liberated by neutralisation with sodium bicarbonate, separated from 25% aqueous alcohol (hyposulphite) in small stout colourless prisms, m. p. 191° (Found : C, 48·3; H, 3·4. $C_{12}H_{10}O_4NSCl$ requires C, 48·1; H, 3·3%).

3-p′-*Acetamidophenylsulphonyl*-p-*xyloquinol*.—*p*-Xyloquinone (3·4 g.) in warm 60% aqueous alcohol (80 c.c.) was condensed with an aqueous solution of *p*-acetamidobenzenesulphinic acid (from 6·7 g. of the sodium salt, 15 c.c. of water, and 35 c.c. of N-hydrochloric acid). The product rapidly separated from a pink solution. Much of the alcohol was distilled away after about an hour on the water-bath, and the *quinol* (7·88 g.) was collected. It separated from 60% aqueous alcohol in colourless hexagonal plates, m. p. 246—247° (Found : C, 57·1; H, 5·1. $C_{16}H_{17}O_5NS$ requires C, 57·3; H, 5·1%).

3-p′-*Aminophenylsulphonyl*-p-*xyloquinol* (XII).—Hydrolysis with aqueous acid was not feasible, but the following procedure was successful. The acetyl derivative (2·83 g.) was refluxed with aqueous-alcoholic hydrochloric acid (24 c.c. alcohol : 16 c.c. concentrated acid) for an hour. The *product* (2·35 g.), obtained on dilution with water and neutralisation with sodium bicarbonate, separated from 25% aqueous alcohol (hyposulphite) in stellate clusters of colourless, lance-shaped needles, m. p. 198—199° (Found : C, 57·1; H, 5·0. $C_{14}H_{15}O_4NS$ requires C, 57·3; H, 5·1%).

2-p-*Tolylsulphonylquinol* (XIV).—This compound was precipitated in quantitative yield on mixing warm concentrated aqueous solutions of *p*-toluenesulphinic acid and benzoquinone in equimolecular proportion. It separated from aqueous alcohol in short, stout, colourless prisms, m. p. 211—212° (Found : C, 59·2; H, 4·7. Calc. for $C_{13}H_{12}O_4S$ : C, 59·1; H, 4·5%). Borsche and Frank (*Annalen*, 1926, **450**, 75) record m. p. 211° for a product obtained from *p*-toluenesulphonhydrazide and benzoquinone.

$pK_a$ *Values*.—Approximate $pK_a$ values were estimated by dissolving accurately weighed amounts of the various compounds in glass-redistilled water with warming and, after cooling to room temperature, adding the calculated volume of N/10-sodium hydroxide solution required for 50% neutralisation, the pH's then being measured at once with the glass electrode. To assess the accuracy of the method it was first applied to a number of sulphonamides which have been carefully examined by Bell and Roblin (*loc. cit.*) and whose figures are quoted in parentheses after those obtained by the present method : sulphanilamide, 10·56 (10·43); sulphadiazine, 6·47 (6·48); sulphadimethylpyrimidine, 7·43 (7·37); sulphanilylacetamide 5·4 (5·38). The following $pK_a$ values were found for compounds described in the present paper : (III), 2·8; (IV), 10·2; (V), 10·6; (IX), 8·4. The alkaline solutions of (IX) rapidly became reddish-brown, but a control experiment showed that the rate of uptake of oxygen in a buffered (pH 8·5) solution from an atmosphere of pure oxygen was not sufficiently high to interfere with the $pK_a$ estimation in air.

The author is grateful to those colleagues mentioned in the text for their co-operation, and in particular to Dr. A. T. Fuller for carrying out numerous *in vitro* antibacterial tests.

NATIONAL INSTITUTE FOR MEDICAL RESEARCH, LONDON, N.W.3. [*Received, May 25th*, 1945.]