691. *Sulphonamides. Part III. Sulphanilamidocarboxyamides as Intestinal Antiseptics; the Influence of* pK_a *and Hydrogen-bonding Capacity.*

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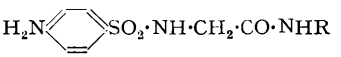
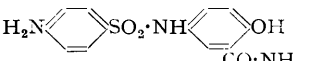
As Brownlee, Green, Tonkin, and Woodbine (unpublished) (cf. Levaditi and Vaisman, *Compt. rend. Soc. Biol.*, 1939, **131**, 33; Swyer and Yang, *Brit. Med. J.*, 1945, I, 149) showed that the three sulphanilamidobenzamides (Gorvin, Parts I and II, *J.*, 1945, 732, 736) are useful intestinal antiseptics, some related amides and imides have been prepared, in most cases by ammonolysis of sulphanilamidocarboxylic esters. Their pharmacological properties suggest that a low degree of absorption from the gut is a general property of sulphanilamidocarboxyamides. Theoretical treatment of this question required a knowledge of pK_a values, and methods for their determination are critically examined.

IN addition to the sulphanilamidobenzamides (Parts I and II; *J.*, 1945, 732, 736) compounds of similar type previously reported include 2- (Migliardi, *Ric. sci.*, 1941, **12**, 1056) and 6-sulphanilamidonicotinamide (Bernstein, Pribyl, Losee, and Lott, *J. Amer. Chem. Soc.*, 1947, **69**, 1158), 3-sulphanilamidopyrazine-2-carboxyamide (Ellingson, Henry, and McDonald, *J. Amer. Chem. Soc.*, 1945, **67**, 1711), and 2-sulphanilamidothiazole-5-carboxyamide (Faith, unpublished results quoted by Florestano and Bahler, *J. Pharm. Exp. Ther.*, 1948, **92**, 196). In the present investigation the following compounds have been prepared (cf. B.P. 562,349); 3- and 5-*sulphanilamidosalicylamide* (as II), 2-, 3- and 4-*sulphanilamidocinnamamide* (as III), 3- and 4-*suphanilamidophthalimide*, 3-*sulphanilamidopicolinamide*, and *sulphanilamidoacetamide* with several of its N-*alkyl* derivatives (I). These substances, with three exceptions, were obtained by the action of aqueous ammonia or alkylamine on the appropriate methyl or ethyl esters (cf. Part I). The



(I.)



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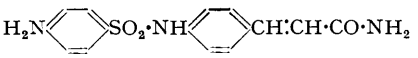

(III.)

two sulphanilamidophthalimides were isolated by hydrolysis of their N^4-*acetyl* derivatives, obtained by the condensation of 3- and 4-aminophthalimide with *N*-acetylsulphanilyl chloride. 3-Sulphanilamidopicolinamide was prepared by the action of aqueous ammonia on *ethyl* 3-$N^{4'}$-*acetylsulphanilamidopicolinate*, followed by selective acid hydrolysis of the acetamido-group (cf. Part II).

The relative ammonolysis rates of the esters of sulphanilamido-acetic, -cinnamic, and -salicylic acid at room temperature (Table I, p. 3309) were in the order expected from a consideration of the environment of the reacting carbalkoxy-group, if it is assumed that attack occurs by an amide ion through a hydrogen-bonded water–ammonia complex (cf. van Velden and Ketelaar, *Chem. Weekblad*, 1947, **43**, 401) according to a suggestion put forward by the author (Part I) and subsequently elaborated by Gordon, Miller, and Day (*J. Amer. Chem. Soc.*, 1948, **70**, 1946; 1949, **71**, 1245). Thus, in ethyl sulphanilamidoacetate the ester group is insulated by the adjacent methylene group and is therefore incapable of any such stabilising resonance as that encountered in ethyl 4-sulphanilamidobenzoate (Part I); ethyl sulphanilamidoacetate reacted very readily with aqueous ammonia and lower alkylamines to give compounds of type (I; R = H or alkyl). In aqueous-ammoniacal solutions of *methyl* or *ethyl* 4-*sulphanilamidocinnamate*, on the other hand, the carbalkoxy-group is stabilised by direct conjugation with the ionised $-SO_2\cdot\bar{N}-$ group with the result that the reactivity of these compounds is of the same very low order as that of the *p*-sulphanilamidobenzoic esters. *Ethyl* 3-*sulphanilamidocinnamate*, however, in which the carbethoxy-group is influenced only indirectly by the stabilising group, reacted with aqueous ammonia considerably more rapidly than did ethyl *m*-sulphanilamidobenzoate. *Methyl* and *ethyl* 5-*sulphanilamidosalicylate* appeared to be more reactive towards aqueous ammonia than were the corresponding *m*-sulphanilamidobenzoic esters, which was somewhat unexpected in view of the general tendency of *ortho*-substituents to impede this type of reaction (cf. Watson, " Modern Theories of Organic Chemistry," 1941, p. 244).

Pharmacological examination of many of the compounds described in this communication and in Parts I and II has been carried out by Dr. G. Brownlee and his colleagues at the Wellcome Research Laboratories, Beckenham. In no case was the antibacterial action equivalent to that

of sulphadiazine, but from the standpoint of intestinal antisepsis the activity may, as in the case of sulphanilylguanidine, be of secondary importance in a compound which undergoes only slight absorption from the gastro-intestinal tract. Although, as pointed out by Bose, Ghosh, and Rakshit (*Quart. J. Pharm. Pharmacol.*, 1946, **19**, 5) the effectiveness of a sulphonamide against intestinal infection may depend on many effects other than poor absorbability, the question of the degree of absorption of sulphonamides from the gut has continued to attract attention from the theoretical as much as from the practical aspect; most speculations have been based, as are those in the present discussion, an the assumption that the determined concentration of drug in the blood-stream over a given period mirrors the absorbability. Thus Krebs and Speakman (*Brit. Med. J.*, 1946, I, 50) have suggested that the degree of absorption of a sulphonamide may be related to its pK_a value,* or rather to the degree to which it is ionised at the pH (7·4) prevailing in the small intestine, low absorption being a consequence of a low degree of ionization of the $-SO_2 \cdot NH-$ group. In support of this hypothesis the authors quote the observation (cf. Kinsman, Moore, and Harrison, *J. Lab. clin. Med.*, 1940, **25**, 1235) that sulphapyridine which is largely (94%) un-ionised at pH 7·4 is absorbed more slowly than the highly ionised sulphathiazole and sulphadiazine. Comparison of Dr. Brownlee's pharmacological results with pK_a measurements (see Tables II and III, for some of our compounds appears superficially to lend support to this hypothesis. Thus *o*-, *m*-, *p*-sulphanilamidobenzamide which have an unusually low degree of absorption from the gut are respectively 80, 91, and 80% un-ionised at pH 7·4. Sulphanilamidoacetamide (99·9% un-ionised) and 4-sulphanilaminocinnamamide (89% un-ionised) are also poorly absorbed. The apparent agreement with the suggestion of Krebs and Speakman is however less striking in the case of 5-sulphanilamidosalicylamide (II), which, although only 64% un-ionised, is reported to be poorly absorbed and about equally as effective as *p*-sulphanilamidobenzamide against intestinal infections. The fundamental difficulty of the hypothesis seems to be that the assumption of absorption of sulphonamides from the gut mainly in the ionised form is contrary to the experience of many workers (cf. Eagle, *J. Pharm. Exp. Ther.*, 1945, **85**, 280) who found that ions of weak acids pass through a wide variety of organic membranes with greater difficulty than do the corresponding undissociated molecules. White, Bell, Bone, Dempsey, and Lee (*ibid*, p. 247) have even suggested that the low permeability of the intestinal mucosa to the ionic form of the drug might account for low blood levels found with certain sulphanilamidocarboxylic acids.

The alternative hypothesis of Rose and Spinks (*Brit. J. Pharmacol.*, 1947, **2**, 65) that the low absorption of certain sulphonamides, *e.g.*, sulphanilylguanidine, may be due to union with a substrate in the gut content, or to the formation of dimeric molecules, through hydrogen-bonding, can probably be extended to include such compounds as the sulphanilamido-derivatives of benzamide, salicylamide, cinnamamide, and acetamide as well as the poorly absorbed 2-sulphanilamidothiazole-5-carboxyamide (Florestano and Bahler, *loc. cit.*), in all of which the presence of the carboxyamido-group indicates a high tendency to hydrogen-bond formation with neighbouring molecules (Hunter, *Chem. and Ind.*, 1941, 32). Such a compound as *p*-sulphanilamidophenyl cyanide, in which the power of hydrogen-bond formation is restricted, will offer less resistance to absorption. It is perhaps significant that *o*-sulphanilamidobenzamide, in which there is a possibility of intra- rather than inter-molecular saturation of the hydrogen-bonding power of the amide group, is more readily absorbed than either the *m*- or the *p*-isomer. The series of *p*-sulphanilamido-*N*-alkylbenzamides (Part II) would also be expected to possess a restricted power of intermolecular hydrogen-bond formation (cf. Rose and Spinks, *loc. cit.*), but this is not reflected in the absorption results which show only the *N*-ethyl and the *N*-*n*-propyl derivatives to be as well absorbed as the parent substance; the *p*-sulphanilamido-*N*-alkylbenzamides are however of high molecular weight and very sparing solubility, factors which may act together to decrease the ease and speed of absorption. A similar argument can hardly be applied in the corresponding group of moderately water-soluble sulphanilamido-*N*-alkylacetamides, in which only the *N*-ethyl derivative is outstandingly better absorbed than the parent substance. While no definite conclusions can be drawn from the results for the alkylated compounds, the poor absorption of sulphanilamidoacetamide itself is in striking contrast to the relatively good absorption of sulphanilamide (cf. Hawkings, *Brit. Med. J.*, 1945, I, 505) and bears out the conclusion that the hydrogen-bonding properties of the carboxyamido-group rather than the pK_a value or the molecular size are primarily responsible for the low absorption of sulphanilamidocarboxyamides in general.

* Methods of determining pK_a are critically examined on pp. 3309, 3310.

Experimental.

Unless otherwise indicated the sulphonamide derivatives were recrystallised from ethanol, using the simple extractor described by Clarke and Kirner (*Org. Synth.*, Coll. Vol. I, 1941, p. 375). All m. p.s are corrected.

5-Sulphanilamidosalicylic Acid.—5-Aminosalicylic acid (7·65 g., 0·05 mol.), dissolved in water (80 c c.) containing sodium hydroxide (5 g., 0·13 mol.), was treated at 40—50° (mechanical shaking) with *N*-acetylsulphanilyl chloride (11·7 g., 0·05 mol.) ground with water into a thin paste. The acetyl group was then removed by boiling the solution for 2 hours with a further quantity (5 g.) of sodium hydroxide. The resulting dark solution was treated with a little sodium dithionite (hydrosulphite) and brought to pH 2—3. The 5-sulphanilamidosalicylic acid (13·8 g., 90%) thus obtained was decolorised by treatment of its ammoniacal solution with charcoal and sodium dithionite, and the reprecipitated acid was crystallised from aqueous ethanol as a mass of felted needles, m. p. 222—223·5° (decomp.) (slow heating) (Found: N, 9·1; S, 10·6. Calc.: N, 9·1; S, 10·4%). Crossley, Northey, and Hultquist (*J. Amer. Chem. Soc.*, 1938, **60**, 2219) record m. p. >285° (decomp.) for this compound, but m. p. 224° is recorded in F.P. 830,754 and U.S.P. 2,270,676.

The N^4-*acetyl* derivative of the above acid was obtained by acidification of the filtered solution after coupling or, less satisfactorily, by allowing 5-aminosalicylic acid to react with *N*-acetylsulphanilyl chloride in pyridine. Crystallisation (charcoal) gave a microcrystalline powder, m. p. *ca.* 265° (decomp.) (slow heating) (Found: N, 8·0; S, 9·1. $C_{15}H_{14}O_6N_2S$ requires N, 8·0; S, 9·15%). This compound is claimed in the above patents to have m. p. 242—245°.

Esters of 5-Sulphanilamidosalicylic Acid.—The acid (29 g.) was refluxed for 5 hours with methanol (120 c.c.) and concentrated sulphuric acid (30 c.c.). The solution was poured into a mixture of ice and 10% aqueous sodium hydroxide (380 c.c.), and sodium carbonate added to neutralise the excess of acid. *Methyl 5-sulphanilamidosalicylate* (26·4 g., 87%) thus obtained was only slightly soluble in ethanol, from which it separated as a crystalline powder, m. p. 188—189° (Found: N, 8·7; S, 10·0. $C_{14}H_{14}O_5N_2S$ requires N, 8·7; S, 9·95%).

A similar procedure was used to prepare the *ethyl* ester (80—85%) which crystallised from aqueous ethanol (charcoal) as a mass of fine needles, m. p. 186—187° (Found: N, 8·3; S, 9·6. $C_{15}H_{16}O_5N_2S$ requires N, 8·3; S, 9·5%). A good yield (77%) was also obtained by the simultaneous esterification and deacetylation of 5-*N*^{4}'-acetylsulphanilamidosalicylic acid under the same conditions.

5-Sulphanilamidosalicylamide.—The methyl ester (12·9 g.) was left for 5 days with aqueous ammonia (80 c.c.; *d* 0·880). Neutralisation gave *5-sulphanilamidosalicylamide* which was decolorised by treatment of its ammoniacal solution with charcoal and sodium dithionite. The reprecipitated amide (10·2 g., 83%) crystallised in small needles, m. p. 221—222·5° (Found: C, 50·2; H, 4·0; N, 13·3; S, 10·4. $C_{13}H_{13}O_4N_3S$ requires C, 50·8; H, 4·3; N, 13·7; S, 10·4%).

Ethyl 5-sulphanilamidosalicylate (10 g.) kept under similar conditions for 8 days gave the amide (8·1 g., 89%) and 5-sulphanilamidosalicylic acid (7%). When the ester (28·7 g.) was heated in an autoclave at 150° for 4 hours with aqueous ammonia (200 c.c.; *d* 0·880) (pressure 225 lbs./sq. in.) only 6·6 g. (25%) of the amide were obtained.

When 5-sulphanilamidosalicylamide (4·0 g.) was treated with acetic anhydride in sodium hydroxide solution (cf. Part I), the N^4'-*acetyl* derivative (3·9 g.) was formed. This on crystallisation gave a felted mass of needles, m. p. 272—273° (Found: C, 51·8; H, 4·7; N, 11·7; S, 9·0. $C_{15}H_{15}O_5N_3S$ requires C, 51·6; H, 4·3; N, 12·0; S, 9·2%).

Reduction of 3-Nitrosalicylic Acid.—A more convenient procedure for the preparation of 3-aminosalicylic acid than those previously recorded (Hübner, *Annalen*, 1879, **195**, 37; Deninger, *J. pr. Chem.*, 1890, **42**, 551; Zahn, *ibid.*, 1900, **61**, 532) consisted in the addition of a suspension of sodium dithionite to a warm neutral solution of sodium 3-nitrosalicylate until the colour had changed from red to pale yellow. The solution was then brought to pH 5 and concentrated under reduced pressure until crystals appeared. This crop, with the addition of subsequent small crystalline deposits obtained on further concentration, amounted to a 47—50% yield of 3-aminosalicylic acid. The method of Zahn (*loc. cit.*) gave a 30% yield, and reduction by means of ferrous sulphate and ammonia gave even less satisfactory results.

3-Sulphanilamidosalicylic Acid.—3-Aminosalicylic acid (10·2 g.), purified by reprecipitation from aqueous ammonia (charcoal), was coupled with *N*-acetylsulphanilyl chloride (15·3 g.) as described for the 5-isomeride. One-tenth of the solution on acidification gave *3-N*^{4}'*-acetylsulphanilamidosalicylic acid* (1·38 g., 59%) which crystallised from aqueous ethanol in prisms, m. p. 265° (decomp.) (Found: N, 8·5; S, 9·1. $C_{15}H_{14}O_6N_2S$ requires N, 8·0; S, 9·15%). The remainder of the solution was hydrolysed with excess of sodium hydroxide and then adjusted to pH 2—3. *3-Sulphanilamidosalicylic acid* (10·3 g., 56%) thus obtained had, after crystallisation from aqueous ethanol, m. p. 217—218° (decomp.) (slow heating) (Found: N, 9·1; S, 10·4. $C_{13}H_{12}O_5N_2S$ requires N, 9·1; S, 10·4%). From the hydrolysed solution 1·95 g. (21%) of unchanged 3-aminosalicylic acid were recovered.

3-Aminosalicylic acid (1·95 g.) reacted similarly with *N*-acetylsulphanilyl chloride (3·5 g.) in pyridine to give 3-*N*^{4}'-acetylsulphanilamidosalicylic acid (2·25 g., 50%). The consistently low yields obtained in the above reactions suggest a low degree of coupling activity in 3-aminosalicylic acid.

Ethyl 3-Sulphanilamidosalicylate.—3-Sulphanilamidosalicylic acid (9·25 g.), esterified with ethanol and concentrated sulphuric acid, gave *ethyl 3-sulphanilamidosalicylate* (6·17 g., 61%) and unchanged acid (1·16 g., 13%). The ester crystallised from aqueous ethanol in fine felted needles, m. p. 176·5° (Found: N, 8·3; S, 9·5. $C_{15}H_{16}O_5N_2S$ requires N, 8·3; S, 9·5%).

3-Sulphanilamidosalicylamide.—The ester (3·7 g.) was kept with aqueous ammonia (*d* 0·880) at room temperature for 8 days. On adjustment of the solution to pH 8—9, *3-sulphanilamidosalicylamide* (3·0 g., 88%) was obtained which, after recrystallisation, formed nodules m. p. 193—194° (Found: C, 50·9; H, 4·3; N, 13·9; S, 10·5. $C_{13}H_{13}O_4N_3S$ requires C, 50·8; H, 4·3; N, 13·7; S, 10·4%). 3-Sulphanilamidosalicylic acid (0·35 g., 10%) was recovered from the filtrate at pH 2—3.

Ethyl 3-Sulphanilamidocinnamate.—3-Aminocinnamic acid, prepared from 3-nitrocinnamic acid by

reduction with ferrous hydroxide (Gabriel and Herzberg, *Ber.*, 1883, **16**, 2038), was coupled with *N*-acetylsulphanilyl chloride in aqueous sodium hydroxide, and the acetyl group removed by boiling with excess of alkali. The yield of crude 3-sulphanilamidocinnamic acid obtained was 55—60%, based on 3-nitrocinnamic acid. On purification the acid formed small crystals, m. p. 214°, with change of form (accompanied by softening or melting) at *ca.* 195° (Ganapathi, *J. Indian Chem. Soc.*, 1938, **15**, 525, recorded m. p. 213°). The acid (11·5 g.) was esterified by refluxing it for 5 hours with ethanol (50 c.c.) and concentrated sulphuric acid (12 c.c.); the resulting *ethyl* 3-*sulphanilamidocinnamate* (11·8 g., 94%) crystallised from aqueous ethanol in needles m. p. 147—148° (Found : C, 58·8; H, 5·5; S, 9·2. $C_{17}H_{18}O_4N_2S$ requires S, 58·9; H, 5·2; S, 9·3%).

3-*Sulphanilamidocinnamamide.*—The ester (0·87 g.) was set aside in aqueous ammonia (5 c.c.; *d* 0·880) for 3 days at room temperature. On adjustment of the solution to pH 8—9, a precipitate of 3-*sulphanilamidocinnamamide* (0·74 g., 96%) was obtained. The amide, which was only slightly soluble in hot ethanol, crystallised in small needles, m. p. 247° (Found : C, 56·7; H, 4·7; N, 13·4; S, 10·0. $C_{15}H_{15}O_3N_3S$ requires C, 56·7; H, 4·8; N, 13·2; S, 10·1%).

When the ester (19·4 g.) was heated in an autoclave with aqueous ammonia (150 c.c.; *d* 0·880) at 150° for 5 hours, the resulting solution gave only 4·7 g. (26%) of the amide, together with a considerable amount of 3-sulphanilamidocinnamic acid.

Methyl 4-*Sulphanilamidocinnamate.*—The most obvious starting-material for this compound was 4-sulphanilamidocinnamic acid, previously prepared by Ganapathi (*loc. cit.*). The coupling of 4-aminocinnamic acid with *N*-acetylsulphanilyl chloride in aqueous alkali did not proceed however in a very satisfactory manner; it was more convenient to carry out this reaction with the ethyl ester.

The ester was prepared in 50% yield from ethyl 4-nitrocinnamate by a modification of the method of Posner (*J. pr. Chem.*, 1910, **82**, 427) : to a hot solution of ethyl 4-nitrocinnamate (7·5 g.) in glacial acetic acid (20 c.c.) were added stannous chloride (25 g.) and hydrochloric acid (20 c.c.; *d* 1·2). The mixture was boiled until all the solid had dissolved, poured on ice, and treated with excess of aqueous sodium hydroxide. The crude product was separated by filtration, dissolved in ethanol, and treated with aqueous sodium dithionite in order to ensure complete reduction. On dilution of the clear alcoholic solution, ethyl 4-aminocinnamate (3·3 g.) was obtained, which from aqueous ethanol formed crystals, m. p. 73° (Kindler, *Ber.*, 1936, **69**, 2805, recorded m. p. 74°, but Heilbron's " Dictionary of Organic Compounds," 1943, I, 70, quotes an earlier figure, m. p. 68—69°).

Ethyl 4-aminocinnamate, warmed in pyridine for 30 minutes with an equivalent amount of *N*-acetylsulphanilyl chloride, gave a quantitative yield of *ethyl* 4-N$^{4'}$-*acetylsulphanilamidocinnamate*, which formed crystals, m. p. 211° (Found : S, 8·35. $C_{19}H_{20}O_5N_2S$ requires S, 8·25%).

The acetylated ester was hydrolysed by boiling it with 5% aqueous sodium hydroxide for an hour. The solution, treated with charcoal and adjusted to pH 2—3, gave 4-sulphanilamidocinnamic acid, which crystallised in small flakes, m. p. *ca.* 247° (decomp.) (Ganapathi, *loc. cit.*, recorded m. p. 239°). The acid (4 g.) was refluxed with methanol (20 c.c.) and concentrated sulphuric acid (4 c.c.) for 4 hours. On neutralisation, *methyl* 4-*sulphanilamidocinnamate* (4 g.) was obtained; this was only slightly soluble in ethanol, but gave therefrom a crystalline powder, m. p. 257° (Found : C, 57·8; H, 4·9; S, 9·8. $C_{16}H_{16}O_4N_2S$ requires C, 57·8; H, 4·9; S, 9·9%). By a similar procedure the *ethyl* ester was prepared, which crystallised in small prisms, m. p. 221—222° (Found : N, 8·4; S, 9·8. $C_{17}H_{18}O_4N_2S$ requires N, 8·1; S, 9·3%).

4-*Sulphanilamidocinnamamide.*—The crude methyl ester (3 g.) was treated with aqueous ammonia (50 c.c.; *d* 0·880) and set aside for a month. On neutralisation, 4-*sulphanilamidocinnamamide* (2·1 g., 75%) was obtained which, after reprecipitation from ammonia and recrystallisation, formed flattened crystals, m. p. 224·5° (Found : C, 56·8; H, 4·8; N, 13·3; S, 10·1. $C_{15}H_{15}O_3N_3S$ requires C, 56·7; H, 4·8; N, 13·2; S, 10·1%). The filtrate from the amide gave a precipitate of 4-sulphanilamidocinnamic acid (0·1 g., 4%) at pH 2—3.

Methyl 2-*Sulphanilamidocinnamate.*—As in the case of the 4-isomeride, the use of the ethyl ester of the aminocinnamic acid rather than the acid itself gave the most satisfactory results. Ethyl 2-aminocinnamate (Friedländer and Weinberg, *Ber.*, 1882, **15**, 1422) was obtained from ethyl 2-nitrocinnamate by reduction with stannous chloride in the manner previously described. The reduction product was in this case separated by extraction with ether and purified by crystallisation from aqueous ethanol. The ester coupled readily with *N*-acetylsulphanilyl chloride in pyridine to give *ethyl* 2-N$^{4'}$-*acetylsulphanilamidocinnamate* (92% yield) which crystallised from aqueous ethanol in needles, m. p. 215° (Found : N, 7·2; S, 8·2. $C_{19}H_{20}O_5N_2S$ requires N, 7·2; S, 8·3%). The acetylated ester was hydrolysed with 5% sodium hydroxide solution to give 2-*sulphanilamidocinnamic acid* (92%) which crystallised from aqueous ethanol in fine needles, m. p. 256° (sharp decomp.) (Found : C, 56·7; H, 4·4. $C_{15}H_{14}O_4N_2S$ requires C, 56·6; H, 4·4%). Esterification with methanol and concentrated sulphuric acid for 4½ hours gave *methyl* 2-*sulphanilamidocinnamate* (94%) which crystallised in fine felted needles, m. p. 190—191° (Found : C, 57·9; H, 5·0. $C_{16}H_{16}O_4N_2S$ requires C, 57·8; H, 4·9%).

2-*Sulphanilamidocinnamamide.*—The crude methyl ester (3·5 g.) was set aside for a month with aqueous ammonia (70 c.c.; *d* 0·880). On partial neutralisation a small amount of tar separated, which was removed by filtration through charcoal. When the solution was adjusted to pH 8 a precipitate of 2-*sulphanilamidocinnamamide* (2·7 g.) was obtained. The amide was only slightly soluble in hot ethanol; it formed crystals, m. p. 237—238° (Found : C, 57·2; H, 4·8; N, 13·1. $C_{15}H_{15}O_3N_3S$ requires C, 56·7; H, 4·8; N, 13·2%). The mother-liquor from the amide gave a small amount of 2-sulphanilamidocinnamic acid at pH 2—3.

3-*Sulphanilamidophthalimide.*—3-Aminophthalimide (cf. Kauffmann and Beisswenger, *Ber.*, 1903, **36**, 2497; Bogert and Jouard, *J. Amer. Chem. Soc.*, 1909, **31**, 488) was conveniently prepared by the reduction of 3-nitrophthalimide (from 3-nitrophthalic acid, *Org. Synth.*, Coll. Vol. I, 1941, p. 408) in aqueous-alcoholic solution with a saturated aqueous solution of sodium dithionite; the yield was approx. 40%. The base (2·4 g.) was warmed with *N*-acetylsulphanilyl chloride (3·5 g.) in pyridine for 2 hours at 80°. After evaporation of the excess of pyridine, 3-N$^{4'}$-*acetylsulphanilamidophthalimide* (3·8 g., 72%) was obtained by shaking the residue with 10% hydrochloric acid; it formed yellow crystalline flakes,

m. p. 240—241° (decomp.) (Found: C, 52·8; H, 3·8; N, 11·75; S, 8·6. $C_{16}H_{13}O_5N_3S$ requires C, 53·5; H, 3·7; N, 11·7; S, 8·9%).

Attempts to deacetylate the above compound by acid hydrolysis always resulted in the formation of some 3-aminophthalimide by fission of the sulphonamido-group; contamination of the product was avoided by adopting the following procedure: 3-$N^{4'}$-Acetylsulphanilamidophthalimide (11 g.) was added to boiling hydrochloric acid (100 c.c.; *d* 1·2), and the solution stirred for 5 minutes. Ice was added, and the solution diluted to 500 c.c. Unchanged acetyl compound (5·3 g.) was filtered off and the solution, having been neutralised with ammonia, was made just acid with acetic acid. 3-*Sulphanilamidophthalimide* (3·5 g., 70% of possible recovery) was obtained, which crystallised from 25% aqueous ethanol (charcoal) in small primrose-yellow needles, m. p. 219° (Found: C, 53·1; H, 3·5; N, 13·3; S, 10·1. $C_{14}H_{11}O_4N_3S$ requires C, 52·95; H, 3·5; N, 13·2; S, 10·1%).

4-*Sulphanilamidophthalimide*.—4-Aminophthalimide, prepared from 4-nitrophthalimide (*Org. Synth.*, Coll. Vol. II, 1943, p. 459) by the method of Bogert and Renshaw (*J. Amer. Chem. Soc.*, 1908, **30**, 1141), was coupled with *N*-acetylsulphanilyl chloride as described for the 3-isomeride. 4-$N^{4'}$-*Acetylsulphanilamidophthalimide*, which was only very slightly soluble in hot ethanol, was obtained as a pale yellow crystalline powder, m. p. 295° (decomp.) (Found: N, 11·6; S, 8·8. $C_{16}H_{13}O_5N_3S$ requires N, 11·7; S, 8·9%).

The acetyl derivative (4·5 g.), refluxed with 10% hydrochloric acid (50 c.c.) and glacial acetic acid (10 c.c.) for 75 minutes, gave 4-*sulphanilamidophthalimide* (0·9 g.) and unchanged substance (1·8 g.); further treatment of the latter with the same reagents (20 and 4 c.c.) for 90 minutes gave the deacetylated product (0·5 g.) and unchanged material (0·5 g.). The combined product (1·4 g., 40%) crystallised from 50% aqueous ethanol in pale yellow prismatic needles, m. p. 266° (Found: N, 13·1; S, 10·0%).

Ethyl 3-N^4-*Acetylsulphanilamidopicolinate*.—3-Aminopicolinic acid, prepared from quinolinimide according to Sucharda (*Ber.*, 1925, **58**, 1729), gave only a small yield of sulphonamide when coupled with *N*-acetylsulphanilyl chloride in pyridine. The acid (7 g.) was therefore esterified by refluxing it for 7 hours in ethanolic hydrogen chloride. *Ethyl* 3-*aminopicolinate* (3·1 g., 37%) crystallised in needles on dilution of its ethereal solution with light petroleum (b. p. 40—60°). The ester was appreciably soluble in aqueous alcohol but crystallised from a small volume of ethanol in prismatic needles, m. p. 131—132°, which readily sublimed (Found: C, 58·5; H, 6·3. $C_8H_{10}O_2N_2$ requires C, 57·8; H, 6·1%). Alcoholic and ethereal solutions of the ester exhibited a violet or blue fluorescence.

The ester (1·66 g.) was warmed for 1 hour at 80° with *N*-acetylsulphanilyl chloride (3 g.) in pyridine. The excess of solvent was removed and the residue treated with dilute hydrochloric acid. On neutralisation with aqueous sodium carbonate, *ethyl* 3-$N^{4'}$-*acetylsulphanilamidopicolinate* (2·23 g., 64%) was precipitated; it crystallised from 50% ethanol (charcoal) in yellowish prismatic needles, m. p. 187—188° (Found: C, 53·5; H, 5·1; N, 11·8. $C_{16}H_{17}O_5N_3S$ requires C, 52·9; H, 4·7; N, 11·6%). When the ester (0·7 g.) was refluxed with ethanol (4 c.c.) and concentrated sulphuric acid (1 c.c.) with a view to removing the acetyl group the molecule was disrupted.

3-$N^{4'}$-*Acetylsulphanilamidopicolinamide*.—The acetylated ester (1·2 g.) was left for 3 days in aqueous ammonia (15 c.c.; *d* 0·88) at room temperature. The solution was then adjusted to pH 9. The precipitate of 3-$N^{4'}$-*acetylsulphanilamidopicolinamide* (1·0 g., 88%) crystallised in yellowish prisms, m. p. 243—244° (Found: C, 50·9; H, 3·7; N, 16·9. $C_{14}H_{14}O_4N_4S$ requires C, 50·3; H, 4·2; N, 16·8%).

When the acetylated ester (0·3 g.) was heated with aqueous ammonia (2 c.c.) in a sealed tube at 150° for 5 hours, 3-$N^{4'}$-acetylsulphanilamidopicolinamide (0·2 g., 69%) was similarly obtained (compare the experiment described below).

3-*Sulphanilamidopicolinamide*.—The acetylated amide (1 g.) was boiled for 1 minute with 50% sulphuric acid (10 c.c.); the clear solution was poured on ice and made slightly alkaline. 3-*Sulphanilamidopicolinamide* (0·64 g., 73%) was obtained which crystallised in small prisms, m. p. 212—213° (Found: C, 49·8; H, 4·3; N, 19·3; S, 10·8. $C_{12}H_{12}O_3N_4S$ requires C, 49·3; H, 4·1; N, 19·2; S, 11·0%).

When ethyl 3-$N^{4'}$-acetylsulphanilamidopicolinate (0·3 g.) was heated with aqueous ammonia (5 c.c.) in a sealed tube at 150° for 15 hours hydrolysis of the acetyl group accompanied ammonolysis, and a small yield of 3-sulphanilamidopicolinamide (0·06 g., 25%) was obtained.

Amides of Sulphanilamidoacetic Acid.—Ethyl sulphanilamidoacetate (cf. Crossley, Northey, and Hultquist, *J. Amer. Chem. Soc.*, 1940, **62**, 532; Cocker, *J.*, 1940, 1574) was prepared by direct esterification of N^4-acetylsulphanilamidoacetic acid (20 g.) which was refluxed in ethanol (90 c.c.) with concentrated sulphuric acid (20 c.c.) for 5 hours. The excess of ethanol was removed, and the solution poured on ice and made alkaline with sodium carbonate. The ester obtained in this way was used without further purification. When shaken with aqueous ammonia (*d* 0·88) the ester reacted rapidly, and neutralisation after 1 hour gave *sulphanilamidoacetamide*. Crystallised from aqueous ethanol, this had m. p. 155° (Found: C, 42·2; H, 4·8; N, 18·3; S, 14·0. $C_8H_{11}O_3N_3S$ requires C, 41·9; H, 4·8; N, 18·3; S, 14·0%); it was readily soluble in water but sparingly so in ethanol.

The substituted amides were obtained in good yield by keeping the ester for 2—3 days in aqueous solutions of methylamine (30%), ethylamine (33%), *n*-propylamine (40%), or *n*-butylamine (40%). The products obtained on neutralisation were crystallised from ethanol or aqueous ethanol to give the following compounds: *sulphanilamido*-N-*methylacetamide*, m. p. 147° and 163—164° (dimorphs) (Found: N, 17·0. $C_9H_{13}O_3N_3S$ requires N, 17·3%), -N-*ethylacetamide*, large crystals, m. p. 126—127° (Found: N, 15·9; S, 12·8. $C_{10}H_{15}O_3N_3S$ requires N, 16·3; S, 12·5%), -N-n-*propylacetamide*, long prisms, m. p. 140° (Found: N, 15·5; S, 11·8. $C_{11}H_{17}O_3N_3S$ requires N, 15·5; S, 11·8%), and -N-n-*butylacetamide*, m. p. 109—110° (Found: N, 14·8; S, 11·2. $C_{12}H_{19}O_3N_3S$ requires N, 14·7; S, 11·2%).

Reactivity of Sulphanilamidocarboxylic Esters towards Ammonia.—The tests were carried out at room temperature in sealed glass tubes using 0·0025 mol. of the ester and aqueous ammonia (5 c.c.; *d* 0·885). The results in Table I are comparable with those recorded for a series of esters in Part I (*loc. cit.*; Table I) as the same standard procedure was used in both cases. The percentage "extent of reaction" is based in each case on the recovery of unchanged ester from weakly alkaline solution in which the reaction products (*i.e.*, the amide and any acid formed by hydrolysis) were soluble; the amount of amide produced was however used as a check on the accuracy of this procedure. The hydrolytic reaction is not significant

under these conditions, although it becomes the main reaction at 150° in the case of ethyl 5-sulphanilamidosalicylate and ethyl 3-sulphanilamidocinnamate (*q. v.*) (cf. Part II).

Absorption Results.—The figures for the absorption of the named compounds (Table II) in mice were obtained by the administration of 25 mg./100 g. (unless otherwise stated) in 10% mucilage of gum acacia to groups of 5 mice *per os*; bleedings of peripheral blood were obtained at intervals and the drug determined in the blood by a modified Bratton–Marshall method. The percentage of drug in un-ionised form was deduced from Table III.

TABLE I.

Relative rates of ammonolysis.

Ester.	Time, days.	Extent of reaction, %.
Ethyl *p*-sulphanilamidobenzoate	148	59
,, 4-sulphanilamidocinnamate	148	61
Methyl *p*-sulphanilamidobenzoate *	15	83
,, 4-sulphanilamidocinnamate	15	53
Ethyl *m*-sulphanilamidobenzoate *	2·8	55
,, 3-sulphanilamidocinnamate *	2·8	100
,, 5-sulphanilamidosalicylate	2·8	100
Methyl *m*-sulphanilamidobenzoate *	1·7	80
,, 5-sulphanilamidosalicylate	1·7	99·5

* Compounds completely in solution at the commencement of the reaction.

TABLE II.

Compound.	Blood concentration, at hours after dosage, in mg./100 ml. of blood, of total drug (free + conjugated). ½.	1.	2.	3.	4½.	6.	Drug in un-ionised form at pH 7·4, %.
Sulphanilylguanidine	3·3	3·9	4·4	3·5	3·7	4·2	100
o-Sulphanilamidobenzamide	6·5	13·1	14·7	12·6	9·5	8·7	80
m- ,,	3·5	3·3	3·9	3·2	3·4	3·4	91
p- ,,	3·3	6·7	6·8	7·2	6·4	—	80
p-Sulphanilamido-*N*-methyl-benzamide	0·5	0·5	0·4	0·2	0·1	0·1	83
,, -*N*-ethyl- ,,	6·0	9·1	5·2	5·4	4·0	2·5	86
,, -*N*-*n*-propyl- ,,	7·6	5·4	5·3	5·5	4·3	2·1	*ca.* 86
,, -*N*-*n*-butyl- ,,	0·2	1·6	0·2	0·3	0·2	0·2	*ca.* 86
,, -*NN*-dimethyl- ,,	2·1	3·2	2·7	2·6	0·6	0·4	86
5-Sulphanilamidosalicylamide	3·2	1·8	1·4	0·5	0·0	0·0	64
4-Sulphanilamidocinnamamide * (50 mg./100 g.)	0·0	3·6	1·8	1·4	0·0	—	89
Sulphanilamido-acetamide	1·2	0·7	0·5	0·1	0·1	0·1	
,, -*N*-methyl-acetamide	1·6	1·4	1·2	0·4	0·2	0·1	
,, -*N*-ethyl- ,,	13·9	14·3	13·3	7·5	4·6	1·1	99·9
,, -*N*-*n*-propyl- ,,	2·4	2·2	1·2	0·3	0·0	—	
,, -*N*-*n*-butyl- ,,	0·6	1·6	0·5	0·1	0·7	—	
p-Sulphanilamidophenyl cyanide	—	—	—	—	30·0	—	58
,, (10 mg./100 g.)	6·7	10·0	10·9	11·4	11·7	11·9	

* No figures obtained with usual dosage.

pK_a *Values.*—Approximate values of pK_a at 20° were established from glass-electrode determinations of pH, using a standard Cambridge pH meter, on aqueous solutions (0·0025M.) of the sulphonamide half-neutralised with 0·1N-sodium hydroxide (carbonate-free) (cf. Walker, *J.*, 1945, 633). As some of the compounds were sparingly soluble in water, consideration was given to the use of 50% ethanol as a solvent (cf. Bell and Roblin, *J. Amer. Chem. Soc.*, 1942, **64**, 2915; Cook, Heilbron, Reed, and Strachan, *J.*, 1945, 864). The assumption of Bell and Roblin (*loc. cit.*) that pK_a values obtained in 50% alcohol can be accurately converted into pK_a (water) is based on the work of Michaelis and Mizutani (*Z. physikal. Chem.*, 1925, **116**, 135) and Mizutani (*ibid.*, 1925, **118**, 318) and on the fact that a smooth curve resulted when values of pK_a (water) were plotted against pK_a (50% ethanol) for six individual sulphonamides. The procedure has now been more fully tested against a larger number of sulphonamides (Tables III and IV) and appears to be less reliable than previously assumed.

Since the dissociation constant of an acid is dependent on the dielectric constant of the solvent (Wynne-Jones, *Proc. Roy. Soc.*, 1933, **140** *A*, 440; Minnick and Kilpatrick, *J. Physical Chem.*, 1939, **43**, 259) it would seem possible in the ideal case to deduce pK_a (water) from the value of pK_a in another solvent, utilising the linear relationship between the free energies of ionisation ($-\boldsymbol{R}T \ln K$) in the two solvents, *i.e.*, a relationship between potential energy terms in the standard equilibrium equations. Such a relation can apply only if the equations contain negligible kinetic-energy terms. Such kinetic-energy terms are, however, in some cases closely related to the interaction of solute with solvent; thus proximity terms due to *ortho*-substituents and, in aliphatic compounds, free rotational and vibrational terms appear in the action of changing the solvent (Hammett, *Trans. Faraday Soc.*, 1938, **34**, 156) as is

shown by comparison of relative acidity constants in water and butanol (Wooten and Hammett, *J. Amer. Chem. Soc.*, 1935, **57**, 2289). Similarly the results of Michaelis and Mizutani (*loc. cit.*) and Mizutani (*loc. cit.*; *Z. physikal Chem.*, 1925, **116**, 350) indicate appreciable irregularity in the effect on pK_a of a change of solvent from water to 60% alcohol both in the aromatic and in the aliphatic series. Hammett ("Physical Organic Chemistry," 1940, p. 259; *J. Amer. Chem. Soc.*, 1937, **59**, 102) concludes that the relative

TABLE III.

	pK_a (water) [8] (0·0025M.).	pK_a (50% w/v EtOH) (0·01M.).	ΔpK_a.	pK_a (water) (lit.).
Sulphanilamide	10·7	—	—	10·56 [1]
Sulphapyridine	8·62	9·8	1·2	8·52 [2]
Sulphathiazole	7·41	8·5	1·1	7·30 [3]
3-Sulphanilamidosalicylamide	7·1	8·1	1·0	—
5-Sulphanilamidosalicylamide	7·65	9·15	1·5	—
o-Sulphanilamidobenzamide	8·0	9·4	1·4	7·7 [4]
m-Sulphanilamidobenzamide	8·45	10·2	1·75	—
p-Sulphanilamidobenzamide	8·02	9·9	1·9	—
p-Sulphanilamido-*N*-methylbenzamide	8·1	10·0	1·9	—
,, -*N*-ethylbenzamide	8·2	10·0	1·8	—
,, -*N*-*n*-propylbenzamide	—	10·1	—	—
,, -*N*-*n*-butylbenzamide	—	10·1	—	—
,, -*NN*-dimethylbenzamide	8·5	10·15	1·65	—
Sulphanilylsulphanilamide	7·63	9·45	1·8	7·85 [5]
4-Sulphanilamidocinnamamide	8·3	10·2	1·9	—
p-Sulphanilamidophenyl cyanide [6]	7·55	9·0	1·45	7·5 [4]
Sulphanilamidoacetamide [7]	10·35	—	—	—
Sulphanilamido-*N*-methylacetamide [7]	10·4	—	—	—
,, -*N*-ethylacetamide [7]	10·25	—	—	—
,, -*N*-*n*-propylacetamide [7]	10·4	—	—	—
,, -*N*-*n*-butylacetamide [7]	10·4	—	—	—

[1] Mean of 6 determinations: 10·5 (Fox and Rose, *Proc. Soc. Exp. Biol. Med.*, 1942, **50**, 142), 10·66 (Schmelkes *et al.*, *ibid.*, p. 145), 10·56 (Walker, *loc. cit.*), 10·43 (Bell and Roblin, *loc. cit.*), 10·65 (Cook *et al.*, *loc. cit.*), 10·58 (Jordan and Taylor, *J.*, 1946, 994).

[2] Mean of 5 determinations: 8·5 (Fox and Rose, *loc. cit.*), 8·29 (Schmelkes *et al.*, *loc. cit.*), 8·4 (Bell and Roblin, *loc. cit.*), 8·7 (Cook *et al.*, *loc. cit.*), 8·7 (Nielson and Wollfbrandt, *Dansk Tidsskr. Farm.*, 1940, **14**, 113).

[3] Mean of 4 determinations: 7·21 (Schmelkes *et al.*, *loc. cit.*), 7·12 (Bell and Roblin, *loc. cit.*), 7·6 (Nielson and Wollfbrandt, *loc. cit.*), 7·26 (Stockton and Johnson, *loc. cit.*).

[4] Cook *et al.* (*loc. cit.*).

[5] Bell and Roblin (*loc. cit.*).

[6] Alternatively, *p*-sulphanilamidobenzonitrile (cf. Part II, *loc. cit.*).

[7] Dissolved in water at room temperature.

[8] Hydrolysis corrections applied where significant.

TABLE IV.

	pK_a (water) (0·0025M.).	pK_a (30% w/v EtOH) (0·01M.).	ΔpK_a.	pK_a (40% w/v EtOH) (0·01M.).	ΔpK_a.	pK_a (50% w/v EtOH) (0·01M.).	ΔpK_a.
Sulphathiazole	7·41	8·07	0·7	8·30	0·9	8·53	1·1
Sulphapyridine	8·62	9·33	0·7	9·55	0·9	9·81	1·2
Sulphanilylsulphanilamide	7·63	8·66	1·0	9·08	1·45	9·45	1·8
p-Sulphanilamidobenzamide	8·02	9·12	1·1	9·53	1·5	9·92	1·9

strengths of a series of acids of a given charge type in one solvent are simply and quantitatively related to those in another only in the limited case of *meta*- and *para*-substituted benzoic acid derivatives. The influence of "special factors" on the sequence of strengths of a series of acids in different solvents has been discussed by Dippy (*J.*, 1941, 550; cf. Davey and Dippy, *J.*, 1944, 411) who does not however mention the varying type and degree of solvation of the hydroxyl group as a possible cause of the anomalous behaviour of *m*-hydroxybenzoic acid when transferred from aqueous to alcoholic solution. Solvent–solute interaction of this type assumes importance when considered in relation to the conclusion of Kolthoff, Lingane, and Larson (*J. Amer. Chem. Soc.*, 1938, **60**, 2512) that the change in pK_a is a function of the distribution constants (D) between the two solvents, of the different molecular and ionic species involved in the acid–base equilibrium: $\Delta pK_a = \log D_{H^+}D_{A^-} - \log D_{HA}$. There appears to be no reported work to show the influence of solvent on the ionisation of an acidic –NH group; but, even if it can be assumed that resonance effects assure the rigidity of such sterically unhindered molecules as sulphanilamide, *p*-sulphanilamidobenzamide, and 4-sulphanilamidocinnamamide (cf. Pauling, *J. Amer. Chem. Soc.*, 1936, **58**, 94) and that the dissociation of NH-compounds, like that of phenols (Boyd and Marle, *J.*, 1914, **105**, 2117; Goldsworthy, *J.*, 1926, 1254; Jenkins, *J.*, 1939, 1137) is not subject to *ortho*-effects, it is very probable that kinetic-energy terms will be introduced with compounds of this type in which are present substituents capable of bringing about a variable degree of association or solvation through hydrogen-bonding.

In Tables III and IV are recorded variations in pK_a for a change of solvent from water to 50% (w/v) ethanol (with a constant change in concentration from 0·0025 to 0·01M.). Sulphanilamide and the sulphanilamidoacetamides gave apparent pK_a values in 50% ethanol of the order of 11·5; these figures are not recorded in the Table in view of the large and somewhat uncertain hydrolysis correction involved in the case of such weak acids. If the compounds sulphapyridine and sulphathiazole are taken as a basis of comparison (cf. Bell and Roblin, *loc. cit.*), the mean value of ΔpK_a (water $\longrightarrow$ 50% ethanol) is 1·15. In most of the compounds tested, ΔpK_a was considerably greater than this standard figure, and in some cases was as high as 1·9. The most divergent compounds include *m*- and *p*-sulphanilamidobenzamide, 4-sulphanilamidocinnamamide, and 4-sulphanilylsulphanilamide, in each of which there is a possibility of association with neighbouring molecules through hydrogen-bonding. In *o*-sulphanilamidobenzamide and in 3- and 5-sulphanilamidosalicylamide, in which there is a possibility of intra- as well as inter-molecular hydrogen bond formation, the values of ΔpK_a are nearer to the standard. Although it is not possible at present to explain fully the irregularities encountered, the results show clearly that pK_a values determined in 50% ethanol are in general reliable only as a rough guide to the corresponding values of pK_a (water); an error at least as great as 0·75 pK_a unit may be involved in the use of a standardisation curve. That a corresponding discrepancy is encountered in solvents containing lower concentrations of ethanol is shown by Table IV. It is evident that the only reasonably accurate method of determination of pK_a (water) using alcoholic solutions is the method of extrapolation (cf. Stockton and Johnson, *J. Amer. Pharm. Assoc.*, 1944, **33**, 383). The recording of ΔpK_a values for many heterocyclic bases (Albert and Goldacre, *J.*, 1946, 706; Albert, Goldacre, and Phillips, *J.*, 1948, 2240) has led workers in that field to a similar conclusion (Albert, personal communication).

Values of pK_a (water) for three of the more sparingly soluble substances in Table III were estimated by a method based on the formation of a supersaturated solution on cooling of a hot aqueous solution of two slightly soluble sulphonamides dissolved in equimolecular proportions. At half-neutralisation the fundamental equation for two weak acids [cf. Michaelis, "Hydrogen Ion Concentration," Vol. I, 1926, p. 47, equation (1*e*)] reduces to $2pH = pK_1 + pK_2$, so that, if pK_1 for one constituent of the mixture is known, pK_2 can be determined. The method is useful for closely related substances which do not interact. Since buffering is at a minimum at the half-neutralisation point it is necessary for accuracy that the two values pK_1 and pK_2 should not differ greatly. The procedure was tested successfully against mixtures of various sulphonamides of known pK_a selected from Table III. When applied to very sparingly soluble sulphonamides it proved to be of somewhat limited applicability; satisfactory results were obtained with *p*-sulphanilamido-*N*-methyl-, -*N*-ethyl- and -*NN*-dimethyl-benzamide in admixture with *p*-sulphanilamidobenzamide, but with the *N*-*n*-propyl and *N*-*n*-butyl derivatives under the same conditions supersaturated solutions could not be obtained.

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