191. *Sulphonamides. Part II. The Action of Amines on Ethyl 4-Sulphanilamidobenzoate. Some Alternative Preparative Methods for Sulphanilamidobenzamides.*

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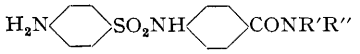
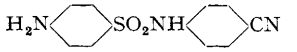
The most interesting of the three sulphanilamidobenzamides (cf. Part I) from the point of view of bacteriostatic activity and low absorption has proved to be the 4-isomer (I; $R_1 = R_2 = H$) (compare Swyer and Yang, *Brit. Med. J.*, 1945, **1**, 149). The preparation of certain derivatives of this compound has therefore been studied, as well as some alternative methods for obtaining the sulphanilamidobenzamides.

THE slow reaction of an ethyl sulphanilamidobenzoate with aqueous ammonia in the cold produces the amide almost exclusively; the more rapid reaction at high temperature, however, results in the simultaneous production of appreciable amounts of acid (Part I). This is evidently due to the increase in the relative concentration of hydroxyl ions in aqueous solutions of ammonia since rising temperature reduces the stability of the hydrogen-bonded ammonia–water complexes. Alkylamines, like ammonia, react readily with ethyl 4-sulphanilamidobenzoate only on heating for several hours at temperatures above 100°, and in all cases the principal reaction is a simple hydrolysis to 4-sulphanilamidobenzoic acid. Substituted amides are produced in small yields; the *methylamide* (I; R′ = H, R″ = Me) (31 per cent.), *ethylamide* (I; R′ = H, R″ = Et) (8 per cent.), and n-*propylamide* (I; R′ = H, R″ = Pr) (1 per cent.) are obtained by this method, but *n*-butylamine, dimethylamine and diethylamine bring about hydrolysis unaccompanied by any detectable amide formation.



(I.)



(II.)

The relative extent of amide formation and hydrolysis of a given ester by an amine at high temperatures must depend largely on the basic strength of the amine, for this factor, by controlling the hydroxyl ion concentration, must determine the rate of hydrolysis of the ester. On the other hand, the rate of amide formation is determined by the nucleophilic reactivity of the reacting amine, or, rather, of the appropriate amine–water complex, and this reactivity would be expected to be greater for the alkylamines than for ammonia if it were not for the higher concentration of anticatalytic lyonium ions in the more strongly basic amine solutions. From the experimental data it seems that, in the cases studied, the hydroxyl ion concentration is high enough to control almost entirely the course of the reaction. It may be objected that some hydrolysis of the amide occurs after its formation; Meyer, however, rejected this possibility in the general case (*Monatsh*, 1906, **27**, 32), and his conclusion is supported by the behaviour of 4-*sulphanilamido*-NN-*dimethylbenzamide* (I; R′ = R″ = Me) (see below), which is not appreciably hydrolysed under the conditions of its attempted preparation from the ester.

A general method for the preparation of alkyl derivatives of 4-sulphanilamidobenzamide of the type discussed above is provided by the preferential acid hydrolysis of their N^4-*acetyl* derivatives, prepared by allowing the appropriately substituted *p*-aminobenzamide to react with *N*-acetylsulphanilyl chloride. Although a certain amount of hydrolysis occurs at the carboxamido group, the alkyl derivatives and the *phenyl* (I; R′ = H, R″ = Ph) and *benzyl* (I; R′ = H, R″ = Ph·CH_2) compounds are reasonably stable to strong acids and are obtained in satisfactory yield by this method. In a similar manner, the 2-, 3-, and 4-sulphanilamidobenzamides are readily prepared from their N^4-acetyl derivatives by acid hydrolysis.

The N^4-acetylsulphanilamidobenzonitriles, prepared from *N*-acetylsulphanilyl chloride and *m*- or *p*-aminobenzonitrile, can also be preferentially hydrolysed at the acetyl group; further hydrolysis of the resulting *sulphanilamidobenzonitrile* (II) with 95 per cent. sulphuric acid or with alkaline hydrogen peroxide provides an alternative route to the 3- and 4-sulphanilamidobenzamides.

EXPERIMENTAL.

The compounds described were in most cases purified by recrystallisation from ethanol, using the simple extractor devised by Clarke and Kirner (*Org. Synth.*, Coll. Vol. I, 1941, 375); this made possible the use of small quantities of solvent, even though many of the substances were of low solubility in ethanol. All m. p.s are corrected. Two or more m. p.s quoted for one compound indicate the existence of polymorphic forms; fusion of the less stable form was followed by resolidification and subsequent melting at the higher temperature.

The Action of Alkylamines on Ethyl 4-Sulphanilamidobenzoate.—(a) *Methylamine.* The ester (7 g.) was heated in an autoclave with 25% aqueous methylamine solution (30 c.c.) at 150° for 6 hours. The liquid was filtered through charcoal and made just acid to phenolphthalein, which brought about the separation of 4-*sulphanilamido*-N-*methylbenzamide* (2·1 g., 31%). Reprecipitation from ammonia followed by recrystallisation gave a crystalline powder, m. p. 236—237° (Found: N, 13·8. $C_{14}H_{15}O_3N_3S$ requires N, 13·8%). 4-Sulphanilamidobenzoic acid (60%) was obtained on making the filtrate just acid to Congo-red. A small yield of the methylamide was also obtained by heating 4-sulphanilamidobenzamide with 33% aqueous methylamine solution for 8 hours at 175°, but the conversion was not complete.

(b) *Ethylamine.* The ester (20 g.) heated in an autoclave with 33% aqueous ethylamine solution (45 c.c.) at 160—170° for 5 hours gave 4-*sulphanilamido*-N-*ethylbenzamide* (1·7 g., 8%) which, after recrystallisation, had m. p. 227·5° (Found: S, 10·1. $C_{15}H_{17}O_3N_3S$ requires S, 10·1%). The mother-liquor contained 4-sulphanilamidobenzoic acid (13·7 g., 76%).

(c) n-*Propylamine.* The ester (9 g.) heated with *n*-propylamine (7·5 c.c.) and water (7·5 c.c.) for 5 hours at 170—180° gave on neutralisation 0·82 g. of a mixture containing some unchanged ester. Fractional crystallisation and precipitation from ammonia gave a substance (0·11 g.), m. p. 242°, raised by authentic propylamide (see below). The original filtrate yielded 4-sulphanilamidobenzoic acid (5·45 g., 67%).

(d) n-*Butylamine*. The ester (5 g.) was heated with *n*-butylamine (5·5 c.c.) and water (5·5 c.c.) for 4 hours at 180°. On making the solution just acid to phenolphthalein, unchanged ester (3·5 g., 70%) was recovered. On acidification of the filtrate the acid (1·1 g., 24%) was obtained.

(e) *Dimethylamine*. The ester (1 g.) placed in a glass tube with 33% aqueous dimethylamine solution (10 c.c.) was heated in an autoclave for 6 hours at 160°. The solution, when acid to Congo-red, precipitated 4-sulphanilamidobenzoic acid (0·73 g., 88%).

(f) *Diethylamine*. The ester (6·4 g., 0·02 mol.) heated in a sealed tube with 40% aqueous diethylamine solution (14·6 c.c., 0·08 mol.) at 180—190° for 6 hours gave unchanged ester (0·73 g., 11%) and 4-sulphanilamidobenzoic acid (4·95 g., 85%). The diethylamine was recovered quantitatively from the mother-liquor as the benzenesulphonyl derivative, and no tertiary base could be detected. Ethanol was present in the final filtrate. The reaction was therefore a simple alkaline hydrolysis.

The Preparation of Substituted p-*Aminobenzamides*.—The *p*-amino-*N*-methyl-, -*N*-ethyl-, -*N*-propyl-, -*N*-butyl-, -*NN*-dimethyl-, -*NN*-diethyl-, and -*NN*-pentamethylene-benzamide were prepared by the method of Wenker (*J. Amer. Chem. Soc.*, 1938, **60**, 1081). The same procedure was applied to the preparation of *p*-amino-*N*-benzylbenzamide (cf. Dermer and King, *J. Org. Chem.*, 1943, **8**, 168) and *p*-amino-*N*-phenylbenzamide (cf. Rivier and Kunz, *Helv. Chim. Acta*, 1932, **15**, 377).

The Coupling of Substituted p-*Aminobenzamides with* N-*Acetylsulphanilyl Chloride*.—The acid chloride (1·1 mol.) was added to a solution of the appropriate compound (1 mol.) dissolved in dry pyridine. After standing on the water-bath for 30 minutes the excess of pyridine was removed under reduced pressure and the residue was shaken with 10% hydrochloric acid. The crude N^4-*acetyl* derivatives were obtained in yields amounting to 90% of the theoretical. The melting points and analyses obtained after recrystallisation are recorded in the table.

When this procedure was applied to *m*- and *p*-aminobenzamide, the compounds N^4-acetyl-3-sulphanilamidobenzamide and N^4-acetyl-4-sulphanilamidobenzamide (cf. Part I) were obtained (cf. also B.P. 486,421).

Compound.	M. p.	Formula.	Found (%).	Required (%).
N^4-*Acetyl*-4-*sulphanilamido*-N-*methylbenzamide*	301°	$C_{16}H_{17}O_4N_3S$	N, 12·2	N, 12·1
,, ,, -N-*ethylbenzamide*	237—238 *	$C_{17}H_{19}O_4N_3S$	N, 11·7	N, 11·6
,, ,, -N-n-*propylbenzamide*	259—260	$C_{18}H_{21}O_4N_3S$	N, 11·2	N, 11·2
,, ,, -N-n-*butylbenzamide*	291—292	$C_{19}H_{23}O_4N_3S$	N, 11·1	N, 10·8
,, ,, -NN-*dimethylbenzamide*	165—166 207—208 231—232	$C_{17}H_{19}O_4N_3S$	N, 11·8	N, 11·6
,, ,, -NN-*diethylbenzamide*	222 243—244	$C_{19}H_{23}O_4N_3S$	N, 10·6	N, 10·8
,, ,, -N-*benzylbenzamide*	300 (decomp.)	$C_{22}H_{21}O_4N_3S$	N, 10·2	N, 9·9
,, ,, -N-*phenylbenzamide*	246—247 270	$C_{21}H_{19}O_4N_3S$	N, 10·2 S, 7·8	N, 10·3 S, 7·8
,, ,, -NN-*pentamethylenebenzamide*	239·5—241	$C_{20}H_{23}O_4N_3S$	N, 10·5 S, 8·2	N, 10·5 S, 8·0
Monohydrate of last compound	159—160 †	$C_{20}H_{25}O_5N_3S$	N, 10·1 S, 7·8	N, 10·0 S, 7·6

* The melt clarified at 244°.

† By crystallisation from aqueous ethanol; it lost water on melting and resolidified as the anhydrous compound.

Hydrolysis of the Acetyl Compounds.—These were refluxed with strong acid until most of the solid had passed into solution; the hot acid liquid was then filtered through glass-wool, cooled by addition of ice and made just alkaline to litmus. The liberated amides were in some cases dissolved in ammonia, filtered through charcoal and reprecipitated, in order to remove coloured impurities before the final recrystallisation from ethanol. The acid concentrations employed in the hydrolysis and the time of heating were capable of considerable variation; in the following examples the figures quoted do not necessarily represent optimum conditions. The volume of acid used was limited to 10 c.c. for each gram of acetyl derivative. The attempted hydrolysis of N^4-acetyl-4-sulphanilamido-*NN*-diethylbenzamide led to the formation of resinous products; in the other cases hydrolysis proceeded mainly at the acetyl group although some 4-sulphanilamidobenzoic acid could usually be isolated from the mother liquor.

4-*Sulphanilamido*-N-*methylbenzamide*.—Refluxing the acetyl compound with 50% sulphuric acid for 30 minutes gave a 66% yield of the methylamide, m. p. 236—237°, identical with the substance described above.

4-*Sulphanilamido*-N-*ethylbenzamide*.—With 50% sulphuric acid, the acetyl derivative gave a 74% yield of ethylamide, m. p. 227·5°, identical with the substance previously described.

4-*Sulphanilamido*-N-n-*propylbenzamide*.—After refluxing with 50% sulphuric acid for 10 minutes, 12% of the acetyl compound remained undissolved; from the solution was obtained an 81% yield of the n-*propylamide*, small rods, m. p. 253—254° (Found : N, 12·7; S, 9·9. $C_{16}H_{19}O_3N_3S$ requires N, 12·6; S, 9·6%).

4-*Sulphanilamido*-N-n-*butylbenzamide*.—The acetyl derivative (78%) was recovered unchanged after refluxing with 50% sulphuric acid for 15 minutes. The action of 65% sulphuric acid, however, brought about complete hydrolysis of the acetyl group in 10 minutes. The *butylamide* crystallised as flattened needles, m. p. 183—184° and 199—200° (Found : N, 12·1; S, 9·1. $C_{17}H_{21}O_3N_3S$ requires N, 12·1; S, 9·2%).

4-*Sulphanilamido*-NN-*dimethylbenzamide*.—Hydrolysis of the acetyl compound with 50% sulphuric acid for 2 minutes, or with hydrochloric acid (*d* 1·2) for 10 minutes gave a 90% yield of the *dimethylamide*, prisms, m. p. 253—254° (Found : N, 13·3; S, 9·9. $C_{15}H_{17}O_3N_3S$ requires N, 13·2; S, 10·1%).

4-*Sulphanilamido*-N-*benzylbenzamide*.—Hydrolysis of the acetyl compound with 65% sulphuric acid for 30 minutes gave a low yield of the *benzylamide*, leaflets, m. p. 188—189° (Found : N, 11·1; S, 8·4. $C_{20}H_{19}O_3N_3S$ requires N, 11·0; S, 8·4%).

4-*Sulphanilamido*-NN-*pentamethylenebenzamide*.—Hydrolysis of the acetyl derivative with 50% sulphuric acid for 20 minutes gave a 28% yield of the *pentamethyleneamide*, prismatic needles, m. p. 204—205° (Found : N, 11·7; S, 9·2. $C_{18}H_{21}O_3N_3S$ requires N, 11·7; S, 8·9%).

4-*Sulphanilamido*-N-*phenylbenzamide*.—Hydrolysis of the acetyl compound with 65% sulphuric acid for 20 minutes gave a 44% yield of the *phenylamide*, microcrystalline powder, m. p. 275° (Found : N, 11·6; S, 8·6. $C_{19}H_{17}O_3N_3S$ requires N, 11·4; S, 8·7%).

4-*Sulphanilamidobenzamide*.—N^4-Acetyl-4-sulphanilamidobenzamide, boiled with 50% sulphuric acid until solution was complete, gave an 80% yield of the amide.

3-*Sulphanilamidobenzamide.*—N^4-Acetyl-3-sulphanilamidobenzamide passed into solution and gave a 72% yield of amide on boiling for one minute with 50% sulphuric acid.

2-*Sulphanilamidobenzamide.*—N^4-Acetyl-2-sulphanilamidobenzamide (Part I) boiled with 50% sulphuric acid for 12 minutes gave a 76% yield of the amide.

4-*Sulphanilamidobenzonitrile.*—*p*-Aminobenzonitrile (1·2 g.) in pyridine (15 c.c.) was treated with *N*-acetylsulphanilyl chloride (2·34 g.) and left for 30 minutes on the water bath. On removing the excess of pyridine and acidifying, N^4-acetyl-4-sulphanilamidobenzonitrile (2·68 g., 85%) (cf. Part I) was obtained. This was hydrolysed with 50% sulphuric acid (25 c.c.) by refluxing for 30 minutes. 4-*Sulphanilamidobenzonitrile* (1·92 g., 82%) was recrystallised from aqueous ethanol to give laminæ, m. p. 178—179·5° (Found: N, 15·4; S, 11·5. $C_{13}H_{11}O_2N_3S$ requires N, 15·4; S, 11·7%).

3-*Sulphanilamidobenzonitrile.*—From *m*-aminobenzonitrile was similarly obtained an 80% yield of N^4-*acetyl*-3-*sulphanilamidobenzonitrile*, m. p. 241° (softening at 232°) (Found: N, 13·6. $C_{15}H_{13}O_3N_3S$ requires N, 13·3%) (B.P. 486,421/1938 gives m. p. 236° for a compound prepared by a similar method). The acetyl compound (6·5 g.), boiled with 50% sulphuric acid (65 c.c.) for 12 minutes gave, in addition to unchanged substance (2·3 g.), 3-*sulphanilamidobenzonitrile* (2·75 g.) crystallising in needles, m. p. 190—191° (Found: N, 15·6; S, 11·6. $C_{13}H_{11}O_2N_3S$ requires N, 15·4; S, 11·7%).

Partial Hydrolysis of the Sulphanilamidobenzonitriles.—3-Sulphanilamidobenzonitrile (1 g.) dissolved readily in 95% sulphuric acid (4 c.c.). After keeping for 18 hours at room temperature the solution was poured into ice-water and made just alkaline to litmus; 3-sulphanilamidobenzamide (0·84 g., 79%) separated in a pure state. A less pure product (0·94 g., 88%) was obtained by treating the nitrile (1 g.) in 10% sodium carbonate solution (10 c.c.) with hydrogen peroxide solution (100 vols., 10 c.c.) and leaving to stand.

4-Sulphanilamidobenzonitrile reacted normally with 95% sulphuric acid to give 4-sulphanilamidobenzamide, although the nitrile was sparingly soluble in the acid. A homogeneous reaction mixture was readily obtained by dissolving the nitrile in a little acetic acid, but the heat evolved on mixing the acetic acid solution with the sulphuric acid tended to produce acetylation unless careful cooling was applied. The nitrile was similarly converted to the amide by hydrogen peroxide under the above conditions.

4-*Sulphanilamido*-NN-*dimethylbenzamide with Dimethylamine.*—An experiment has been previously described in which ethyl 4-sulphanilamidobenzoate was heated with aqueous dimethylamine solution in an autoclave. In another glass tube in the same autoclave was contained a solution of the dimethylamide (1 g.) similarly dissolved in the amine solution (10 c.c.). From this tube unchanged dimethylamide (0·954 g.) was recovered after heating under the previously described conditions.

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