

190. Sulphonamides. Part I. The Action of Ammonia on Sulphanilamidobenzoic Esters in the Light of the General Theory of Ester Ammonolysis.

By JOHN H. GORVIN.

The three isomeric sulphanilamidobenzoic acids have been studied by several groups of workers (cf. Northey, *Chem. Reviews*, 1940, **27**, 85; Marchant, Lucas, and McClelland, *Canadian J. Res.*, 1942, **20 B**, 5), and are reported to show little bacteriostatic activity. The *amides* (as I) derived from these acids are of interest as intestinal antiseptics in the chemotherapy of bacillary dysentery, as they resemble sulphanilylguanidine and succinylsulphathiazole in being poorly absorbed from the gut (Brownlee, Green, Tonkin, and Woodbine, *unpublished results*). In this investigation the preparation of the amides by the action of ammonia on the corresponding esters was studied (cf. B.P. 562,349). In order to explain the low rate of reaction at room temperature the general behaviour of substituted ethyl benzoates towards aqueous ammonia was also explored; the results are of interest in connection with the mechanism of formation of amides from esters.

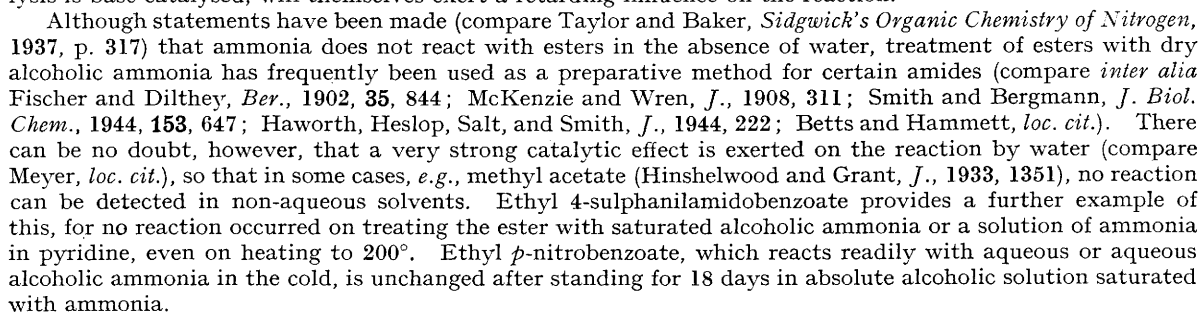
THE ethyl esters of the 2-, 3-, and 4-sulphanilamidobenzoic acids (compare Marchant *et al.*, *loc. cit.*) are very resistant to the action of aqueous ammonia in the cold, but good yields of the corresponding *sulphanilamidobenzenamides* (I represents the 4-isomer) are obtained by heating the esters for several hours with concentrated ammonia at 150°. The low reactivity at room temperature is illustrated by the case of ethyl 3-sulphanilamidobenzoate, which, although immediately soluble in cold aqueous ammonia, has reacted only to the extent of about 70 per cent. after five days. The *methyl* ester, in spite of its lower solubility in ammonia, reacts almost completely under the same conditions, which supports the general conclusion of Meyer (*Monatsh.*, 1906, **27**, 42) that methyl esters react more rapidly than the ethyl analogues (compare also Morrell, *J.*, 1914, 2701; French and Wrightsman, *J. Amer. Chem. Soc.*, 1938, **60**, 50). The ethyl esters of the 2- and 4-sulphanilamidobenzoic acids, and even the *methyl* ester of the 4-acid, react with aqueous ammonia in the cold considerably more slowly than does ethyl 3-sulphanilamidobenzoate.

According to Branch and Calvin (*The Theory of Organic Chemistry*, 1941, p. 415; compare also Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 690), the reaction of an ester with aqueous ammonia is an example of generalized base catalysis, and it may therefore be represented by a mechanism similar to that suggested for the alkaline hydrolysis of esters (compare Watson, *Modern Theories of Organic Chemistry*, 1941, p. 125). This representation of the mechanism corresponds with the earlier viewpoint of Meyer (*loc. cit.*, p. 35), who observed that amide formation takes place most readily in the case of esters derived from such strong acids as trichloroacetic, but tends to proceed slowly in the case of esters of weak acids, *e.g.*, trimethylacetic. Kinetic studies carried out in development of these ideas have been conducted in liquid ammonia (cf. Fernelius and Bowman, *Chem. Reviews*, 1940, **26**, 23) or in alcoholic ammonia (Betts and Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 1568); the results obtained indicate that in these solvents a given series of esters will show variations of reactivity towards ammonia tending in the same direction as the variations of reactivity in alkaline hydrolysis.

Aqueous ammonia, although a most useful preparative reagent for amides, is not suitable for accurate kinetic studies owing to the complicating factors introduced by the low solubility of the ester. It has been found, however, that the substituted ethyl benzoates show sufficient variation in reactivity towards aqueous ammonia for a semi-quantitative study to give results of some significance. These indicate that the effect of substituents on the reactivity of ethyl benzoate at 18° is in the order: $p\text{-NO}_2 > m\text{-NO}_2 > \text{H}, m\text{-NH}_2 > p\text{-CH}_3 > p\text{-OCH}_3, p\text{-NH}_2, p\text{-OH}$, in agreement with the corresponding order obtained for alkaline hydrolysis (Kindler, *Annalen*, 1926, **450**, 1; 1927, **452**, 90; Ingold and Nathan, *J.*, 1936, 222; Evans, Gordon and Watson, *J.*, 1937, 1430; Tommila and Hinshelwood, *J.*, 1938, 1801; Westheimer, *J. Amer. Chem. Soc.*, 1940, **62**, 1892). An essentially similar order of reactivity is found in solutions of aqueous ammonia diluted with alcohol to increase the solubility of the esters.

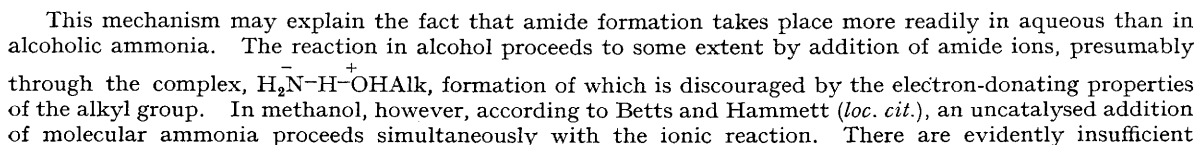
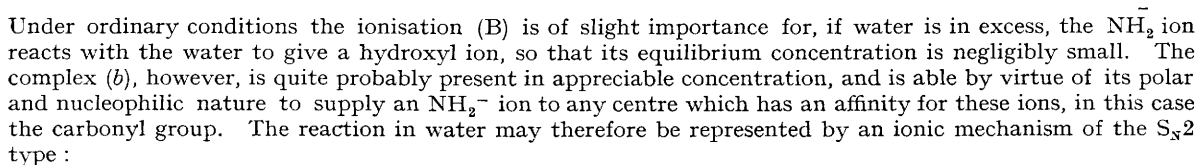
In the most highly resistant group of compounds studied, ethyl 4-sulphanilamidobenzoate reacts with aqueous ammonia rather more readily than either ethyl *p*-amino- or ethyl *p*-hydroxy-benzoate. The apparent high stability of ethyl *p*-aminobenzoate may possibly be due to its insolubility, as it appears to be relatively more reactive in alcoholic aqueous ammonia. Ethyl *p*-hydroxybenzoate, however, is completely soluble in ammonia, and ethyl 4-sulphanilamidobenzoate is soluble to a considerable extent, so the principal cause of the

slight extent. Ethyl 3-sulphanilamidobenzoate, dissolved in cold aqueous ammonia, reacts more slowly than ethyl *m*-aminobenzoate kept under the same conditions as an oily emulsion. The negative charge is unable to exert its full stabilising effects in the *m*-position, but it does appear to confer an appreciable degree of extra stability to the carbethoxy group. Nothing can be concluded about the magnitude of this effect from the available data, however as the two cases under discussion are not strictly comparable; the sulphonamide solution contains an equivalent concentration of ammonium ions which, on the assumption that the ammonolysis is base-catalysed, will themselves exert a retarding influence on the reaction.

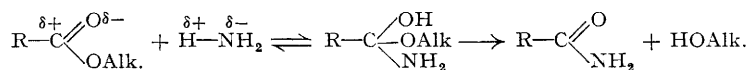


The solvolysis of esters in liquid ammonia and in amines has been shown to be acid-catalysed (by "onium" ions) (Fellinger and Audrieth, *J. Amer. Chem. Soc.*, 1938, **60**, 579; Audrieth and Kleinberg, *J. Org. Chem.*, 1938, **3**, 312). As a result of studies on the solvolysis of esters in *n*-butylamine, Glasoe, Scott, and Audrieth (*J. Amer. Chem. Soc.*, 1941, **63**, 2965) conclude that the accelerating effect of water on reactions of this type is due to the increase in concentration of the catalytically active "onium ions." There seems to be no real evidence, however, that this explanation holds for systems in which the molar ratio of water to amine is high. Ammonolysis of phenylacetic esters in methanol is retarded by ammonium ions (Betts and Hammett, *loc. cit.*), and has been shown to be partly a base-catalysed reaction: it therefore seems permissible in the absence of further evidence to accept the contention of Branch and Calvin (*op. cit.*) that the reaction of esters with amines in an aqueous medium is also base-catalysed. The progressively accelerating effect of water on the solvolysis studied by Glasoe, Scott, and Audrieth may very well involve a change from an acid- to a base-catalysis.

If the interaction of ammonia molecules with water is considered, it appears that aqueous ammonia must contain a variety of unstable hydrogen-bonded complexes of which the types (a) and (b) represent the simplest forms :



amide ions available to control the reaction completely, so that some part is played by the more sluggish molecular process:



Moreover, in alkaline hydrolysis it is generally assumed that the intervention of a water molecule is necessary for the removal of the alkoxy group, possibly according to the mechanism suggested by Lowry (see Waters, *Physical Aspects of Organic Chemistry*, 1942, Chap. 12), in which the required proton is supplied by the water molecule (see also Watson, *Trans. Faraday Soc.*, 1941, **37**, 712). The lower proton-donating ability of the alcohol molecules (Danner, *J. Amer. Chem. Soc.*, 1922, **44**, 2832; Faulkner and Lowry, *J.*, 1926, 1938) would partly account for the sluggishness of ammonolysis in alcoholic solution, assuming that a similar mechanism is involved.

It is not improbable that the molecular process is also involved in the reaction occurring in aqueous ammonia. As Hughes and Ingold have pointed out (*J.*, 1935, 252), this type of mechanism is facilitated by ionising solvents owing to the stabilisation of fractional charges in the transition state of the reaction; attack by a neutral ammonia molecule would thus proceed more readily in water than in a non-aqueous solvent, although not so readily as attack by an amide ion.

EXPERIMENTAL.

(Melting points are corrected.)

Esterification of the Sulphanilamidobenzoic Acids.—The 2-, 3-, and 4-sulphanilamidobenzoic acids were prepared by the action of *N*-acetylsulphanil chloride on the appropriate aminobenzoic acid (Koloff, *J. Amer. Chem. Soc.*, 1938, **60**, 950), the acetyl group being subsequently removed by alkaline hydrolysis (Crossley, *ibid.*, 2217). The acids (25 g.) were esterified by refluxing for at least 5 hours with concentrated sulphuric acid (25 c.c.) and alcohol (100 c.c.); the solutions were poured into a mixture of ice and 10% sodium hydroxide solution (320 c.c.), and made just alkaline with sodium carbonate to give the esters in almost quantitative yield. Ethyl 4-sulphanilamidobenzoate was also obtained by the esterification of *N*⁴-acetyl-4-sulphanilamidobenzoic acid, the acetyl group being removed in the process.

The following esters were prepared: methyl 3-sulphanilamidobenzoate, crystals from methanol, m. p. 165–166° (Found: N, 9.3; S, 10.5. $\text{C}_{14}\text{H}_{13}\text{O}_4\text{N}_3\text{S}$ requires N, 9.2; S, 10.5%); methyl 4-sulphanilamidobenzoate, crystals from methanol, m. p. 235–236° (Found: S, 10.7%); ethyl 2-sulphanilamidobenzoate, prisms from ethanol, m. p. 168.5° (Marchant *et al.*, *loc. cit.*, gave m. p. 165.5°); ethyl 3-sulphanilamidobenzoate, plates from ethanol, m. p. 106.5–107.5°, resolidifying and melting again at 153° (Marchant *et al.* gave m. p. 105°) (Found: S, 10.0. Calc.: S, 10.0%); ethyl 4-sulphanilamidobenzoate, thin plates from a large volume of ethanol, m. p. 243° (softening at 237°) (Marchant *et al.* gave m. p. 235°).

4-Sulphanilamidobenzamide (I).—Ethyl 4-sulphanilamidobenzoate (42.5 g.) was heated with aqueous ammonia (300 c.c., *d* 0.880) in an autoclave for 5 hours at 150°, the pressure rising to 200 lbs./sq. in. After cooling, the contents of the autoclave were mixed with charcoal and filtered. Sulphuric acid (50%) was added to the ice-cooled liquid until the mixture was no longer alkaline to phenolphthalein, but remained alkaline to litmus. Filtration gave 4-sulphanilamidobenzamide (26 g., 67%). The mother-liquor gave 4-sulphanilamidobenzoic acid (9.1 g., 31%) on making the filtrate just acid to Congo-red. The amide was purified by reprecipitation from ammonia, followed by recrystallisation from ethanol to give thin plates, m. p. 201–202° (Found: N, 14.5; S, 10.9. $\text{C}_{13}\text{H}_{13}\text{O}_3\text{N}_3\text{S}$ requires N, 14.4; S, 11.0%).

3-Sulphanilamidobenzamide. (a) Ethyl 3-sulphanilamidobenzoate (120 g.) was heated in an autoclave for 5 hours at 150° with aqueous ammonia (900 c.c., *d* 0.880). Proceeding as described above 3-sulphanilamidobenzamide (79 g., 72%) was obtained together with 3-sulphanilamidobenzoic acid (22.5 g., 21%). The amide was reprecipitated from ammonia and recrystallised from a large volume of ethanol to give needles, m. p. 217–218° (Found: N, 14.4; S, 10.9. $\text{C}_{13}\text{H}_{13}\text{O}_3\text{N}_3\text{S}$ requires N, 14.4; S, 11.0%). (b) Methyl 3-sulphanilamidobenzoate (1.0 g.) was treated with ammonia (4.0 c.c., *d* 0.885) and left at 20° in a closed tube. The solid gradually went into solution, and after 5 days the clear liquid was neutralised, giving 3-sulphanilamidobenzamide (0.88 g., 93%). The ethyl ester, which was immediately soluble in ammonia, reacted in the same way but complete conversion to the amide required about 8 days at room temperature.

2-Sulphanilamidobenzamide.—Ethyl 2-sulphanilamidobenzoate (35 g.) was heated with aqueous ammonia (300 c.c., *d* 0.880) in an autoclave for 3 hours at 150°. On making the solution neutral to phenolphthalein there was obtained 2-sulphanilamidobenzamide (24 g., 75%), and acidification of the mother-liquors gave 2-sulphanilamidobenzoic acid (4.3 g., 13%). The amide was purified by reprecipitation from ammonia and by recrystallisation from aqueous ethanol or benzene; it was obtained in thin plates, m. p. 175–176° (Found: C, 53.6; H, 4.6; S, 10.8. $\text{C}_{13}\text{H}_{13}\text{O}_3\text{N}_3\text{S}$ requires C, 53.6; H, 4.5; S, 11.0%). Ethyl 2-sulphanilamidobenzoate did not react appreciably on standing with ammonia solution for a week at room temperature.

The Reactivity of Substituted Ethyl Benzoates towards Ammonia.—(a) *Reaction in aqueous ammonia.* The tests were carried out at 18° in sealed glass test-tubes, using 0.005 mol. of the ester and aqueous ammonia (10 c.c., *d* 0.885). Slight variations in ammonia concentration may have occurred between the various groups of tests, but in any single group the molar concentration of reactants was constant. The esters, purified by recrystallisation or distillation, were present as finely powdered solids or as oily emulsions, with the exception of ethyl 3-sulphanilamidobenzoate and ethyl *p*-hydroxybenzoate, which were soluble in the reacting solution. Agitation was not continuous, but each member of a group received the same treatment throughout. At the end of the tests, the ammonia was removed by neutralisation or under reduced pressure, and the reaction products separated by taking advantage of their relative solubilities. The esters were soluble in ligroin (b. p. 40–60°) or in chloroform but the amides, in general, were insoluble in these solvents. The sulphonamides were separated in weakly alkaline solution, in which only the amides were soluble. As far as possible the results in Table I were arrived at by determining the unreacted ester; when practical considerations made it more convenient to determine the amount of amide formed, results are given in terms of a minimum degree of reactivity. It appeared that the tendency towards formation of the carboxylic acid is very slight in the aromatic series in the cold; amide formation is certainly the predominating reaction among the more reactive members of the series.

(b) *Reaction in aqueous alcoholic ammonia.* Similar tests were performed (Table II), using a mixture of aqueous ammonia (5 c.c., *d* 0.885) and ethanol (5 c.c.) for the same weight of ester (0.005 mol.). This mixture dissolved most of the esters completely. Ethyl *p*- and *m*-nitrobenzoate were, however, only partially soluble, and ethyl 4-sulphanilamidobenzoate, which is almost insoluble in cold alcohol, dissolved to such a slight extent that this may explain its unexpectedly low reactivity.

TABLE I.

Group.	Ester.	Time (days).	Extent of reaction, %.
1	Ethyl <i>p</i> -nitrobenzoate	0.25	27
	" <i>m</i> -nitrobenzoate	0.25	22
2	" <i>p</i> -nitrobenzoate	2.0	87
	" <i>m</i> -nitrobenzoate	3.0	82
	" benzoate	7.9	< 75
	" <i>m</i> -aminobenzoate	7.9	100
	" 3-sulphanilamidobenzoate	7.9	100
	" <i>p</i> -toluate	29	< 47
	" <i>p</i> -hydroxybenzoate	29	20
	" <i>p</i> -aminobenzoate	29	15
	" 4-sulphanilamidobenzoate	5.1	45
3	Ethyl 4-sulphanilamidobenzoate	29	27
	" anisate	29	< 26
	" <i>p</i> -hydroxybenzoate	29	19
	" <i>p</i> -aminobenzoate	29	15
	" 3-sulphanilamidobenzoate	5.0	72
4	" <i>m</i> -aminobenzoate	5.0	88
	" <i>m</i> -aminobenzoate	7.0	97

TABLE II.

Ester.	Time (days).	Extent of reaction, %.
Ethyl <i>p</i> -nitrobenzoate	1.0	60
" <i>m</i> -nitrobenzoate	1.0	44
" <i>m</i> -aminobenzoate	17	19
" 3-sulphanilamidobenzoate	17	24
" <i>p</i> -toluate	61	< 32
" anisate	61	< 10
" <i>p</i> -aminobenzoate	61	16
" <i>p</i> -hydroxybenzoate	61	8.5
" 4-sulphanilamidobenzoate	61	4.0

(c) *Reaction in anhydrous solvents.* Ethyl *p*-nitrobenzoate (1.95 g.) was dissolved in a saturated solution of dry ammonia in absolute ethanol (20 c.c.) and kept in a sealed vessel for 18 days at room temperature. On evaporation of excess of solvent and dilution with water, the ester was recovered quantitatively in an unchanged state.

Ethyl 4-sulphanilamidobenzoate (5 g.) was heated in an autoclave for 6 hours with a saturated solution of dry ammonia gas in ethanol (100 c.c.). The temperature rose to 200°, and the pressure to 350–450 lbs./sq. in. After cooling and removing the alcoholic ammonia under reduced pressure, the ester was recovered unchanged. Similarly, no reaction was detected when the ester (7 g.) was heated for 6 hours at 210° with pyridine (50 c.c.) saturated with dry ammonia.

Acetylation of the Sulphanilamidobenzenamides.—Experiments were carried out to obtain acetyl derivatives for pharmacological study. Direct acetylation of the amide under mild conditions was effective; more strenuous acetylation tended to dehydrate the amide group. Results are also recorded of attempts to obtain the desired product through the acetylated ester. Two of the following compounds, the preparation of which has been claimed in patent literature without proof of identity, are now recorded as new.

Action of Acetic Anhydride on 4-Sulphanilamidobenzenamide.—The amide (5.8 g.), dissolved in 10% sodium hydroxide solution (16 c.c.), was treated with acetic anhydride and sodium hydroxide by alternate additions. Final acidification gave *N*⁴-acetyl-4-sulphanilamidobenzenamide (5.4 g.), which, after recrystallisation from a large volume of ethanol, had m. p. 286° (decomp.) (Found: N, 12.7; S, 9.7. $C_{15}H_{15}O_4N_3S$ requires N, 12.6; S, 9.6%) (B.P. 486.421/1938 gives m. p. 255°). When the amide (2 g.) was refluxed for 1½ hours with acetic anhydride (20 c.c.), evaporation of excess solvent and neutralisation with sodium hydroxide gave *N*⁴-acetyl-4-sulphanilamidobenzenitrile, which, when recrystallised from ethanol, had m. p. 252–253° (Found: C, 57.2; H, 4.0; N, 13.3; S, 10.2. $C_{15}H_{13}O_3N_3S$ requires C, 57.1; H, 4.2; N, 13.3; S, 10.2%).

Acetylation of Ethyl 4-Sulphanilamidobenzoate.—The ester (10 g.) was refluxed with acetic anhydride (100 c.c.) for 1 hour. Evaporation of excess solvent and neutralisation gave ethyl *N*⁴-diacetyl-4-sulphanilamidobenzoate (11.7 g., 92%), which, after recrystallisation from ethanol, had m. p. 202° (Found: C, 56.4; H, 4.9; S, 7.6. $C_{19}H_{20}O_6N_2S$ requires C, 56.4; H, 5.0; S, 7.9%).

When heated with aqueous ammonia (*d* 0.880) in an autoclave for 3 hours at 150°, the diacetyl ester gave ethyl *N*⁴-acetyl-4-sulphanilamidobenzoate (52%), which crystallised from aqueous ethanol in needles, m. p. 223° (Found: N, 7.8; S, 8.6. $C_{17}H_{18}O_5N_2S$ requires N, 7.7; S, 8.9%) (B.P. 486.421/1938 gives m. p. 220°). From the mother-liquor of the reaction *N*⁴-acetyl-4-sulphanilamidobenzoic acid was obtained. When heated with aqueous ammonia (*d* 0.880) in an autoclave for 20 hours at 150°, the reaction products were 4-sulphanilamidobenzenamide (40%) and 4-sulphanilamidobenzoic acid (56%).

Acetylation of 3-Sulphanilamidobenzenamide.—The amide (5.8 g.) was acetylated in the manner previously described for the 4-amide, giving *N*⁴-acetyl-3-sulphanilamidobenzenamide (4.5 g., 68%). After recrystallisation from ethanol, it had m. p. 222–223° (Found: N, 12.7. $C_{15}H_{15}O_4N_3S$ requires N, 12.6%).

Acetylation of Ethyl 2-Sulphanilamidobenzoate.—The ester (16 g.) was refluxed with acetic anhydride (160 c.c.) for 20 minutes. After concentration and neutralisation, the crude product was recrystallised from ethanol to give ethyl *N*⁴-diacetyl-2-sulphanilamidobenzoate (10.8 g., 54%), m. p. 199° (Found: C, 56.2; H, 4.9; N, 7.1. $C_{19}H_{20}O_6N_2S$ requires C, 56.4; H, 5.0; N, 6.9%). The diacetyl ester (10 g.) was heated with aqueous ammonia (80 c.c., *d* 0.880) for 2½ hours at 150° in an autoclave. On making neutral to phenolphthalein, there was obtained *N*⁴-acetyl-2-sulphanilamidobenzenamide (6.4 g., 78%). After recrystallisation from much ethanol it had m. p. 263° (decomp.) (Found: C, 54.0; H, 4.5; N, 12.5. $C_{15}H_{15}O_4N_3S$ requires C, 54.0; H, 4.5; N, 12.6%).

The author's thanks are due to Mr. D. T. Warren for experimental assistance, and to Messrs. A. Bennett and H. C. Clarke for the microanalyses.

WELLCOME LABORATORIES OF TROPICAL MEDICINE, LONDON, W.C.1.

[Received, July 4th, 1945.]