

### 35. Some Sulphonyl Derivatives of Amidines and Imino-ethers.

By H. J. BARBER.

Some sulphonyl derivatives of imino-ethers have been prepared and converted into the corresponding amidines, which can exist in two isomeric forms.

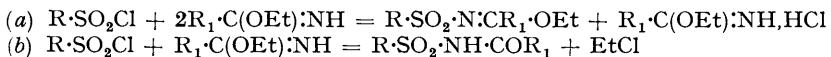
THE structure associated with the therapeutic activity of sulphonamides of heterocyclic derivatives such as sulphapyridine, sulphathiazole, and sulphadiazine is  $p\text{-NH}_2\text{C}_6\text{H}_4\text{SO}_2\text{NH}\cdot\text{C:N}\cdot$ . Sulphonyl derivatives of amidines have this structure with the sole difference that the second nitrogen atom is not a member of a heterocyclic system. Preliminary indications from the biological point of view were unfavourable, and this line of work was therefore not pursued far, being abandoned early in 1939 when these experiments were carried out. The recent patent of J. R. Geigy A.-G. (B.P. 538,822), which covers similar ground, now makes publication of these results desirable. Geigy claims the conversion of benzenesulphonyl acylamides and arylamides (I,  $\text{R} = \text{C}_6\text{H}_4\text{NO}_2$  or  $\text{C}_6\text{H}_4\text{NHAc}$ ) into the imino-chlorides (II), which give the amidines (III).



This type of reaction was discovered 83 years ago by Gerhardt, who described the preparation of  $N$ -benzenesulphonylbenzamidine (III;  $\text{R}, \text{R}_1 = \text{Ph}$ ) and  $N$ -*p*-toluenesulphonylbenzamidine (*Ann. Chim.*

*Phys.*, 1858, **53**, 303). Wolkowa (*Ber.*, 1872, **5**, 141) also prepared these compounds. In these laboratories, G. Newbery (unpublished communication) prepared 4-acetamidobenzenesulphonylbenzamidine (III; R = C<sub>6</sub>H<sub>4</sub>·NHAc, R<sub>1</sub> = Ph) by direct condensation of the sulphonyl chloride with the amidine at first in pyridine solution. Pyridine as a condensing agent was unsatisfactory and gave poor yields, presumably because amidines are generally much stronger bases than pyridine. Geigy, however, described this method. Aqueous sodium hydroxide gave excellent yields, acetone solutions or suspensions of the two reagents being used. Newbery also submitted his product to hydrolysis, mild conditions giving the sulphanilylbenzamide (I). (III; R = C<sub>6</sub>H<sub>4</sub>·NH<sub>2</sub>, R<sub>1</sub> = Ph) and more drastic treatment the sulphanilylbenzamide (I).

Sulphonyl imino-ethers of the type (IV) were obtained by condensation of sulphonyl chlorides with imino-ether bases. Again pyridine was not a satisfactory condensing agent, and the best method found was to employ two molecules of the imino-ether base. The reaction was not quite simple and, since the amide type (I) was also obtained, it is possible that the reaction may proceed in two directions, *viz.* :



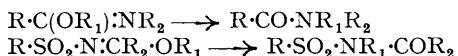
These sulphonyl imino-ethers reacted with ammonia to give the expected sulphonyl amidines, but in certain cases it was possible to isolate an unstable form of amidine which was very easily converted into the stable form identical with that obtained by condensation of the amidine and the sulphonyl chloride. It is suggested that the two forms may be represented by (III) (unstable) and R·SO<sub>2</sub>·NH·CR<sub>1</sub>·NH (V) (stable).

Isolation of isomeric pairs of amidines had hitherto only been achieved in cases where all the hydrogen atoms have been fully substituted (cf. Sidgwick, "Organic Chemistry of Nitrogen," p. 156) and some confirmation of the proposed structures was therefore sought.

Hydrolysis of the two forms might take place differently, (III) giving R·SO<sub>2</sub>·NH<sub>2</sub> + R<sub>1</sub>·CO·NH<sub>2</sub> and (V) giving R·SO<sub>2</sub>·NH·COR<sub>1</sub> + NH<sub>3</sub>. The ease with which the labile isomer passed into the stable form precluded definite conclusions being drawn, but, since some sulphonamide was usually formed from the labile amidine (III) whereas the stable form (V) was hydrolysed exclusively to the mixed amide (I), the evidence is in favour of the above interpretation of the isomerism.

The sulphonyl amidine (V; R = C<sub>6</sub>H<sub>4</sub>·NO<sub>2</sub>, R<sub>1</sub> = Ph) underwent a remarkably smooth decomposition on heating, sulphur dioxide being lost and 4-nitrophenylbenzamidine being formed. The isomeric form corresponding to (III) appeared to be less readily decomposed, but, as isomerisation to the stable form was probably proceeding rapidly at the somewhat high temperature of desulphoxylation, the distinction was not a sharp one. The sulphonyl imino-ether (IV; R = C<sub>6</sub>H<sub>4</sub>·NO<sub>2</sub>, R<sub>1</sub> = Ph) having a similar structure does not desulphoxylate in this way, but is extremely stable to heat.

It was thought that a rearrangement of sulphonyl imino-ethers similar to that investigated by Chapman (*J.*, 1925, **127**, 1992) might be induced :



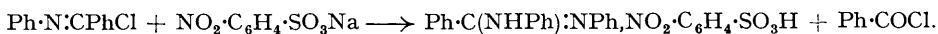
In the case of acetanilide-*p*-sulphonylbenzimino-ether (IV; R<sub>1</sub> = C<sub>6</sub>H<sub>4</sub>·NHAc, R<sub>1</sub> = Ph) a change occurred on melting, the original compound, m. p. 100—102°, being transformed into one, m. p. 136—137°, having different physical properties but reacting in the same way with ammonia as the lower-melting form. This is probably a case of dimorphism. Similar changes have not been observed with other sulphonyl imino-ethers and no suggestion of structural rearrangement was found experimentally with the different types examined.

Mumme and Hesse (*Ber.*, 1910, **43**, 889) have shown that imino-chlorides react with sodium salts of carboxylic acids to give imino-esters :



The analogous case for sulphonic acids is shown in the second scheme.

An attempt to realise the latter hypothetical reaction was made in the case where R = Ph, R<sub>1</sub> = Ph, and R<sub>2</sub> = C<sub>6</sub>H<sub>4</sub>·NO<sub>2</sub>. Under the conditions needed to promote reaction, more complex changes occurred; benzoyl chloride was evolved and the main product was the *p*-nitrobenzenesulphonate of *NN'*-diphenylbenzamidine :



Various compounds were prepared in endeavours to identify this product.

#### EXPERIMENTAL.

**4-Nitrobenzenesulphonyl Chloride.**—Technical *p*-nitrochlorobenzene (400 g.) was dissolved in boiling alcohol (1400 c.c.), and a solution of sodium disulphide, prepared by dissolving sulphur (21 g.) in molten hydrated sodium sulphide (80 g.), run in at such a rate as to maintain a vigorous reaction; the mixture was boiled for a further  $\frac{1}{2}$  hour. After cooling, the disulphide was washed with alcohol and with water and suspended in a mixture of acetic acid (1300 c.c.) and water (200 c.c.) in a deep 2 l. vessel, and a rapid stream of chlorine passed in. The temperature rose rapidly to about 75° and after about 1½ hours nearly complete solution was obtained. The hot solution was filtered and added to water (10 l.). The sulphonyl chloride solidified at once and was washed with water and dried in a vacuum. It then contained about 20% of 4 : 4'-dinitrodiphenyl sulphoxide and was used for certain preparations where this impurity could readily

be removed—*p*-nitrobenzenesulphonamide, for example. Crystallisation did not give an economical and complete purification. Distillation gave the pure sulphonyl chloride (268 g.), m. p. 79–80°, b. p. 143–144°/1·5 mm. This preparation was carried out repeatedly with success, but on one occasion spontaneous decomposition set in early in the course of distillation. This was attributed to the presence of *p*-nitrobenzenesulphenyl chloride occluded in the sulphonyl chloride and arising through incomplete oxidation at the chlorination stage. Appropriate precautions were always taken when carrying out this distillation.

**4-Nitrobenzenesulphonylbenzimino-ether.**—Benziminoethyl ether (75 g.) was added to a solution of 4-nitrobenzenesulphonyl chloride (55 g.) in dry acetone (150 c.c.) and left overnight at 30–35°. The benzimino-ether hydrochloride, which separated almost quantitatively, was removed, and the acetone solution evaporated to a syrup, which crystallised on addition of alcohol. The product, recrystallised from alcohol, formed slender prisms, m. p. 129–130°. Yield, 55–60% (Found : N, 8·5.  $C_{15}H_{14}O_5N_2S$  requires N, 8·4%).

**N-4-Nitrobenzenesulphonylbenzimidine** (B.P. 538, 822, p. 5).—(a) Benzamidine hydrochloride (1·9 g.), suspended in acetone (10 c.c.), was treated with sodium hydroxide (0·8 g.) in water (2 c.c.), a solution of 4-nitrobenzenesulphonyl chloride (2·2 g.) in acetone (10 c.c.) added, and the whole vigorously shaken for about 10 minutes. Water (100 c.c.) was then added and the required amidine crystallised (yield 2·7 g., 88%). It formed heavy diamond plates from alcohol, m. p. 179° (decomp.) (Found : N, 13·9.  $C_{15}H_{11}O_4N_2S$  requires N, 13·8%).

(b) 4-Nitrobenzenesulphonylbenzimino-ether (1·0 g.) was suspended in alcohol (50 c.c.), 6% alcoholic ammonia (20 c.c.) added, and the whole stirred. The solid rapidly dissolved and the product soon began to separate in clusters of small prisms. These were collected after about 5 minutes. If left longer, the much denser crystals of the other form began to appear and eventually the change was complete. It was conveniently followed on a microscope slide. The product first obtained had m. p. 159–165° after preliminary softening (Found : N, 13·8%). Recrystallisation from alcohol, if carried out rapidly, did not affect the m. p. or crystalline form, but prolonged boiling produced the higher-melting form. The most striking difference between the two isomers was the difference in the ease of decomposition. The isomer of lower m. p. decomposed only at 195–200°, whereas the isomer of higher m. p. decomposed rapidly at or immediately above its m. p.

**Action of Heat on N-4-Nitrobenzenesulphonylbenzimidine.**—0·4 G. was heated in a glycerol bath at 200° until evolution of sulphur dioxide had ceased. The product (0·3 g., 95%), which solidified on cooling, crystallised from alcohol in short, heavy, yellow prisms, m. p. 167–168°, having all the properties of an amidine (Found : N, 17·7.  $C_{12}H_{11}O_2N_3$  requires N, 17·4%).

**4-Acetamidobenzenesulphonylbenzimino-ether.**—Benzimino-ether hydrochloride (7·9 g.) was suspended in pyridine (20 c.c.), acetanilide-*p*-sulphonyl chloride (9·6 g.) added, and the mixture stirred at 70° until a clear solution was obtained. The product, which separated when poured into water (400 c.c.), crystallised from 50% alcohol in colourless short prisms, m. p. 100–102° (Found : N, 8·35.  $C_{17}H_{18}O_4N_2S$  requires N, 8·1%).

When the above product was kept at 110–120° for a few minutes, resolidification set in. The product after recrystallisation from alcohol then had m. p. 136–137° (Found : N, 8·35%). This form was less soluble in alcohol and crystallised in a much denser form than the form of lower m. p. It appeared to react more slowly with alcoholic ammonia.

**4-Acetamidobenzenesulphonylbenzimidine.**—*a*-Form. 4-Acetamidobenzenesulphonylbenzimino-ether, *a*- or *β*-form (1·0 g.), was suspended in alcohol (5 c.c.), and 10% ethyl alcoholic ammonia (1 c.c.) added. On stirring, the ether rapidly dissolved and the solution was at once cooled in ice. The product (0·5 g., 55%) separated in small prisms and was collected after a few minutes. This product melts at 180–185°, the behaviour varying considerably with the rate of heating. It is probable that isomerisation is proceeding during heating. If the substance is placed in the bath at 185–187°, it melts sharply to a clear liquid (Found : N, 13·3.  $C_{15}H_{15}O_3N_2S$  requires N, 13·5%).

This isomer can be recrystallised from alcohol or acetic acid without change of m. p., but is converted into the isomer of higher m. p. by alcoholic ammonia. The change from the light prismatic form to the heavy rhombic form can readily be followed.

The *β*-form, m. p. 208–210°, was obtained by more prolonged action of alcoholic ammonia as above. This was identical with the product obtained on condensation of acetanilide-*p*-sulphonyl chloride with benzamidine by G. Newbery, to whom I am indebted for samples and information.

**4-Aminobenzenesulphonylbenzimino-ether.**—4-Nitrobenzenesulphonylbenzimino-ether (3·3 g.), dissolved in acetone (60 c.c.), was reduced with hydrogen (at 2 atm. and room temperature) in presence of platinum oxide catalyst (0·1 g.). The theoretical uptake was usually obtained in about 15 minutes. After removal of catalyst and solvent the residue was crystallised from benzene (prisms) and then from alcohol. The yield from a number of such operations was 75%; m. p. 98° (Found : N, 9·3.  $C_{15}H_{16}O_3N_2S$  requires N, 9·2%).

**4-Aminobenzenesulphonylbenzimidine.**—Treatment of the imino-ether with alcoholic ammonia under conditions similar to those employed in the other cases gave an *α*-form, m. p. 155–160°. It melted incompletely if heated slowly, but melted completely if placed in a block at 170° or above (Found : N, 15·3.  $C_{13}H_{10}O_2N_3S$  requires N, 15·3%). The *β*-form, m. p. 205–207°, was identical with the product obtained by Newbery (Found : N, 15·0%).

**4-Nitrobenzenesulphonylacetimino-ether.**—Acetimino-ether (11 g.) was added to 4-nitrobenzenesulphonyl chloride (14 g.) dissolved in ether (60 c.c.), and the mixture kept overnight at about 25°. The acetimino-ether hydrochloride which separated (5 g.; calc., 7·8 g.) was removed, and the ethereal solution evaporated. The residue was recrystallised rapidly from alcohol (20 c.c.). Yield 5 g., m. p. 87–88° (Found : N, 10·4.  $C_{10}H_{12}O_5N_2S$  requires N, 10·3%). In an experiment where the reaction was carried out in boiling ether most of the product was 4-nitrobenzenesulphonacetamide, m. p. 194°.

**Interaction of N-Phenylbenzimino-chloride and Sodium 4-Nitrobenzenesulphonate.**—The imino-chloride (5 g.) and the sodium salt (6 g., dried at 115° to constant weight) were intimately mixed and heated gradually to 180°; benzoyl chloride then began to distil. After 1½ hours the mixture was cooled and lixiviated with a little water and ether. The NN'-diphenylbenzimidine *p*-nitrobenzenesulphonate, after crystallising twice from alcohol (short heavy prisms), had m. p. 240–241°. Yield 1·1 g. (Found : C, 63·1, 62·8; H, 4·4–4·5; N, 8·8.  $C_{25}H_{21}O_5N_3S$  requires C, 63·1; H, 4·5; N, 8·8%). On treatment with cold sodium hydroxide solution this substance yielded diphenylbenzimidine, m. p. 145–147°, undepressed by an authentic specimen.

**N-p-Nitrobenzenesulphonyl-o-phenylbenzimino-ether.**—4-Nitrobenzenesulphonylbenzimino-chloride (m. p. 164–165°. Geigy, loc. cit., gives m. p. 160–162°) (3·25 g.) was added to a solution of sodium hydroxide (0·5 g.) in phenol (5 g.) at 40°. Reaction was immediate and was completed by warming for 20 mins. at 100°. After cooling, the mixture was treated with water and made alkaline with sodium hydroxide. The crystalline product was collected, washed with water, and dried. Yield, 3·75 g. It formed short heavy prisms from acetone, m. p. 173–174° (Found : C, 60·0; H, 3·9; N, 7·35.  $C_{19}H_{14}O_5N_2S$  requires C, 59·7; H, 3·7; N, 7·3%). On heating at various temperatures no change of m. p. was observed. At 280–285° decomposition set in with some evolution of sulphur dioxide.

**Di-4-nitrobenzenesulphonanilide.**—4-Nitrobenzenesulphonyl chloride (2·2 g.) was heated with sodium-4-nitrobenzenesulphonanilide (3·0 g.) for 1 hr. at 150–200°. The solid product was triturated with water made alkaline with sodium

hydroxide. It formed heavy prisms from pyridine, m. p. 264° (Found : N, 9.1.  $C_{18}H_{18}O_8N_2S_2$  requires N, 9.1%). This substance was remarkable in that it could be recrystallised unchanged from boiling concentrated nitric acid.

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RESEARCH DIVISION, MAY & BAKER LIMITED, DAGENHAM.

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