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## Sulfonamides in the Benzimidazole, Benzothiazole and Benzotriazole Series

BY C. F. H. ALLEN, ALAN BELL AND C. V. WILSON

Conspicuously absent from the chemical literature are sulfonamides in the benzimidazole, benzothiazole and benzotriazole series. One reason for this may have been the lack of the corresponding sulfonic acids until the last decade.<sup>1,2</sup> Moreover, although the sulfonic acids are now available, they cannot be converted into the necessary sulfonyl chlorides by the usual methods, nor can the chlorides be prepared by the use of chlorosulfonic acid. A reaction appears to take place between this reagent and the heterocycle, but it is one of salt formation, for, on making the reaction product alkaline, the starting material is recovered unchanged. Benzimidazoles, however, after several hours of treatment with chlorosulfonic acid,<sup>2</sup> yield a sulfonic acid. Benzotriazole does not give a sulfonic acid under the same conditions; N-acetylbenzotriazole was unaffected by this reagent.

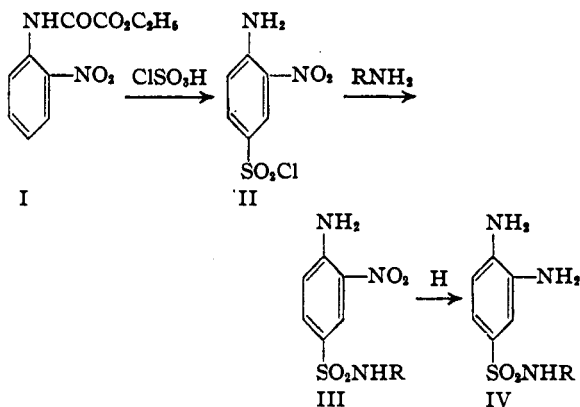
As a general reaction, the formation of sulfonic acids by ring closure of suitable *ortho* diamines is of doubtful utility, owing to the inaccessibility of the requisite starting materials, except 3,4-diaminobenzenesulfonic acid.<sup>3,4,5,6</sup> Even in this last instance we have failed to find references to the benzimidazole-5-sulfonic and benzotriazole-5-sulfonic acids, but we have found their preparations to be straightforward.

However, if there were other reactive groups in the molecule, the conversion of  $-\text{SO}_3\text{H}$  to  $-\text{SO}_2\text{Cl}$ , without attacking the substituents, would be very difficult, even if it were possible. Since we had some interest in 2-mercapto derivatives, this method could not be used. A 2-mercaptobenzothiazole-5-sulfonic acid,<sup>7</sup> salts of 2-mercaptobenzimidazole-5-sulfonic acid,<sup>8</sup> and a benzotriazolesulfonic acid,<sup>9</sup> have been reported previously. 2-Aminobenzothiazole-6-sulfonamide appears in a table of compounds in a recent paper,<sup>10</sup> but its original source was not avail-

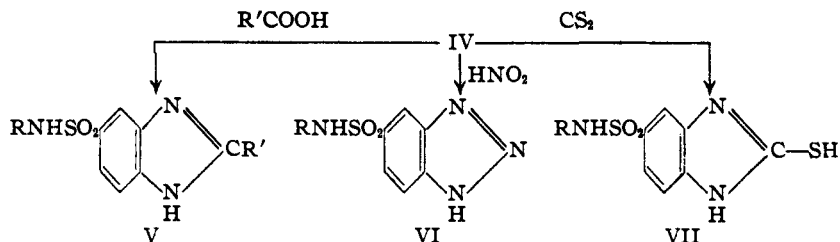
able nor was a method of preparation indicated.

Two procedures were therefore devised, whereby the sulfonamido group was introduced into the molecule prior to ring closure. The starting materials were relatively simple known substances.

In the first procedure, ethyl *o*-nitrophenylloxamate I,<sup>11</sup> was converted to 3-nitro-4-amino-benzenesulfonyl chloride in a single reaction by a treatment with chlorosulfonic acid—the protecting group was hydrolyzed off during the manipulation.



The sulfonyl chloride II was then treated with an amine to form a sulfonamide III. Finally, the nitro group was reduced and the resulting diamine IV closed to whatever heterocyclic ring system was desired. By this procedure there were pre-



pared 5-sulfonamidobenzimidazoles V, 5-sulfonamidobenzotriazole VI, (R = H), and 2-mercapto-5-sulfonamidobenzimidazoles, VII.

The second procedure started with the known<sup>12</sup> 3-nitro-4-chlorobenzenesulfonyl chloride, which was converted into a sulfonamide VIII. Upon treatment with hydrazine, this afforded 6-sulfonamidobenzimidazoles IX, whereas with carbon disulfide and sodium polysulfide, 2-mercapto-5-sulfonamidobenzothiazoles X resulted.

Von Auwers<sup>13</sup> described an indazolesulfonylchloride, prepared from a sodium indazolesulfon-

(11) Pickard, Allen, Bowdler and Carter, *J. Chem. Soc.*, **81**, 1568 (1902).

(12) P. Fischer, *Ber.*, **24**, 3788 (1891).

(13) Von Auwers and Kleiner, *J. prakt. Chem.*, **118**, 75 (1928).

(1) Sulfonation of benzimidazoles, (a) Swiss Patent 163,005; 164,730-6 [C. A., **28**, 2918 (1934)]; (b) German Patent 578,488 [Frdl., **20**, 843 (1935)]; (c) U. S. Patent 2,036,525 [C. A., **30**, 3546 (1936)].

(2) Use of chlorosulfonic acid: (a) German Patent 605,687 [Frdl., **21**, 1279 (1937)]; (b) French Patent 45,661 [C. A., **30**, 3910 (1936)].

(3) Zincke and Kuchenbecker, *Ann.*, **330**, 23 (1904).

(4) Nietzki and Lerch, *Ber.*, **21**, 3221 (1888).

(5) Post and Hardtung, *Ann.*, **205**, 100 (1880).

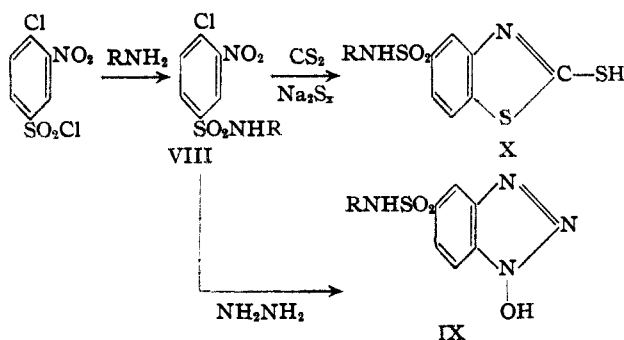
(6) Ruggli and Hinovker, *Helv. Chim. Acta*, **17**, 973 (1934).

(7) Teppema and Sebrell, *THIS JOURNAL*, **49**, 1754 (1927).

(8) Swiss Patent 126,127 [C. A., **23**, 849 (1929)].

(9) Fieser and Martin, *THIS JOURNAL*, **57**, 1838 (1935).

(10) Arnold, Helmert, Möbus, Frigge and Rau, *Ber.*, **76**, 372 (1942).



ate, but, when we employed sodium benzimidazolesulfonate under identical conditions, no sulfonyl chloride could be isolated.

The reactions outlined appear to be of general utility, and make available previously unknown types of substances.

### Experimental

3-Nitro-4-aminobenzenesulfonyl chloride has previously been obtained by treating *o*-nitraniline directly with chlorosulfonic acid;<sup>14</sup> although the yield was not given, on repeating the procedure, there was obtained only 3–4% yield of crude material, not easily purified. It was incorrectly reported by Goslich,<sup>15</sup> whose error was corrected by P. Fischer.<sup>12</sup> It is still uncorrected in the latest edition of Beilstein's "Handbuch".<sup>16</sup> On treating the oxamic ethyl ester<sup>11</sup> with chlorosulfonic acid, an excellent yield of this chloride resulted; the oxalo group was hydrolyzed off during the manipulation.

To 187 g. of chlorosulfonic acid was added 45 g. of ethyl *o*-nitrophenyloxamate,<sup>11</sup> and the mixture was heated for three hours on the steam-bath. The cooled solution was then added slowly to chipped ice; the solid was filtered, washed, dried, and recrystallized from benzene. The yield of chloride (II), m. p. 152–3°, was 15 g. It was converted to the known 3-nitro-4-aminobenzenesulfonamide, m. p. 206–207°, which was identical with a specimen prepared as directed by Fischer.<sup>13</sup>

**3-Nitrosulfanilamides.**—The general procedure was to warm for one-half hour on the steam-bath a mixture of equivalent amounts of the acid chloride and the amine, with 1.5 equivalents of potassium or sodium acetate in about five times its weight of acetic acid. In this way there were prepared *N'*-(4'-acetaminophenyl)-3-nitrosulfanilamide (XI; III, R = 4-acetaminophenyl), and *N'*-(2'-hydroxyphenyl)-3-nitrosulfanilamide (XII; III, R = 2-hydroxyphenyl). Their properties are collected in Table I.

**3-Nitro-4-chlorobenzenesulfonamides.**—These were prepared by the same general procedure. In this way there were obtained *N*-(4'-chlorophenyl)-3-nitro-4-chlorobenzenesulfonamide (XIII; VIII, R = 4-chlorophenyl), *N*-(4'-acetaminophenyl)-3-nitro-4-chlorobenzenesulfonamide (XIV; VIII, R = 4-acetaminophenyl), *N*-(2'-hydroxyphenyl)-3-nitro-4-chlorobenzenesulfonamide (XV; VIII, R = 2-hydroxyphenyl), *N*-(2'-hydroxy-4'-methylphenyl)-3-nitro-4-chlorobenzenesulfonamide (XVI; VIII, R = 2-hydroxy-4-methylphenyl).

**3,4-Diaminobenzenesulfonamide (XVII; IV, R = H)** was secured by reducing the 3-nitro-4-aminobenzenesulfon-

amide preferably in the presence of a Raney nickel catalyst but also by the use of sodium hydrosulfite.

***N*-β-Hydroxyethyl Derivatives.**—*N*-β-Hydroxyethyl-3-nitro-4-chlorobenzenesulfonamide, XVIII, was obtained as follows: to a boiling solution of 10 g. of 3-nitro-4-chlorobenzenesulfonyl chloride in 100 cc. of benzene was added 5 cc. of ethanolamine. The oil that separated was dissolved by the addition of a minimum of alcohol, the solution concentrated to a small volume, and diluted. After the last of the benzene had been removed, the solid that separated was crystallized from hot water.

*N*<sup>1</sup>,*N*<sup>4</sup>-Di-β-hydroxyethyl-3-nitrosulfanilamide, XIX, was prepared in a similar manner, but using an excess of ethanolamine; the use of dioxane as a solvent was also satisfactory; there was no separation of an oil and the dioxane was evaporated on the steam-bath.

**5-Sulfonamidobenzimidazole (XX; V; R, R' = H),** and **2-methyl-5-sulfonamidobenzimidazole (XXI; V, R = H, R' = CH<sub>3</sub>)** were obtained by ring closure of 3,4-diaminobenzenesulfonamide, employing the desired acid and its sodium salt in the usual manner, and heating for at least three hours.

**5-Sulfonamidobenzotriazole (XXII; VI, R = H)** was prepared as follows: 2 g. of 3,4-diaminobenzenesulfonamide was dissolved in 20 cc. of water, 1.3 cc. of acetic acid, and 0.2 cc. of concentrated hydrochloric acid by warming. The solution was cooled to 10°, and 1 g. of sodium nitrite in 5 cc. of water was added all at once. After several color changes, the solid that separated was filtered, treated in hot aqueous solution with Norite, and allowed to crystallize.

Benzazimidoles were prepared by refluxing for two to three hours a mixture of the appropriate 3-nitro-4-chlorobenzenesulfonamide with twice its weight of 85% hydrazine hydrate in an equal volume of alcohol. They were not recrystallized; all melt with more or less violent decomposition. In this way there were secured 6-sulfonamidobenzazimidole (XXIII; IX, R = H), 6-sulfon-(2'-hydroxyanilido)-benzazimidole (XXIV; IX, R = 2-hydroxyphenyl), and 6-*N*-β-hydroxyethylsulfonamidobenzazimidole (XXV; IX, R = β-hydroxyethyl).

**2-Mercaptobenzimidazoles:** 2-mercapto-5-sulfon-(2'-hydroxyanilido)-benzimidazole (XXVI; VII, R = 2-hydroxyphenyl). A solution of 8.6 g. of *N'*-(2'-hydroxyphenyl)-3-nitrosulfanilamide in 25 cc. of alcohol was reduced in the presence of a Raney nickel catalyst at 90°, under 40 lb. pressure. The diamine was not isolated, but the catalyst filtered from the cooled solution. After the addition of 5 cc. of carbon disulfide and enough 40% sodium hydroxide solution to make it alkaline, it was heated overnight on the steam-bath, the solution concentrated to a small volume, diluted, and acidified with hydrochloric acid. The precipitate was filtered, washed, and dissolved in warm sodium carbonate solution. After treatment with a decolorizing carbon, it was acidified, and the precipitate filtered, washed and dried. The mercapto derivative so obtained melts, with decomposition, at 265°.

All these mercapto derivatives are slowly decomposed in solution, and are less pure after attempted recrystallizations. Sulfur analyses tend to give low results, but are useful in showing how many sulfur atoms have been introduced into the molecule.

Similarly, 2-mercapto-5-sulfon-(4'-acetaminoanilido)-benzimidazole (XXVII; VII, R = 4-acetaminophenyl) was obtained from the nitrosulfanilamide XI; upon hydrolysis for two hours on the steam-bath, using 12 g. of the acetyl derivative, 24 cc. of hydrochloric acid and 100 cc. of alcohol, the 2-mercapto-5-sulfon-(4'-anilidobenzimidazole) (XXVIII; VII, R = 4-aminophenyl) was formed.

**2-Mercaptobenzothiazoles:** 2-mercapto-5-sulfon-(4'-chloroanilido)-benzothiazole (XXIX; X, R = 4-chlorophenyl) was prepared by heating a mixture of 5.8 g. of sodium sulfide, 4.8 g. of sulfur, and 28 cc. of water until solution was complete, and then adding 8.5 parts of *N*-(4'-chlorophenyl)-3-nitro-4-chlorobenzenesulfonamide and 5 cc. of carbon disulfide, and warming on the steam-bath for

(14) German Patent 526,171 [*Frdl.*, 17, 522 (1932)].

(15) Goslich, *Ann.*, 180, 103 (1876).

(16) Beilstein-Prager-Jacobson, "Organische Chemie," Vol. 14, p. 709.

TABLE I  
 PROPERTIES OF NEW SUBSTANCES

No.	Solvent	M. p., °C.	Yield, %	Empirical formula	Analyses, %	
					Calcd.	Found
XI	Acetic acid	265-266	80	C <sub>14</sub> H <sub>14</sub> N <sub>4</sub> O <sub>8</sub> S		
XII	Alcohol	205-206	70	C <sub>12</sub> H <sub>11</sub> N <sub>3</sub> O <sub>6</sub> S	N, 13.6	N, 13.6
XIII	Benzene	120-121 <sup>a</sup>	77	C <sub>12</sub> H <sub>9</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>4</sub> S	Cl, 20.5	Cl, 20.4
XIV		188-190	79	C <sub>14</sub> H <sub>12</sub> ClN <sub>3</sub> O <sub>6</sub> S		
XV	Benzene	143-145	37	C <sub>12</sub> H <sub>9</sub> ClN <sub>2</sub> O <sub>6</sub> S	N, 8.5	N, 8.4
XVI	Benzene	155-156	47	C <sub>12</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>6</sub> S	N, 8.2	N, 8.0
XVII	Water	174-175	80	C <sub>8</sub> H <sub>9</sub> N <sub>3</sub> O <sub>5</sub> S	N, 22.5	N, 22.6
XVIII	Water	125	84	C <sub>8</sub> H <sub>9</sub> ClN <sub>3</sub> O <sub>5</sub> S	N, 10.0	N, 10.2
XIX	Water	158	85	C <sub>14</sub> H <sub>16</sub> N <sub>4</sub> O <sub>6</sub> S	N, 13.8	N, 13.6
XX	Alcohol	213-214	28	C <sub>7</sub> H <sub>7</sub> N <sub>3</sub> O <sub>5</sub> S	N, 21.3	N, 20.8
XXI	Alcohol	221	44	C <sub>8</sub> H <sub>9</sub> N <sub>3</sub> O <sub>5</sub> S	N, 19.9	N, 19.5
XXII	Water	236-237	71	C <sub>8</sub> H <sub>9</sub> N <sub>4</sub> O <sub>5</sub> S	N, 28.3	N, 28.3
XXIII		222 <sup>b</sup>	50	C <sub>8</sub> H <sub>8</sub> N <sub>4</sub> O <sub>5</sub> S	N, 26.2	N, 26.2
XXIV		228 <sup>b</sup>	70	C <sub>12</sub> H <sub>16</sub> N <sub>4</sub> O <sub>6</sub> S	N, 18.3	N, 18.1
XXV		168 <sup>b</sup>	20	C <sub>8</sub> H <sub>10</sub> N <sub>4</sub> O <sub>6</sub> S	N, 21.7	N, 21.9
XXVI		265 <sup>b</sup>	54	C <sub>13</sub> H <sub>11</sub> N <sub>3</sub> O <sub>5</sub> S <sub>2</sub>	N, 13.1	N, 12.8
XXVII			68	C <sub>14</sub> H <sub>14</sub> N <sub>4</sub> O <sub>8</sub> S <sub>2</sub>		
XXVIII		240-242 <sup>b</sup>	95	C <sub>12</sub> H <sub>12</sub> N <sub>4</sub> O <sub>5</sub> S <sub>2</sub>	{ C, 49.2 H, 3.5 S, 26.9	{ C, 48.8 H, 3.6 S, 25.1
XXIX		208-210 <sup>b</sup>	55	C <sub>12</sub> H <sub>9</sub> ClN <sub>2</sub> O <sub>5</sub> S <sub>2</sub>	S, 28.5	S, 27.8
XXX		284-285 <sup>b</sup>	38	C <sub>13</sub> H <sub>12</sub> N <sub>3</sub> O <sub>5</sub> S <sub>2</sub> <sup>c</sup>	N, 8.2	N, 8.3
XXXI	Alcohol	246-248 <sup>b</sup>	53	C <sub>13</sub> H <sub>10</sub> N <sub>7</sub> O <sub>5</sub> S <sub>2</sub>		
XXXII		218-220 <sup>b</sup>	65	C <sub>14</sub> H <sub>12</sub> N <sub>3</sub> O <sub>5</sub> S <sub>2</sub>		

<sup>a</sup> Prepared in acetone, using two equivalents of the amine instead of acetic acid and sodium acetate. <sup>b</sup> With decomposition. <sup>c</sup> Upon hydrolysis the free amine, m. p. 230-232°, was formed.

three hours. After filtering, the filtrate (at 20°) was acidified. The remainder of the treatment was similar to that in the previous example.

By a similar procedure there were prepared 2-mercapto-5-sulfon-(4'-acetaminoanilido)-benzothiazole (XXX; X, R = 4-acetaminophenyl), 2-mercapto-5-sulfon-(2'-hydroxyanilido)-benzothiazole (XXXI; X, R = 2-hydroxyphenyl), and 2-mercapto-5-sulfon-(2'-hydroxy-4'-methyl-anilido)-benzothiazole (XXXII; X, R = 2-hydroxy-4-methylphenyl).

### Summary

A series of reactions is described, by which

it is possible to obtain in considerable variety the hitherto unknown sulfonamides in the benzimidazole, benzotriazole, and benzothiazole series.

By these procedures there have been prepared 5-sulfonamidobenzimidazoles, 5-sulfonamidobenzotriazole, 6-sulfonamidobenzazimidoles, 2-mercapto-5-sulfonamidobenzimidazoles and 2-mercapto-5-sulfonamidobenzothiazoles.

ROCHESTER, N. Y.

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## NOTES

### 1,3:2,4-Dibenzylidene-D-sorbitol

BY S. J. ANGYAL AND J. V. LAWLER

In their recent exhaustive paper, Wolfe, Hann and Hudson<sup>1</sup> proved that in dibenzylidene-D-sorbitol (m. p. 219-220°) the benzylidene groups are attached to carbon atoms 1,2,3,4 of D-sorbitol. They were unable, however, to assign a definite structure.

At the time their paper reached us, we were engaged in similar research. Our results agree with theirs, but in one respect we were able to go

(1) Wolfe, Hann and Hudson, *THIS JOURNAL*, **64**, 1493 (1942).

further. By careful hydrolysis of dibenzylidene-D-sorbitol with acetic acid in alcohol, we were able to isolate a monobenzylidene-D-sorbitol identical with Vargha's 2,4-monobenzylidene-D-sorbitol.<sup>2</sup> As under these mild conditions no migration is likely, we feel entitled to assign the 1,3:2,4 structure to dibenzylidene-D-sorbitol.

In a similar way we obtained 1,3:2,4-dibenzylidene-D-sorbitol from tribenzylidene-D-sorbitol,<sup>3</sup> which proves that the latter has the structure 1,3:2,4:5,6-tribenzylidene-D-sorbitol.

(2) Vargha, *Ber.*, **66**, 23, 1337 (1935).

(3) Karrer and Büchi, *Helv. Chim. Acta*, **20**, 86 (1937).