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The Syntheses of 7-Sulphamylpyrido[2,3-*e*]-1,2,4-Thiadiazine-1,1-Dioxide, 5-Sulphamylpyrido[4,3-*e*]-1,2,4-Thiadiazine-1,1-Dioxide and Certain of Their Derivatives

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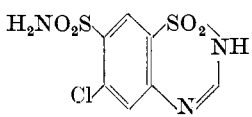
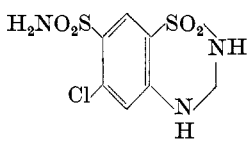
Earlier communications[1, 2, 3, 4] from these laboratories have disclosed a new class of diuretic agents which are derivatives of 1,2,4-benzothiadiazine-1,1-dioxide. The clinical utility of 6-chloro-7-sulphamyl-1,2,4-benzothiadiazine-1,1-dioxide* (I) and its 3,4-dihydro derivative† (II) have prompted the synthesis of some of



(I)



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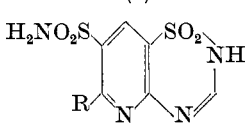

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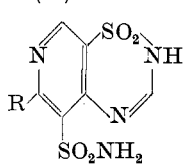


(IV)

the 'aza' analogues of these compounds, i.e., analogues of (I) and (II) in which the benzene nucleus is replaced by the pyridine nucleus. Two of the four possible isomeric forms were studied. These included some substituted 7-sulphamylpyrido[2,3-*e*]-1,2,4-thiadiazine-1,1-dioxides (III), 5-sulphamylpyrido[4,3-*e*]-1,2,4-thiadiazine-1,1-dioxides (IV), and their 3,4-dihydro derivatives.

* Chlorothiazide, 'DIURIL' (Trademark of Merck and Company).

† Hydrochlorothiazide, 'HydroDIURIL' (Trademark of Merck and Company).

The required intermediates for the first series were 2-amino-3,5-pyridinedisulphonamide (VIa) and its 6-substituted derivatives. In the second series, 4-amino-3,5-pyridinedisulphonamide (XII) was the key compound. In each case these intermediates were then cyclized to the desired products.

When this study was initiated, 3,5-pyridinedisulphonic acid[5, 6] was the only disulphonated pyridine described in the literature; furthermore, the method of synthesis from piperidine was impractical and the yield was poor. In a search for a better synthetic method, we tried refluxing both pyridine and pyridine-*N*-oxide with chlorosulphonic acid for 100 h. In neither case was an appreciable amount of the corresponding 3,5-pyridinedisulphonyl chloride produced.

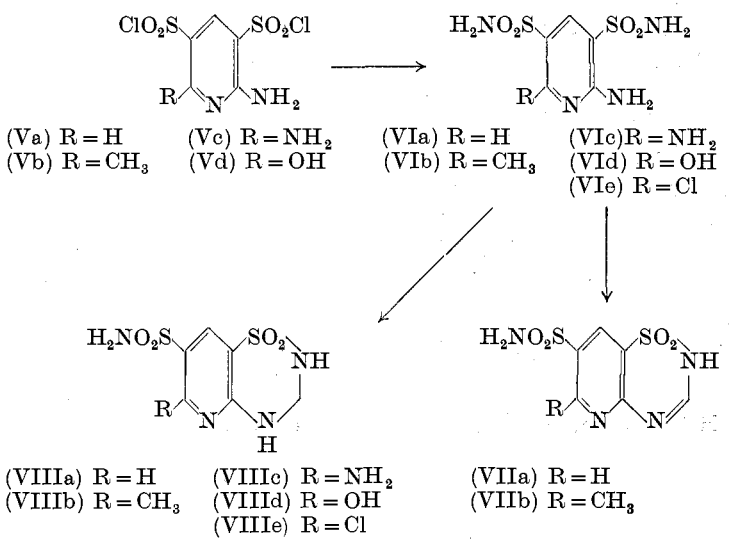
However, an amino group in the 2- or 4-position of the pyridine ring greatly facilitated sulphonation. Thus, when 2-aminopyridine was heated with chlorosulphonic acid at 150° for 116 h followed by treatment with thionyl chloride, 2-amino-3,5-pyridinedisulphonyl chloride (Va) was obtained in 79 per cent yield. One factor that doubtlessly contributed to the success of this synthesis was the high order of stability of 2-aminopyridine and its reaction products to the rigorous conditions of the reaction.

A second activating group in the 6-position of the pyridine nucleus further facilitated sulphonation. After heating for only 12 h under the conditions described, 2,6-diaminopyridine was converted to 2,6-diamino-3,5-pyridinedisulphonyl chloride (Vc) in 74 per cent yield. Likewise, 2-amino-6-hydroxypyridine gave the corresponding 3,5-disulphonyl chloride (Vd) in 72 per cent yield after 12 h of heating.

With 2-amino-6-methylpyridine, competing side reactions became a problem. In order to obtain optimum yields, it was necessary to terminate the reaction after 18 h even though there had been only a 28 per cent conversion to the desired disulphonyl chloride (Vb). Under similar reaction conditions, 2-amino-6-methylpyridine-1-oxide[7] also produced 2-amino-6-methyl-3,5-pyridinedisulphonyl chloride (Vb). It is not known whether the oxygen atom was lost before or after sulphonation but the yield was not improved when the *N*-oxide was employed.

The chlorosulphonation of 2-amino-4-methylpyridine or of 2-amino-4,6-dimethylpyridine has yielded mixtures from which

no pure products have been isolated. Vigorous evolution of hydrogen chloride, indicating that reaction had taken place, occurred in each case. The products of the reaction, however, both before and after treatment with ammonia, consisted of intractable mixtures.



(Va) R = H (Vb) R = CH_3 (Vc) R = NH_2 (Vd) R = OH

(VIa) R = H (VIb) R = CH_3 (VIc) R = NH_2 (VId) R = OH (VIe) R = Cl

(VIIIa) R = H (VIIIb) R = CH_3 (VIIIc) R = NH_2 (VIIId) R = OH (VIIIe) R = Cl

(VIIa) R = H (VIIb) R = CH_3

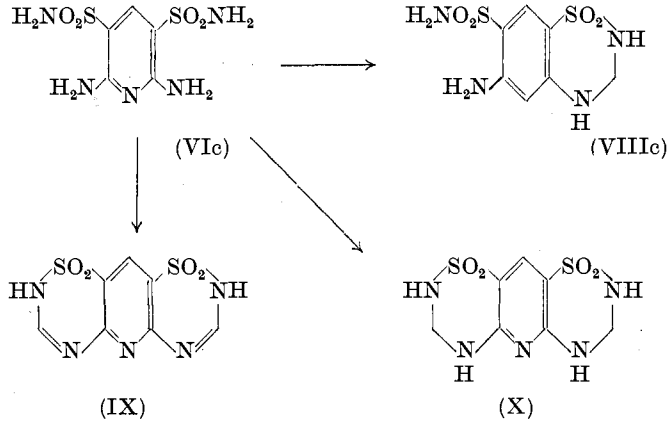
4-Aminopyridine was converted to 4-amino-3,5-pyridinedisulphonyl chloride (XI) in 74 per cent yield by heating with chlorosulphonic acid for 115 h. The disulphonamides were readily produced by dissolving the disulphonyl chlorides in liquid ammonia. In each case, the conversion was rapid and the yield was usually excellent. 2-Amino-6-chloro-3,5-pyridinedisulphonamide (VIe) was prepared by the interaction of the corresponding 6-hydroxy compound (VId) with a mixture of phosphorus pentachloride and phosphorus oxychloride followed by treatment of the reaction product with ammonia.

Cyclization of the amino-3,5-pyridinedisulphonamides to the corresponding pyrido[2,3-*e*] or [4,3-*e*]-1,2,4-thiadiazine-1,1-dioxide was carried out by methods very similar to those described for the benzene analogues.[1, 2] In general, this involved interaction with a carboxylic acid or its derivative. In one case, the acyclic acyl

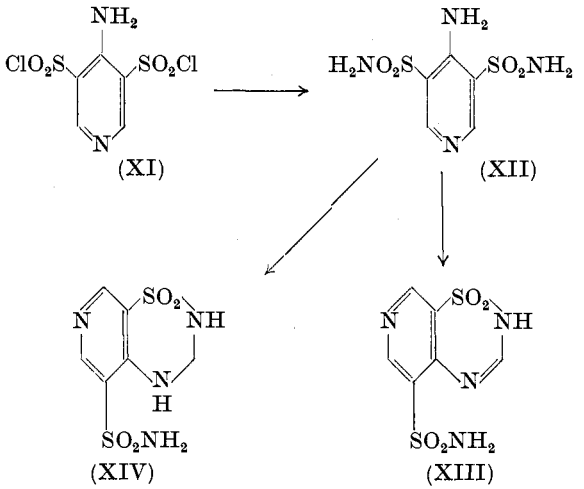
intermediate was isolated. It was observed that cyclization in the benzene series generally proceeded more readily than in the pyridine series. Furthermore, the 2-amino-3,5-pyridinedisulphonamides cyclized with greater facility than 4-amino-3,5-pyridinedisulphonamide.

The pyrido[2,3-*e*]-1,2,4-thiadiazine-1,1-dioxides were prepared by refluxing the appropriate amino-3,5-pyridinedisulphonamide with 100 per cent formic acid. The reaction proceeded smoothly for the conversion of (VIa) to (VIIa) (R = H) and for the transformation of (VIb) to (VIIb) (R = CH_3) but with (VId) (where R = OH) the procedure failed.

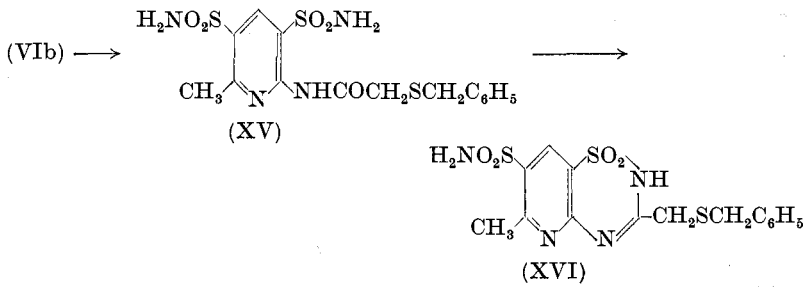
The interaction of 2,6-diamino-3,5-pyridinedisulphonamide (VIc) with formic acid appears to proceed stepwise since mixtures are formed in which the tricyclic product (IX) becomes more predominant as the reaction progresses. The best synthesis of (IX) consisted in boiling (VIc) with formamide for 5 min. Under these conditions, the yield was 95 per cent.



Cyclization of 4-amino-3,5-pyridinedisulphonamide (XII) proved to be considerably more difficult than the corresponding 2-amino isomer (VIa). Refluxing for long periods with 100 per cent formic acid gave no reaction. However, treatment with boiling formamide afforded a 38 per cent yield of 5-sulphamylpyrido[4,3-*e*]-1,2,4-thiadiazine-1,1-dioxide (XIII).

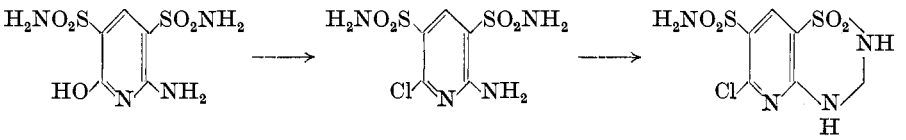


3-Benzylmercaptomethyl-6-methyl-7-sulphamylpyrido[2,3-*e*]-1,2,4-thiadiazine-1,1-dioxide (XVI) was prepared by the conventional two-step process involving conversion of (VIb) to the corresponding 2-benzylmercaptoacetamido derivative (XV) followed by cyclization in alcoholic triethylamine.



The compounds in the '3,4-dihydro' series, i.e., the 3,4-dihydropyrido[2,3-*e*] and [4,3-*e*]-1,2,4-thiadiazine-1,1-dioxides, were generally prepared from the required amino-3,5-pyridinedisulphonamide and exactly one molar equivalent of formaldehyde. The cyclizations were carried out in aqueous solution, usually under weakly alkaline conditions. The yields were good and, by avoiding an excess of formaldehyde, the side reactions were minimized and the purification of the products simplified.

2-Amino-3,5-pyridinedisulphonamide (VIa) was converted to 3,4-dihydropyrido[2,3-*e*]-1,2,4-thiadiazine-1,1-dioxide (VIIIa) in 85 per cent yield. The yield of the 6-methyl derivative (VIIIb) was 71 per cent. 2-Amino-6-hydroxy-3,5-pyridinedisulphonamide (VId) was readily converted to the 6-hydroxy derivative (VIIId) in 85 per cent yield in contrast with its failure to react with formic acid. The 6-chloro derivative (VIIIe), which was prepared in 59 per cent yield, is one of the two possible isomeric 'azahydrochlorothiazides'.



(VId) (VIe) (VIIIe)

With 2,6-diamino-3,5-pyridinedisulphonamide (VIc), it was possible to obtain predominantly either the dicyclic (VIIIc) or the tricyclic derivative (X) by employing either one or two molar equivalents of formaldehyde in the reaction.

5-Sulphamyl-3,4-dihydropyrido[4,3-*e*]-1,2,4-thiadiazine-1,1-dioxide (XIV) was produced in 80 per cent yield by the interaction of 4-amino-3,5-pyridinedisulphonamide (XII) and formaldehyde under the conditions employed for the 2-amino series.

Since the completion of this study in our laboratories, some of the compounds of the 'azathiazide' class have been reported in the literature.[8,9]

Biological Results

Each of the sulphonamides prepared in this study was assayed for its diuretic and saluretic activity in either dogs or rats, and in some instances in both species. Both oral and parenteral administration were employed.

In general, the activity of each compound was comparable with, although somewhat less potent than, that of its 1,2,4-benzothiadiazine analogue. Thus, the 'dihydro' series, i.e. sulphamyl-3,4-dihydropyrido[2,3-*e*] and [4,3-*e*]-1,2,4-thiadiazine-1,1-dioxides, were more active than the corresponding 'aromatic' series, i.e. sulphamylpyrido[2,3-*e*] and [4,3-*e*]-1,2,4-thiadiazine-1,1-dioxides,

which, in turn, were more active than the acyclic amino-3,5-pyridinedisulphonamides.

The introduction of either a 6-methyl group or a 3-benzylmercaptomethyl group in the 7-sulphamylpyrido[2,3-*e*]-1,2,4-thiadiazine-1,1-dioxide molecule produced an increase in activity. Likewise, the introduction of either a methyl or a chloro-group in the 6-position of 7-sulphamyl-3,4-dihydropyrido[2,3-*e*]-1,2,4-thiadiazine-1,1-dioxide increased potency.

The 6-chloro derivative was somewhat more active than the corresponding 6-methyl derivative. On the other hand, the introduction of a 6-hydroxyl group markedly reduced the activity.

The number of the sulphamylpyrido[4,3-*e*]-1,2,4-thiadiazine-1,1-dioxides studied was not adequate to permit a rigorous comparison with the sulphamylpyrido[2,3-*e*]-1,2,4-thiadiazine series. However, the members of the [2,3-*e*] series were consistently more active than those of the [4,3-*e*] series. This relative activity of the two series is not surprising. In the 1,2,4-benzothiadiazine series, the location of the sulphamyl group in the 7-position is critical for optimal activity. In the [4,3-*e*] series, the location of this essential sulphamyl group in the 7-position is not possible since a nitrogen atom occupies this position.

From the present preliminary study, no extensive data are available on potassium excretion. However, no marked differences were observed between the members of these pyrido analogues and the corresponding 1,2,4-benzothiadiazines.

Experimental*

2-Amino-3,5-pyridinedisulphonyl chloride (Va). Under anhydrous conditions, 2-aminopyridine (Matheson, Coleman and Bell) (47 g, 0·5 mole) was added to a mechanically stirred flask containing chlorosulphonic acid (583 g, 5 moles), the temperature being kept below 15°. The mixture was stirred and gradually heated to 150° and then held at this temperature (reflux) for 116 h. The solution was cooled, thionyl chloride (146·6 ml, 2 mole) added, and the stirred solution gradually heated to 125° over a period of 2 h. The contents of the flask were cooled and added dropwise to a beaker of crushed ice (1·2 kg) which was cooled in a

* All melting points are corrected.

bath containing Dry Ice and 2-methoxyethanol. The solid that separated was removed by filtration. This material consisted of a mixture of (Va) and a salt thereof. The solid was extracted with boiling benzene to remove the (Va). The residue was converted to (Va) by warming with water and extracting with boiling benzene. The combined benzene extracts were filtered, concentrated to incipient precipitation and cooled. The yield of (Va) was 114 g (79 per cent). Several recrystallizations from benzene, with concomitant treatment with decolourizing charcoal, gave white crystalline material melting at 137·5–139° (d.).*

Anal. Calcd. for $C_5H_4Cl_2N_2O_4S_2$: C, 20·63; H, 1·38; N, 9·62; S, 22·03. Found: C, 21·01; H, 1·38; N, 9.60; S, 21·92.

2-Amino-3,5-pyridinedisulphonamide (VIa). Liquid ammonia (154 g, 8·9 mole) was placed in a beaker cooled in a bath containing Dry Ice and 2-methoxyethanol. The liquid was stirred and (Va) (30 g, 0·103 mole) was added portionwise over a period of 30 min. Excess ammonia was removed by evaporation and the residue was crystallized from water. The yield of crystalline (VIa) was 24·2 g (93 per cent). After several more recrystallizations from water, the white, crystalline (VIa) melted at 229·5–231° (d.).†

Anal. Calcd. for $C_5H_8N_4O_4S_2$: C, 23·80; H, 3·20; N, 22·21; S, 25·42. Found: C, 23·93; H, 3·14; N, 22·15; S, 25·53.

7-Sulphamylpyrido[2,3-e]*-1,2,4-thiadiazine-1,1-dioxide* (VIIa). A solution of (VIa) (7·57 g, 0·03 mole) in 99–100 per cent formic acid (50 ml) was refluxed under anhydrous conditions for 40 h. After several hours heating, a white solid began to separate. After cooling, this was removed by filtration and the filtrate concentrated and cooled to obtain more product. The combined yield was 6·9 g (89 per cent). After two recrystallizations from formic acid, the white crystalline (VIIa) melted at 319–320° (d.),‡ pK_a 6·4, 8·8.

Anal. Calcd. for $C_6H_6N_4O_4S_2$: C, 27·48; H, 2·31; N, 21·36. Found: C, 27·68; H, 2·37; N, 21·23.

7-Sulphamyl-3,4-dihydropyrido[2,3-e]*-1,2,4-thiadiazine-1,1-dioxide* (VIIIa). A solution of (VIa) (7·57 g, 0·03 mole), ethanol (90 ml), sodium hydroxide (430 mg, 0·0107 mole), water (10 ml) and

* A m.p. of 137–139° has been reported.[9]

† M.p.'s of 222–223° (uncorr.) and 232–234° have been reported. [8,9]

‡ M.p.'s of 332–334° (uncorr.)[8] and 323–325°[9] have been reported.

aqueous formaldehyde (3·04 g, 0·0375 mole) was stirred mechanically and heated on a steam bath for 2·5 h. The solution was acidified with 2N hydrochloric acid (2 ml) and concentrated to dryness at reduced pressure. The residue was suspended in water (*ca* 20 ml), filtered, and washed with a little water. The yield was 6·7 g (85 per cent). The solid was dissolved in 28 per cent ammonium hydroxide, filtered, and the filtrate was heated to remove the ammonia, whereby (VIIIa) separated. Further purification can be effected by crystallization from water, or, better, by repeatedly dissolving in cold dilute aqueous sodium hydroxide and precipitating with dilute hydrochloric acid. The purified (VIIIa) melted at 289·5–291° (d.),* pK_a 7·6, 9·3.

Anal. Calcd. for $C_6H_8N_4O_4S_2$: C, 27·27; H, 3·05; N, 21·20. Found: C, 27·72; H, 3·35; N, 20·92.

2-Amino-6-methyl-3,5-pyridinedisulphonyl chloride (Vb). 2-Amino-6-methylpyridine (Reilly Tar and Chemical) (108·1 g, 1 mole) and chlorosulphonic acid (1165·3 g, 10 mole) were refluxed for 18 h as described for (VIa). After cooling and addition of thionyl chloride (476 g, 4 mole), the mixture was gradually heated to reflux over a period of 3 h. After cooling and pouring on to crushed ice, the product was extracted with benzene. The benzene extract was dried over sodium sulphate and the solvent removed by distillation at reduced pressure. The yield of crude (Vb) was 86·2 g (28 per cent). After several recrystallizations from methylcyclohexane, pure (Vb) melted at 132–133° (d.).†

Anal. Calcd. for $C_6H_6Cl_2N_2O_4S_2$: C, 23·61; H, 1·98; N, 9·18. Found: C, 23·91; H, 2·10; N, 9·09.

2-Amino-6-methyl-3,5-pyridinedisulphonamide (VIb). Compound (Vb) (85·2 g, 0·279 mole) was added to liquid ammonia (309 g, 18·2 mole) as described for the preparation of (VIa). After evaporation of the excess ammonia, the resulting solid was recrystallized from water (800 ml) with concomitant treatment with decolourizing charcoal. The yield of VIb was 47·2 g (64 per cent). After several recrystallizations from water, the product melted at 245·5–247° (d.).‡

Anal. Calcd. for $C_6H_{10}N_4O_4S_2$: C, 27·06; H, 3·79; N, 21·04. Found: C, 27·52; H, 3·56; N, 20·89.

* Reported m.p.,[8] 269–270° (uncorr.).

† Reported m.p.,[9] 132–133°.

‡ Reported m.p.'s, 235–236° (uncorr.),[6] and 249–251°.[9]

6-Methyl-7-sulphamylpyrido[*2,3*-e]-*1,2,4-thiadiazine-1,1-dioxide* (VIIb). Compound VIb (14·65 g, 0·055 mole) in 99–100 per cent formic acid (120 ml) was refluxed under anhydrous conditions for 40 h. The yield was 12·5 g (82 per cent). After recrystallization from formic acid and then acetic acid, the product melted at 322–323° (d.).*

Anal. Calcd. for $C_7H_8N_4O_4S_2$: C, 30·42; H, 2·92; N, 20·28. Found: C, 30·52; H, 2·73; N, 20·12.

6-Methyl-7-sulphamyl-3,4-dihydropyrido[*2,3*-e]-*1,2,4-thiadiazine-1,1-dioxide* (VIIIb). Compound (VIb) (14·65 g, 0·055 mole), 2·48 per cent aqueous formaldehyde (66·5 g, 0·055 mole), 0·883N aqueous ammonia (3·1 ml, 0·00275 mole) and water (61 ml) were refluxed for 2·5 h. After addition of 10·78N aqueous ammonia (4·85 g, 0·052 mole) and water (329 ml), refluxing was continued for another hour. The yield of product which separated upon cooling was 10·9 g (71 per cent). The product was purified as described for (VIIIa), m.p. 277–278° (d.).†

Anal. Calcd. for $C_7H_{10}N_4O_4S_2$: C, 30·21; H, 3·62; N, 20·13. Found: C, 30·07; N, 3·90; N, 20·01.

3-Benzylmercaptomethyl-6-methyl-7-sulphamylpyrido[*2,3*-e]-*thiadiazine-1,1-dioxide* (XVI). Compound (VIb) (12·8 g, 0·048 mole), benzylmercaptoacetyl chloride[10,11] (9·65 g, 0·048 mole) and dry dioxane (225 ml) were stirred and refluxed under anhydrous conditions for 20 h. The (VIb) slowly dissolved and *2-benzylmercaptoacetamido-6-methyl-3,5-pyridinedisulphonamide* (XV) gradually separated. The mixture was cooled and filtered, and the solid washed with dioxane. The crude (XV), 6·9 g. (34 per cent), m.p. 237–239° (uncorr.), was used in the next step without purification.

Crude (XV) (6·9 g, 0·0157 mole) was dissolved in a solution of 25 per cent triethylamine in methanol (100 ml). After standing at room temperature overnight, the solvent was removed by distillation at reduced pressure and the residue was recrystallized three times from a 3:1 ethanol–water mixture. The yield was 4·5 g (70 per cent), m.p. 255–256·5° (d.).

Anal. Calcd. for $C_{15}H_{16}N_4O_4S_3$: C, 43·67; H, 3·91; N, 13·58. Found: C, 43·71; H, 4·12; N, 13·51.

* Reported m.p.'s 309–310° (uncorr.),[8] and 316° (dec).[9]

† Reported m.p. 265–267°.[9]

2,6-Diamino-3,5-pyridinedisulphonyl chloride (Vc). 2,6-Diaminopyridine (Reilly Tar and Chemical) (36 g, 0·33 mole) and chlorosulphonic acid (583 g, 5 moles) were refluxed for 12 h. The mixture was cooled and treated with thionyl chloride (96·6 g, 1·32 mole) and gradually heated to 120° over a period of 8 h. The cooled reaction mixture was poured on to crushed ice (1 kg) as described for (Va) and the light brown product was collected on a filter, washed with water and dried. The yield was 74·8 g (74 per cent). After several recrystallizations from acetonitrile, (Vc) melted at 213–214·5° (d.).

Anal. Calcd. for $C_5H_5Cl_2N_3O_4S_2$: C, 19·62; H, 1·65; Cl, 23·16; N, 13·72; S, 20·95. Found: C, 19·90; H, 1·89; Cl, 22·96; N, 13·68; S, 21·20.

2,6-Diamino-3,5-pyridinedisulphonamide (VIc). Compound (Vc) (9·74 g, 0·0317 mole) was added to liquid ammonia (468 g, 2·75 mole) as described for (VIa). After recrystallization of the crude product from water, the yield was 7·73 g (91 per cent). Further recrystallization from water gave (VIc) melting at 246·5–248° (d.).

Anal. Calcd. for $C_5H_9N_5O_4S_2$: C, 22·47; H, 3·40; N, 26·20; S, 23·99. Found: C, 22·90; H, 3·35; N, 26·19; S, 23·89.

6-Amino-7-sulphamyl-3,4-dihydro[*2,3*-e]-*1,2,4-thiadiazine-1,1-dioxide* (VIIIc). Compound (VIc) (5 g, 0·0186 mole), 2·48 per cent aqueous formaldehyde (22·5 g, 0·0186 mole), 0·883N aqueous ammonia (0·75 ml, 0·00066 mole) and water (20·8 ml) were stirred and refluxed for 2 h. Then 10·78N aqueous ammonia (1·52 ml, 0·0164 mole) and water (145 ml) were added and refluxing continued for 40 min. The mixture was filtered to remove some solid material (910 mg). Upon cooling the filtrate, (VIIIc) separated. The yield was 3·62 g (70 per cent). Purification was carried out as described for (VIIIa), m.p. 244–245°.

Anal. Calcd. for $C_6H_9N_5O_4S_2$: C, 25·80; H, 3·25; N, 25·08. Found: C, 25·55; H, 3·46; N, 24·91.

The 910 mg of insoluble material was recrystallized by dissolving in conc. ammonium hydroxide, concentrating and cooling, m.p. 274–275° (d.). This material was shown to be (X) by mixed m.p. and analysis.

Anal. Calcd. for $C_7H_9N_5O_4S$: C, 28·86; H, 3·11; N, 24·05. Found: C, 28·56; H, 3·22; N, 24·19.

*Pyrido[2,3-*e*,6,5-*e*]bis[1,2,4]thiadiazine-1,1,9,9-tetroxide* (IX). Compound (VIc) (5·35 g, 0·02 mole) was dissolved in boiling formamide (20 ml) and the boiling solution filtered. The total heating time was 5 min. The filtrate was quickly cooled, whereby 4·5 g (95 per cent) of crystalline (IX) separated. The product was purified by recrystallization from formamide, then by dissolving in aqueous ammonia and reprecipitating with dilute hydrochloric acid, and finally by recrystallization from dimethylformamide. The pure crystalline (IX) did not melt below 360°.

Anal. Calcd. for $C_7H_5N_5O_4S_2$: C, 29·27; H, 1·75; N, 24·38. Found: C, 29·32; H, 2·05; N, 24·19. pK_a = 5·6, 7·6.

*3,4,6,7 - Tetrahydropyrido[2,3-*e*,6,5-*e*] - bis[1,2,4]thiadiazine - 1,1,9,9-tetroxide* (X). Compound (VIc) (5 g, 0·0186 mole), 2·48 per cent aqueous formaldehyde (45 g, 0·0186 mole), 0·883N ammonium hydroxide (0·75 ml, 0·00066 mole) and water (20·8 ml) were stirred and refluxed for 7 h. Then 10·78N aqueous ammonia (3·04 ml, 0·0328 mole) and water (237 ml) were added and stirring and refluxing continued for 1·25 h. The yield of white solid that separated during the reaction was 2·98 g (55 per cent). The product was purified as described for (VIIIa), and melted at 274·5–275° (d.).

Anal. Calcd. for $C_7H_9N_5O_4S_2$: C, 28·86; H, 3·11; N, 24·05. Found: C, 28·94; H, 3·46; N, 24·00.

2-Amino-6-hydroxy-3,5-pyridinedisulphonamide (VId). 2-Amino-6-hydroxypyridine (Aldrich Chemical Company material purified by recrystallization from isopropyl alcohol, m.p. 209–210°) (72·7 g, 0·66 mole) and chlorosulphonic acid (654 ml, 10 moles) were refluxed for 12 h. After cooling and addition of thionyl chloride (194 ml, 2·63 mole), the mixture was gradually heated to reflux over 3·5 h.

After pouring on to crushed ice (4 kg) as described for (Va), the cold aqueous mixture was extracted with ethyl acetate (3 × 400 ml). The combined filtrates were treated with decolourizing charcoal, dried over anhydrous sodium sulphate, and filtered, and the solvent was removed by distillation under reduced pressure. The light grey solid residue weighed 145·6 g (72 per cent) and represented crude *2-amino-6-hydroxy-3,5-pyridinedisulphonyl chloride* (Vd). This material was not purified before use in the next step.

Crude (Vd) (145·6 g, 0·474 mole) was added to liquid ammonia (450 ml) and isolated as described for (VIa). The yield was 106 g (83 per cent). The crude product was purified by dissolving it in conc. aqueous ammonia, treating the solution with decolourizing charcoal, filtering, concentrating and cooling. After a final recrystallization from water, the m.p. was 282–283·5° (d.).

Anal. Calcd. for $C_5H_8N_4O_5S_2$: C, 22·39; H, 3·01; N, 20·88. Found: C, 22·73; H, 3·23; N, 20·83.

6-Hydroxy-7-sulphamyl-3,4-dihydropyrido[*2,3*-e]-*1,2,4-thiadiazine-1,1-dioxide* (VIIId) was prepared from (VId) (4·5 g, 0·0167 mole) as described for (VIIIb). The yield was 4 g (85 per cent). After repeated dissolution in cold dilute sodium hydroxide and precipitation with dilute acetic acid, the m.p. was 273–274° (d.).

Anal. Calcd. for $C_6H_8N_4O_5S_2$: C, 25·70; H, 2·88; N, 19·98. Found: C, 25·86; H, 3·09; N, 19·85.

2-Amino-6-chloro-3,5-pyridinedisulphonamide (VIe). Compound (VId) (57·7 g, 0·215 mole) and phosphorus oxychloride (625 ml) was stirred and refluxed under anhydrous conditions for 30 h. At various intervals, phosphorus pentachloride was added to the reaction mixture. After 2 h, 194 g was added and after 7·5 h, 44·9 g, and after 15·5 h, a final addition of 8·3 g was made. The reaction mixture was concentrated to dryness at reduced pressure and the residue added to liquid ammonia as described for (VIa). Trituration of the crude product with water gave 7·6 g; another 4·1 g was obtained by concentration of the aqueous mother liquor. The yield of crude product from the two steps was 11·7 g (19 per cent). After several recrystallizations from a 2:1 ethanol–water mixture, m.p. 275° (d.).

Anal. Calcd. for $C_5H_7ClN_4O_4S_2$: C, 20·94; H, 2·46; Cl, 12·37. N, 19·54; Found: C, 21·64; H, 2·68; Cl, 11·88; N, 19·65.

6-Chloro-7-sulphamyl-3,4-dihydropyrido[*2,3*-e]-*1,2,4-thiadiazine-1,1-dioxide* (VIIIe) was prepared from (VIe) (4·79 g, 0·016 mole) as described for (VIIIb). The crude yield was 2·95 g (59 per cent). Purification was carried out by repeatedly dissolving in dilute sodium hydroxide and precipitating with dilute acetic acid. Finally, the product was crystallized from a 2:1 ethanol–water mixture. The yellow crystalline (VIIIe) melted at 280° (d.).

Anal. Calcd. for $C_6H_7ClN_4O_4S_2$: C, 24·13; H, 2·36; Cl, 11·87; N, 18·76. Found: C, 24·36; H, 2·50; Cl, 11·55; N, 19·23.

4-Amino-3,5-pyridinedisulphonyl chloride (XI). 4-Aminopyridine (Aldrich Chemical Company material recrystallized from benzene, m.p. 155–157°) (33·3 g, 0·35 mole) and chlorosulphonic acid (229 ml, 3·5 mole) were refluxed for 115 h, then treated with thionyl chloride (103·2 ml, 1·2 mole) and gradually heated to 120° over 3 h. The mixture was cooled, poured on to ice (1·3 kg) and then diluted (to 3 l.) with ice water. The solid was removed by filtration and the mother liquor extracted with benzene. The extract was dried and the solvent removed by distillation under reduced pressure. The combined yield was 75·6 g (74 per cent). After several recrystallizations from methylcyclohexane, the product melted at 123–125°.

Anal. Calcd. for $C_5H_4Cl_2N_2O_4S_2$: C, 20·63; H, 1·38; N, 9·62. Found: C, 20·88; H, 1·37; N, 9·58.

4-Amino-3,5-pyridinedisulphonamide (XII) was prepared from (XI) and liquid ammonia as described for (VIb). The yield was 91 per cent. After several recrystallizations from water, the product melted at 284·5–285·5° (d.).

Anal. Calcd. for $C_5H_8N_4O_4S_2$: C, 23·80; H, 3·20; N, 22·21; S, 25·42. Found: C, 24·02; H, 3·27; N, 22·33; S, 25·31.

5-Sulphamylpyrido[*4,3*-e]-*1,2,4-thiadiazine-1,1-dioxide* (XIII). Compound (XII) (12·93 g, 0·05 mole) was slowly added to boiling formamide (40 ml). After boiling for 15 min, the solution was cooled in ice and water (60 ml) added. The solid that separated along with that recovered from the mother liquors weighed 6 g (38 per cent). The product was dissolved in cold dimethylformamide and gradually treated with water, whereby the product crystallized. Repetition of this process gave (XIII), melting at 330–331° (d.).

Anal. Calcd. for $C_6H_6N_4O_4S_2$: C, 27·48; H, 2·31; N, 21·36. Found: C, 27·80; H, 2·51; N, 21·44.

5-Sulphamyl-3,4-dihydropyrido[*4,3*-e]-*1,2,4-thiadiazine-1,1-dioxide* (XIV) was prepared from (XII) (5 g, 0·0197 mole) as described for (VIIIb). The yield was 4·16 g (80 per cent). After purification as described for (VIIIa), the product melted at 269–270° (d.).

Anal. Calcd. for $C_6H_8N_4O_4S_2$: C, 27·27; H, 3·05; N, 21·20; S, 24·27. Found C, 26·82; H, 3·24; N, 21·22; S, 24·52.

Summary. A number of 7-sulphamylpyrido[2,3-*e*]-1,2,4-thiadiazine-1,1·dioxides including those containing substituents at the 3· or 6-position as well as their 3,4·dihydro derivatives were synthesized. 5·Sulphamylpyrido[4,3·*e*]-1,2,4·thiadiazine·1,1·dioxide and its 3,4-dihydro derivative were prepared. The compounds were assayed for their diuretic and saluretic activity and found to be comparable to although somewhat less potent than the corresponding 1,2,4·benzothiadiazine analogues.

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References

[1] Novello, F. C. and Sprague, J. M. *J. Amer. chem. Soc.*, **79**, 2028 (1957)
[2] Novello, F. C. and Sprague, J. M. 132nd Meeting of the American Chemical Society, New York, September 8–13 (1957); Abstracts, p. 32–0
[3] Sprague, J. M. *Ann. N.Y. Acad. Sci.*, **71**, 328 (1958)
[4] Novello, F. C., Bell, S. C., Abrams, E. L. A., Ziegler, C. and Sprague, J. M. *J. org. Chem.*, **25**, 970 (1960)
[5] Hoffmann, L. and Koenigs, W. *Ber. dtsch. chem. Ges.*, **16**, 727 (1883)
[6] Koenigs, W. and Geigg, R. *Ber. dtsch. chem. Ges.*, **17**, 589 (1884)
[7] Adams, R. and Mujano, S. *J. Amer. chem. Soc.*, **76**, 2785 (1954)
[8] Yale, H. L., Losse, K. and Bernstein, J. *J. Amer. chem. Soc.*, **82**, 2042 (1960)
[9] Ciba Ltd. South African Patent No. 594,079 and No. 594,080, Oct. 16, 1959; Indian Patent No. 66,425, August 14, 1960; Australian Patent No. 53,925 and No. 53,926, Oct. 22, 1959
[10] Stoner, G. G. and Dougherty, G. *J. Amer. chem. Soc.*, **63**, 1481 (1941)
[11] Lesser, R. and Mehrlander, A. *Ber. dtsch. chem. Ges.*, **56**, 1642 (1923)