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Heterocyclic Disulphonamides and Their Diuretic Properties*

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Introduction

The search for a clinically effective diuretic agent has been the task and goal of medicinal chemists for well over fifty years. Due to the importance of this area of medical research, it is of interest to review briefly its development.

Although it had been known for many years that mercurated compounds exhibited significant diuretic effects, it was not until 1950 that chloromerodrin (I)[1]† was developed and introduced as an orally active and consistently effective diuretic agent (see Chart I). However, the most widely known mercurial today probably is merallureide (II)[2]‡ because of its relatively low toxicity. Another compound which caused very good diuresis when administered parenterally was diglucomethoxane (III)[3].§

Three points of interest stimulated further research in this field, namely, the desire for (1) less toxic compounds, (2) orally effective compounds, and (3) non-mercurial diuretics.

Since the work of Emil Fischer and Wilhelm Traube the xanthines and purines have been known to act as diuretics. One that has stood the test of time as a mild diuretic is theophylline (IV). Recently, Schmidt, Eichenberger and Druey[4] have prepared compound (V), an isomer of caffeine, and have found it to act very much like the latter substance when tested in laboratory animals. In the pyrimidine class, amino*iso*metradine (VI)[5],‖ has been studied clinically.

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† Neohydrin ®.

‡ Mercuhydrin ®.

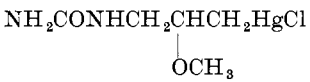
§ Mersoben ®.

‖ Rolicton ®.

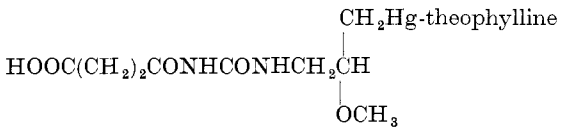
However, the most fruitful results in this investigation have been in sulphonamide derivatives. This was influenced by Pitts'[6]

Chart I

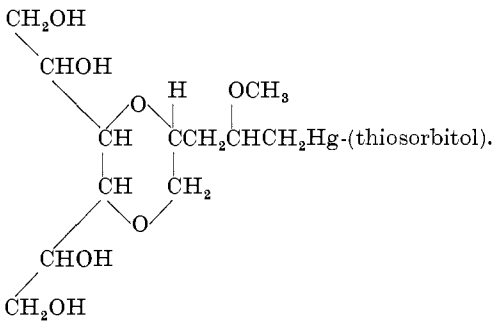
A. *Mercurials*



I

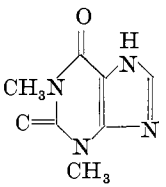


II

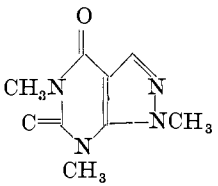


III

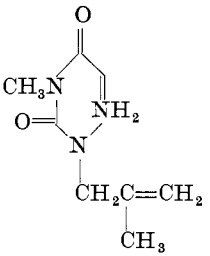
B. *Pyrimidines and Purines*



IV

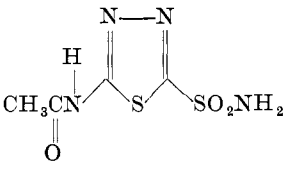


V

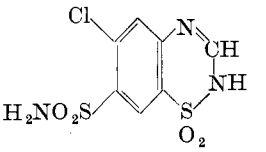


VI

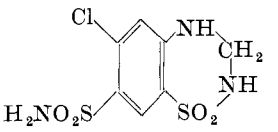
C. *Sulphonamides*



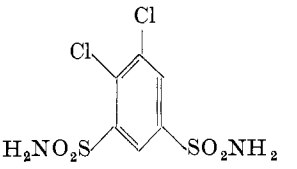
VII



VIII



IX



X

finding that sulphonamides inhibited the enzyme carbonic anhydrase. Thus, many sulphonamides were prepared and clinically tested. In 1953, acetazolamide (VII)[7]* was introduced as the first potent, orally active non-mercurial diuretic. Its effectiveness was based on its carbonic anhydrase inhibitory action.

In 1957 a dramatic entry was made into the diuretic field with chlorothiazide (VIII)† a compound first prepared by Novello and Sprague.[8] This sulphonamide derivative was more closely related in its action to the mercurials than to the carbonic anhydrase inhibitors.

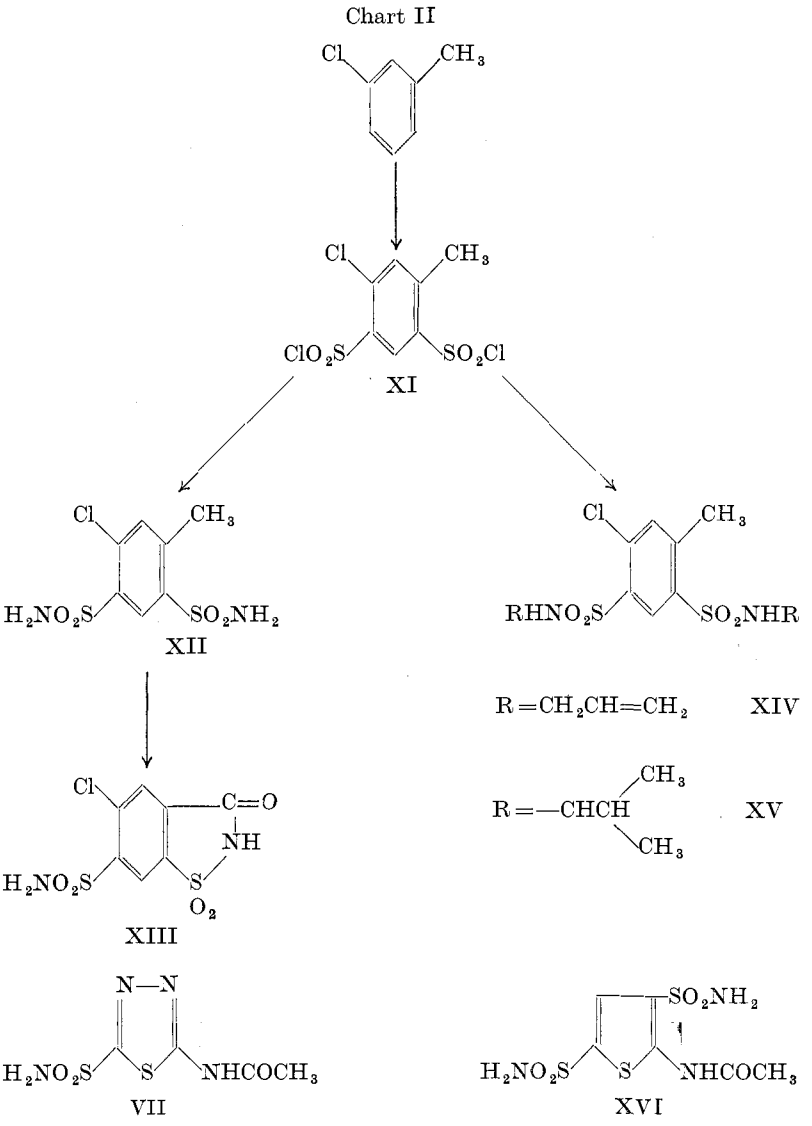
At about this time CIBA's interest in diuretics and sulphonamides led to the discovery and introduction of hydrochlorothiazide (IX),[9]‡ a compound which was found to be fifteen to twenty times as potent as chlorothiazide when tested in humans. It was also our experience, as well as that of Novello and Sprague, that certain *m*-benzenedisulphonamides elicited a marked diuresis. One of the compounds prepared by Novello and Sprague showing this effect is 5,6-dichloro-*m*-benzenedisulphonamide (X).

New Disulphonamides

The chlorosulphonation of *m*-chlorotoluene (see Chart II) according to the method outlined by Lustig and Katscher[10] gave

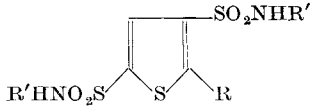
* Diamox ®. † Diuril ®. ‡ Esidrix ®.

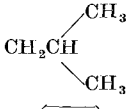
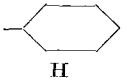
Chart II



rise to a good yield of disulphonyl chloride (XI) which on treatment with ammonia yielded 4-chloro-6-methyl-*m*-benzenedisulphonamide (XII). This compound was found to be $\frac{1}{10}$ as

Table I. Thiophen disulphonamides



R	R′	m.p. °C	Formula	Calcd.			Found		
				C	H	N	C	H	N
Cl	H	214–215	$C_4H_5ClN_2O_4S_3$	17·41	1·86	10·15	17·80	1·83	10·30
Br	H	229–232	$C_4H_5BrN_2O_4S_3$	14·96	1·57		15·05	1·71	
CH_3	H	195–196	$C_5H_8N_2O_4S_3$	23·48	3·15	10·95	23·48	3·16	11·13
C_2H_5	H	205–206	$C_6H_{10}N_2O_4S_3$			10·36			10·22
C_2H_5		121–122	$C_{14}H_{26}N_2O_4S_3$			7·32			7·20
C_2H_5		118–120	$C_{18}H_{30}N_2O_4S_3$			6·45			6·23
C_3H_7(*iso*)	H	210–212	$C_7H_{12}N_2O_4S_3$	29·56	4·25	9·85	29·32	4·17	9·54
C_3H_7(*n*)	H	160–162	$C_7H_{12}N_2O_4S_3$	29·56	4·25	9·85	29·51	4·31	9·83

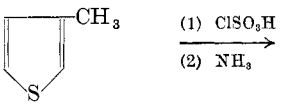
active as hydrochlorothiazide when tested in dogs. Oxidation of (XII) with sodium dichromate in 70 per cent sulphuric acid at 50° led to the formation of a saccharin-type compound (XIII) which also had diuretic activity. The *N*,*N*′-disubstituted disulphonamides (XIV and XV) were found to be inactive.

In order to correlate the aromatic and heterocyclic aspects of this problem, a number of thiophen disulphonamides were prepared. The first of these to be synthesized was 5-acetamido-2,4-thiophen disulphonamide (XVI), a compound closely related to acetazolamide. This compound was found to exhibit only slight diuretic activity when tested in rats. Several other 2-substituted thiophen disulphonamides were prepared in the usual manner in order to increase the activity, and these results are listed in Table I.[12]

Observations on diuretic activity were made on groups of 4–8 rats which had been fasted for 18 h. These were given an oral dose of 1·25 mg/kg of the test compound. This was immediately followed by a fluid load of 0·2 per cent sodium chloride solution, calculated on the basis of 5 per cent of the body weight. The rats were then placed in metabolism cages and urine volumes measured at 30 min intervals over a 3 h period. The total amount of sodium and potassium excreted for the 3 h period was determined by flame photometry. The diuretic activity of these compounds was then compared with hydrochlorothiazide as a standard.

5-Chloro-2,4-thiophen disulphonamide was found to be $\frac{1}{10}$ as active as hydrochlorothiazide. Surprisingly enough, the corresponding 5-bromo derivative was inactive. However, the 5-alkyl-2,4-thiophen disulphonamides showed a significant diuretic effect. Outstanding in this group is 5-ethyl-2,4-thiophen disulphonamide which elicited $\frac{1}{5}$ the diuretic effect as hydrochlorothiazide.

It was thus of interest to study the effect of the 3-alkylthiophen disulphonamides. Thus, 3-methylthiophen was reacted with excess chlorosulphonic acid to give a yellow oil which resisted crystallization. Amination of this oil gave a crude precipitate which upon recrystallization from ethanol gave a colourless crystalline substance, m.p. 236–238°. Upon standing, the alcohol filtrate deposited crystals, m.p. 164–165°. These substances were designated as (XVII) and (XVIII) respectively.



XVII

m.p. 235–238°
$\lambda_{max.}$ 244 mμ
$\epsilon = 7304$
$\lambda_{min.}$ 218 mμ
$\epsilon = 2,430$

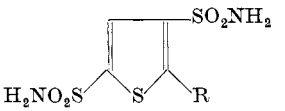
XVIII

m.p. 168°
$\lambda_{max.}$ 253 mμ
$\epsilon = 11,000$
$\lambda_{min.}$ 218 mμ
$\epsilon = 1,580$

It is obvious from the nature of the reactants that only the 2,4- and 2,5-disulphonamide derivatives can be formed. The infrared spectra of (XVII) and (XVIII) were quite similar. However, it appeared that the ultraviolet absorption data might be used for structural elucidation. The literature[13] records the preparation and unequivocal proof of structure of 2,4-thiophen disulphonamide (m.p. 218°). This compound was prepared and its ultraviolet absorption data is recorded in Table II along with other

Table II. Ultraviolet absorption spectra of thiophen disulphonamides

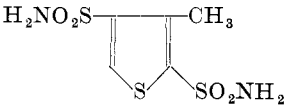
2,4-Thiophen disulphonamides



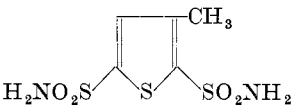
R	$\lambda_{max.}$	ϵ	$\lambda_{min.}$	ϵ
H	242	7560	217	2370
Cl	256	8800	224	2430
Br	259	9780	225	2740
CH_3	245	7670	220	2540
C_2H_5	247	8100	220	2460

2,4-thiophen disulphonamides. Apart from the polar effects of the halogens and the inductive influence of the alkyl groups, these compounds have maxima and minima and extinction coefficients which are closely in line with compound (XVII). Consequently,

we have tentatively assigned (XVII) as 3-methyl-2,4-thiophen disulphonamide and (XVIII) as 3-methyl-2,5-thiophen disulphonamide.



XVII

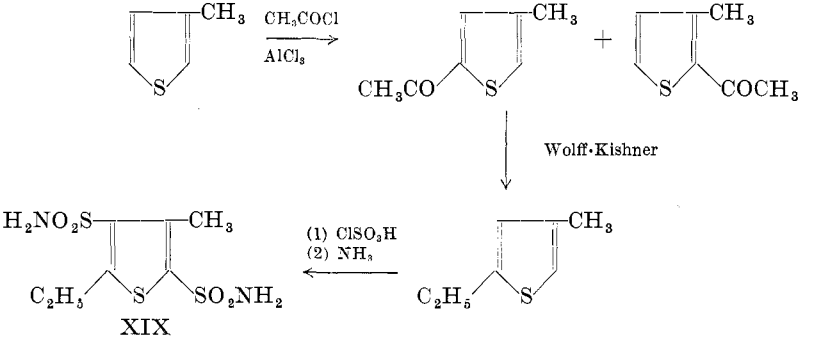


XVIII

The diuretic properties of these compounds were unusual. 3-Methyl-2,5-thiophen disulphonamide was $\frac{1}{5}$ as active as hydrochlorothiazide, whereas its isomer, 3-methyl-2,4-thiophen disulphonamide, was weakly active. Moreover, as was the case with 4-chloro-6-methyl-*m*-benzenedisulphonamide, substitution on the sulphamyl nitrogens resulted in complete loss of diuretic effect. It is of interest to note that all of the active compounds in this series caused pronounced potassium excretion.

Finally, these data demonstrated that the 5-ethyl and 3-methyl derivatives were the most effective agents. Consequently, it was decided to incorporate both of these groups in the same molecule.

Friedel-Craft's acetylation of 3-methylthiophene yielded two products, 3-methyl-2-acetylthiophen and 4-methyl-2-acetyl-



XIX

thiophen, which were separated by distillation.[14] Wolff-Kishner reduction of the 4-methyl derivative followed by chlorosulphonation and amination yielded the desired 5-ethyl-3-methyl-2,4-thiophen disulphonamide (XIX). This compound was tested for its diuretic properties and was found to be weakly active.

Experimental*

5-Chlorotoluene-2,4-disulphonyl chloride (XI). *m*-Chlorotoluene (50 g, 0·4 mole) was added dropwise with stirring to 280 ml of chlorosulphonic acid in a 3 l. round bottom, 3-necked flask cooled in an ice bath. Sodium chloride (270 g) was added portionwise over a period of 1–2 h and the mixture then heated gradually in an oil bath to 150°. After 3 h at this temperature, the flask was cooled in an ice bath and the contents were treated with one l. of cold water. The product was extracted with ether and the extract washed with water and dried over sodium sulphate. After removal of the ether on a steam bath, the residual solid material was recrystallized from benzene-hexane to give analytically pure product, m.p. 122–123°, in 73 per cent yield.

Anal. Calcd. for $C_7H_5Cl_3O_4S_2$: C, 25·98; H, 1·58. Found: C, 26·22; H, 1·72.

6-Chloro-4-methyl-m-*benzenedisulphonamide* (XII). Twenty grams (0·06 mole) of (XI) was treated at 0° with 100 ml of 28 per cent ammonium hydroxide. The mixture was then heated on a steam bath for 1 h, chilled and the product collected on a filter and washed with water. After recrystallization from 50 per cent. aqueous ethyl alcohol, a 40 per cent yield of product, m.p. 250°, was obtained.

Anal. Calcd. for $C_7H_9ClN_2O_4S_2$: C, 29·52; H, 3·18; N, 9·84. Found: C, 29·74; H, 3·37; N, 10·02.

N,N′-*Diallyl-6-chloro-4-methyl*-m-*benzenedisulphonamide* (XIV). This compound was prepared by treating compound (XI) (3·23 g, 0·01 mole) with a 30 per cent water solution of allylamine at 0°. A 35 per cent yield of product, m.p. 133–134°, recrystallized from ethyl alcohol : water (1 : 2) was obtained.

Anal. Calcd. for $C_{13}H_{17}ClN_2O_4S_2$: C, 42·79; H, 4·70. Found: C, 42·78; H, 4·91.

N,N′-*Di*iso*butyl-6-chloro-4-methyl*-m-*benzenedisulphonamide* (XV), m.p. 163–164°, was obtained by the same procedure using a 50 per cent water solution of *iso*butylamine.

Anal. Calcd. for $C_{15}H_{25}ClN_2O_4S_2$: C, 49·37; H, 6·91. Found: C, 49·52; H, 6·53.

*5-Chloro-6-sulphamyl-1,2-benzo*isothiazolin-3-one *1,1-dioxide*

* All melting points reported are uncorrected.

(XIII). Compound XII (9·63 g, 0·034 mole) was dissolved in 50 ml of concentrated sulphuric acid in a 3-necked round bottom flask, fitted with a thermometer and stirrer. To this was added slowly 11·15 g (0·037 mole) of sodium dichromate dihydrate. The temperature of the reaction mixture immediately rose to 45–50°. The mixture was stirred at this temperature for one h, and the green mixture was then poured onto ice with stirring. The light tan precipitate was collected on a filter, washed with water and air dried. Two recrystallizations from ethyl acetate gave 4·3 g of pure product, m.p. 274–275°.

Anal. Calcd. for $C_7H_5ClN_2O_5S_2$: C, 28·34; H, 1·70; N, 9·46. Found: C, 28·60; H, 1·65; N, 9·43.

In Tables I and II are outlined the physical and analytical data for the 5-substituted-2,4-thiophen disulphonamides and their *N*,*N'*-disulphamyl derivatives. A typical method for the preparation of these compounds is as follows:

5-Ethyl-2,4-thiophen disulphonamide. To 335 ml of chlorosulphonic acid chilled to −10° in an ice salt bath, there was added dropwise with vigorous stirring 50 g (0·44 mole) of 2-ethylthiophen. The temperature of the reaction mixture was maintained between −10° and −5°. Sodium chloride (312 g) was added over a 2 h period while maintaining the temperature of the reaction at 0°. After allowing the reaction mixture to warm up to room temperature slowly, it was heated at 150° for 3 h. After cooling the flask in an ice water bath, the reaction mixture was decomposed slowly with one l. of ice water. The product was extracted with ether, the extract washed with water and dried over sodium sulphate. After removal of the ether on the steam bath, the residual disulphonyl chloride compound was recrystallized from benzene-hexane, m.p. 102–103°.

Anal. Calcd. for $C_6H_6Cl_2O_4S_3$: C, 23·31; H, 1·95. Found: C, 23·05; H, 1·93.

In several cases the disulphonyl chloride compound was obtained as an oil which resisted all attempts at crystallization. In these cases, the oil was treated directly with the aminating agent.

The disulphonamide was prepared by treating the disulphonyl chloride derivative with ammonium hydroxide as previously described. Yield of pure product, m.p. 205–206°, obtained after ethyl alcohol recrystallization was 45 per cent.

3-Methylthiophen disulphonamides. Forty-nine grams (0·5 mole) of 3-methylthiophen was treated with chlorosulphonic acid in the same manner as described for 2-ethylthiophen. After work-up of the ether extract a dark brown oil remained which could not be obtained in crystalline form. This oil was treated with 150 ml of 28 per cent ammonium hydroxide at 0° and the mixture then heated at 90°–100° for 1 h. On chilling in an ice bath a brown precipitate was obtained which was collected on a filter, washed with water and dried to yield 18 g of crude product. This was recrystallized from ethyl alcohol using Norite. The colourless crystalline powder was collected and melted at 236–238°. This has been assigned structure (XVII), *3-methyl-2,4-thiophen disulphonamide.*

Anal. Calcd. for $C_5H_8N_2O_4S_3$: C, 23·43; H, 3·15. Found: C, 23·70; H, 3·26.

The mother liquors on standing deposited colourless needles which melted at 168°. This compound has been assigned the structure of *3-methyl-2,5-thiophen disulphonamide* (XVIII).

Anal. Calcd. for $C_5H_8N_2O_4S_3$: C, 23·43; H, 3·15; N, 10·93. Found: C, 23·80; H, 3·10; N, 11·12.

Thiophen was sulphonated according to the method outlined above. The product obtained melted at 218° and compares with that reported previously by Jaekel and also by Steinkopf.[13] The structure of this compound was rigorously proven by Steinkopf.

5-Ethyl-3-methyl-2,4-thiophen disulphonamide (XIX). The Wolff-Kishner reduction of 2-acetyl-4-methylthiophen gave a 23 per cent yield of 2-ethyl-4-methylthiophene, b.p. 154–167°/730 mm.

Twenty-four grams (0·158 mole) of 2-ethyl-4-methylthiophen was added dropwise with stirring to 145 ml of chlorosulphonic acid chilled to −10°. During the addition the temperature was maintained at −5°. Then 135 g of sodium chloride was added over a 2 h period at 0°. After heating the contents of the flask at 150° in an oil bath for 4 h, the reaction mixture was chilled and decomposed with ice water. The disulphonyl chloride was extracted with ether, the ether extract washed with water and then dried over sodium sulphate. Removal of the ether yielded a yellow oil (39 g) which was treated at 0° with 200 ml of 28 per cent ammonium hydroxide. After heating the mixture on the

steam bath for one h, the reaction mixture was chilled in an ice bath. The precipitate was collected on a filter, washed with water and recrystallized from ethyl alcohol to yield 5-ethyl-3-methyl-2,4-thiophen disulphonamide, m.p. 228–230°.

Anal. Calcd. for $C_7H_{12}NO_4S_3$: C, 29·56; H, 4·25. Found: C, 29·37; H, 4·21.

Summary. The diuretic effect of some thiophen disulphonamides is comparable to that of the analogous benzene derivatives and to chlorothiazide. The most potent one in this series, 5-ethyl-2,4-thiophen disulphonamide, is about 1/5 as active as hydrochlorothiazide. These thiophen disulphonamides also cause excessive excretion of potassium.

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[11] Lew, H. Y. and Noller, C. R. *J. Amer. chem. Soc.*, **72,** 5715 (1950)
[12] While work in this series was in the state of completion the Hoechst Co. of Germany was issued, on February 1, 1959, the South African Pat. No 3495A-58 for some 5-alkyl-2,4-disubstituted thiophene disulphonamides
[13] (*a*) Jaekel, H. *Ber.* **19,** 184 (1886)
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