SULFANILAMIDOQUINOXALINES

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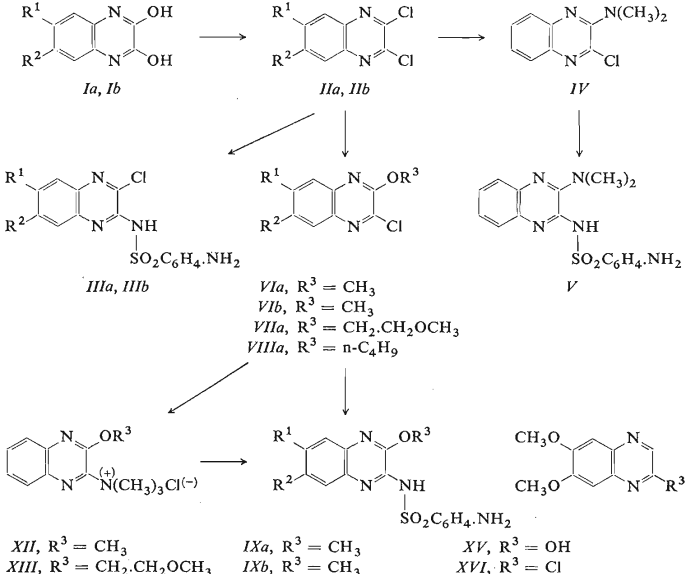
3-Dimethylamino-, 3-methoxy-, 3-(2-methoxyethoxy)- and 3-n-butoxy-2-chloroquinoxaline (*IV*, *VIa*, *VIIa*, *VIIIa*) were prepared from 2,3-dihydroxyquinoxaline (*Ia*) *via* 2,3-dichloro derivative *IIa*. In analogy, 2-chloro-3,6,7-trimethoxyquinoxaline (*VIb*) was prepared from 2,3-dihydroxy-6,7-dimethoxyquinoxaline (*Ib*). Reaction of 4,5-dimethoxy-*o*-phenylenediamine with the hemiacetal of ethyl glyoxylate yielded 2-hydroxy-6,7-dimethoxyquinoxaline (*XV*) which was converted to the 2-chloro derivative *XVI*. Condensation of 4,5-methylenedioxy-1,2-phenylenediamine (*XVIII*) with the diethyl ester of mesoxalic acid yielded the ethyl ester of 3-hydroxy-6,7-methylenedioxy-2-quinoxalinecarboxylic acid (*XIX*) which was chlorinated to the 3-chloro derivative *XX* and saponified to the acid *XXI*. This acid was decarboxylated to 2-chloro-6,7-methylenedioxyquinoxaline (*XXII*). Reactions of the chloro derivatives *IIa*, *IIb*, *IV*, *VIa*, *VIb*, *VIIa*, *VIIIa*, *XVI* and *XXII* either directly with sulfanilamide or after conversion to trimethylammonium salts *XII* and *XIII*, resulted in the sulfonamides *IIIa*, *IIIb*, *V*, *IXa*, *IXb*, *Xa*, *XIa*, *XIVa*, *XVII* and *XXIII*. In comparison with sulfadimidine, 2-dimethylamino-, 2-methoxy- and 2-(2-methoxyethoxy)-3-sulfanilamidoquinoxaline had a significantly higher antibacterial effect toward *Streptococcus pyogenes β-haemolyticus* and *Staphylococcus pyogenes aureus*.

In a previous communication[1] we dealt with the chemical and pharmaceutical research of compounds derived from 3-hydroxy-6,7-dialkoxy-2-quinoxalinecarboxylic acids. It was the aim of the present work to prepare several new sulfanilamidoquinoxalines for bacteriological screening. Of this group, literature reports exist on 3-methoxy-, 5-methoxy- and 6-methoxy-2-sulfanilamidoquinoxaline[2-4].

For the preparation of all the sulfonamides we used as principal intermediates the corresponding 2-chloro derivatives. In their preparation we proceeded from the well-known 2,3-dihydroxyquinoxaline (*Ia*) obtained by condensation of 1,2-phenylenediamine with the diethyl ester of oxalic acid[5,6] which was converted in the usual way *via* the 2,3-chloro derivative *IIa* (using partial alkoxylation) to the corresponding 2-chloro-3-alkoxyquinoxalines (Scheme 1). In this way, 3-methoxy-, 3-(2-methoxyethoxy)- and 3-n-butoxy-2-chloroquinoxaline (*VIa*, *VIIa*, *VIIIa*) were prepared. Similarly, using partial amination, we obtained 3-dimethylamino-2-chloroquinoxaline (*IV*). Condensation of 4,5-dimethoxy-1,2-phenylenediamine with the diethyl ester of oxalic acid we obtained 2,3-dihydroxy-6,7-dimethoxyquinoxaline (*Ib*) which was converted *via* the 2,3-dichloro derivative *IIb* to 2-chloro-3,6,7-trimethoxyquinoxaline (*VIb*). Condensation of 4,5-dimethoxy-1,2-phenylenediamine with the hemi-

acetal of ethyl glyoxylate resulted in 2-hydroxy-6,7-dimethoxyquinoxaline (*XV*) which was processed to the 2-chloro derivative *XVI* with the aid of phosphorus oxychloride. In the preparation of 2-chloro-6,7-methylenedioxyquinoxaline *XXII* we proceeded somewhat differently (Scheme 2). Using the reaction of 4,5-methylenedioxy-1,2-phenylenediamine (*XVIII*) with the diethyl ester of mesoxalic acid we prepared the ethyl ester of 3-hydroxy-6,7-methylenedioxy-2-quinoxalinecarboxylic acid (*XIX*) which was first converted to the 2-chloro derivative *XX* and this was saponified to the acid *XXI*. Decarboxylation of this acid yielded 2-chloro-6,7-methylenedioxyquinoxaline (*XXII*).

The alkoxy-2-chloroquinoxalines thus prepared were processed to the corresponding 2- or 3-sulfanilamidoalkoxyquinoxalines either by a direct reaction with

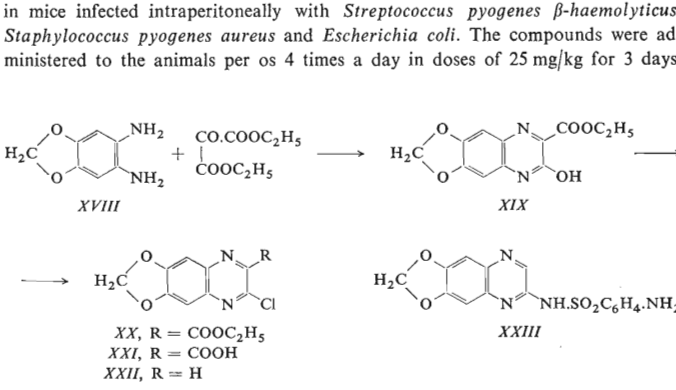


SCHEME 1

sulfanilamide in dimethylformamide in the presence of anhydrous potassium carbonate (method *A*) or according to Klötzer and Bretschneider[7] after amination with trimethylamine by the reaction of the thus obtained quinoxalinyltrimethylammonium chloride with a sodium salt of sulfanilamide (method *B*).

2-Methoxy-3-sulfanilamidoquinoxaline (*IXa*) was described by Stevens and coworkers[3]. Reaction of N^4-acetylsulfanilamide with 2-chloro-2-methoxyquinoxaline in nitrobenzene in the presence of potassium carbonate and Cu-bronze yielded after a complicated isolation 2·8% of a compound melting at 263–264°C. In this laboratory, sulfonamide *IXa* was prepared by both the above methods and the products obtained were purified by precipitation from an ammonia solution and by crystallization. Chromatographically uniform preparations had in both cases a m.p. 229–230°C. The substantial difference in the melting points obtained here and that of Stevens' preparation led to the idea that according to Stevens' procedure the 2-methoxy-3-sulfanilamidoquinoxaline may have been hydrolyzed with sodium hydroxide to which the compound is rather sensitive as was found here. Hence, the sulfonamide *IXa* was heated with 2·5M-NaOH for 3 h in a boiling-water bath which are the conditions used by Stevens and coworkers[3] during isolation of their product. According to thin-layer chromatography on silica gel the reaction mixture contains a small amount of the starting methoxy compound *IXa* but a majority of 2,3-dihydroxyquinoxaline *Ia* and 2-hydroxy-3-sulfanilamidoquinoxaline *Xa* which was also isolated. It is thus assumed that the compound designated by Stevens and coworkers[3] as 2-methoxy-3-sulfanilamidoquinoxaline was a mixture containing predominantly the 2-hydroxy derivative *Xa*.

Sulfonamides *IIIa*, *IIIb*, *V*, *IXa*, *IXb*, *XIa*, *XIVa*, *XVII* and *XXIII* were tested in mice infected intraperitoneally with *Streptococcus pyogenes β-haemolyticus*, *Staphylococcus pyogenes aureus* and *Escherichia coli*. The compounds were administered to the animals per os 4 times a day in doses of 25 mg/kg for 3 days.



SCHEME 2

The sulfonamides *V*, *VIa* and *XIVa* showed a better effect against streptococcal and staphylococcal infection than did sulfadimidine (2-sulfanilamido-4,6-dimethylpyrimidine) which was used as a reference standard in these tests.

EXPERIMENTAL

The melting points were determined in Kofler's block. Samples for elementary analysis were dried for 2 h in oil-pump vacuum (about 0·2 Torr) over phosphorus pentoxide at a temperature proportional to the melting point of the compound.

2-Chloro-3-dimethylaminoquinoxaline (*IV*)

12·2 g 2,3-dichloroquinoxaline[8] was dissolved under stirring in 200 ml 0·6 M ethanolic solution of dimethylamine. After 4 days, the solution was concentrated by distillation *in vacuo*, the residue was mixed with water (60 ml) and made alkaline with sodium carbonate. The precipitated product was crystallized from methanol and had a melting point of 63—63·5°C. The yield was 13·2 g (98·5%). For $C_{10}H_{10}ClN_3$ (207·7) calculated 57·84% C, 4·85% H, 17·07% Cl, 20·23% N; found: 58·18% C, 4·93% H, 16·87% Cl, 20·25% N.

2-Chloro-3-methoxyquinoxaline (*VIa*)

Modification of the procedure[3] made it possible to increase the yield. A solution of sodium methanolate (1·25 g sodium in 150 ml methanol) was added dropwise over a period of 2 h to a suspension of 10 g 2,3-dichloroquinoxaline[6,7] in 375 ml methanol. The mixture was stirred at room temperature for 5 h. Methanol was then distilled away and the residue mixed with 40 ml water. The precipitated product was removed by filtration, washed with water and dried in air. The yield was 9·0 g (93%), m.p. 74—77°C. Reference[3] gives m.p. 74—75°C.

2-Chloro-3-(2-methoxyethoxy)quinoxaline (*VIIa*)

The compound was prepared in analogy to *VIa* by a reaction of *IIa* with sodium 2-methoxyethanolate. Yield 87·4%, m.p. 53—55°C. For $C_{11}H_{11}ClN_2O_2$ (238·7) calculated: 55·36% C, 4·65% H, 14·85% Cl, 11·74% N; found: 55·27% C, 4·72% H, 14·98% Cl, 11·83% N.

2-Chloro-3-n-butoxyquinoxaline (*VIIIa*)

The compound was prepared in analogy to *VIa* by a reaction of *IIa* with sodium butanolate. Yield 7·0 g (59%), m.p. 25—29°C. For $C_{12}H_{13}ClN_2O$ (236·7) calculated: 60·89% C, 5·50% H, 14·98% Cl, 11·86% N; found: 59·40% C, 5·14% H, 14·85% Cl, 11·87% N.

2,3-Dihydroxy-6,7-dimethoxyquinoxaline (*Ib*)

22·8 g 4,5-dinitroveratrol was hydrogenated in 250 ml ethanol with Raney Ni (10 g) at 60—70°C to 4,5-diaminoveratrol[1]. The filtrate after removal of the catalyst was mixed with 90 ml diethyl ester of oxalic acid, the reaction mixture was heated slowly to 175—180°C and maintained at that temperature for 4 h. After cooling, the precipitated product was filtered and washed with ethanol. Yield 18·3 g (82%) of a compound melting at about 360°C (under decomposition). Sample for analysis was purified by precipitation from an alkaline solution with dilute acetic acid and by washing with hot water. It then melted above 360°C (under decomposition). For $C_{10}H_{10}N_2O_4$ (222·2) calculated: 54·05% C, 4·54% H, 12·61% N; found: 53·75% C, 4·46% H, 12·78% N.

2,3-Dichloro-6,7-dimethoxyquinoxaline (*IIb*)

A mixture of 10·0 g *Ib* and 100 ml phosphorus oxychloride was stirred and slowly heated to boiling temperature and refluxed for 3 h. At reduced pressure, the remaining oxychloride was distilled off and the warm (60°C) residue was poured into ice-cold water and neutralized with ammonia. The precipitated product was filtered, washed with water and dried in air. Yield 10·2 g (88%), m.p. 192 to 195°C. A sample for analysis was recrystallized from a mixture of cyclohexane and benzene (1 : 1) and melted at 198—199°C. For $C_{10}H_8Cl_2N_2O_2$ (259·1) calculated: 46·36% C, 3·11% H, 27·37%Cl, 10·81% N; found: 46·41% C, 3·09% H, 27·50% Cl, 10·86% N.

2-Chloro-3,6,7-trimethoxyquinoxaline (*VIb*)

Sodium methylate (0·24 g sodium in 50 ml methanol) was added dropwise over an hour to a solution of 2·59 g *IIb* in 130 ml methanol, whereupon the reaction mixture was stirred and heated to the boiling temperature and refluxed to disappearance of the alkaline reaction (1 h). The product precipitated upon cooling was filtered and washed with water. Yield 2·02 g (79·2%), m.p. 180·5—181·5°C. After two-fold crystallization from ethanol the m.p. did not change. For $C_{11}H_{11}ClN_2O_3$ (254·7) calculated: 51·88% C, 4·35% H, 13·93% Cl, 11·00% N; found: 51·73% C, 4·28% H, 15·65% Cl, 11·19% N.

2-Hydroxy-6,7-dimethoxyquinoxaline (*XV*)

A freshly prepared solution of 4,5-diaminoveratrol[1] (prepared by catalytic hydrogenation of 11·4 g 4,5-dinitroveratrol) in 125 ml ethanol was mixed with aqueous-ethanolic solution of hemiacetal of ethyl glyoxylate[9] and the mixture was heated slowly to boiling under a reflux condenser. After 3 h the heating was terminated, the mixture cooled and the precipitate filtered and washed with water and ethanol. Yield 5·2 g (51%), m.p. 260—266°C. A sample for analysis was crystallized from dimethylformamide and melted at 262—266°C. For $C_{10}H_{10}N_2O_3$ (206·2) calculated: 58·25% C, 4·89% H, 13·58% N; found: 58·95% C, 5·21% H, 13·68% N.

2-Chloro-6,7-dimethoxyquinoxaline (*XVI*)

A mixture of 8·22 g *XV* and 50 ml phosphorus oxychloride was heated to boiling. After 1 h of boiling it was cooled and poured into ice-cold water. Neutralization with ammonia yielded 4·45 g (49·7%) of a compound melting at 152—155°C. A sample for analysis was crystallized from ethanol and melted at 154—156·5°C. For $C_{10}H_9ClN_2O_2$ (224·6) calculated: 53·46% C, 4·04% H, 15·78% Cl, 12·47% N; found: 53·56% C, 4·06% H, 15·83% Cl, 12·49% N.

Ethyl Ester of 3-Hydroxy-6,7-methylenedioxy-2-quinoxalinecarboxylic Acid (*XIX*)

A solution of 10·6 g 4,5-dinitro-1,2-methylenedioxybenzene[10,11] in 100 ml ethanol was hydrogenated on Raney Ni at room temperature. After 5 h, the absorption was terminated (consumption of 6·7 litres at 22°C and 750 Torr). The catalyst was filtered and the formed 4,5-diamino-1,2-methylenedioxybenzene (*XVIII*) was condensated without isolation in an ethanolic solution with 19·5 g diethylmesoxalate by refluxing for 2·5 hr. After cooling, the precipitated product was filtered and washed with water and ethanol. Yield 8·8 g (67),% m.p. 258—259°C (under decomposition). A sample for analysis was crystallized from dioxane and melted at 258—264°C (under decomposition). For $C_{12}H_{10}N_2O_5$ (262·2) calculated: 54·97% C, 3·84% H, 10·68% N; found: 54·76% C, 4·18% H, 10·82% N.

Ethyl Ester of 3-Chloro-6,7-methylenedioxy-2-quinoxalinecarboxylic Acid (*XX*)

8·0 g ester *XIX* was stirred and heated to boiling temperature in 50 ml phosphorus oxychloride. After 1 h of boiling the reaction mixture was poured into ice-cold water and neutralized with 5M-NaOH (150 ml). On the following day, the precipitated product was filtered, washed with water and, while moist, recrystallized from ethanol. Yield 4·4 g (51·5%), m.p. 128—132°C. A sample for analysis was crystallized from ethanol and melted at 132—133°C. For $C_{12}H_9ClN_2O_4$ (280·7) calculated: 51·35% C, 3·23% H, 12·63% Cl, 9·98% N; found: 51·57% C, 3·22% H, 12·70% Cl, 9·90% N.

2-Chloro-6,7-methylenedioxyquinoxaline (*XXII*)

5·6 g ester *XX* was refluxed in a solution of 3·0 g anhydrous sodium carbonate in 200 ml 75% ethanol for 5 h. The reaction mixture was then decolourized with charcoal and evaporated to dryness. The residue was dissolved in a small amount of water and acidified with a small amount of hydrochloric acid. The precipitated 3-chloro-6,7-methylenedioxy-2-quinoxalinecarboxylic acid (*XXI*) was filtered, washed with water and dried. Yield 4·2 g (83·2%) of a compound melting at 210—214°C. Gram-equivalent determined by potentiometric titration: 256·1; for $C_{10}H_5ClN_2.O_4$ calculated: 252·6. 4·1 g acid *XXI* was heated for 10 min to 205°C in diphenyl ether (25 ml). The reaction mixture was diluted with light petroleum and the precipitated product was filtered on the following day and washed with light petroleum. A total of 2·6 g compound (80%) melting at 126—130°C was obtained. A sample for analysis was crystallized from ethanol and melted at 136—138°C. For $C_9H_5ClN_2O_2$ (208·6) calculated: 51·81% C, 2·42% H, 17·00% Cl, 13·43% N; found: 52·06% C, 2·44% H, 16·99% Cl, 13·34% N.

2-Chloro-3-sulfanilamidoquinoxaline (*IIIa*)

A mixture of 4·0 g *IIa*, 3·44 g sulfanilamide, 2·8 g anhydrous sodium carbonate and 15 ml dimethylformamide was heated under stirring for 45 min to 145—150°C. Dimethylformamide was then distilled off at reduced pressure. The residue was dissolved in 100 ml hot water and 5 ml ammonia, the solution was decolourized with charcoal and the product precipitated from warm (35—45°C) filtrate. The product was filtered, stirred with hot water and filtered again. Yield 6·3 g (93·6%), m.p. 208—212°C. The sample for analysis was twice precipitated from dilute ammonia with hydrochloric acid. The m.p. remained unchanged. For $C_{14}H_{11}ClN_4O_2S$ (334·8) calculated: 50·22% C, 3·31% H, 10·59% Cl, 16·74% N, 9·58% S; found: 50·45% C, 3·46% H, 10·38% Cl, 16·85% N, 9·52% S.

2-Chloro-3-sulfanilamido-6,7-dimethoxyquinoxaline (*IIIb*)

A mixture of 4·15 g *IIb*, 2·75 g sulfanilamide, 2·2 g anhydrous potassium carbonate and 15 ml dimethylformamide was heated for 2 h to 145—155°C and further treated as for the preparation of *IIIa*. Yield 2·75 g (44%), m.p. 270—275°C. Sample for analysis was dissolved in dilute ammonia and the solution concentrated *in vacuo* for crystallization. The product was then recrystallized from 50% acetic acid and melted at 276°C. For $C_{16}H_{15}ClN_4O_4S$ (394·8) calculated: 48·67% C, 3·83% H, 8·98% Cl, 14·19% N, 8·12% S; found: 48·73% C, 3·92% H, 9·13% Cl, 14·28% N, 8·26% S.

2-Dimethylamino-3-sulfanilamidoquinoxaline (*V*)

8·6 g sulfanilamide and 4·15 g anhydrous potassium carbonate were added to a solution of 6·22 g *IV* in 30 ml dimethylformamide. The mixture was heated to 150°C and maintained at this tem-

perature for 90 min. It was then distilled at reduced pressure to remove dimethylformamide and the residue was mixed with water (35 ml) and ammonia. After heating to 80°C the insoluble residue was filtered, washed with water (10 ml) and the filtrate decolourized with charcoal. On cooling, a crystalline product precipitated and another fraction was obtained by neutralization of the mother liquor with dilute hydrochloric acid. Yield 5·8 g (56·4%), m.p. 200—202°C. Further crystallization from methanol did not appreciably alter the melting point. For $C_{16}H_{17}.N_5O_2S$ (343·4) calculated: 55·96% C, 4·99% H, 20·39% N, 9·34% S; found: 55·56% C, 5·33% H, 19·58% N, 9·14% S.

(3-Methoxy-2-quinoxalinyl)trimethylammonium Chloride (*XII*)

5·8 g *VIa* was dissolved in 25 ml 3·6M benzene solution of trimethylamine and the solution left to stand at room temperature for 10 days. The quaternary salt was then filtered and washed with benzene. Yield 3·5 g (46%). Attempts at crystallization were not successful. For $C_{12}H_{16}.ClN_3O$ (243·7) calculated: 14·54% Cl^-; found: 14·04% Cl^-.

2-Methoxy-3-sulfanilamidoquinoxaline (*IXa*)

Method A: A mixture of 3·0 g *VIa*, 2·65 g sulfanilamide, 2·15 g anhydrous potassium carbonate and 15 ml dimethylformamide was heated under stirring to 150°C until carbon dioxide evolution stopped (45 min). The dimethylformamide was distilled off at reduced pressure and the residue was dissolved in hot water with an addition of ammonia. After decolourizing with charcoal, the product was precipitated with dilute hydrochloric acid and then reprecipitated from an ammonia solution. The product obtained (4·5 g) melted at 180—205°C. Crystallization from acetone yielded an insoluble compound melting at 278—280°C, which did not show a depression upon mixing with 2-hydroxy-3-sulfanilamidoquinoxaline (*Xa*). Concentration of the mother liquor yielded 3·6 g of a compound melting at 205—210°C which was further crystallized from a mixture of acetone and water (2 : 1) and then from methanol to reach a m.p. of 227—230°C. It was chromatographically uniform. Paper chromatography was done in butanol–ammonia–water (5 : 2 : 2). For $C_{15}H_{14}N_4O_3S$ (330·3) calculated: 54·54% C, 4·27% H, 16·96% N, 9·70% S; found: 54·00% C, 4·35% H, 17·00% N, 9·87% S.

Method B: 2·54 g *XII* was added in parts under stirring to a melted mixture of the sodium salt of sulfanilamide and 4·7 g acetamide at 100–120°C. The melt was maintained at 100–110°C for further 20 min whereupon it was poured into 80 ml water, neutralized with dilute hydrochloric acid and made alkaline again with sodium carbonate (3·0 g). The precipitated excess sulfanilamide was filtered after several hours and the filtrate made acid to pH 3—5. The precipitated product was filtered on the following day, washed with water and, while moist, was dissolved in a mixture of 50 ml water and 10 ml ammonia. The solution was decolourized with charcoal and concentrated at reduced pressure almost to dryness. The crystalline residue was filtered, washed with water and recrystallized first from 50% methanol, then from acetone and finally from methanol. The chromatographically uniform product melted at 229—230°C and showed no depression upon mixing with compound obtained under *A*.

2-n-Butoxy-3-sulfanilamidoquinoxaline (*XIa*)

The compound was prepared from *VIIIa* by method *A*. Yield 59%, m.p. 175°C. A sample for analysis was crystallized from methanol and melted at 178—179°C. For $C_{18}H_{20}N_4O_3S$ (372·4) calculated: 58·05% C, 5·41% H, 15·04% N, 8·61% S; found: 57·96% C, 5·44% H, 15·08% N, 8·76% S.

2,6,7-Trimethoxy-3-sulfanilamidoquinoxaline (*IXb*)

The sulfonamide was prepared from the chloro derivative *VIb* by method *A*. Yield 40%, m.p. 223—226°C (water–dimethylsulfoxide 1 : 1). For $C_{17}H_{18}N_4O_5S$ (390·4) calculated: 52·30% C, 4·65% H, 14·35% N, 8·21% S; found: 52·57% C, 4·94% H, 14·35% N, 8·45% S.

2-(2-Methoxyethoxy)-3-sulfanilamidoquinoxaline (*XIVa*)

A solution of 48·0 g *VIIa* in 205 ml 2·61M trimethylamine in benzene was left to stand for 10 days and the precipitated quaternary ammonium salt *XIII* was filtered. Since it was quite hygroscopic it was used directly for the reaction with sulfanilamide. A mixture of 23·8 g acetamide and 29·5 g sodium sulfanilamide was melted by heating to 140—150°C and, after cooling to 100°C, it was mixed with 15·0 g quaternary ammonium salt *XIII*. The melt was kept at 110°C for another 25 min whereupon it was poured into 400 ml water. After alkalinization with sodium carbonate, the insoluble residue was filtered, the filtrate decolorized with charcoal and, at about 80°C, precipitated with hydrochloric acid. The product (6·2 g) crystallized from methanol and then melted at 182 to 184°C. For $C_{17}H_{18}N_4O_4S$ (374·4) calculated: 54·54% C, 4·84% H, 14·96% N, 8·56% S; found: 54·62% C, 4·83% H, 15·44% N, 8·52% S.

2-Sulfanilamido-6,7-dimethoxyquinoxaline (*XVII*)

A mixture of 3·36 g *XVI*, 2·58 g sulfanilamide, 3·45 g anhydrous potassium carbonate and 8·5 ml dimethylformamide was stirred and refluxed for 2 h. Dimethylformamide was then distilled off at reduced pressure. The distillation residue was dissolved in 100 ml water with an addition of ammonia, decolourized with charcoal and the filtrate neutralized with dilute hydrochloric acid to a weakly acid reaction. The precipitated product (1·7 g) was extracted with 1M ammonia and the solution obtained was evaporated at reduced pressure practically to dryness. The precipitated crystalline sulfonamide was crystallized from 50% dimethyl sulfoxide and from a large amount of water. In both cases a chromatographically pure compound was obtained, m.p. 256—258°C (yield 1·4 g, 26%). For $C_{16}H_{16}N_4O_4S$ (360·4) calculated: 53·32% C, 4·48% H, 15·54% N, 8·89% S; calculated: 53·10% C, 4·49% H, 15·46% N, 8·86% S.

2-Sulfanilamido-6,7-methylenedioxyquinoxaline (*XXIII*)

A mixture of 2·1 g *XXII*, 3·9 g sodium sulfanilamide and 10 ml dimethylformamide was heated for 1 h to 140°C. The reaction mixture was then mixed with 50 ml water and the insoluble fraction was filtered while hot and washed with water. The crude product was dissolved in 50 ml water with an addition of 2 ml 5M-NaOH, decolourized with charcoal and neutralized while hot to a weakly acid reaction with dilute hydrochloric acid. Finally, it was crystallized from 50% ethanol m.p. 301—302°C. Yield 0·43 g (12·5%). For $C_{15}H_{12}N_4O_4S$ (344·3) calculated: 52·32% C, 3·51% H, 16·27% N, 9·31% S; found: 52·59% C, 3·58% H, 16·31% N, 9·48% S.

Alkaline Hydrolysis of 2-Methoxy-3-sulfanilamidoquinoxaline (*IXa*)

A solution of 2·0 g *IXa* in 37 ml 2·5M-NaOH was heated for 3 h in a boiling water bath. The reaction mixture was then neutralized with 5M-HCl (pH 4·5), the precipitated product was removed by filtration and washed with water. A total of 1·63 g (79%) compound melting at 275—278°C was obtained which, according to chromatography on a thin layer of silica gel G (2-propanol-23% ammonia) contained 2-hydroxy-3-sulfanilamidoquinoxaline (*Xa*) as the main component, together with a small amount of the starting substance *IXa*, 2,3-dihydroxyquinoxaline *Ia* and another

unidentified compound. The mixture was dissolved in a mixture of 1M-NH_3 (10 ml) and water (20 ml) and then subjected to fractional precipitation with 1M-CH_3COOH. Three fractions weighing 1·00, 0·22 and 0·10 g were obtained. The first fraction which was chromatographically purest was dissolved while hot in water (15 ml) with an addition of several drops of ammonia. Cooling in a refrigerator resulted in a crystalline ammonium salt (chromatographically homogeneous) which was filtered, dissolved in water and decomposed with dilute acetic acid. The precipitated product (0·42 g, 22·6%) melted at 277·5—278·5°C. For $C_{14}H_{12}N_4O_3S$ (316·3) calculated: 53·15% C, 3·82% H, 17·71% N, 10·13% S; found: 53·46% C, 3·84% H, 17·62% N, 10·16% S.

The analyses were done at the analytical department of this Institute (headed by Dr J. Körbl) The antibacterial tests were conducted by the bacteriological department of this Institute (headed by Dr A. Šimek).

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