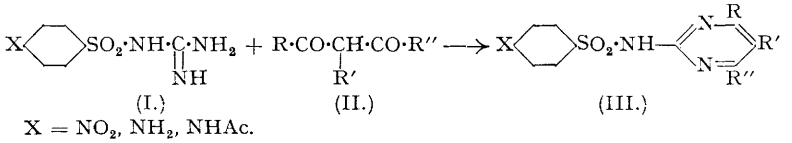
181. 2-p-*Aminobenzenesulphonamidopyrimidines. Preparation by a Novel Route.*

By F. L. Rose and G. Swain.

The preparation is described of a series of sulphanilamide derivatives of pyrimidine by allowing *p*-nitro-, *p*-amino- or *p*-acetamido-benzenesulphonylguanidine to react with β-diketones or β-ketocarboxylic esters.

The sulphanilamides derived from amines of the heterocyclic series provide some of the most active antibacterial drugs of this class. The methods commonly used for their preparation have been adequately reviewed elsewhere (Northey, *Chem. Rev.*, 1940, **27**, 85). The more important require the condensation, usually in an anhydrous acid-binding solvent such as pyridine, of the heterocyclic amine with *p*-nitro- or *p*-acetamido-benzenesulphonyl chloride, followed by conversion of the *para*-substituent to amino. Few attempts have been made to synthesise these substances by building up the heterocyclic ring on to a preformed sulphonamide group.

An analogous route to compounds of the sulphapyrimidine (sulphadiazine) class was described by Haworth and Rose (B.P. 552,887) and is, in part, recorded here in detail. It involved condensation of *p*-nitro-, *p*-amino- or *p*-acetamido-benzenesulphonylguanidine with β-diketones or β-ketocarboxylic esters :



(I.) (II.) (III.)

X = NO_2, NH_2, NHAc.

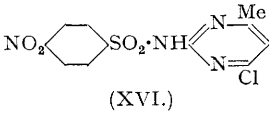
Since the synthesis of the desired product could be effected with readily available compounds (I) this process offered technical advantages over the sulphonyl chloride method which invariably requires anhydrous reaction conditions. Similar condensations to those described here have been recorded independently by the Soc. Chem. Ind. Basle (B.P. 566,571), Cilag (B.P. Appln. 4613/44, and by Ganapathi, Deliwala, and Shirsat (*Proc. Ind. Acad. Sc.*, 1942, **16**, No. 2, Series A, 115) who allowed (I) (X = NH_2 and AcNH) to react with ethyl acetoacetate and its α-alkyl derivatives in the presence of sodium ethoxide. We have found it unnecessary to use this condensing agent since the reaction proceeded smoothly in most cases by heating to a sufficiently high temperature. The reaction has been examined in every case with (I) (X = NO_2, NH_2 and AcNH), but was not equally successful with all three *p*-substituents. Thus the reaction was facile between (I) (X = NO_2, NHAc) and ethyl acetoacetate in excess of the latter under reflux, between (I) (X = NO_2, NH_2) and ethyl oxaloacetate in boiling pyridine, between (I) (X = NHAc) and ethyl oxaloacetone at 130°, and between (I) (X = NH_2) and acetylacetone at 110°. On the other hand, the reaction was sluggish or gave undesired products between (I) (X = NO_2, NH_2) and ethyl oxaloacetone and (I) (X = NO_2, NHAc) and acetylacetone. In the latter case, (I) (X = NHAc) gave a good yield when the reaction was effected in boiling glacial acetic acid in the presence of anhydrous sodium acetate. The condensations with acetylacetone have been extended to the use of homologous β-diketones such as propionylacetone and 3-methylacetylacetone. The pyrimidine derivatives thus prepared are listed below :

Compound No.	(I). X.	(II).	(III). R.	R′.	R″.
(IV)	NO_2	Ethyl acetoacetate	CH_3	H	OH
(V)	AcNH	,, ,,	CH_3	H	OH
(VI)	NO_2	Ethyl oxaloacetate	$CO_2C_2H_5$	H	OH
(VII)	NH_2	,, ,,	$CO_2C_2H_5$	H	OH
(VIII)	AcNH	Ethyl oxaloacetone	$CO_2C_2H_5$	H	CH_3
(IX)	NO_2	Acetylacetone	CH_3	H	CH_3
(X)	NH_2	,,	CH_3	H	CH_3
(XI)	AcNH	,,	CH_3	H	CH_3
(XII)	NH_2	3-Methylacetylacetone	CH_3	CH_3	CH_3
(XIII)	NH_2	Propionylacetone	C_2H_5	H	CH_3
(XIV)	NH_2	Dipropionylmethane	C_2H_5	H	C_2H_5
(XV)	NH_2	Hexoylacetone	α-C_5H_{11}	H	CH_3

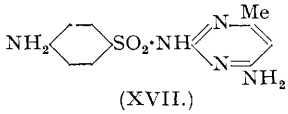
The most important of the above reactions was that which resulted in the formation of 2-*p*-aminobenzenesulphonamido-4 : 6-dimethylpyrimidine (X). As a result of the availability of this substance by this route it has been introduced into medical practice for the treatment of bacterial infections (Macartney, Smith, Luxton, Ramsey and Goldman, *Lancet*, 1942, i, 639; Rose, Martin and Bevan, *J. Pharm. Exp. Therap.*, 1943, **77**, 127). In consequence, its preparation has been the subject of intensive study which need not be reported here in detail. In general, the condensation of (I) (X = NH_2, "sulphaguanidine") with acetylacetone has been shown to proceed readily at temperatures above 110°, and was best effected by using excess diketone as solvent, or by adding a diluent such as acetic acid, phenol or ethanol (pressure reaction). Isolation and purification of the product was facilitated by its solubility in dilute alkali. The parent sulphaguanidine was not soluble in these conditions. The yield was largely independent of the excess diketone used and most of the sulphonylguanidine was accounted for, either as the required reaction product or by recovery unchanged after treatment of the gummy by-products with dilute mineral acid, suggesting that these contained unstable condensation products. These might be anil derivatives, involving the condensation of acetylacetone with the aromatic amine group, or acyclic systems in which the two carbonyl groups of the diketone have condensed with the guanidine groups from two different molecules. All the initial preparations of (X) made over a period of several months in our laboratories by a number of different workers, whether directly from sulphaguanidine or *via* the nitro-compound (IX), were isolated after low temperature drying as the hemihydrate, m. p. 178—180° (corr.). The solubility of this material in water was 192 mg./100 c.c. at 37°. These characteristics corresponded well with those recorded by Caldwell, Kornfeld and Donnell (*J. Amer. Chem. Soc.*, 1941, **63**, 2188) and Sprague, Kissinger and Lincoln (*ibid.*, 1941, **63**, 3028) for the same product prepared by a sulphonyl chloride reaction. A single later preparation (1942) was subsequently found to be anhydrous, to have m. p. 197—198° (corr.) and to be rather less soluble in water at 37° (62 mg./100 c.c.). Examination of reference samples of earlier preparations and of those stored some distance away showed that they all had the higher m. p. Attempts to prepare the hydrated metatastable form have since failed, nor does it appear to have arisen during the later work of Roblin, Winnek and English (*ibid.*, 1942, **64**, 567) when repeating the earlier researches of Caldwell *et al.* (*loc. cit.*), although the former workers observed a tendency of aqueous solutions to supersaturate. The change from metastable to stable form produced no observable differences in antibacterial properties of the drug, measured either *in vitro* or *in vivo*.

The relatively high water solubility of (X) was advantageous from the therapeutic standpoint in reducing the risk of renal damage during elimination from the body. In this connection it may be noted that the corresponding compounds carrying one or no methyl groups in the pyrimidine nucleus are recorded as much less soluble (about 10—15 mg./100 c.c. at 37°). The introduction of a third methyl group in position 5 (XII), however, reduced solubility to this same level.

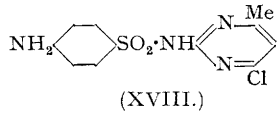
Compound (IV) with phosphoryl chloride gave the corresponding 6-chloro-derivative (XVI), which reacted in hot phenol with ammonia gas to give the corresponding 6-amino-derivative. This, reduced in hot ethanol with iron in the presence of a little hydrochloric acid, gave the diamine (XVII).



(XVI.)



(XVII.)

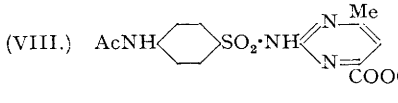


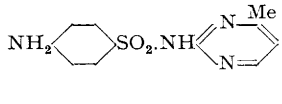
(XVIII.)

Compound (IV) was similarly reduced to the corresponding amine. Attempts to reduce (XVI) to (XVIII) in the same manner failed, but reduction with ferrous sulphate in cold dilute ammonia was successful. Compound (XVIII) dissolved in dilute hydrochloric acid, showed the presence of the primary amino-group by the diazo-reaction. It was obtained pure by rapid recrystallisation from ethanol, but the solution in dilute hydrochloric acid deposited a precipitate on heating for a short time, presumably through inter-molecular condensation.

The condensation of ethyl oxaloacetone with (I) (X = AcNH) has provided an indirect route to 2-*p*-aminobenzenesulphonamido-4-methylpyrimidine (XIX, "Sulphamerazine"). The reaction product (VIII) was saponified with remarkable ease by treatment for a short time with cold dilute sodium hydroxide, and the

(VIII.)





(XIX.)

carboxylic acid group was then easily removed by heating the free acid either alone or, better, in dimethylaniline (Rose and Swain, B.P. 569,228). Finally, the acetyl group was removed with hot dilute hydrochloric acid. The reactivity of the ester group of (VIII) was also shown by formation of the amide in good yield following solution in cold dilute ammonia. The preparation of the un-methylated sulphonamide corresponding to (XIX) by oxidation of the two pyrimidine methyl groups of the acetyl derivative of (X) to carboxyl followed by decarboxylation, was unsuccessful. Potassium permanganate used in the theoretical amount in the presence of magnesium sulphate gave a high yield of (I) (X = AcNH). It was not apparent whether the breakdown of the pyrimidine ring preceded or followed oxidation of the methyl groups.

Condensation of ethyl oxaloacetate with (I) (X = NO_2 or NH_2) giving (VI) and (VII), respectively, gave the highest yield with the sodio-derivative of the ester reacting in boiling pyridine. The carboxylic ester group

was less reactive with dilute sodium hydroxide or ammonia than that of (VIII), being unchanged by treatment for a short time with either. Reduction of (VI) gave a product identical with (VII) and the amine prepared either way was obtained pure in the form of golden yellow needles. The incidence of colour in such a compound was unusual and there was no reason to doubt the structure assigned to it. Solutions in organic solvents and dilute alkalis retained the yellow colour, whereas the solution in dilute hydrochloric acid was colourless.

Experimental.

2-p-*Nitrobenzenesulphonamido*-4-*hydroxy*-6-*methylpyrimidine* (IV).—*p*-Nitrobenzenesulphonylguanidine (Roblin, Williams, Winnek and English, *J. Amer. Chem. Soc.*, 1940, **62**, 2002; 2·5 g.) and ethyl acetoacetate (12·5 c.c.) were refluxed for 1½ hours and the alcohol and water formed in the reaction were allowed to escape. The solid precipitated on cooling was washed on to a filter with a little methanol and crystallised from acetic acid in pale yellow prisms (1·5 g.), m. p. 220—222° (Found : C, 41·9; H, 3·05; N, 17·65. $C_{11}H_{10}O_5N_4S$ requires C, 41·9; H, 3·2; N, 18·1%).

2-p-*Aminobenzenesulphonamido*-4-*hydroxy*-6-*methylpyrimidine* (III, X = NH_2, R = OH, R′ = H, R″ = CH_3).—Compound (IV) (3·2 g.), water (50 c.c.), conc. hydrochloric acid (2 c.c.) and iron filings (15 g.) were refluxed with stirring for 1 hour, made alkaline with caustic soda and filtered. The filtrate was cooled and neutralised with acetic acid. The precipitate was filtered off, dried (2·1 g.) and recrystallised from dilute acetic acid. It was obtained in colourless prisms, m. p. 251°; Ganapathi *et al.* (*loc. cit.*) give m. p. 253—254° (Found : C, 46·55; H, 4·1; N, 19·9. Calc. for $C_{11}H_{12}N_4O_3S$: C, 47·1; H, 4·4; N, 20·0%).

2-p-*Acetamidobenzenesulphonamido*-4-*hydroxy*-6-*methylpyrimidine* (V).—*p*-Acetamidobenzenesulphonylguanidine (2·5 g.) (Marshall, Bratton, White, Litchfield, *Bull. Johns Hopkins Hosp.*, 1940, **67**, 163) and ethyl acetoacetate (12·5 c.c.) were refluxed for 1½ hours allowing the volatile products of the reaction to escape. The crystalline solid which precipitated on cooling was separated and recrystallised from wet β-ethoxyethanol; colourless plates, m. p. 271—273° (Ganapathi *et al.*, *loc. cit.*, give m. p. 273°) (Found : N, 17·2. $C_{13}H_{14}N_4O_4S$ requires N, 17·4%).

Ethyl 2-p-*Nitrobenzenesulphonamido*-4-*hydroxy*-*pyrimidine*-6-*carboxylate* (VI).—*p*-Nitrobenzenesulphonylguanidine (4·9 g.), ethyl oxaloacetate (sodium derivative, 4·0 g.) and pyridine (15 c.c.) were refluxed together for 1½ hours. The reaction mixture was diluted with water (150 c.c.), made alkaline with sodium hydroxide, and filtered from undissolved solid. The filtrate was acidified with hydrochloric acid, the crystalline precipitate filtered off and recrystallised from aqueous ethanol; yellow needles, m. p. 195° (decomp.) (1·1 g.), (Found : C, 41·6; H, 3·3; N, 15·3. $C_{13}H_{12}O_5N_4S$ requires C, 42·3; H, 3·3; N, 15·25%).

Ethyl 2-p-*Aminobenzenesulphonamido*-4-*hydroxy*-*pyrimidine*-6-*carboxylate* (VII).—(a) Compound (VI) (1·6 g.) was dissolved in water (50 c.c.) and concentrated ammonia solution (15 c.c.) at 50°, and ferrous sulphate crystals (8·3 g.) in water (30 c.c.) stirred in during 15 minutes. The suspension was filtered, the filtrate made acid with hydrochloric acid, treated with decolourising charcoal and refiltered. The pale yellow filtrate was made alkaline with ammonia and then neutralised with acetic acid. The precipitate (0·4 g.) recrystallised from a water–ethanol mixture in pale yellow needles, m. p. 212—214° (decomp.) (Found : C, 46·35; H, 4·2; N, 16·25. $C_{13}H_{14}O_5N_4S$ requires C, 46·15; H, 4·15; N, 16·6%). (b) *p*-Aminobenzenesulphonylguanidine (Roblin, Williams, Winnek and English, *loc. cit.*, 46 g.) ethyl oxaloacetate (sodium derivative, 42 g.) and pyridine (100 c.c.) were refluxed together for 1 hour. The excess pyridine was removed under reduced pressure and the syrupy residue shaken with water (500 c.c.), filtered and the filtrate made acid with acetic acid. The semi-solid precipitate was purified by dissolving in cold dilute ammonia, treating with decolourising charcoal and reprecipitating with acetic acid. The product recrystallised from water–ethanol in pale yellow needles (7·1 g.), m. p. 212—214° (decomp.), undepressed by admixture with material made by (a). The yellow colour was not removed by further treatment with decolourising charcoal and since the colour persisted in material made by routes (a) and (b) it was considered to be inherent in the compound.

Ethyl 2-p-*Acetamidobenzenesulphonamido*-4-*methylpyrimidine*-6-*carboxylate* (VIII).—*p*-Acetamidobenzenesulphonylguanidine (60 g.) and ethyl oxaloacetone (90 g.) were heated together for 6 hours in an oil-bath kept at 145—160°. Ethanol (100 c.c.) was added to the brown pasty mass whilst still hot and the mixture cooled, filtered and the crystalline solid washed with a little fresh solvent (68 g., m. p. 214—215°). It crystallised from ethanol in faintly yellow prisms, m. p. 224—225° (decomp.) (Found : C, 49·95; H, 4·7; N, 14·7. $C_{16}H_{18}O_5N_4S$ requires C, 50·8; H, 4·8; N, 14·8%).

2-p-*Acetamidobenzenesulphonamido*-4-*methylpyrimidine*-6-*carboxylic Acid*.—(III, X = AcNH, R = CH_3, R′ = H, R″ = COOH).—The above ethyl ester (crude reaction product, 68 g.) was stirred for 30 minutes at 20—25° in water (250 c.c.) and sodium hydroxide (40% solution, 150 c.c.). The solution was filtered from a little insoluble material and, after standing a further 1 hour, the filtrate was nearly neutralised at 0° with hydrochloric acid. Some hydrolysis of the acetamido-group occurred (diazo-reaction), and acetic anhydride (24 c.c.) was therefore stirred in during 30 minutes. The solution was made strongly acid with hydrochloric acid and the precipitate converted to a crystalline filterable form by adding the whole to boiling water (2000 c.c.). After cooling, the solid was collected (55·4 g., m. p. 252—254° decomp.). It crystallised in colourless needles from water–butanol–ethanol mixture (5 : 3 : 4), m. p. 250° (decomp.) (Found : C, 48·2; H, 4·55; N, 16·2. $C_{14}H_{14}O_5N_4S$ required C, 48·0; H, 4·0; N, 16·0%).

2-p-*Acetamidobenzenesulphonamido*-4-*methylpyrimidine* (III, X = AcNH, R = CH_3, R′ = R″ = H).—The above carboxylic acid (55·3 g.) was stirred in dimethylaniline (80 c.c.) for 3 hours in a bath kept at 220—230° and, after cooling, the solid was washed on to a filter with benzene. It formed small prisms, (46·5 g.), m. p. 242—244° undepressed by admixture with specimen made by the method of Roblin, Williams, Winnek and English (*loc. cit.*).

2-p-*Aminobenzenesulphonamido*-4-*methylpyrimidine* (III, X = NH_2, R = CH_3, R′ = R″ = H).—The solution obtained by refluxing the above acetamido-compound (14 g.) with N-hydrochloric acid (70 c.c.) for ¾ hour was decolourised with charcoal, filtered and made alkaline with ammonia. The solid (8·1 g.), m. p. 224—226°, crystallised from ethyl alcohol in colourless prisms (5·4 g.), m. p. 230—231° undepressed in admixture with an authentic specimen.

2-p-*Acetamidobenzenesulphonamido*-4-*methylpyrimidine*-6-*carboxylamide* (III, X = AcNH, R = CH_3, R′ = H, R″ = $CONH_2$).—(VIII, 2 g.) was dissolved in 3N ammonia (60 c.c.) and, after standing, the solution was acidified with dilute hydrochloric acid. The precipitate (1·9 g., m. p. 267—270°) was recrystallised from aqueous ethanol (2 : 1) and obtained in colourless prisms (1·5 g.), m. p. 272—274° (decomp.) (Found : C, 45·95; H, 4·65; N, 19·15. $C_{14}H_{15}O_4N_5S,H_2O$ requires C, 45·8; H, 4·6; N, 19·1%).

2-p-*Nitrobenzenesulphonamido*-4 : 6-*dimethylpyrimidine* (IX).—*p*-Nitrobenzenesulphonylguanidine (2·5 g.), acetylacetone (2 c.c.) and glacial acetic acid (2 c.c.) were refluxed for 3 hours. The solid, precipitated on adding water, was dissolved in dilute ammonia, filtered and reprecipitated with hydrochloric acid. It crystallised from dilute acetic acid in pale yellow prisms (0·4 g.), m. p. 215° (Found : N, 19·2. $C_{12}H_{12}O_4N_4S$ requires N, 19·2%).

2-p-*Aminobenzenesulphonamido*-4 : 6-*dimethylpyrimidine* (X).—(a) Compound (IX) (1·5 g.) was dissolved in water (80 c.c.) and concentrated ammonia (16 c.c., *d* 0·88) at 50°. A solution of ferrous sulphate crystals (10 g.) in water (40 c.c.) was added and the suspension stirred 15 minutes at 50° and filtered. The filtrate was made acid with acetic acid and the precipitate collected. When crystallised from water and dried at 40°, it formed colourless prisms (0·8 g.), m. p.

176—178° with initial melting and resolidification at 127—130° (Found: C, 50·4; H, 5·0; N, 19·5. $C_{12}H_{14}O_2N_4S,\frac{1}{2}H_2O$ requires C, 50·2; H, 5·2; N, 19·5%). The solubility in water at 37° was 192 mg./100 c.c. determined by a diazo-colourimetric method. Caldwell, Kornfeld and Donnell (*loc. cit.*) give m. p. 178—180° (corr.) and Sprague, Kissinger and Lincoln (*J. Amer. Chem. Soc.*, 1941, **63**, 3028) give m. p. 175·5—176·5° for anhydrous material prepared from the sulphonyl chloride and 2-amino-4:6-dimethylpyrimidine. The former record a solubility of 150 mg./100 c.c. at 29°. 2-*p*-Acetamidobenzenesulphonamido-4:6-dimethylpyrimidine (XI) was obtained as colourless prisms by warming the amine in acetic acid with a little acetic anhydride and adding water, m. p. 244° (Found: N, 17·5. Calc. for $C_{14}H_{12}O_3N_4S$: N, 17·7%). Solubility 115 mg./100 c.c. in water at 37°. Caldwell *et al.* and Sprague *et al.* give m. p. 246·8—247° corr. and 240—241·5°, respectively. (XI) was also obtained directly (21·7 g.) by refluxing for 17 hours a mixture of (I) (X = AcNH, 25·6 g.), acetylacetone (15 g.), acetic acid (75 g.) and anhydrous sodium acetate. (b) *p*-Aminobenzenesulphonylguanidine (85 g.) and acetylacetone (48 c.c.) were stirred together for 21 hours in a bath kept at 160—165° (internal temperature 110—120°). The water formed during the reaction was allowed to escape. On cooling and adding methanol (170 c.c.), crystals of crude 2-*p*-aminobenzenesulphonamido-4:6-dimethylpyrimidine separated (70 g.). A little recrystallised from water gave material identical with that made by (a). Later preparations gave material, m. p. 197—198° and solubility 62 mg./100 c.c. at 37° (Found: C, 51·5; H, 4·65; N, 20·3. Calc. for $C_{12}H_{14}O_2N_4S$: C, 51·8; H, 5·0; N, 20·1%). Roblin, Winnek and English (*loc. cit.*) give m. p. 198—199° (corr.) and solubility 75 mg./100 c.c. at 37°, for their product made by using a sulphonyl chloride and m. p. 249—250° for the acetyl derivative.

The methanol filtrate obtained above was evaporated under reduced pressure. The residual gum did not solidify even after long standing under water but when warmed with dilute hydrochloric acid and then made alkaline with caustic soda, *p*-aminobenzenesulphonylguanidine (22 g.) was recovered.

2-p-*Aminobenzenesulphonamido*-4:5:6-*trimethylpyrimidine* (XII).—*p*-Aminobenzenesulphonylguanidine (10·7 g.) and 3-methylacetylacetone were condensed together as (b) above. The crude product crystallised from β-ethoxyethanol in colourless prisms, m. p. 234—235·5°. Solubility in water, 15 mg./100 c.c. at 37° (Found: N, 19·0. $C_{13}H_{16}O_2N_4S$ requires N, 19·2%).

2-p-*Aminobenzenesulphonamido*-4-*methyl*-6-*ethylpyrimidine* (XIII).—*p*-Aminobenzenesulphonylguanidine (21·4 g.), propionylacetone (12·5 g.), glacial acetic acid (8 c.c.) and *n*-amyl alcohol (40 c.c.) were refluxed for 16 hours. The cooled solution was extracted with 3N sodium hydroxide (70 c.c.) and the aqueous extract made acid with acetic acid. The semi-solid precipitate was dissolved in hot dilute hydrochloric acid, the solution decolourised with charcoal and neutralised with ammonia. The precipitate was collected, washed and dried at 100°, and, when crystallised from *n*-butanol formed colourless prisms (10·7 g.) m. p. 160—162° (Found: N, 19·2. $C_{13}H_{16}O_2N_4S$ requires N, 19·2%).

2-p-*Aminobenzenesulphonamido*-4:6-*diethylpyrimidine* (XIV), similarly prepared, using dipropionylmethane (14 g.), crystallised in colourless prisms from methanol (1·8 g.), m. p. 153—154° (Found: N, 18·3. $C_{14}H_{18}O_2N_4S$ requires N, 18·4%).

2-p-*Aminobenzenesulphonamido*-4-*methyl*-6-n-*amylpyrimidine* (XV). *p*-Aminobenzenesulphonylguanidine (8·6 g.), hexoylacetone (Morgan and Holmes, *J.*, 1924, **125**, 760, 6·2 g.) and *cyclo*hexanol (16 c.c.) were refluxed for 18 hours. The reaction product when worked up as for the 4-methyl-6-ethyl homologue, adding benzene to give better separation of the *cyclo*hexanol-dilute caustic soda mixture, gave colourless prisms (4·9 g.) from aqueous methanol (4·9 g.), m. p. 134—137° (Found: N, 16·5. $C_{16}H_{22}O_2N_4S$ requires N, 16·8%).

4-*Chloro*-2-p-*nitrobenzenesulphonamido*-6-*methylpyrimidine* (XVI).—Compound (IV) (5 g.) and phosphoryl chloride were refluxed together for ½ hour, cooled and added to ice water. The precipitate was separated, dissolved at 40° in water (200 c.c.), rendered alkaline with sodium hydroxide, decolourised with charcoal and precipitated with dilute acetic acid. The crystalline solid was separated, washed with water and dried (4 g.) under reduced pressure over potassium hydroxide, m. p. 203—205° (Found: Cl, 10·5. $C_{11}H_9O_4N_4SCl$ requires Cl, 10·8%).

4-*Chloro*-2-p-*aminobenzenesulphonamido*-6-*methylpyrimidine* (XVIII).—Compound (XVI) (5·5 g.) was dissolved in water (100 c.c.) and ammonia (*d* 0·88; 40 c.c.) and ferrous sulphate crystals (30 g.) in water (50 c.c.) stirred in at 20°. The suspension was stirred during 20 minutes and filtered. The filtrate was successively made acid with hydrochloric acid (adding decolourising charcoal and refiltering), alkaline with ammonia, then neutral with acetic acid. The crystalline precipitate (3 g.) recrystallised from ethanol in colourless rectangular prisms, m. p. 138—140° decomp. (Found: Cl, 11·4. $C_{11}H_{11}O_2N_4SCl$ requires Cl, 11·9%).

2-p-*Aminobenzenesulphonamido*-4-*amino*-6-*methylpyrimidine* (XVII).—Ammonia gas was passed into a solution of (XVI, 5 g.) in phenol (20 g.) heated in a bath kept initially at 100° then raised to 140° during 15 minutes, and kept at that temperature for a further 15 minutes. The cooled reaction mixture was diluted with water, neutralised with acetic acid and the phenol removed in steam. The clear hot supernatant solution was decanted from insoluble matter and, on cooling, deposited colourless crystals. The nitro-compound (1·8 g.), m. p. 200—205° was not further purified but was reduced during refluxing and stirring for 40 minutes in water (100 c.c.) to which iron filings (10 g.) and concentrated hydrochloric acid (2 c.c.) had been added. Sodium hydroxide was added until alkaline and the hot suspension filtered. The hot filtrate was neutralised with acetic acid, and the crystalline precipitate which formed on cooling recrystallised from water in colourless prisms (1·0 g.), m. p. 250—252° (Found: C, 46·3; H, 5·1; N, 24·55. $C_{11}H_{13}O_2N_5S,\frac{1}{3}H_2O$ requires C, 46·3; H, 4·8; N, 24·6%).

Oxidation of 2-p-*Acetamidobenzenesulphonamido*-4:6-*dimethylpyrimidine.*—Potassium permanganate (31·6 g.) was added over 1 hour to a mixture of 2-*p*-acetamidobenzenesulphonamido-4:6-dimethylpyrimidine (XI, 13·9 g.), water (800 c.c.) and anhydrous magnesium sulphate (18 g.) stirred at 95—100°. When the permanganate colour was discharged the suspension was filtered. The filtrate, on cooling, deposited colourless crystals (10 g.), m. p. 257°, undepressed on admixture with authentic specimen of (I, X = AcNH). Refluxing with N-hydrochloric acid (80 c.c.) gave after neutralisation and recrystallisation from water a crystalline solid, m. p. 185°, undepressed in admixture with authentic (I, X = NH_2).

Imperial Chemical Industries Ltd., Research Laboratories,
Hexagon House, Blackley, Manchester, 9.

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