21. p-*Aminobenzenesulphonamide Derivatives of Pyrimidine as Antibacterial Agents.*

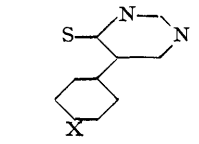
By F. L. Rose and G. A. P. Tuey.

A number of sulphanilamides derived from aminopyrimidines have been prepared and investigated. Those from 2-amino-4 : 6-dialkoxypyrimidines showed unusual pharmacodynamic properties in that they were retained in the blood stream of experimental animals for an exceptional period of time. Exchange of one alkoxy group for another has been observed in the 2-amino-4 : 6-dialkoxypyrimidine series.

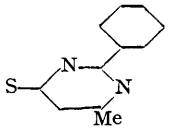
Following the observation by Ewins, Phillips, and Newberry (B.P. 516,288) that the introduction of an α-pyridyl residue into the sulphonamide group of sulphanilamide led to an enhancement of antibacterial activity, many analogous preparations have been made with other heterocyclic systems. For a review of the literature up to 1940 see Northey, *Chem. Rev.*, 1940, **27**, 85.

In general, an effect similar to that observed in the case of sulphapyridine has been found with other analogous compounds containing heterocyclic rings particularly when the sulphonamido group was in the α-position to the tertiary nitrogen atom of the heterocyclic nucleus. The enhanced *in vivo* activity can be attributed to two factors, (*a*) an increase in the intrinsic antibacterial action of the drug as measured by increased *in vitro* activity and (*b*) an improvement in pharmacological properties resulting in the attainment of a higher concentration of the drug in the blood or tissues of the infected host. The incidence of these two factors is particularly marked in the case of the sulphanilamides derived from 2-aminopyrimidine (see, for example, Schmidt, Hughes, Badger, and Schmidt, *J. Pharmacol.*, 1944, **81**, 17; Schmidt, Sealer, and Hughes, *ibid.*, p. 43). Compounds of this type were first described by Roblin, Williams, Winnek, and English (*J. Amer. Chem. Soc.*, 1940, **62**, 2002) who prepared them by interaction of *p*-nitrobenzenesulphonyl chloride and aminopyrimidines followed by reduction of the nitro group. A different route, involving reaction of a *p*-substituted benzenesulphonylguanidine with a β-diketone or β-ketocarboxylic ester, has also been described by Rose and Swain (*J.*, 1945, 689) and others. A very considerable number of sulphanilamidopyrimidines are described in the literature and, although antibacterial activity is not recorded in every instance, it is possible to generalise to a limited extent on the relation between chemical structure and biological effect. 2-*p*-Aminobenzenesulphonamidopyrimidine (" sulphadiazine ") exhibits a high degree of antibacterial activity *in vitro* and persistence in the blood stream of experimental animals. The introduction of a methyl group into position 4- of the pyrimidine nucleus (" sulphamerazine ") is said to produce an even more persistent drug. Two methyl groups in positions 4- and 6- (IV : " sulphamezathine ") reduce intrinsic antibacterial activity somewhat,

but a marked increase in water solubility minimises the incidence of renal blockage during clearance from the animal body. Further chemical variations of the parent compound have been described (see for example, Caldwell, Kornfeld, and Donnell, *J. Amer. Chem. Soc.*, 1941, **63**, 2188; Sprague, Kissinger, and Lincoln, *ibid.*, 1941, **63**, 3028; G. de Sütö-Nagy and Johnson, *ibid.*, 1941, **63**, 3234; Joiner and Spoerri, *ibid.*, 1941, **63**, 1929; Roblin, Winnek, and English, *ibid.*, 1942, **64**, 567; Anderson, Faith, Marson, Winnek, and Roblin, *ibid.*, 1942, **64**, 2902; Backer and Grevenstuck, *Rec. trav. chim.*, 1942, **61**, 291), but no compound having improved properties appears to have been obtained. Nevertheless, we have continued during the past few years investigations of this type of sulphanilamide, and now record the chemical work with brief description of biological activity. Only sulphonamides derived from 2-amino- and 4-amino-pyrimidines have been examined and the emphasis has been on compounds which would exhibit favourable pharmacological properties. It appeared that the 4-*p*-aminobenzenesulphonamidopyrimidines were deficient in this respect (Roblin, Winnek, and English, *loc. cit.*), but it was considered that the introduction of substituents such as phenyl into the pyrimidine nucleus might overcome the defect. Suitably substituted aminopyrimidines have been described by Davies and Piggot (*J.*, 1945, 347) and Davies, Johnson, and Piggott (*ibid.*, p. 352), and the compounds (I) have been prepared by reaction with *p*-nitrobenzenesulphonyl chloride followed by reduction of the nitro group.



(X = H, Cl, and MeO).
(I.)



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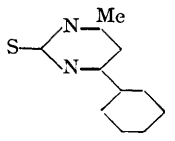

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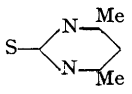

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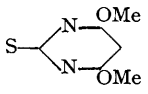
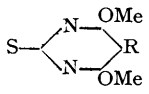
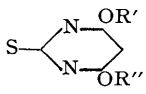


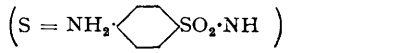
(V.)



(VI.)



(VII.)



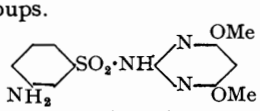
The related compound (II) and the 2-sulphanilamido derivative (III) were prepared in a similar manner. These compounds have been examined by Dr. A. R. Martin for *in vitro* and *in vivo* activity against the hæmolytic streptococcus. Only (I, X = H) was more effective than sulphanilamide and this substance was also more persistent in the blood stream of mice than the latter drug. It is, however, only sparingly soluble in water (3·5 mg./100 c.c. at 37°).

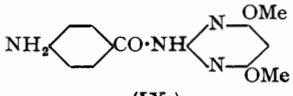
In view of the interest, already mentioned, in 2-sulphanilamido-4 : 6-dimethylpyrimidine (IV), an analogous preparation (V) was made in which the methyl groups were replaced by methoxyl. Related compounds containing one methoxyl group substituted into the pyrimidine nucleus have been described by Roblin, Winnek, and English (*loc. cit.*) but do not appear to have been of special interest. Compound (V), however, exhibited a higher degree of persistence in the blood stream of mice than any other sulphanilamide drug examined in these laboratories. It was also more active *in vitro* against experimental streptococcal infections. This substance was also unusual in that its acetyl derivative, although devoid of *in vitro* activity, was almost as effective *in vivo* as the free amine. This was shown to be due to a rapid de-acetylation in the animal body. These results will be published in detail elsewhere. The parent 2-amino-4 : 6-dimethoxypyrimidine was described by Fisher and Johnson (*J. Amer. Chem. Soc.*, 1932, **54**, 727); it was made by heating 4 : 6-dichloro-2-aminopyrimidine and sodium methoxide under pressure at 160—170°. It has now been shown that this reaction, which proceeds by stepwise replacement of the chlorine atoms, can be effected at atmospheric pressure. The first chlorine atom was rapidly replaced by methoxyl by heating in excess of methanol or more slowly by stirring the reactants together at room temperature. Addition of xylene to the reaction mixture and removal of the excess alcohol by distillation, finally refluxing for some hours, gave a 77·5% yield of the dimethoxy derivative. The aminopyrimidine was converted into the sulphanilamide by allowing it to react with 4-nitro- or 4-acetamido-benzenesulphonyl chloride and reducing or hydrolysing the resulting product; the second method gave the better yield.

The high antibacterial activity of (V) led us to prepare other dialkoxy compounds of the same type. Thus methyl and ethyl were introduced into the 5-position of the pyrimidine nucleus (VI : R = Me or Et). As in the case of type (IV) (Rose and Swain, *loc. cit.*) such substitution led to a marked reduction in solubility in water. Compound (VI, R = Et) was sparingly soluble, and so were its sodium salt and hydrochloride. The parent aminopyrimidines were made in a manner analogous to that used for (V) by condensing the appropriately substituted ethyl malonate with guanidine, converting the product into the dichloro compound by means of phosphoryl chloride and into the final substance by the action of sodium methoxide in boiling xylene. Higher homologues of (V) (VII, R′ = R″ = Et, Pr$^{\alpha}$, Pr$^{\beta}$, Bu$^{\alpha}$, $-C_2H_4\cdot O\cdot Et$) were prepared similarly through the corresponding *p*-nitrobenzenesulphonamides, followed by reduction of the nitro group. Where R′ = R″ = Bu$^{\alpha}$ or $-C_2H_4\cdot O\cdot Et$ the final products were most conveniently isolated as the sodium salts. Compounds of type (VII, R′ = R″) were also prepared as follows: 4-chloro-2-amino-6-methoxypyrimidine was treated with

the higher sodium alkoxides by heating in excess of the corresponding alcohol or in xylene. In all cases examined (ethoxide, propoxide, butoxide), the dialkoxypyrimidines isolated from the reaction mixtures were mainly the symmetrical 4 : 6-diethoxy, dipropoxy and dibutoxy derivatives, respectively. It was apparent, therefore, that replacement of the methoxy group by the higher alkoxy groups had occurred, analogous to the ester interchange reaction in the carboxylic acid series. This phenomenon emphasised the essentially acid character of the hydroxyl groups substituted in the 4- and 6-positions of pyrimidine. Further experiments showed that the converse replacement of higher by lower alkoxy groups was possible, since 4-chloro-2-amino-6-ethoxypyrimidine gave considerable amounts of the dimethoxy derivative when treated with sodium methoxide in excess methanol. This suggested that the final reaction products constituted an equilibrium mixture the nature of which depended on which alcohol or alkoxide was present in excess; in accordance with this it was subsequently found that reaction of 4-chloro-2-amino-6-methoxypyrimidine with rather less than a molar quantity of sodium ethoxide in the absence of excess ethanol, gave substantial yields of the required asymmetric 2-amino-4-methoxy-6-ethoxypyrimidine. This compound was converted to its sulphanilamide derivative through condensation with *p*-acetamidobenzenesulphonyl chloride.

Biological examination of compounds (VI) and (VII) has shown them to be less effective than (V) against infections in mice, although all retain a high degree of persistence in the blood of the experimental animal, but at a lower average level than that given by (V). The reason for the unique pharmacological properties of this type of substance is now being investigated. It was thought, however, that some preliminary insight into the phenomenon might be gained by examination of compounds such as (VIII) and (IX), which would indicate how far the persistence effect was due to the 2-amido-4 : 6-dimethoxypyrimidine moiety or to the sulphanilamide structure as a whole. These compounds were made by condensation of the aminopyrimidine with *m*-nitrobenzenesulphonyl chloride and *m*-nitrobenzoyl chloride, respectively, and reduction of the nitro groups.


(VIII.)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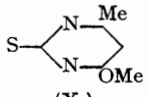
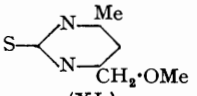

(X.)


(XI.)

Only (VIII) behaved similarly to (V) indicating that the sulphonamide group may be essential but that the primary amino group need not be in the *para* position. In this connection it should be noted that *p*-aminobenzoic acid is very rapidly removed from the blood stream of mice (Martin and Rose, *Biochem. J.*, 1945, **39**, 91). Two further compounds (X) and (XI) bearing some relation to (V), in that both carry methoxy substituents, were made.

Compound (X) was prepared by the method used for the preparation of (VIII), and (XI) was made by condensation of *p*-aminobenzenesulphonylguanidine (" sulphaguanidine ") with 1-methoxypentane-2 : 4-dione in the manner described by Rose and Swain (*loc. cit.*). The same compound prepared by the sulphonyl chloride route has been described by Backer and Grevenstuck (*loc. cit.*). Neither (X) nor (XI) was superior to sulphanilamide in antibacterial activity.

Experimental.

2-Aminopyrimidine Intermediates.—*2-Amino-4 : 6-dimethoxypyrimidine.* Sodium (9·6 g.) was dissolved in methanol (160 c.c.), dry xylene (160 c.c.) added followed by 4 : 6-dichloro-2-aminopyrimidine (32·8 g., Büttner, *Ber.*, 1903, **36**, 2228). After the initial vigorous reaction, the mixture was heated in an oil-bath at 140—150° for 3 hours, allowing the methanol to distil away, benzene (100 c.c.) and water (200 c.c.) added and, after filtration, the benzene layer was distilled away. 2-Amino-4 : 6-dimethoxypyrimidine distilled at 252°/760 mm. (24 g., m. p. 92—93°). The *picrate*, prepared in methanol, crystallised from methanol–*β*-ethoxyethanol in yellow needles, m. p. 208° (Found : N, 21·9. $C_6H_9O_2N_3$,$C_6H_3O_7N_3$ requires N, 21·8%). According to Fisher and Johnson (*loc. cit.*) the base has m. p. 95°.

2-Amino-4 : 6-diethoxypyrimidine was prepared similarly from sodium (7·2 g.), ethanol (75 c.c.), xylene (50 c.c.) and 4 : 6-dichloro-2-aminopyrimidine (24·6 g.); it distilled at 265—266°/760 mm. (21·2 g., colourless crystals, m. p. 101°, from benzene) (Found : C, 51·85; H, 7·1; N, 22·5. $C_8H_{13}O_2N_3$ requires C, 52·4; H, 7·1; N, 22·9%). The *picrate*, prepared in methanol, crystallised from ethanol in yellow needles, m. p. 162° (Found : N, 20·15. $C_8H_{13}O_2N_3$,$C_6H_3O_7N_3$ requires N, 20·3%).

2-Amino-4 : 6-di-n-propoxypyrimidine was prepared from sodium (4·6 g.), *n*-propanol (100 c.c.), xylene (50 c.c.), and 4 : 6-dichloro-2-aminopyrimidine (16·5 g.); it distilled at 184°/42 mm. (16 g., colourless crystals, m. p. 72°, from ligroin) (Found : C, 57·05, H, 7·8; N, 19·45. $C_{10}H_{17}O_2N_3$ requires C, 56·9; H, 8·1; N, 19·9%). The *picrate*, prepared in methanol, crystallised from *β*-ethoxyethanol in yellow needles, m. p. 188° (Found : N, 19·15. $C_{10}H_{17}O_2N_3$,$C_6H_3O_7N_3$ requires N, 19·1%).

*2-Amino-4 : 6-di-*iso*propoxypyrimidine* was prepared using quantities as for *n*-propoxy derivative; it distilled at 160°/30 mm. (13·8 g., colourless crystals, m. p. 90°, from ligroin) (Found : C, 56·55; H, 7·55; N, 19·35. $C_{10}H_{17}O_2N_3$ requires C, 56·9; H, 8·1; N, 19·9%). The *picrate*, prepared in and recrystallised from methanol, formed yellow needles, m. p. 108° (Found : N, 19·1. $C_{10}H_{17}O_2N_3$,$C_6H_3O_7N_3$ requires N, 19·1%).

2-Amino-4 : 6-di-n-butoxypyrimidine, prepared from sodium (7·2 g.), *n*-butanol (150 c.c.), xylene (50 c.c.), and 4 : 6-dichloro-2-aminopyrimidine (24·6 g.), distilled at 192°/17 mm. (27·9 g., colourless needles, m. p. 58°, from ligroin) (Found : C, 60·3; H, 8·45; N, 17·35. $C_{12}H_{21}O_2N_3$ requires C, 60·2; H, 8·8; N, 17·6%). The *picrate*, prepared in and recrystallised from methanol, formed yellow needles, m. p. 182—183° (Found : N, 17·75. $C_{12}H_{21}O_2N_3$,$C_6H_3O_7N_3$ requires N, 17·9%).

2-Amino-4 : 6-di-(β-ethoxyethoxy)-pyrimidine. Sodium (4·6 g.) was dissolved in *β*-ethoxyethanol (70 c.c.) and 4 : 6-dichloro-2-aminopyrimidine (16·5 g.) added. After the initial vigorous reaction the mixture was heated for 4 hours in an oil-bath 160—180°. Excess *β*-ethoxyethanol was removed under reduced pressure, the residue treated with water, extracted twice with ether, and the ether layer distilled. The aminopyrimidine boiled at 228—230°/12 mm. (24 g.

colourless viscous liquid). The *picrate*, prepared in methanol, crystallised from aqueous methanol in yellow needles, m. p. 121° (Found: C, 42·9; H, 4·55; N, 16·45. $C_{12}H_{21}O_4N_3,C_6H_3O_7N_3$ requires C, 43·2; H, 4·8; N, 16·8%).

4-*Chloro*-2-*amino*-6-*methoxypyrimidine*. Sodium (23 g.) was dissolved in methanol (300 c.c.), 4 : 6-dichloro-2-aminopyrimidine (82 g. finely powdered) added, the suspension was stirred at laboratory temperature for 24 hours and filtered. The solid was washed with methanol, then with water to remove sodium chloride and dried at 60° (63 g., m. p. 159—162°). It crystallised from toluene (500 c.c.) in colourless needles (47 g., m. p. 164—166°) (Found: Cl, 22·7. Calc. for $C_5H_6ON_3Cl$:Cl, 22·3%). Gabriel and Colman (*Ber.*, 1903, **36**, 3381) give m. p. 168—169°.

4-*Chloro*-2-*amino*-6-*ethoxypyrimidine*, prepared similarly from sodium (3·5 g.), ethanol (100 c.c.), and 4 : 6-dichloro-2-aminopyrimidine (16·4 g.), was isolated from the alcoholic filtrate by adding water (500 c.c.) and crystallised twice from ligroin (6 g., colourless prisms, m. p. 87°) (Found: Cl, 21·0; N, 23·85. $C_6H_8ON_3Cl$ requires Cl, 20·95; N, 24·1%).

2-*Amino*-4-*methoxy*-6-*ethoxypyrimidine*. (i) A mixture of sodium (4·4 g.) in ethanol (60 c.c.) and xylene (50 c.c.) with 4-chloro-2-amino-6-methoxypyrimidine (15 g.) was heated in an oil-bath at 170° for 8 hours, the alcohol being allowed to distil away. The only isolated product, obtained as above, was 2-amino-4 : 6-diethoxypyrimidine (7·7 g., m. p. 101—102°, undepressed in admixture with authentic sample). A similar experiment in which methanol replaced ethanol and 4-chloro-2-amino-6-ethoxypyrimidine the corresponding methoxy derivative gave, likewise, 2-amino-4 : 6-dimethoxypyrimidine (3·3 g., m. p. 91°; undepressed in admixture with authentic sample). It was probable that in both cases the required methoxyethoxy pyrimidine was formed to some extent during the reactions but was not isolated. (ii) Sodium (2·5 g.) was dissolved in a mixture of ethanol (17 c.c.) and xylene (50 c.c.) and the excess alcohol distilled away. 4-Chloro-2-amino-6-methoxypyrimidine (17·5 g.) was added, the mixture was refluxed for 2 hours and, after diluting with benzene, was extracted with hydrochloric acid (200 c.c., 5N). The aqueous layer was made alkaline with sodium hydroxide, the precipitated oil taken into ether, dried over potassium hydroxide and distilled. The fraction boiling at 226—228°/736 mm. was collected (9·7 g.), crystallised from ligroin and twice from water. 2-*Amino*-4-*methoxy*-6-*ethoxypyrimidine* formed colourless needles, m. p. 98° (Found: N, 24·4. $C_7H_{11}O_2N_3$ requires N, 24·8%). The *picrate*, prepared in ethanol, crystallised from water in yellow plates, m. p. 185—186° (Found: C, 39·05; H, 3·95; N, 21·4. $C_7H_{11}O_2N_3,C_6H_3O_7N_3$ requires C, 39·2; H, 3·6; N, 21·1%).

2-*Amino*-4 : 6-*dimethoxy*-5-*methylpyrimidine*. 4 : 6-Dichloro-2-amino-5-methylpyrimidine (10·9 g., prepared by the method of Gabriel and Colman starting with diethyl α-methylmalonate in place of diethyl malonate), sodium (4·3 g.) in methanol (45 c.c.) and xylene (50 c.c.) were heated together for 4 hours in an oil-bath at 160—170°. The reaction mixture, worked up as above, gave 2-*amino*-4 : 6-*dimethoxy*-5-*methylpyrimidine* in colourless crystals (5 g., m. p. 112—114°) from ligroin (Found: N, 24·6. $C_7H_{11}O_2N_3$ requires N, 24·8%).

2-*Amino*-4 : 6-*dimethoxy*-5-*ethylpyrimidine*, prepared analogously, gave colourless crystals, m. p. 92—94°, from ligroin (Found: N, 22·55. $C_8H_{13}O_2N_3$ requires N, 22·95%).

Sulphanilamide Derivatives.—2-p-*Aminobenzenesulphonamido*-4 : 6-*dimethoxypyrimidine* (V). (i) 2-Amino-4 : 6-dimethoxypyrimidine (15·5 g.), *p*-acetamidobenzenesulphonyl chloride (23·4 g.), and pyridine (30 c.c.) were mixed and heated at 60—70° for 1 hour, then at 40° for 16 hours. The granular mass, obtained on adding water, was purified by boiling with a mixture of methanol (50 c.c.) and water (20 c.c.) and recrystallised from aqueous β-ethoxyethanol giving 2-p-*acetamidobenzenesulphonamido*-4 : 6-*dimethoxypyrimidine*, m. p. 235° (Found: N, 16·1. $C_{14}H_{16}O_5N_4S$ requires N, 15·9%). The acetyl group was removed by boiling with N-NaOH (200 c.c.) for 6 hours and treating the product with decolorising charcoal successively in alkaline and in hydrochloric acid solution, finally precipitating with ammonia. 2-p-*Aminobenzenesulphonamido*-4 : 6-*dimethoxypyrimidine* gave colourless crystals, m. p. 171·5°, from methanol (Found: C, 46·75; H, 4·9; N, 17·85; MeO, 19·7. $C_{12}H_{14}O_4N_4S$ requires C, 46·5; H, 4·5; N, 18·1; MeO, 20·0%). (ii) 2-Amino-4 : 6-dimethoxypyrimidine (3·1 g.), *p*-nitrobenzenesulphonyl chloride (4·5 g.) and pyridine (5 c.c.) were mixed, warmed to 60°, and then set aside at 20° for 48 hours. The resultant paste was washed with water by decantation, dissolved in cold dilute sodium hydroxide, decolorised with charcoal and neutralised with acetic acid. The precipitate was dried (3·9 g.). The crude nitro compound (6·8 g.) was reduced by refluxing for 6 hours with iron filings (6 g.) in β-ethoxyethanol (20 c.c.) and concentrated hydrochloric acid (0·5 c.c.). The reduction mixture was added to water (200 c.c.) containing 2N-sodium carbonate (25 c.c.) and filtered. The filtrate was neutralised with acetic acid. The precipitate (tar + crystals), formed on standing, was purified by solution successively in dilute hydrochloric acid and sodium hydroxide. The product was contaminated with coloured impurities and only after repeated crystallisation from methanol had m. p. 175·5°, undepressed in admixture with material made by method (i).

2-p-*Aminobenzenesulphonamido*-4 : 6-*diethoxypyrimidine* (VII, R′ = R″ = Et), prepared by method (ii), the intermediate nitro derivative (crystallised, m. p. 156°, from ethanol) being reduced in ethanol, gave colourless crystals, m. p. 140°, from aqueous β-ethoxyethanol (Found: N, 15·4; S, 8·85. $C_{14}H_{18}O_4N_4S,2H_2O$ requires N, 15·0; S, 8·55%).

2-p-*Aminobenzenesulphonamido*-4 : 6-*di*-n-*propoxypyrimidine* (VII, R′ = R″ = Pr$^{\alpha}$), prepared by method (ii) (effecting the reduction of the nitro compound in *n*-propanol in place of β-ethoxyethanol), gave colourless crystals, m. p. 128—129°, from methanol (Found: N, 15·25; S, 8·75. $C_{16}H_{22}O_4N_4S$ requires N, 15·3; S, 8·75%).

2-p-*Aminobenzenesulphonamido*-4 : 6-*di*-iso*propoxypyrimidine* (VII, R′ = R″ = Pr$^{\beta}$), prepared similarly to *n*-propoxy derivative and crystallised from methanol, had m. p. 159—160° after drying under reduced pressure at 80° (Found: N, 15·25; S, 8·9. $C_{16}H_{22}O_4N_4S$ requires N, 15·3; S, 8·75%).

2-p-*Aminobenzenesulphonamido*-4 : 6-*di*-n-*butoxypyrimidine* (VII, R′ = R″ = Bu$^{\alpha}$) was prepared by method (ii). The intermediate nitro derivative was purified through its sparingly soluble *sodium salt*; yellow leaflets, m. p. 140°, from aqueous methanol (Found: C, 46·6; H, 5·6; S, 6·9; Na, 4·65. $C_{18}H_{23}O_4N_4SNa,H_2O$ requires C, 46·5; H, 5·4; S, 6·9; Na, 4·95%). The reduction of the nitro compound was carried out in butanol in place of β-ethoxyethanol; this allowed the sodium salt of the amine to crystallise from the hot alkaline filtrate; colourless crystals, m. p. 275° (after drying at 110°), from butanol (Found: C, 48·45; H, 5·95; N, 12·9; S, 7·3; Na, 5·4. $C_{18}H_{25}O_4N_4SNa,1\frac{1}{2}H_2O$ requires C, 48·7; H, 6·3; N, 12·65; S, 7·2; Na, 5·2%).

2-p-*Aminobenzenesulphonamido*-4-*methoxy*-6-*ethoxypyrimidine* (VII, R′ = Me, R″ = Et) was prepared by a modification of method (i). The intermediate acetamido derivative was not isolated but was hydrolysed directly by adding 12 equivalents of 5N-NaOH and distilling away the pyridine in steam during 20 minutes. The crude base was precipitated with acetic acid and purified by clarifying successively the solutions in dilute hydrochloric acid and dilute aqueous ammonia, finally crystallising from benzene; colourless prisms, m. p. 127—128° (Found: C, 48·5; H, 4·65; N, 17·1. $C_{13}H_{16}O_4N_4S$ requires C, 48·2; H, 4·9; N, 17·3%).

2-p-*Aminobenzenesulphonamido*-4 : 6-*dimethoxy*-5-*methylpyrimidine* (VI, R = Me) was prepared similarly by the modification of method (i). The amine was isolated as its sodium salt on cooling after steam distillation of the pyridine; it was dissolved in hot water, converted into free sulphonamide with acetic acid, and recrystallised from aqueous dioxan; it had m. p. 227—228° (Found: S, 9·6. $C_{13}H_{16}O_4N_4S$ requires S, 9·85%).

2-p-*Aminobenzenesulphonamido*-4 : 6-*dimethoxy*-5-*ethylpyrimidine* (VI, R = Et) was prepared and isolated analogously; it was crystallised from *o*-dichlorobenzene (or aqueous dioxan) and obtained in colourless plates, m. p. 234—236° (Found: S, 9·2. $C_{14}H_{18}O_4N_4S$ requires S, 9·45%); it was not readily soluble either in dilute acids or in alkalis.

4-p-*Aminobenzenesulphonamido*-5-*phenylpyrimidine* (I, X = H). *p*-Nitrobenzenesulphonyl chloride (4·5 g.) was

condensed with 4-amino-5-phenylpyrimidine (3·4 g., Davies *et al.*, *loc. cit.*) in pyridine (10 c.c.) on the water-bath for 2 hours. The crude nitro compound obtained on adding dilute hydrochloric acid was partly purified by extraction with dilute sodium hydroxide and reprecipitation with acid, and reduced by refluxing for 3·5 hours in water (50 c.c.), concentrated hydrochloric acid (2 c.c.) and iron filings (10 g.). The base was isolated by making alkaline with sodium hydroxide, filtering and neutralising the filtrate with acetic acid. It formed colourless plates from aqueous β-ethoxyethanol, m. p. 253—255° (Found: N, 17·2. $C_{16}H_{14}O_2N_4S$ requires N, 17·2%).

4-p-*Aminobenzenesulphonamido*-5-p-*anisylpyrimidine* (I, X = OMe), colourless needles from aqueous β-ethoxyethanol, m. p. 269° (Found: N, 16·25. $C_{17}H_{16}O_3N_4S$ requires N, 16·5%), and 4-p-*aminobenzenesulphonamido*-5-p-*chlorophenylpyrimidine* (I, X = Cl), colourless prisms from aqueous β-ethoxyethanol, m. p. 267° (Found: N, 15·05. $C_{16}H_{13}O_2N_4SCl$ requires N, 15·2%), were prepared analogously.

2-p-*Aminobenzenesulphonamido*-4-*phenyl*-6-*methylpyrimidine* (III), prepared by method (ii) from 2-amino-4-phenyl-6-methylpyrimidine (Evans, *J. pr. Chem.*, 1893, **48**, 513), formed colourless crystals from β-ethoxyethanol m. p. 236° (Found: C, 60·2; H, 4·65; N, 16·3. $C_{17}H_{16}O_2N_4S$ requires C, 60·0; H, 4·7; N, 16·45%).

6-p-*Aminobenzenesulphonamido*-2-*phenyl*-4-*methylpyrimidine* (II), prepared by method (ii) from 6-amino-2-phenyl-4-methylpyrimidine (Pinner, *Ber.*, 1887, **20**, 2363), was recrystallised from ethanol. It had m. p. 210—211° (Found: N, 16·35. $C_{17}H_{16}O_2N_4S$ requires N, 16·45%).

2-p-*Aminobenzenesulphonamido*-4-*methoxy*-6-*methylpyrimidine* (X), prepared by method (ii) from 2-amino-4-methoxy-6-methylpyrimidine (m. p. 154—155°, from the chloro compound and sodium methoxide) and reducing the intermediate nitro derivative (m. p. 256°) with iron filings in β-ethoxyethanol, formed colourless crystals from methanol, m. p. 195° (Found: C, 48·95; H, 5·2; N, 18·4. $C_{12}H_{14}O_3N_4S$ requires C, 49·0; H, 4·5; N, 19·0%).

2-p-*Aminobenzenesulphonamido*-6-*methyl*-4-*methoxymethylpyrimidine* (XI). *p*-Aminobenzenesulphonylguanidine (4·3 g.), 1-methoxypentane-2 : 4-dione (3·4 g., prepared by a method analogous to that used by Sommelet (*Bull. Soc. chim.*, 1907, **4**, 382) for the ethoxy compound), amyl alcohol (6 c.c.), and acetic acid (2 c.c.) were heated together for 16 hours in an oil-bath at 150°. A dilute sodium hydroxide extract of the reaction mixture was clarified with decolorising charcoal and neutralised with dilute acid. The semi-solid precipitate crystallised when stirred with methanol and was recrystallised from the same solvent, giving 1·1 g., m. p. 167—170° (Found: C, 51·05; H, 5·75; N, 17·8; MeO, 10·1. $C_{13}H_{16}O_3N_4S$ requires C, 50·7; H, 5·2; N, 18·2; MeO, 9·75%).

Miscellaneous Amides.—2-m-*Aminobenzenesulphonamido*-4 : 6-*dimethoxypyrimidine* (VIII). *m*-Nitrobenzenesulphonyl chloride (11·1 g.), 2-amino-4 : 6-dimethoxypyrimidine (8·5 g.) and pyridine (50 c.c.) were kept at 90° for 1 hour. The reaction mixture was stirred with dilute hydrochloric acid and the dark gummy residue was dissolved in dilute sodium hydroxide, clarified with decolorising charcoal, and the precipitate with acetic acid collected and crystallised from aqueous β-ethoxyethanol (3·0 g., m. p. 149—151°). This was reduced in methanol solution with hydrogen at atmospheric temperature and pressure in the presence of nickel. The residue after filtration from catalyst and distillation of the solvent, crystallised in colourless needles from butanol (1·2 g., m. p. 134°) (Found: N, 17·75. $C_{12}H_{14}O_4N_4S$ requires N, 18·1%).

2-p-*Aminobenzamido*-4 : 6-*dimethoxypyrimidine* (IX). *p*-Nitrobenzoyl chloride (9·3 g.), 2-amino-4 : 6-dimethoxypyrimidine (7·8 g.) and pyridine (20 c.c.) were mixed at 50—60° and then kept at 40° for 16 hours. Water (100 c.c.) was added, the precipitate stirred in boiling ethanol (30 c.c.), and the suspension cooled and filtered. The crude nitro compound (11·8 g.) was reduced with iron filings (12 g.) by refluxing for 6 hours in ethanol (150 c.c., 95%) and concentrated hydrochloric acid (0·5 c.c.). Sodium carbonate was then added and the hot suspension filtered. The filtrate was evaporated to dryness, the residue digested in cold dilute sodium hydroxide, filtered and reprecipitated with acetic acid. The solid, crystallised from aqueous β-ethoxyethanol (charcoal), gave 4·4 g., m. p. 191° (Found: C, 57·45; H, 5·55; N, 19·8. $C_{13}H_{14}O_3N_4$ requires C, 57·0; H, 5·1; N, 20·4%).

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