46. *Sulphonamides derived from Substituted Anilines.*

By A. H. Cook, I. M. Heilbron, and K. J. Reed.

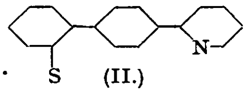
A variety of sulphanilamidophenyl-pyridines, -phenylpyridines, -lutidines, -thiazoles, and one sulphanilamidophenylpyrimidine have been synthesised, usually from the appropriate substituted aniline. Many of these sulphonamides showed considerable antibacterial action *in vitro*, though *in vivo* tests revealed disadvantages.

AMONG the most successful of the sulphonamide drugs have been those with the sulphanilamido-group attached directly to a heterocyclic system as in sulphapyridine. There have been many attempts to improve the action of these drugs, *e.g.*, by inserting a single methylene group between the sulphanilamido-system and the heterocyclic ring, by using polynuclear ring-systems such as quinolyl or acridyl, or by preparing sulphanilamidobenzene derivatives.

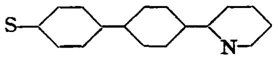
Recent work in these laboratories (see, *e.g.*, Heilbron, Hey, and Lambert, J., 1940, 1279) had provided a variety of pyridylanilines of known orientation and it seemed worth while to prepare the corresponding sulphanilamides by interaction with acetylsulphanilyl chloride and removal of the acetyl group in the usual manner. The resulting *compounds* (I) thus resembled sulphapyridine except that a benzene ring was inserted between the sulphanilamido- and the pyridyl group.

Promising *in vitro* and *in vivo* tests suggested that the anti-bacterial effect might remain when two benzene rings were inserted between the sulphanilamide and the pyridyl residue, or when the pyridyl ring in compounds (I) was replaced by the thiazole ring. Accordingly 2-amino- and 4-amino-4'-α-pyridyldiphenyl were converted into *sulphonamides* (II) and (III) respectively. The acetyl derivatives of these compounds were almost insoluble in dilute acid or alkali and, although the anticipated sulphonamide nature was confirmed, they were of no obvious practical value; attention was therefore redirected to those sulphonamides with only one ring separating the sulphanilamide and the heterocyclic group. It is interesting that (IV), prepared from α-4-aminobenzylpyridine, had considerable potency compared with α-4-*sulphanilamidophenylpyridine* (V). Compounds (VI)—(IX) were prepared in the normal manner from the appropriate amines. (VIII) was also prepared from the requisite amine and *p*-nitrobenzenesulphonyl chloride, followed by reduction. 2-Phenyl-4-methylthiazole had previously been nitrated (Friedman, Sparks, and Adam, *J. Amer. Chem. Soc.*, 1937, **59**, 2262) to a mononitro-compound. Thiobenzamide, obtained in excellent yield by refluxing benzonitrile with alcoholic ammonium sulphide, was converted into the thiazole, but repetition of these workers' nitration procedure gave a mixture. After separation, one component was shown to be the 4'-*nitro*-compound by oxidation to *p*-nitrobenzoic acid, and since it yielded the second component on further nitration, the latter must be formulated as 2' : 4'-*dinitrophenyl-4-methylthiazole*. In consequence of these difficulties in the preparation of 2-*p*-aminophenyl-4-methylthiazole *p*-acetamidothiobenzamide was condensed with bromoacetone, and 2-p-*acetamidophenyl-4-methylthiazole* hydrolysed to the required base. The corresponding sulphonamide (X) was prepared in the normal manner, and in similar fashion the isomeric sulphonamide (XI) also was obtained.

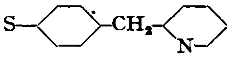
(I.)



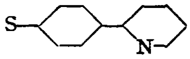
(II.)



(III.)

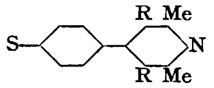


(IV.)

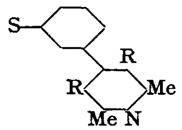


(V.)

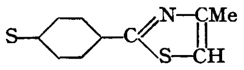
(S = p-NH$_2$·C$_6$H$_4$·SO$_2$·NH)



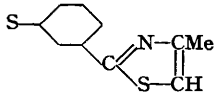
(VI.) R = CO$_2$Et
(VII.) R = H



(VIII.) R = CO$_2$Et
(IX.) R = H



(X.)



(XI.)

Attempts were then made to synthesise 2-*o*-aminophenyl-4-methylthiazole by similar steps. However, *o*-acetamidobenzonitrile on heating with ethanolamine and alcoholic hydrogen sulphide afforded mainly 2-methyl-4-thioquinazolone (cf. Bogert, Brenemann, and Hand, *J. Amer. Chem. Soc.*, 1903, **25**, 376) and only a very small yield of the required o-*acetamidothiobenzamide*. Moreover, acetylation of *o*-aminobenzonitrile yielded some 2-methylquinazolone in addition to the normal acetyl compound. This undesired cyclisation was prevented by working with o-*acetylsulphanilamidobenzonitrile*; this was converted into o-*acetylsulphanilamidothiobenzamide*, and the latter condensed with bromoacetone to give 2-o-*acetylsulphanilamidophenyl-4-methylthiazole*, hydrolysis of which gave the required *sulphonamide* directly.

2-Phenyl-4 : 6-dimethylpyrimidine had been previously nitrated by Ochiai *et al.* (*J. Pharm. Soc. Japan*, 1939, **59**, 462), though it appears that the constitution of the mononitro-product was not ascertained. We had no difficulty in obtaining the same compound, but as it was oxidised to *m*-nitrobenzoic acid, it must be unexpectedly formulated as the *m*-nitro-compound. It was converted by the ordinary reactions into 2-m-*sulphanilamidophenyl-4* : 6-*dimethylpyrimidine*.

The antibacterial potency of most of the above compounds was compared with that of sulphapyridine in the Department of Experimental Medicine, Glaxo Laboratories Ltd., under the direction of Dr. J. Ungar, to whom our thanks are due. They were tested in synthetic medium and in most cases in 1% glucose and in 10% serum broth against several organisms. The results are in the table. *In vivo* tests (mice infected with *Streptococcus* or *Pneumococcus* and the drugs administered orally, by intraperitoneal or rarely intramuscular injection) showed some of these compounds to be probably less toxic than sulphapyridine, though they were either less effective or had disadvantageous solubilities.

Compound.	Solubility in synthetic medium.	Inhibition in synthetic medium.	Inhibition in glucose broth.
α-2-Sulphanilamidophenylpyridine	Insol. 1/10,000	Nil	Nil
β-2-Sulphanilamidophenylpyridine *	Insol. 1/50,000	*B. subtilis* 1/100,000	Nil
α-3-Sulphanilamidophenylpyridine *	Insol. 1/10,000	*Staph.* 1/5000 *Strep.* 1/500,000 *B. subtilis* 1/100,000	*Strep.* 1/5000 *Pneumo.* 1/50,000
α-4-Sulphanilamidophenylpyridine	Sol. 1/10,000	*B. coli* 1/5000 *Strep.* 1/10,000 *B. subtilis*, slight	*Strep.* 1/5000 *Pneumo.* 1/50,000
γ-4-Sulphanilamidophenylpyridine	Insol. 1/5000	*Strep.* 1/200,000 *B. subtilis* 1/100,000	*Strep.* 1/5000
α-4-Sulphanilamidobenzylpyridine *	Insol. 1/50,000	*Strep.* 1/50,000 *B. subtilis* 1/500,000	*Pneumo.* 1/100,000
2-(*o*-Sulphanilamidophenyl)-4-methylthiazole	Insol. 1/50,000	*B. subtilis* 1/500,000	Nil
2-(*m*-Sulphanilamidophenyl)-4-methylthiazole	Insol. 1/10,000	*Staph.* 1/1000	Nil
2-(*p*-Sulphanilamidophenyl)-4-methylthiazole	Insol. 1/10,000	*Strep.* 1/500,000 *B. subtilis* 1/100,000	*Strep.* 1/10,000 *Pneumo.* slight
3 : 5-Dicarbethoxy-4-(*m*-sulphanilamidophenyl)-2 : 6-lutidine	Insol. 1/10,000	Nil	Not tried
4-(*m*-Sulphanilamidophenyl)-2 : 6-lutidine	Insol. 1/10,000	*Staph.* 1/1000	Not tried
3 : 5-Dicarbethoxy-4-(*p*-sulphanilamidophenyl)-2 : 6-lutidine	Insol. 1/50,000	*Staph.*, *Strep.* *B. subtilis, coli*, slight inhib.	Nil Nil
2-(*p*-Sulphanilamidophenyl)-4 : 6-dimethylpyrimidine	Insol. 1/10,000	*Staph.* 1/5000 *B. coli* 1/1000	Not tried
Sulphapyridine *	Insol. 1/5000	*Pneumo.* 1/10,000 *Strep.* 1/100,000 *B. subtilis* 1/10^6	Nil

* In these cases, the effects of *p*-aminobenzoic acid was examined. The effect of the sulphonamides (1/1000) on *B. subtilis* was completely neutralised by the natural vitamin (1/5000).

EXPERIMENTAL.

Sulphanilamidophenylpyridines.—α-2-, β-2-, α-3-, α-4-, and γ-4-Aminophenylpyridines were obtained by the methods of Heilbron, Hey, and co-workers (J., 1940, 349, 355). α-3-Aminophenylpyridine, previously described as an oil, was obtained as a solid crystallising in rhombs, m. p. 72—74°, from light petroleum (Found: C, 78·1, 77·7; H, 6·0, 6·05. Calc. for $C_{11}H_{10}N_2$: C, 77·8; H, 5·9%). The amines were dissolved or suspended in pyridine (*ca.* 6 mols.) and treated slowly with *N*-acetylsulphanilyl chloride (1 mol.) in the cold. The mixtures were heated at 100° for 1 hour, and the acetylsulphanilyl compounds precipitated with water and allowed to crystallise; they were freely soluble in dilute sodium hydroxide solution. The following were prepared: α-2-N^4-*Acetylsulphanilamidophenylpyridine*, small prismatic needles, m. p. 150—151°, from ethanol (Found: C, 62·1; H, 4·5. $C_{19}H_{17}O_3N_3S$ requires C, 62·1; H, 4·6%). β-2-N^4-*Acetylsulphanilamidophenylpyridine*, needles, m. p. 168·5—169°, from dilute ethanol (Found: C, 62·05; H, 4·9%). α-3-N^4-*Acetylsulphanilamidophenylpyridine*, pale yellow needles, m. p. 223—225°, from ethanol (Found: C, 62·4; H, 4·85%). α-4-N^4-*Acetylsulphanilamidophenylpyridine*, needles, m. p. 241·5°, from acetone–light petroleum (Found: C, 62·25; H, 4·8%). γ-4-N^4-*Acetylsulphanilamidophenylpyridine*, prisms, m. p. 272°, from ethanol (Found: C, 61·9; H, 4·85%).

The acetyl compounds were refluxed with 2N-hydrochloric acid (10 vols.) for 1 hour. The clear cold solution was treated with sufficient 2N-sodium hydroxide to dissolve the precipitate first formed, the alkaline solution decolorised with charcoal, and the sulphonamide precipitated by neutralisation. In the case of the 4-γ-isomeride the hydrochloride of the sulphonamide separated from the cold acid solution; it was suspended in water, converted into the soluble sodium salt, decolorised and precipitated as usual. With the preceding exception the sulphonamides were freely soluble in dilute acid or alkali and gave azo-dyes on diazotisation and coupling. The following were prepared: α-2-*Sulphanilamidophenylpyridine*, pale yellow prisms, m. p. 200°, from acetone–water (Found: C, 62·9; H, 4·5. $C_{17}H_{15}O_2N_3S$ requires C, 62·7; H, 4·6%). β-2-*Sulphanilamidophenylpyridine*, prisms, m. p. 186—186·5°, from dilute ethanol (Found: C, 62·8; H, 4·8%). α-3-*Sulphanilamidophenylpyridine*, plates, m. p. 170°, from dilute ethanol (Found: C, 62·9; H, 4·85%). α-4-*Sulphanilamidophenylpyridine*, needles, m. p. 257·5°, from ethanol (Found: C, 62·5; H, 5·0%). γ-4-*Sulphanilamidophenylpyridine*, pale yellow needles, m. p. 217—218°, from ethanol–water (Found: C, 62·9; H, 4·6%).

α-4-Aminobenzylpyridine (Tschitschibabin, Kuindishi, and Benewolenskara, *Ber.*, 1925, **58**, 1583) (9 g.) in pyridine (25 c.c.) was treated with acetylsulphanilyl chloride (12 g.); after 12 hours, addition of water precipitated α-4-N^4-*acetylsulphanilamidobenzylpyridine* (17·8 g.); it crystallised in needles, m. p. 217—219°, from dilute ethanol (Found: C, 63·35; H, 5·0. $C_{20}H_{19}O_3N_3S$ requires C, 63·0; H, 5·0%). Hydrolysis with 2N-hydrochloric acid (10 vols.) for 30 mins. in the normal manner afforded α-4-*sulphanilamidobenzylpyridine* (14·5 g.). It formed prismatic needles, m. p. 154°, from dilute ethanol (Found: C, 63·8; H, 4·9. $C_{18}H_{17}O_2N_3S$ requires C, 63·7; H, 5·0%).

Sulphanilamidopyridyldiphenyls.—The *N*^{4}-acetyl compounds were prepared in excellent yields from the aminopyridyldiphenyls (Heilbron, Hey, and Lambert, *loc. cit.*) as with the aminophenylpyridines above. 2′-N^4-*Acetylsulphanilamido*-4-α-*pyridyldiphenyl* formed needles, m. p. 193—194°, from acetone–light petroleum. 4′-N^4-*Acetylsulphanilamido*-4-α-*pyridyldiphenyl* separated from ethanol in needles, m. p. 275—277° (Found: C, 67·3; H, 4·95. $C_{25}H_{21}O_3N_3S$ requires C, 67·7; H, 4·75%). Hydrolysis of the acetyl compounds was effected by boiling with dilute hydrochloric acid for ½—1 hr. and neutralising the solution. 2′-*Sulphanilamido*-4-α-*pyridyldiphenyl* crystallised from dilute ethanol in small plates, m. p. 164—165° (Found: C, 69·2; H, 4·9. $C_{23}H_{19}O_2N_3S$ requires C, 68·8; H, 4·75%); 4′-*sulphanilamido*-4-α-*pyridyldiphenyl*, crystallised from acetic acid, had m. p. 298—299° (Found: C, 68·6; H, 4·8. $C_{23}H_{19}O_2N_3S$ requires C, 68·8; H, 4·75%).

Sulphanilamidophenyl-lutidines.—Acetylsulphanilyl chloride (1·22 g.) was warmed for 1 hr. at 100° with ethyl 4-*p*-aminophenyl-2 : 6-dimethylpyridine-3 : 5-dicarboxylate (Cook, Heilbron, and Steger, J., 1943, 413) (1·7 g.) and pyridine (10 c.c.), and the product (2·6 g., m. p. 242—243°) precipitated with water (50 c.c.); the N^4-*acetylsulphanilyl* derivative separated from dilute ethanol in prismatic needles, m. p. 243—244° (Found: C, 60·4; H, 5·35. $C_{27}H_{29}O_7N_3S$ requires C, 60·1; H, 5·4%). Hydrolysis of the acetyl derivative (2·3 g.) with boiling 2N-hydrochloric acid (25 c.c.) for 30 mins. and neutralisation of the suspension gave *ethyl* 4-p-*sulphanilamidophenyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* (2·0 g.); it separated from dilute alcohol as a solvate, and from benzene it formed small prismatic needles, m. p

164—165° (Found : C, 60·25; H, 5·45. $C_{25}H_{27}O_6N_3S$ requires C, 60·3; H, 5·4%). The corresponding 4-*m*-sulphanilamido-compound was prepared (*a*) similarly in about the same yield from ethyl 4-*m*-aminophenyl-2 : 6-dimethylpyridine-3 : 5-dicarboxylate (Cook, Heilbron, and Steger, *loc. cit.*) and (*b*) from the amine and *p*-nitrobenzenesulphonyl chloride. (*a*) *Ethyl* 4-m-N^4-*acetylsulphanilamidophenyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* separated from dilute ethanol or acetone–light petroleum in needles, m. p. 196—197° (Found : C, 60·4; H, 5·6. $C_{27}H_{29}O_7N_3S$ requires C, 60·1; H, 5·4%). *Ethyl* 4-m-*sulphanilamidophenyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* formed prisms, m. p. 158—159°, from ethanol (Found : C, 60·45; H, 5·6. $C_{25}H_{27}O_6N_3S$ requires C, 60·3; H, 5·4%). (*b*) The amine (2·0 g.) was kept for 15 hrs. with *p*-nitrobenzenesulphonyl chloride (1·3 g.) in pyridine (5 c.c.), and crude *ethyl* 4-(3′-p-*nitrobenzenesulphonamidophenyl*)-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* precipitated with water (100 c.c.); it separated from benzene–light petroleum (charcoal) in pale yellow prisms, m. p. 150—151° (Found : C, 57·2; H, 5·2. $C_{25}H_{25}O_8N_3S$ requires C, 56·9; H, 4·8%). The nitro-compound (1 g.) was added slowly to a suspension of iron dust (2 g.) in ethanol (6 c.c.) and 15% hydrochloric acid (1 c.c.). The whole was heated on the steam-bath for 2 hrs., and the solutions made alkaline and decolorised with charcoal. Evaporation and neutralisation gave the sulphanilamido-compound identical with that prepared in (*a*).

4-m-N^4-*Acetylsulphanilamidophenyl*-2 : 6-*dimethylpyridine* was prepared by heating acetylsulphanilyl chloride (6·6 g.) with 4-*m*-aminophenyl-2 : 6-dimethylpyridine (4·5 g.) in pyridine (60 c.c.) for 1 hr. at 100°, and adding water (350 c.c.); recrystallisation from dilute ethanol gave needles, m. p. 267—268° (Found : C, 63·6; H, 5·5. $C_{21}H_{21}O_3N_3S$ requires C, 63·8; H, 5·3%). Hydrolysis was effected only by boiling in 20% aqueous sodium hydroxide for 30 mins. 4-m-*Sulphanilamidophenyl*-2 : 6-*dimethylpyridine* (yield, 5·0 g. or 64% over-all) crystallised from acetone in large prisms, m. p. 269—270° (Found : C, 64·3; H, 5·5. $C_{19}H_{19}O_2N_3S$ requires C, 64·6; H, 5·4%).

Sulphanilamidophenylthiazoles.—*o*-Acetamidobenzonitrile (20 g.) was heated (autoclave) for 1 hr. at 100° with a mixture of ethanol (240 c.c.) and triethanolamine (40 c.c.) previously saturated with hydrogen sulphide at 0°. Filtration and concentration gave *o*-acetamidothiobenzamide (18·6 g.), m. p. 221—222° after crystallisation from ethanol. The thioamide (10 g.), bromoacetone (5· 4c.c.), and ethanol (100 c.c.) were refluxed for 1 hr. On cooling, a hydrobromide separated, from which neutral impurities were extracted with ether and the free base liberated with ice-cold sodium hydroxide solution. Crystallisation from *cyclo*hexanol–light petroleum gave 2-o-*acetamidophenyl*-4-*methylthiazole* in yellow needles (0·2 g.), m. p. 116—117° (Found : C, 62·4; H, 5·2. $C_{12}H_{12}ON_2S$ requires C, 62·1; H, 5·2%). The alkaline solution on acidification yielded 4-thio-2-methyldihydroquinazolone, m. p. 220° (decomp.), identified as its picrate, m. p. 203—205° (Bogert, Breneman, and Hand, *loc. cit.*).

Acetylsulphanilyl chloride (51 g.) was heated with *o*-aminobenzonitrile (24·6 g.) in pyridine (100 c.c.) for 1 hour at 100°. The *product* (59·5 g.), m. p. 217—220°, separated in solvated form from dilute ethanol but in unsolvated needles, m. p. 224°, from acetone–light petroleum (Found : C, 56·9; H, 4·4. $C_{15}H_{13}O_3N_3S$ requires C, 57·1; H, 4·15%). Ethanol (30 c.c.), saturated with ammonia and then with hydrogen sulphide, was heated with the nitrile for 12 hrs. at 100°. Evaporation and addition of water precipitated a solid mixture of the original nitrile and *o*-acetylsulphanilamidothiobenzamide, which was separated by several crystallisations from dilute ethanol, the thioamide, m. p. 200° (decomp.), being obtained from the mother-liquors. The crude thioamide (16 g.) was refluxed for 1 hr. with ethanol (200 c.c.) and bromoacetone (5 c.c.). Removal of solvent in a vacuum, addition of water, and purification of the solid by solution in alkali and precipitation with acid gave 2-o-N^4-*acetylsulphanilamidophenyl*-4-*methylthiazole* (4·1 g.), which separated from dilute ethanol in prisms, m. p. 168·5—169° (Found : C, 55·7; H, 4·4. $C_{18}H_{17}O_3N_3S_2$ requires C, 55·8; H, 4·4%). Hydrolysis of the acetyl compound (4·0 g.) with boiling 2N-hydrochloric acid (40 c.c.) for 1 hr. and neutralisation (charcoal) gave 2-o-*sulphanilamidophenyl*-4-*methylthiazole* (2·9 g.), which separated from ethanol in large prismatic needles, m. p. 178° (Found : C, 55·8; H, 4·7. $C_{16}H_{15}O_2N_3S_2$ requires C, 55·6; H, 4·4%).

m-Acetamidobenzonitrile (20 g.) was heated for 1 hour with ethanol (240 c.c.) and triethanolamine (40 c.c.) previously saturated with hydrogen sulphide at 0°. Concentration gave crude m-*acetamidothiobenzamide* (16 g.), which separated in prisms, m. p. 177—178° (decomp.), from acetone–light petroleum (Found : C, 55·35; H, 5·2. $C_9H_{10}ON_2S$ requires C, 55·6; H, 5·2%). The thioamide was converted into 2-m-*acetamidophenyl*-4-*methylthiazole* (yield, 57%) as with the *o*-isomeride above; crystallisation from benzene–light petroleum gave prisms, m. p. 130—131° (Found : C, 62·15; H, 5·1. $C_{12}H_{12}ON_2S$ requires C, 62·1; H, 5·2%). Hydrolysis of the acetyl compound (7 g.) with 10 vols. of boiling 6N-hydrochloric acid for 15 mins. and neutralisation of the solution gave 2-m-*aminophenyl*-4-*methylthiazole* (5·5 g.), which separated from light petroleum in small prisms, m. p. 46—48° (Found : C, 63·1; H, 5·3. $C_{10}H_{10}N_2S$ requires C, 63·1; H, 5·3%). Introduction of the acetylsulphanilyl residue and removal of the acetyl group was effected in excellent yield by the methods used in preceding cases. 2-m-N^4-*Acetylsulphanilamidophenyl*-4-*methylthiazole* formed needles, m. p. 233°, from acetone–light petroleum (Found : C, 56·0; H, 4·6. $C_{18}H_{17}O_3N_3S_2$ requires C, 55·6; H, 4·4%). 2-m-*Sulphanilamidophenyl*-4-*methylthiazole* separated from dilute ethanol in small prisms, m. p. 188—189° (Found : C, 55·7; H, 4·35. $C_{16}H_{15}O_2N_3S_2$ requires C, 55·6; H, 4·4%).

The following appears to be an improvement on existing preparations of thiobenzamide. Benzonitrile (50 g.) was refluxed for 2 hrs. with 16% aqueous ammonium sulphide (300 c.c.) and ethanol (250 c.c.). Evaporation to dryness and crystallisation of the residue three times from water gave the pure compound (35 g.), m. p. 116°. Nitration of 2-phenyl-4-methylthiazole by the method of Friedman, Sparks, and Adam (*loc. cit.*) gave a mixture from which 2-2′ : 4′-*dinitrophenyl*-4-*methylthiazole* was obtained as the less soluble component by fractional crystallisation from *cyclo*hexane; it formed yellow needles, m. p. 154—155° (Found : C, 45·3; H, 2·65. $C_{10}H_7O_4N_3S$ requires C, 45·3; H, 2·65%). 2-4′-Nitrophenyl-4-methylthiazole, m. p. 107°, was conveniently separated from the mixture by its preferential solution in 16% hydrochloric acid; it was evidently identical with the compound described by Friedman, Sparks, and Adam.

2-*p*-Aminophenyl-4-methylthiazole, better prepared *via* *p*-acetamidothiobenzamide, was converted into the sulphanilyl derivative in the manner of other preparations in this paper. 2-p-N^4-*Acetylsulphanilamidophenyl*-4-*methylthiazole* (yield, 81%) separated from ethanol in prismatic needles, m. p. 255—256° (Found : C, 55·9; H, 4·45. $C_{18}H_{17}O_3N_3S_2$ requires C, 55·8; H, 4·4%). 2-p-*Sulphanilamidophenyl*-4-*methylthiazole* (yield after crystallisation, 85%) separated from dilute ethanol in needles, m. p. 202—203° (Found : C, 55·4; H, 4·4. $C_{16}H_{15}O_2N_3S_2$ requires C, 55·6; H, 4·4%).

2-*m*-Nitrophenyl-4 : 6-dimethylpyrimidine (Ochiai *et al.*, *loc. cit.*), m. p. 157·5°, was oxidised with a boiling solution of potassium permanganate in acetic acid and 5N-sulphuric acid. *m*-Nitrobenzoic acid, m. p. and mixed m. p. with authentic material 140°, was obtained. The corresponding amine was converted into the sulphonamide in the usual manner. 2-m-N^4-*Acetylsulphanilamidophenyl*-4 : 6-*dimethylpyrimidine* (yield, theoretical) separated from acetone or a large volume of ethanol in prisms, m. p. 246—248° (Found : C, 60·6; H, 5·2. $C_{20}H_{20}O_3N_4S$ requires C, 60·6; H, 5·1%). 2-m-*Sulphanilamidophenyl*-4 : 6-*dimethylpyridine* (yield, 74% after recrystallisation) formed small prisms, m. p. 206—207°, from dioxan–light petroleum (Found : C, 61·0; H, 5·2. $C_{18}H_{18}O_2N_4S$ requires C, 61·0; H, 5·1%).

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