56. *The Conversion of Sucrose into Pyridazine Derivatives. Part I. 3-Sulphanilamido-6-methylpyridazine.*

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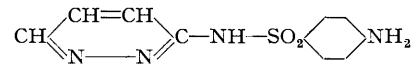
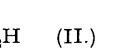
The synthesis of 3-amino-6-methylpyridazine from lævulic acid is described. The preparation of the sulphanilamide derived from it has been achieved and its chemotherapeutic properties are discussed. Some structural aspects of the pyridazone intermediates are also mentioned.

Sulphanilamide derivatives of six-membered ring diazines have achieved marked success as chemotherapeutic agents for use in combating certain bacterial infections, but the diazine molecules used have been those of the pyrimidine and pyrazine series only. It seems that only one sulphanilamide derivative of pyridazine, namely 3-sulphanilamidopyridazine (I), has been described fully. This compound was prepared and its chemotherapeutic properties described by Anderson, Faith, Musson, Roblin, and Winneck (*J. Amer. Chem. Soc.*, 1942, **64**, 2902) who obtained it *via* Gabriel's 3-chloropyridazine (*Ber.*, 1909, **42**, 655). 3-Sulphanilamidopyridazine possessed high bacteriostatic activity *in vitro*, was capable of being absorbed strongly, and could be obtained in high concentration in the blood stream, but unfortunately and unexpectedly its activity *in vivo* was extremely low.

(I.) 

 (II.)

We have been interested in the pyridazine and pyridazone derivatives that can be obtained from lævulic acid (II), and in this paper is described the synthesis from this raw material of another sulphanilamide derivative of pyridazine, namely 3-*sulphanilamido*-6-*methylpyridazine* (IX),* together with the results of our investigations on the intermediate compounds used in this synthesis.

The new sulphanilamido-compound was found to possess high bacteriostatic activity in routine bacteriostatic tests—in fact it showed considerably greater activity than sulphathiazole with which it is compared in Table I. Moreover in its solubility (61) and that of its *N*-acetyl

Table I.

	Blood medium.	Broth medium.					Synthetic medium.		
Compound.	*Str. Hæmolyticus.*	*Str. Hæmolyticus.*	*B. Coli.*	*Pseudomonas æruginosa.*	*Staph. aureus.*	*Clostridium Welchii.*	*B. Coli.*	*Pseudomonas æruginosa.*	*Staph. aureus.*
3-Sulphanilamido-6-methylpyridazine	0·06	7	0·5	20	500	0·5	0·05	0·5	1·0
Sulphathiazole	0·3	15	5	5	100	5	0·03	7	2·0

The figures represent mg. of compound/100 c.c. necessary to prevent growth of the organism.

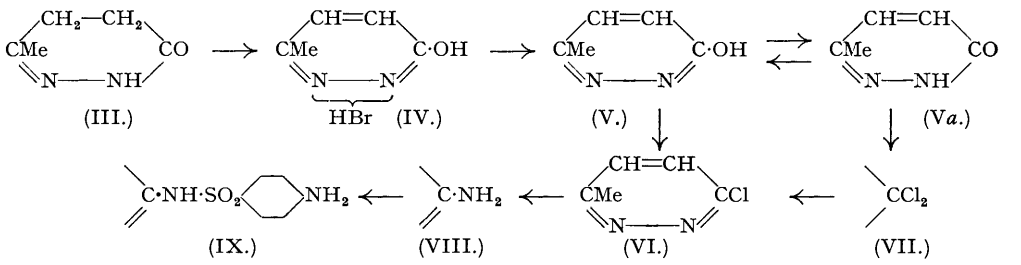
derivative (39) it appeared to offer advantages over sulphathiazole (40) and its *N*-acetyl derivative (3·3) (solubilities in parentheses in mg./100 c.c. of solution). More extensive biological work on this compound is in progress and the results will be published elsewhere.

Ethyl lævulate was condensed with hydrazine hydrate, either at room temperature or by heating for a short time, and 6-methyl-3-pyridazinone (III) was obtained in almost quantitative yield. This compound was first obtained by Curtius (*J. pr. Chem.*, 1894, **50**, 522) who believed he had obtained the hydrazide of lævulic acid until the true position was demontrated by Wolff (*Annalen*, 1912, **394**, 98). This substance could also be obtained by dry distillation of ethyl lævulate semicarbazone.

The 6-methyl-3-pyridazinone (III) was then converted into the corresponding pyridazone. This operation was first carried out by Poppenberg (*Ber.*, 1901, **34**, 3263) who treated 6-methyl-3-pyridazinone with bromine in acetic acid solution. Poppenberg obtained 6-methyl-3-pyridazone of m. p. 143° directly from this solution and made no mention of any other product

* While tests on this compound were being carried out, a patent (B.P. 563,629) granted to the American Cyanamide Co. was published in which this compound and others were described, although no details as to its preparation other than the introduction of the sulphanilamide residue to the pyridazine nucleus were given.

of the reaction. We, however, could not repeat the experiment as described by this author, and in fact we found the reaction was much more complicated.



When 6-methyl-3-pyridazinone was treated with bromine according to Poppenberg's conditions, hydrazine hydrobromide first separated, and after this had been removed a compound which clearly possessed salt-like properties crystallised out. This was 6-*methyl*-3-*pyridazone monohydrobromide* (IV) and was obtained in 76% yield. The mother liquors gave a product soluble in ether which was identified as βδ-dibromolævulic acid. It was clear that during the bromine treatment, which amounts to a dehydrogenation, part of the 6-methyl-3-pyridazinone had suffered cleavage, giving hydrazine, isolated as its hydrobromide, and lævulic acid, which in the presence of bromine is converted into the dibromo-derivative.

The dehydrogenation was then carried out under different conditions, so as to try to eliminate cleavage of the diazine ring. Table II shows the results of these experiments, from which it is seen that when the reaction is carried out under anhydrous conditions, no secondary reaction occurs, and an almost theoretical yield of 6-methyl-3-pyridazone hydrobromide was obtained.

TABLE II.

Experimental conditions.	Hydrazine dihydrobromide.	6-Methyl 3-pyridazone monohydrobromide.	βδ-Dibromolævulic acid.
According to Poppenberg (*loc. cit.*)	28·8	111·9 (76·6%)	47·6
Bromine in acetic acid at room temp.	48·4	92·6 (63·5%)	74·5
Bromine in acetic acid at 0°	67·0	76·6 (52·5%)	93·8
Bromine in acetic acid (anhydrous conditions)	Nil	145·4 (99·5%)	Nil

The figures given refer to g. of each compound obtained from 100 g. of 6-methyl-3-pyridazinone monohydrate.

The decomposition of 6-methyl-3-pyridazone hydrobromide to the free base can be carried out under a variety of conditions. The hydrobromide is readily decomposed by sodium acetate solution, by liquid ammonia, or merely by boiling water. We have obtained the best yields by using the second method. The resulting 6-*methyl*-3-*pyridazone* (V or V*a*) can easily be reconverted into the hydrobromide or hydrochloride by treatment in dry alcohol with the appropriate hydrogen halide.

6-Methyl-3-pyridazinone was converted into the pyridazone derivative by two alternative methods. Paal and Koch (*Ber.*, 1903, **36**, 2538) and Paal and Kuhn (*ibid.*, 1907, **40**, 4598) had used nitrous acid to dehydrogenate compounds similar to that under discussion; 6-methyl-3-pyridazinone was therefore converted to the corresponding pyridazone by treatment with sodium nitrite and dilute acetic acid. More recently Borsche (*Annalen*, 1941, **548**, 74) had used chromium trioxide in acetic acid solution to dehydrogenate similar compounds. When 6-methyl-3-pyridazinone was treated with these reagents it was converted into 6-methyl-3-pyridazone, but only in very poor yield.

The next step in the synthesis of the sulphanilamide required the preparation of 3-chloro-6-methylpyridazine (VI). Poppenberg (*loc. cit.*) had obtained this by chlorination of 6-methyl-3-pyridazone with phosphoryl chloride, but recorded no yield. We have found that this reaction could be carried out in such a way as to give the 3-chloro-derivative in 95% yield. In addition we tried an alternative method. Phosphorus pentachloride with anhydrous 6-methyl-3-pyridazone gave a product which although not clearly defined was apparently 3 : 3-dichloro-6-methyldihydropyridazine (VII). This on distillation decomposed with elimination of hydrogen chloride giving 3-chloro-6-methylpyridazine. Alternatively, the 3 : 3-dichloro-compound (VII) could be decomposed with the formation of 3-chloro-6-methyl-

pyridazine by treatment with sodium hydroxide solution. However the yield of this material obtained by the last two methods did not compare with that obtained by the treatment of 6-methyl-3-pyridazone with phosphoryl chloride. The chloropyridazine gave a crystalline *monohydrochloride* and *monohydrobromide*, although Poppenberg (*loc. cit.*) stated that it did not form salts.

By treatment with aqueous ammonia at high temperature the 3-chloro-derivative was converted into 3-*amino*-6-*methylpyridazine* (VIII) in about 50% yield, but some 6-methyl-3-pyridazone was obtained also. With methyl alcoholic ammonia, a slightly higher yield (60%) of amine was obtained, together with a very small amount of 3-*methoxy*-6-*methylpyridazine*, identified as its *hydrochloride*, which was synthesised by treatment of 3-chloro-6-methylpyridazine with sodium methoxide.

3-Amino-6-methylpyridazine formed only mono-salts (a *hydrochloride* and a *picrate*). It also formed a beautifully crystalline *acetyl* derivative, which also formed only mono-salts (a *hydrochloride* and a *hydrobromide*).

To introduce the sulphanilamido-residue, we have used both the usual procedures. Thus the amine was condensed with *N*-acetylsulphanilyl chloride in pyridine solution, and 3-N-*acetylsulphanilamido*-6-*methylpyridazine* was obtained in 84% yield. It was possible to effect some condensation in chloroform, without the presence of another base—that is, by making use of the basic nature of the pyridazine ring for absorption of hydrogen chloride—but the yield was only 25%. The *N*-acetyl group was easily removed by hydrolysis with either aqueous sodium hydroxide or dilute hydrochloric acid, and 3-sulphanilamido-6-methylpyridazine (IX) obtained in 87% yield. (IX) formed a *dihydrochloride*.

The amine (VIII) was also condensed with *p*-nitrobenzenesulphonyl chloride in pyridine solution, but the yield of 3-p-*nitrobenzenesulphonamido*-6-*methylpyridazine* was only 46%, and reduction of this compound was accompanied by secondary reactions so that only a 21% yield of the sulphanilamide was obtained.

Experimental.

6-*Methyl*-3-*pyridazinone*.—(1) Ethyl lævulate (84·5 g.) and hydrazine hydrate (50/50 w/w, 55·7 g.) were mixed, and ethyl alcohol was added until a homogeneous mixture was obtained. The solution was boiled under reflux for 1 hour and then left overnight. The crystals which had separated were collected, and a second crop obtained on evaporation of the mother liquor. The product recrystallised from water in large colourless rhombs, m. p. 82°. Yield, 76 g. (practically quantitative). This was 6-methyl-3-pyridazinone monohydrate. A sample was dried in a vacuum at 110° and the resulting anhydrous compound recrystallised from benzene; it had 105° (Wolff, *loc. cit.*, gives m. p. 104—105°) (Found: C, 54·2; H, 6·7; N, 25·8. Calc. for $C_5H_6ON_2$: C, 53·6; H, 7·0; N, 25·0%).

(2) Ethyl lævulate semicarbazone (2·62 g.) was subjected to dry distillation. The distillate (1·03 g.) crystallised on cooling. It recrystallised from water in large rhombic crystals, m. p. 82° alone or in admixture with 6-methyl-3-pyridazinone obtained as above. Yield, 72%.

The Action of Bromine on 6-*Methyl*-3-*pyridazinone*.—(a) *Poppenberg's method* (*loc. cit.*). 6-Methyl-3-pyridazinone monohydrate (31·9 g.) was dissolved in warm glacial acetic acid (100 g.) and bromine (12·17 c.c.) was slowly added. Thereafter the mixture was heated at 100° for 15 minutes. Hydrazine hydrobromide (9·2 g.) [m. p. 207° (decomp.) after recrystallisation from glacial acetic acid] separated and was filtered off. By next day the filtrate had deposited 6-*methyl*-3-*pyridazone hydrobromide* (35·7 g.); after recrystallisation from glacial acetic acid this had m. p. 184·5—185°, and boiling water, boiling pyridine, or liquid ammonia decomposed it with formation of 6-methyl-3-pyridazone and bromide ions (Found: C, 31·5; H, 3·6; N, 14·4. $C_5H_7ON_2Br$ requires C, 31·4; H, 3·7; N, 14·7%). The mother liquors on evaporation yielded crude βδ-dibromolævulic acid as a syrup (15·2 g.), which crystallised after long standing with alcohol; recrystallised from ligroin (b. p. 60—80°) it yielded shining white needles, m. p. 112—113°, not depressed in admixture with pure βδ-dibromolævulic acid (Found: C, 21·6; H, 2·3. Calc. for $C_5H_6O_3Br_2$: C, 21·8; H, 2·1%).

(b) *At room temperature*. To 6-methyl-3-pyridazinone monohydrate (47·5 g.) dissolved in glacial acetic acid (125 c.c.) was slowly added bromine (37 c.c.) at room temperature. When 14 c.c. of the bromine had been added, minute crystals began to separate, and after completion of the addition the hydrazine hydrobromide (23 g.) was collected. The filtrate was kept overnight and the crystals of 6-methyl-3-pyridazone hydrobromide, which separated, were filtered off; ether added to the filtrate precipitated a second crop (total yield, 44 g.). The mother liquors were evaporated to a syrup of crude βδ-dibromolævulic acid (32 g.).

(c) *Under ice-cold conditions*. 6-Methyl-3-pyridazinone monohydrate (20·0 g.) was dissolved in glacial acetic acid (60 c.c.) and the solution cooled in an ice-bath. Bromine (16 c.c.) was slowly added with shaking. When exactly half the bromine had been added hydrazine hydrobromide (13·4 g.) separated (at this stage hydrogen bromide was evolved). The filtrate after the removal of this was kept overnight; 6-methyl-3-pyridazone hydrobromide (13·5 g.) had then separated and was collected. Evaporation of the mother liquors gave a syrup of crude βδ-dibromolævulic acid (18·8 g.).

Dehydrogenation of 6-*Methyl*-3-*pyridazinone under Anhydrous Conditions*.—6-Methyl 3-pyridazinone monohydrate (165 g.) was dehydrated by heating at 120°/15 mm. for 4 hours. The anhydrous product was dissolved in freshly distilled glacial acetic acid (350 c.c.), and bromine (110·5 c.c.) slowly added at room temperature without cooling. No hydrazine hydrobromide separated. The solution was kept

overnight; crystals had then separated, and were collected. A further crop was obtained by addition of ether to the mother liquors. The combined products had m. p. 184° and were practically pure 6-methyl-3-pyridazone monohydrobromide. Yield, 240 g. (quantitative).

6-*Methyl*-3-*pyridazone Monohydrate.*—(*a*) 6-Methyl-3-pyridazone monohydrobromide (22·4 g.) was suspended in glacial acetic acid (85 c.c.) and freshly fused and powdered sodium acetate (13·5 g.) added. The mixture was heated under reflux for 1 hour, evaporated to dryness, and the residue extracted with boiling chloroform. The extracts were dried ($MgSO_4$), the chloroform was removed by evaporation, and the residue, 6-methyl-3-pyridazone, recrystallised from water as the *monohydrate*, m. p. 119—123°. Yield, 12·9 g.; 86% (Found: C, 47·3; H, 6·1. $C_5H_6ON_2,H_2O$ requires C, 46·9; H, 6·3%).

(*b*) 6-Methyl-3-pyridazone monohydrobromide (1·14 g.) was dissolved in cold water, and a solution containing sodium hydroxide (1 mol., 0·24 g.) added. After evaporation to dryness the residue was extracted with chloroform, and 6-methyl-3-pyridazone monohydrate isolated as above. Yield, 0·47 g.; 72%.

(*c*) 6-Methyl-3-pyridazone monohydrobromide (5·04 g.) was dissolved in liquid ammonia (100 c.c.) and the solution allowed to evaporate overnight under anhydrous conditions. The residue was extracted with ether, and after removal of the solvent 6-methyl-3-pyridazone was obtained as above. Yield, 3·4 g.; 82%.

(*d*) 6-Methyl-3-pyridazone monohydrobromide (1 g.) was dissolved in water (10 c.c.) and the solution was boiled. Thereafter it was neutralised with silver carbonate, filtered, and evaporated to dryness. The residue was extracted with chloroform, and the extract, after being dried ($MgSO_4$), was evaporated to dryness. 6-Methyl-3-pyridazone was obtained after recrystallisation from water. Yield, 0·55 g.; 82%.

The monohydrate was dehydrated by heating it at 120° for 2 hours in a vacuum. The resulting anhydrous *compound*, m. p. 138°, crystallised from acetone in colourless needles (Found: C, 54·2; H, 5·7; N, 25·9. $C_5H_6ON_2$ requires C, 54·5; H, 5·4; N, 25·4%).

(*e*) 6-Methyl-3-pyridazinone (2·84 g.) was dissolved in glacial acetic acid (25 c.c.) and chromium trioxide (2·2 g.) was added to the solution. The mixture was kept overnight, and the pasty mass extracted with acetone. The solvents were removed from the extract and the solid residue was recrystallised from water; colourless plates (0·6 g., 20%), m. p. 120—123°, alone or in admixture with 6-methyl-3-pyridazone monohydrate.

(*f*) 6-Methyl-3-pyridazinone monohydrate (3·22 g.) was dissolved in water (50 c.c.) and sodium nitrite (1·8 g.) followed by dilute acetic acid was added. Next day the mixture was evaporated to dryness, and the residue extracted with acetone. The extract was dried ($MgSO_4$) and the solvent removed. The residue was recrystallised from water; white plates (0·03 g., 10%), m. p. 120—123° alone or in admixture with 6-methyl-3-pyridazone monohydrate.

6-*Methyl*-3-*pyridazone Monohydrochloride.*—Anhydrous 6-methyl-3-pyridazone (0·1 g.) was dissolved in absolute alcohol (5 c.c.) and the solution cooled to 0°, and treated with dry hydrogen chloride. The *hydrochloride* separated as a white solid; this was filtered off and recrystallised from dry alcohol–ether; m. p. 176—176·5° (Found: C, 41·5; H, 4·7. $C_5H_7ON_2Cl$ requires C, 41·0; H, 4·8%).

The hydrobromide was prepared in the same way. It had m. p. 183—184° and was identical with the product of the treatment of 6-methyl-3-pyridazinone with bromine (Found: C, 31·1; H, 3·4; N, 14·4%.

3-*Chloro*-6-*methylpyridazine.*—(*a*) Anhydrous 6-methyl-3-pyridazone (19·4 g.) was heated with phosphorus oxychloride (75 c.c.) at 100° for 30 minutes. The excess of phosphorus oxychloride was removed by distillation and crushed ice carefully added to the residue. The product was made alkaline to brilliant-yellow with 5N-sodium hydroxide. Thereafter it was exhaustively extracted with ether, the ether extracts were dried ($MgSO_4$), and the solvent was removed. The solid which remained was recrystallised from ligroin (b. p. 40—60°); shining white needles, m. p. 58° (yield, 19·4 g., 96%).

(*b*) Anhydrous 6-methyl-3-pyridazone (6·8 g.; 1 part) and phosphorus pentachloride (34 g.; 5 parts) were intimately mixed and heated on an oil-bath at 100° for 1 hour. Hydrogen chloride was evolved. After being allowed to cool, crushed ice was added, and the product made alkaline with sodium hydroxide solution. Thereafter it was extracted with chloroform and the extract dried ($MgSO_4$), filtered, and evaporated to a brown liquid (*A*) (6·8 g.) which was probably 3 : 3-dichloro-6-methyldihydropyridazine. This on attempted distillation at 150° (bath temperature)/15 mm. decomposed, and crystals of 3-chloro-6-methylpyridazine monohydrochloride appeared in the distillate.

The liquid (*A*) (1·3 g.) and 10% sodium hydroxide solution (10 c.c.) were boiled under reflux for 0·5 hours, filtered (charcoal), and the filtrate extracted with ether. The extract was dried ($MgSO_4$), filtered, and the solvent removed. There remained a solid which recrystallised from ligroin and had m. p. 58° alone or in admixture with 3-chloro-6-methylpyridazine. Yield, 0·25 g.; 26%.

3-*Chloro*-6-*methylpyridazine Monohydrobromide.*—3-Chloro-6-methylpyridazine (0·1 g.) was dissolved in absolute alcohol (3 c.c.), the solution cooled in ice, and dry hydrogen bromide passed in to precipitate the *hydrobromide* which recrystallised in long pink needles, m. p. 220° (decomp.) (Found: N, 13·5; total halide, 54·5. $C_5H_6N_2ClBr$ requires N, 13·4; total halide, 55·1%). The *monohydrochloride*, prepared similarly, separated from alcohol–ether in slightly pink needles, m. p. 250° (with darkening) (Found: N, 16·4. $C_5H_6N_2Cl_2$ requires N, 16·8%).

3-*Amino*-6-*methylpyridazine.*—(*a*) 3-Chloro-6-methylpyridazine (17·25 g.) was dissolved in dry methyl alcohol (1 l.) saturated at 0° with ammonia, and the solution heated at 175° for 2 days in an autoclave. The solution was then filtered and concentrated in a vacuum. The residue was treated with barium hydroxide (31·7 g. in 250 c.c. of water) at 80° in an atmosphere of nitrogen. The solution was evaporated to dryness and the residue extracted once with benzene (Extract *A*) and then with chloroform (Extract *B*). All these later operations were conducted in an atmosphere of nitrogen.

Extract *A* was dried ($CaCl_2$), and the solvent removed. A moist residue remained, which was extracted with warm water. The solid dissolved, and from the solution 3-amino-6-methylpyridazine was isolated, m. p. 225°. Yield, 4·4 g. A brown liquid did not dissolve in the water, and this was separated and dried. It was then dissolved in absolute ethyl alcohol, and dry hydrogen chloride was

bubbled through the solution. On addition of ether, a solid separated and was collected (0·2 g.). After recrystallisation from ethyl alcohol it had m. p. 131—132° not depressed in admixture with an authentic specimen of 3-methoxy-6-methylpyridazine monohydrochloride. Hence it appeared that the brown oil was 3-methoxy-6-methylpyridazine.

Extract *B* was dried ($MgSO_4$) and the solvent was removed. The solid residue of 3-amino-6-methylpyridazine (8·9 g., 60%) recrystallised from water in white rhombs, m. p. 224—225°. It was basic, soluble in alcohol and water, slightly soluble in chloroform, but insoluble in ether. It formed a complex with silver nitrate which was decomposed by nitric acid (Found: C, 55·2; H, 6·2; N, 38·2. $C_5H_7N_3$ requires C, 55·0; H, 6·4; N, 38·3%). The *monohydrochloride*, prepared by the action of dry hydrogen chloride in ice-cold solution, separated from alcohol in colourless plates, m. p. 237° (Found: C, 41·6; H, 5·40. $C_5H_8N_3Cl$ requires C, 41·2; H, 5·5%). The *monopicrate* separated from alcohol in yellow needles, m. p. 220—221° (Found: C, 38·8; H, 3·3; N, 25·2. $C_{11}H_{10}O_7N_6$ requires C, 39·1; H, 2·9; N, 24·9%).

(*b*) 3-Chloro-6-methylpyridazine (4·1 g.) was heated at 150° for two days with ammonia (*d*, 0·88) in an autoclave. Thereafter the solution was filtered (charcoal), evaporated to dryness, and the residue dissolved in water and treated with sodium hydroxide (1 mol.) at 100° for 1 hour. The solution was acidified with dilute hydrochloric acid and evaporated to dryness. The thoroughly dried residue was extracted with chloroform (*A*) and then with alcohol (*B*).

Extract *A* was evaporated to dryness; the residue recrystallised from water in white plates of 6-methyl-3-pyridazone, m. p. 123—124° (1 g., 28·6%).

Extract *B* was evaporated to dryness; the residue of 3-amino-6-methylpyridazine hydrochloride was dissolved in the minimum amount of water, cooled to 0°, and made alkaline with sodium hydroxide. The solution was filtered (charcoal) and kept overnight. The crystals which had separated were 3-amino-6-methylpyridazine, m. p. 225° (1·7 g., 48·5%).

3-*Methoxy*-6-*methylpyridazine*.—3-Chloro-6-methylpyridazine (2·0 g.) was dissolved in dry methyl alcohol (150 c.c.), containing sodium (5 g.), and the solution boiled under reflux for 2 hours. After evaporation to dryness, excess of aqueous potassium hydroxide was added, and the resulting solution extracted with benzene. The extract was dried ($MgSO_4$) and the benzene removed. The *methoxy*-compound (0·70 g., 36·8%) distilled as a colourless liquid which soon turned red; b. p. 210°, $n_D^{21°}$ 1·5014 (Found: N, 22·5. $C_6H_8ON_2$ requires N, 22·6%). Much red polymer remained in the flask. The *hydrochloride*, prepared by the action of dry hydrogen chloride in ice-cold solution, crystallised from ethyl alcohol in large colourless deliquescent plates, m. p. 137—138° (Found: C, 44·6; H, 5·8. $C_6H_9ON_2Cl$ requires C, 44·8; H, 5·6%).

3-*Acetamido*-6-*methylpyridazine*.—3-Amino-6-methylpyridazine (0·3 g.) was boiled for 15 minutes with fused sodium acetate (0·4 g.) and acetic anhydride (5 c.c.). Thereafter the solution was poured into water, and the solution neutralised with sodium bicarbonate and extracted with chloroform. The extract, after being dried ($MgSO_4$), was evaporated to dryness and the residual *acetyl* derivative recrystallised from water. Yield, 0·31 g. (45%), m. p. 214—215° (Found: C, 55·5; H, 5·9; N, 27·8. $C_7H_9ON_3$ requires C, 55·6; H, 5·9; N, 27·8%). The *monohydrochloride*, prepared by the action of dry hydrogen chloride in alcoholic solution, crystallised from alcohol–ether in white plates, m. p. 235° (decomp.) (Found: Cl, 18·9. $C_7H_{10}ON_3Cl$ requires Cl, 18·9%). The *monohydrobromide*, which was unstable, formed crystals, m. p. 206° (Found: Br, 36·6. $C_7H_{10}ON_3Br$ requires Br, 36·2%).

3-N-*Acetylsulphanilamido*-6-*methylpyridazine*.—(*a*) *N*-Acetylsulphanilyl chloride (2·88 g., 1·1 mols.) in dry pyridine (20 c.c.) was added to a suspension of 3-amino-6-methylpyridazine (1·354 g., 1 mol.) also in dry pyridine. The mixture was kept at room temperature for 24 hours, and then poured into water containing sodium hydroxide (0·5 g., 1 mol.) and concentrated. The *compound* separated as a yellow solid which recrystallised from acetic acid–water in white cubes, which turned pink on standing; m. p. 247—247·5° (Found: C, 51·0; H, 4·7; N, 18·4. $C_{13}H_{14}O_3N_4S$ requires C, 51·0; H, 4·6; N, 18·3%). Yield, 3·2 g. (84%). Solubility in water at 15°, 39 mg./100 c.c. of solution.

(*b*) 3-Amino-6-methylpyridazine (0·48 g.) was dissolved in dry chloroform (20 c.c.) and to the solution was added *N*-acetylsulphanilyl chloride (1·1 g.) also in dry chloroform (10 ml.). The mixture was kept at 45° for 30 minutes. The chloroform was removed, and sodium hydroxide (0·18 g.) in water (10 c.c.) were added. On concentrating the solution an oil separated, which crystallised. After recrystallisation from acetic acid–water it had m. p. 247° alone or in admixture with 3-*N*-acetylsulphanilamido-6-methylpyridazine. Yield, 0·30 g. (22·3%).

3-*Sulphanilamido*-6-*methylpyridazine*.—(*a*) 3-*N*-Acetyl-6-methylsulphanilamidopyridazine (1·9 g.) was dissolved in aqueous sodium hydroxide solution (0·7 g. in 7 c.c.) and the mixture heated under reflux for 45 minutes. It was then allowed to cool, filtered (charcoal), and made just acid with dilute hydrochloric acid. The solid which then separated was recrystallised from hot water; yellow needles, m. p. 195—196° (Found: C, 50·2; H, 4·3; NH_2 (nitrite titration), 6·0. $C_{11}H_{12}O_2N_4S$ requires C, 50·0; H, 4·5; NH_2, 6·1%). Yield, 1·45 g. (87%). The *dihydrochloride*, prepared by the action of dry hydrogen chloride in alcoholic solution, crystallised from alcohol–water in white plates, m. p. 215° (Found: C, 39·3; H, 3·9. Cl, 11·8. $C_{11}H_{14}O_2N_4Cl_2S$ requires C, 39·3; H, 3·9; Cl, 11·8%).

(*b*) 3-*N*-Acetyl-6-methylsulphanilamidopyridazine (0·03 g.) was heated under reflux for 1 hour with 2N-hydrochloric acid (7 c.c.). When cool, the solution was neutralised with sodium hydroxide solution. A yellow solid separated and was collected. After recrystallisation from water it had m. p. 195—196°, alone or in admixture with 3-sulphanilamido-6-methylpyridazine. Yield, 0·02 g. (80%). Solubility in water at 15°, 61 mg./100 c.c. of solution.

(*c*) 3-Amino-6-methylpyridazine (0·37 g.) suspended in dry pyridine was treated with *p*-nitrobenzenesulphonyl chloride (0·82 g., 1·1 mols.), dissolved in dry pyridine, at 0°. After 24 hours at room temperature, water containing sodium hydroxide (0·13 g., 1 mol.) was added, and the mixture evaporated until a solid began to separate. This 3-p-*nitrobenzenesulphonamido*-6-*methylpyridazine* was collected and recrystallised from alcohol–water; pale yellow crystals, m. p. 161° (Found: C, 44·5; H, 3·3. $C_{11}H_{10}O_4N_4S$ requires C, 44·8; H, 3·4%). Yield, 0·47 g. (46%).

The above nitro-compound (0·39 g.) was dissolved in dry methyl alcohol (150 c.c.) and hydrogenated

over Raney nickel at room temperature. After being filtered the solution was evaporated. The residue was dissolved in water, filtered (charcoal), and allowed to cool; a yellow solid then separated, m. p. 196—197°, alone or in admixture with 3-sulphanilamido-6-methylpyridazine. Yield, 0·07 g. (21%). A brown oil was also formed which would not crystallise. The crystalline sulphonamide was readily converted by treatment with acetic anhydride–acetic acid into 3-*N*-acetylsulphilamido-6-methylpyridazine, m. p. 247°.

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