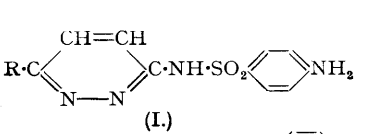
445. *The Conversion of Sucrose into Pyridazine Derivatives. Part IV. Further Sulphanilamides derived from 6-Methyl-3-pyridazone.*

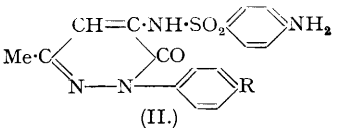
By R. F. Homer, Hilda Gregory, W. G. Overend, and L. F. Wiggins.

A method of synthesis of 3-sulphanilamidopyridazine from the 6-methyl-3-pyridazone obtained from lævulic acid (Overend and Wiggins, *J.*, 1947, 239) is described. The bacteriostatic activity of this compound compared with that of 3-sulphanilamido-6-methylpyridazine is discussed. 5-*Sulphanilamido*-2 : 6-*dimethyl*-3-*pyridazone* has been obtained; this, however, has no marked bacteriostatic activity *in vitro*.

Parts I and II (*J.*, 1947, 239, 549) of this series described several sulphanilamides, containing the pyridazine or pyridazone nucleus, which had been obtained using lævulic acid as the essential intermediate. 3-Sulphanilamido-6-methylpyridazine (I; R = Me) (Part I) was shown to possess a very high bacteriostatic activity *in vitro* against various micro-organisms. 4-Sulphanilamido-2-phenyl-6-methyl-3-pyridazone (II; R = H) (Part II) also derived from lævulic acid through its phenylhydrazone, also possessed considerable activity in routine bacteriostatic tests, but this was less marked than that shown by (I; R = Me) or sulphathiazole, although, despite the presence of the phenyl residue, it possessed better solubility properties than the latter compound. 4-Sulphanilamido-2-*p*-nitrophenyl-6-methyl-3-pyridazone (II; R = NO_2) was also made, but this was too sparingly soluble to be of use.



(I.)



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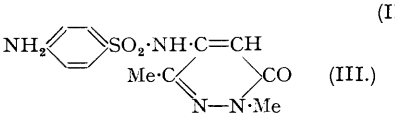


(III.)

The effect of (I; R = Me) in mice has now been investigated by Dr. A. T. Fuller of the National Institute for Medical Research. Dr. Fuller's tests indicate that (I; R = Me) is better than sulphanilamide against *Streptococcus hæmolyticus* (Richards) infection in mice. Furthermore, although it failed to protect mice against 100 lethal doses of staphylococcus, it was more efficient than sulphathiazole when used against 5. In an examination of its effect, compared with that of sulphathiazole, against *Clostridium welchii* in guinea pigs, it was found that there was little difference in the effectiveness of the two drugs, though with (I; R = Me) the occurrence of *Cl. welchii* at the injection site in the survivors was less than that occurring when sulphathiazole was used.

Since these results seemed promising it was thought worth while to prepare other sulphanilamide derivatives of pyridazine and 3-pyridazone, and 5-*sulphanilamido*-2 : 6-*dimethyl*-3-*pyridazone* (III) and 3-sulphanilamidopyridazine (I; R = H) are now described; the latter, first made by Anderson, Faith, Marson, Roblin, and Winneck (*J. Amer. Chem. Soc.*, 1942, **64**, 2902), has now been made from lævulic acid.

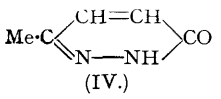
5-Sulphanilamido-2 : 6-dimethyl-3-pyridazone has been obtained in the following way.

5-Chloro-2 : 6-dimethyl-3-pyridazone on treatment with aqueous ammonia under pressure readily gave 5-*amino*-2 : 6-*dimethyl*-3-*pyridazone* characterised as the *hydrochloride*, *picrate*, and *acetyl* derivative. This amine with *p*-acetamidobenzenesulphonyl chloride afforded 5-(p-*acetamidobenzenesulphonamido*)-2 : 6-*dimethyl*-3-*pyridazone*, which on hydrolysis yielded 5-*sulphanilamido*-2 : 6-*dimethyl*-3-*pyridazone* (III). This formed a characteristic *monohydrochloride*. The behaviour of (III) in bacteriostatic tests is shown below, where it is seen that although it does possess some activity, this is much less than that shown by sulphathiazole.

	Strep. hæmolyticus.		*Staph. aureus.*		*B. coli.*	
Compound.	Blood medium.	Broth medium.	Synth. medium.	Broth medium.	Synth. medium.	Broth medium.
5-Sulphanilamido-2 : 6-dimethyl-3-pyridazone	2	10	500	1000	2	50
Sulphathiazole	0·2	—	1	—	0·05	5

The figures represent mg. of compound/100 c.c. of solution necessary to prevent growth of organisms.

3-Sulphanilamidopyridazine (I; R = H) was first obtained by Anderson *et al.* (*loc. cit.*) through the 3-chloropyridazine obtained by Gabriel (*Ber.*, 1909, **42**, 655) from 2-ketoglutaric acid by condensation with hydrazine. The product, 3-pyridazinone-6-carboxylic acid was dehydrogenated to form 3-pyridazone-6-carboxylic acid which was then decarboxylated to 3-pyridazone. This with phosphoryl chloride gave 3-chloropyridazine. This compound has now been obtained from lævulic acid in the following way. 6-Methyl-3-pyridazone (IV) is readily made from lævulic acid (Part I, *loc. cit.*). Now it has been found that the methyl group in this compound can be easily oxidised by means of potassium dichromate and sulphuric acid to give, in 70% yield, 3-pyridazone-6-carboxylic acid (V), identical with Gabriel's compound (*loc. cit.*). The dichromate–sulphuric acid method of oxidation was far superior to the nitric acid oxidation which Paal and Dencks (*Ber.*, 1903, **36**, 491) used to oxidize 3-phenyl-6-methylpyridazine to 3-phenylpyridazine-6-carboxylic acid. Under Paal and Denck's conditions only minute yields of (V) were obtained from 6-methylpyridazone.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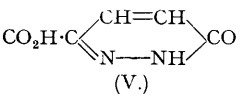
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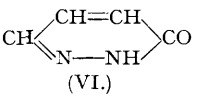
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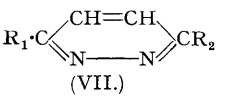
(VII.)

(V) was readily transformed into the characteristic *ethyl* ester and the 6-*carbamyl* derivative. It was readily decarboxylated at its melting point, to yield 3-pyridazone (VI) in 88% yield. Treatment of this with phosphoryl chloride gave 3-chloropyridazine (VII; R_1 = H, R_2 = Cl) in high yield. This compound was not very stable since it darkened and liquefied even on being kept at 0° in a vacuum. Its hydrochloride was also unstable in air. A possible alternative method of preparation of (VII; R_1 = H, R_2 = Cl) was by oxidation of 3-chloro-6-methylpyridazine (VII; R_1 = Me, R_2 = Cl) followed by decarboxylation of the 3-*chloropyridazine*-6-*carboxylic acid* (VII; R_1 = CO_2H, R_2 = Cl) produced. Attempts to decarboxylate 3-chloropyridazine-6-carboxylic acid were abandoned when the extreme instability of 3-chloropyridazine even at low temperatures and under anhydrous conditions was confirmed. Some aspects of the preparation and properties of the acid are, however, of interest. Attempts to oxidise 3-chloro-6-methylpyridazine with nitric acid according to the method of Paal and Dencks (*loc. cit.*) failed, and led only to removal of the chlorine atom with formation of 6-methyl-3-pyridazone. Oxidation with potassium dichromate and sulphuric acid, however, afforded the 6-carboxylic acid in 65% yield. The acid was identical with the product of chlorination of 3-pyridazone-6-carboxylic acid with phosphoryl chloride, though the yield of the 3-chloro-compound by the latter procedure was only 38%. The chlorine atom in this compound was extremely labile and was completely removed by refluxing with 2% ethyl-alcoholic hydrogen chloride, which gave ethyl pyridazone-6-carboxylate only.

Treatment of 3-chloropyridazine with methyl-alcoholic ammonia under pressure resulted in the formation of 3-aminopyridazine (VII; R = H, R_2 = NH_2), identical with that described by Anderson (*loc. cit.*), in good yield. This on treatment with *p*-acetamidobenzenesulphonyl chloride gave 3-(p-*acetamidobenzenesulphonamido*)*pyridazine*, which, on hydrolysis with either dilute alkali or acid, afforded 3-sulphanilamidopyridazine, m. p. 175°. Anderson *et al.* (*loc. cit.*) record m. p. 189—190° for this compound. We were unable to raise the melting point of our compound to this value even by repeated recrystallisation.

The American authors first made this compound and reported that, although it possessed a remarkably high activity in bacteriostatic tests against *Esch. coli* yet against streptococcal and pneumococcal infection in mice it was practically inactive. This, in view of the high activity of 3-sulphanilamido-6-methylpyridazine *in vitro* and *in vivo*, appeared very remarkable, and one of the reasons for the preparation of 3-sulphanilamidopyridazine was to enable a biological re-examination of it to be made. Dr. A. T. Fuller has tested this compound against *Strep. hæmolyticus* (Richards) in mice and he finds that it is more active than sulphanilamide itself when given orally, but is inactive when given intraperitoneally. Although Anderson *et al.* gave no details of their method of testing 3-sulphanilamidopyridazine, the inference is that they did so intraperitoneally, which would account for their statement that this substance was inactive *in vivo*.

Experimental.

Treatment of 5-Chloro-2 : 6-dimethyl-3-pyridazone with Ammonia.—5-Chloro-2 : 6-dimethyl-3-pyridazone (Part III, preceding paper) (7·8 g.) was dissolved in aqueous ammonia (*d*, 0·88) (750 c.c.) and heated at 160° for 60 hours in an autoclave. The mixture was evaporated to dryness under reduced pressure, and the residue extracted with chloroform in an atmosphere of nitrogen. The extract was dried ($MgSO_4$) and evaporated to a thick syrup which crystallised on trituration with acetone. The

crude material, recrystallised from acetone, gave 5-*amino*-2 : 6-*dimethyl*-3-*pyridazone* (4·0 g.; 58%), m. p. 163° (Found : C, 51·4; H, 6·2; N, 29·7. $C_6H_9ON_3$ requires C, 51·8; H, 6·4; N, 30·2%).

A small quantity of the amine was dissolved in absolute alcohol and the solution saturated with hydrogen chloride. White crystals of the *hydrochloride* separated, and after recrystallisation from absolute alcohol containing a little hydrogen chloride had m. p. *ca.* 245° (decomp.) (Found : C, 41·6; H, 5·8. $C_6H_9ON_3$,HCl requires C, 41·2; H, 5·7%). The amine (0·5 g.) was dissolved in a little water, and picric acid (1 mol.) dissolved in alcohol added. The precipitated *picrate* was collected and recrystallised from water to form yellow needles (0·06 g.), m. p. 130° (Found : N, 23·2. $C_{12}H_{12}O_8N_6$ requires N, 22·8%).

The amine (0·6 g.) was refluxed with fused sodium acetate (3 g.) and acetic anhydride (20 c.c.) for ½ hour. The mixture was poured into water, neutralised with sodium carbonate, and extracted with chloroform. The dried ($MgSO_4$) extract was evaporated to dryness; the crude *acetyl* derivative recrystallised from water in colourless needles (0·4 g.), m. p. 227° (60%) (Found : C, 53·3; H, 6·1; N, 23·9. $C_8H_{11}O_2N_3$ requires C, 53·0; H, 6·0; N, 23·2%).

5-(p-*Acetamidobenzenesulphonamido*)-2 : 6-*dimethyl*-3-*pyridazone*.—The amine (5·0 g.) and *p*-acetamidobenzenesulphonyl chloride (8·5 g.) were separately dissolved in dry pyridine, the solutions mixed, and the mixture kept at 40° for 1 hour. It was then poured into water, sodium hydroxide (1·45 g., 1 mol) added, and the solution distilled with much water to remove pyridine. A yellowish solid separated, and was filtered off and recrystallised from alcohol–acetic acid. 5-(p-*Acetamidobenzenesulphonamido*)-2 : 6-*dimethyl*-3-*pyridazone* (2·2 g.) separated as pink microcrystals, m. p. 263° (Found : C, 49·8; H, 4·8. $C_{14}H_{16}O_4N_4S$ requires C, 50·0; H, 4·8%).

5-*Sulphanilamido*-2 : 6-*dimethyl*-3-*pyridazone*.—The acetyl derivative (1·5 g.) was refluxed with 10% aqueous sodium hydroxide (20 c.c.) for ¾ hour. On being neutralised with hydrochloric acid the solution deposited a yellow solid which was collected and recrystallised from aqueous alcohol, forming yellow needles of 5-*sulphanilamido*-2 : 6-*dimethyl*-3-*pyridazone monohydrate* (1·2 g.), m. p. 113—123° (Found : C, 46·4; H, 5·2. $C_{12}H_{14}O_3N_4S,H_2O$ requires C, 46·2; H, 5·15%). The *anhydrous* compound had m. p. 207° (Found : N, 19·4. $C_{12}H_{14}O_3N_4S$ requires N, 19·1%).

The sulphanilamido-compound (0·05 g.) was shaken with acetic anhydride (3 c.c.) and 5N-acetic acid (3 c.c.). After a few minutes, crystals of the acetyl derivative (0·05 g.) separated, m. p. 262° alone or in admixture with an authentic specimen.

The sulphanilamide monohydrate (50 mg.) was dissolved in dry methyl alcohol and the solution was saturated with hydrogen chloride. On addition of ether, a yellowish powder was precipitated, which, when recrystallised from methyl alcohol containing a little hydrogen chloride, formed pale yellow needles of the *hydrochloride monohydrate* (40 mg.), m. p. 180° (decomp.) (Found : C, 41·1; H, 4·8; N, 16·2. $C_{12}H_{14}O_3N_4S,HCl,H_2O$ requires C, 41·4; H, 4·9; N, 16·1%).

Oxidation of 6-*Methyl*-3-*pyridazone*.—(a) *By dilute nitric acid.* 6-Methyl-3-pyridazone (3·0 g.) was heated with nitric acid (10%; 15 c.c.) for 5 hours at 160°. On cooling, crystals separated which were recrystallised from water, giving 3-pyridazone-6-carboxylic acid monohydrate (0·05 g.), m. p. 257°. Gabriel (*loc. cit.*) gives the same m. p. (Found : C, 38·2; H, 3·5; N, 17·8. Calc. for $C_5H_4O_3N_2,H_2O$: C, 38·0; H, 3·8; N, 17·7%). The mother liquors were evaporated to dryness; the residue, recrystallised from water, gave 6-methyl-3-pyridazone (0·015 g.), m. p. 122—123° alone or in admixture with starting material.

(b) *By concentrated nitric acid.* 6-Methyl-3-pyridazone (1·0 g.) was heated with concentrated nitric acid (20 c.c.) in an evaporating basin on a water-bath. Complete evaporation of the acid and recrystallisation of the residue from water gave 100% recovery of the unchanged starting material.

(c) *By potassium dichromate and concentrated sulphuric acid.* To a mechanically stirred solution of 6-methyl-3-pyridazone (5·0 g.) in concentrated sulphuric acid (50 c.c.) potassium dichromate (13·4 g.; 1 mol.) was added in small quantities as a finely ground powder. When the reaction started, as indicated by the development of a green coloration, the flask was cooled in cold water before the addition of potassium dichromate was continued. After the addition was completed, stirring was continued for a further 2 hours, then the viscous green mixture was poured on crushed ice. The colourless crystalline powder which separated was collected, washed with alcohol and ether, then recrystallised from hot water giving needles of 3-pyridazone-6-carboxylic acid monohydrate (4·35 g.; 68·4%), m. p. 257°. The results of further experiments carried out under slightly varied conditions are tabulated below.

6-Methyl-3-pyridazone, g.	$K_2Cr_2O_7$, g.	H_2SO_4, c.c.	Temp.	Yield. G.	Yield. %
5	13·4 (1 mol.)	50	40°	4·31	68·0
5	13·4 ,,	50	50	4·28	68·0
5	13·4 ,,	30	30—50	4·2	67·5
5	16·08 (1·2 mol.)	50	30—50	4·62	72·5
50	160·8 ,,	500	30—50	46·15	72·4

Ethyl 3-*pyridazone*-6-*carboxylate*. 3-Pyridazone-6-carboxylic acid (2·0 g.) was heated under reflux with 2% ethyl-alcoholic hydrogen chloride for 6 hours on a water-bath. The mixture was thereafter neutralised with lead carbonate and filtered, and the filtrate evaporated to dryness under reduced pressure. Recrystallisation of the residue from hot water gave glistening white flakes of *ethyl* 3-*pyridazone*-6-*carboxylate monohydrate* (2·0 g.; 84%), m. p. 102° (Found : C, 45·5; H, 5·2; N, 15·4. $C_7H_8O_3N_2,H_2O$ requires C, 45·2; H, 5·4; N, 15·1%). The anhydrous *ester* had m. p. 122° (Found : C, 50·2; H, 4·7; N, 16·0. $C_7H_8O_3N_2$ requires C, 50·0; H, 4·8; N, 16·6%).

6-*Carbamyl*-3-*pyridazone*. A solution of ethyl 3-pyridazone-6-carboxylate (0·3 g.) in ethyl alcohol was saturated with ammonia at 0° and the solution kept at 0° overnight. Crystals separated which were collected, and after being recrystallised from water gave 6-*carbamyl*-3-*pyridazone*, m. p. 304° (decomp.) (Found : C, 43·3; H, 3·9; N, 30·5. $C_5H_5O_2N_3$ requires C, 43·2; H, 3·6; N, 30·2%).

Oxidation of 3-Chloro-6-methylpyridazine.—(*a*) 3-Chloro-6-methylpyridazine (5 g.) (Part I, *loc. cit.*) and 5% nitric acid (150 c.c.) were heated at 160° for 5 hours in a sealed tube. After cooling, the solution was evaporated to dryness; the syrup remaining solidified on addition of water. The solid after recrystallisation from water had m. p. 124—125° alone or in admixture with 6-methyl-3-pyridazone monohydrate. Yield 3·6 g.

(*b*) To a mechanically stirred solution of 3-chloro-6-methylpyridazine (1·8 g.) in concentrated sulphuric acid (10 c.c.), finely powdered potassium dichromate (5·0 g., 20% excess) was added slowly, the temperature being kept below 50°. When the addition was complete, stirring was continued for a further 2 hours at 50°. The oxidation was still not complete, as indicated by the yellowish-green coloration. Thereafter the mixture was heated for a further 2 hours on a boiling water-bath. The viscous, dark green liquid was cooled and added to crushed ice, and the solution extracted with ether. The ethereal extract was dried ($MgSO_4$) and evaporated to dryness, and the residue recrystallised from water, giving *3-chloropyridazine-6-carboxylic acid* (1·45 g.; 65·3%), m. p. 146° (Found: C, 37·5; H, 2·2; N, 17·1. $C_5H_3O_2N_2Cl$ requires C, 37·8; H, 1·9; N, 17·6%).

Chlorination of 3-Pyridazone-6-carboxylic Acid.—3-Pyridazone-6-carboxylic acid (3·0 g.) was heated under reflux with phosphoryl chloride (50 c.c.) for 0·5 hour. Most of the excess of phosphoryl chloride was removed under reduced pressure, crushed ice added, and the mixture extracted with ether. The etheral extract was dried ($MgSO_4$) and evaporated to a colourless crystalline solid which was recrystallised from water, giving 3-chloropyridazine-6-carboxylic acid (1·25 g.; 38·0%), m. p. 146° alone or in admixture with the product obtained by oxidation of 3-chloro-6-methylpyridazine.

3-Chloropyridazine-6-carboxylic acid (0·85 g.) was heated under reflux with 2% ethyl-alcoholic hydrogen chloride (40 c.c.) for 6 hours. The resulting solution was neutralised with barium carbonate and filtered, and the filtrate evaporated to dryness. The residue recrystallised from water in rosettes of needles (0·53 g.; 59%), m. p. 121—122° alone or in admixture with ethyl pyridazone-6-carboxylate (Found: N, 16·3. Calc. for $C_7H_8O_3N_2$: N, 16·6%).

3-Pyridazone.—Anhydrous 3-pyridazone-6-carboxylic acid (10·0 g.) was heated gently in a distilling flask until, after fusion of the crystalline mass, the evolution of carbon dioxide subsided. On being heated more strongly, the crude product distilled and solidified in long needles. After repetition of the distillation, followed by recrystallisation of the product from acetone–ethyl alcohol–ligroin, long needles of 3-pyridazone (6·0 g.; 88·0%), m. p. 103° (cf. Gabriel, *loc. cit.*), separated.

3-Chloropyridazine.—Phosphoryl chloride (10 c.c.) was added slowly to 3-pyridazone (3·0 g.). When the vigorous reaction which immediately ensued had slowed down, the mixture was heated on a water-bath for 2 hours at 67°. The excess of phosphoryl chloride was removed under reduced pressure, and the dark brown residue poured on crushed ice. The resulting solution was neutralised with sodium carbonate and extracted with ether, and the ethereal extract dried ($MgSO_4$). Evaporation of the ether at 0° under reduced pressure gave a white crystalline residue, which on careful recrystallisation from ether–ligroin (b. p. 40—60°) gave shiny flakes of 3-chloropyridazine (2·56 g.; 70·8%), m. p. 29° (cf. Gabriel, *loc. cit.*). These quickly decomposed even when kept in a vacuum desiccator at 0°. The hydrochloride was obtained by dissolving the base (0·1 g.) in anhydrous ethyl alcohol and saturating the solution with dry hydrogen chloride at 0°. Crystals, m. p. 122°, separated, but these decomposed too quickly for analytical results to be obtained.

3-Aminopyridazine.—3-Chloropyridazine (15 g.) was heated with methyl alcohol (750 c.c.) saturated with ammonia at 0° in an autoclave at 175° for 2 days. The dark brown solution thereby obtained was filtered and evaporated to dryness under reduced pressure in an atmosphere of nitrogen. The residue was extracted several times with hot ethyl acetate, and the crystals which separated on cooling were collected. Evaporation of the ethyl acetate yielded more of this material which was crude 3-aminopyridazine. The residue, insoluble in ethyl acetate, was heated with barium hydroxide (20 g.) in water (300 c.c.) for 1 hour in an atmosphere of nitrogen, and the mixture thereafter evaporated to dryness and extracted with ethyl acetate. A further crop of crystals was obtained from this extract. Recrystallisation of the total crude product gave 3-aminopyridazine (8·1 g.; 65%), m. p. 169—170° (Found: C, 50·8; H, 5·5; N, 43·6. Calc. for $C_4H_5N_3$: C, 50·5; H, 5·3; N, 44·2%).

3-(p-Acetamidobenzenesulphonamido)pyridazine.—A solution of *p*-acetamidobenzenesulphonyl chloride (14·0 g., 2% excess) in dry pyridine (80 c.c.) was added to 3-aminopyridazine (5·0 g.) also dissolved in dry pyridine (*ca.* 200 c.c.). The resulting dark red solution was kept for 24 hours at room temperature, then poured into water containing sodium hydroxide (1 mol.). The mixture was distilled with water until all the pyridine had been removed; a dark brown oil then separated and slowly solidified. Recrystallisation from water gave *3-(p-acetamidobenzenesulphonamido)pyridazine* (9·35 g.; 60·7%), m. p. 106—107° (Found: C, 49·1; H, 4·0. $C_{12}H_{12}O_3N_4S$ requires C, 49·3; H, 4·1%).

Hydrolysis. (*a*) 3-(*p*-Acetamidobenzenesulphonamido)pyridazine (1·35 g.) was heated with 10% sodium hydroxide solution (15 c.c.) on a boiling water-bath for ½ hour, and the resulting solution was neutralised (litmus) with dilute hydrochloric acid. The free base which separated on standing was collected and recrystallised from water to give 3-sulphanilamidopyridazine as yellow crystals (0·6 g.; 52%), m. p. 175°; solubility at room temp., 0·192 mg./100 c.c. of solution. The m. p. was not raised even by 3 further recrystallisations. Anderson *et al.* (*loc. cit.*) give m. p. 189—190° (Found: C, 47·9; H, 4·2; N, 22·7. Calc. for $C_{10}H_{10}O_2N_4S$: C, 48·0; H, 4·0; N, 22·4%).

(*b*) 3-(*p*-Acetamidobenzenesulphonamido)pyridazine (0·5 g.) was heated with 2N-hydrochloric acid (10 c.c.) on a boiling water-bath for 1 hour. Dilute sodium hydroxide was then added until the solution became turbid and an oil separated which gradually solidified. The solid was collected and recrystallised from water, giving 3-sulphanilamidopyridazine (0·26 g.; 60·7%), m. p. 175° alone or in admixture with the product obtained above by alkaline hydrolysis.

The sulphanilamido-compound (0·1 g.) could be reacetylated, by heating it with acetic anhydride (5 c.c.) and sodium acetate (0·2 g.) for 30 minutes, to 3-(*p*-acetamidobenzenesulphonamido)pyridazine, m. p. 106—107° alone or in admixture with the compound obtained by direct condensation of *p*-acetamidobenzenesulphonyl chloride with 3-aminopyridazine.

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THE A. E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM, 15. [*Received, February* 16*th*, 1948.]