442. *The Conversion of Sucrose into Pyridazine Derivatives. Part VII. Some Sulphone Derivatives of 6-Methylpyridazine and 6-Methyl-3-pyridazone.*

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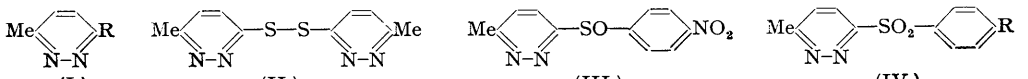
The synthesis of *p*-aminophenyl 6-methyl-3-pyridazyl sulphone and some attempts to prepare *p*-aminophenyl 6-methylpyridaz-3-on-2-yl sulphone are described.

Sulphanilamide derivatives incorporating pyrimidine and pyrazine residues have been used with marked success in chemotherapy. Similar derivatives of pyridazine are less well known but one of them, 3-sulphanilamido-6-methylpyridazine (Overend and Wiggins, *J.*, 1947, 239; Roblin and Winnek, B.P. 563,629), shows promise of usefulness inasmuch as it displays a greater bacteriostatic activity than does sulphathiazole when examined under *in vitro* conditions. In recent years it has been shown that certain sulphones have powerful bacteriostatic activity. Thus, it has been shown that the 4 : 4′-diaminodiphenyl sulphone of Fromm and Wittman (*Ber.*, 1908, **41**, 2264) has a hundred times the curative effect of sulphanilamide on hæmolytic streptococcal infections in mice. Moreover, it has some chemotherapeutic efficacy in cases of

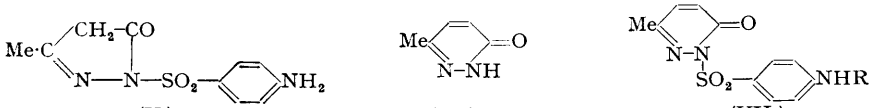
experimental tuberculosis (Feldman, Hinshaw, and Moses, *Amer. J. Med. Sci.*, 1944, **207**, 290), but its toxicity diminishes its clinical value. More recently, in attempts to find less toxic analogues the phenyl residues have been replaced by certain heterocyclic groups, and Bambas (*J. Amer. Chem. Soc.*, 1945, **67**, 668) has shown that the bacteriostatic activity is maintained so long as at least one phenyl group is left in the molecule—when both phenyl groups are replaced by heterocyclic residues, the activity vanishes. Moreover, Tullar and Banks (Abstracts of the St. Louis Meeting of the Amer. Chem. Soc., Division of Med. Chem., 1944, No. 5) demonstrated that for maintenance of activity it was necessary to include at least one amino-group situated *para* with respect to the sulphone group. It was also shown that only one amino-group was necessary to give an active substance. Thus, *p*-aminophenyl *p'*-hydroxyphenyl sulphone exhibited bacteriostatic activity. With these facts in our mind, the preparation of sulphone derivatives of pyridazine was attempted.



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

In Part V of this series (*J.*, 1948, 2199) methods were described for the preparation of 3-mercapto-6-methylpyridazine (I; R = SH) and for its conversion into 3-ethylthio-6-methylpyridazine (I; R = SEt). Now it has been found possible to oxidise this either with acid potassium permanganate at 0° or with 30% hydrogen peroxide at room temperature, to yield crystalline 6-*methyl*-3-*pyridazyl ethyl sulphone* (I; R = SO_2·Et). Attempts to prepare 3-phenylthio-6-methylpyridazine by heating 3-mercapto-6-methylpyridazine with iodobenzene at 150—160° were unsuccessful and instead *di*-(6-*methyl*-3-*pyridazyl*) *disulphide* (II) and unchanged starting material were isolated. This disulphide was also obtained when 3-mercapto-6-methylpyridazine was treated with aqueous ammonia, and the original thiol was regenerated by treatment with dilute sodium hydroxide solution followed by acidification. However, 3-mercapto-6-methylpyridazine condensed with *p*-bromonitrobenzene in the presence of alcoholic sodium methoxide at 80°, to give crystalline 3-p-*nitrophenylthio*-6-*methylpyridazine* (I; R = *p*-NO_2·C_6H_4·S·) in moderate yield. Oxidation of this with 30% hydrogen peroxide did not give the expected sulphone (IV; R = NO_2), but instead p-*nitrophenyl* 6-*methyl*-3-*pyridazyl sulphoxide* (III) was formed. The same compound was obtained when the theoretical amount of potassium permanganate was used as the oxidizing agent, although an excess of permanganate gave p-*nitrophenyl* 6-*methyl*-3-*pyridazyl sulphone* (IV; R = NO_2), which was also obtained when the sulphoxide itself was oxidized with potassium permanganate. Catalytic reduction of *p*-nitrophenyl 6-methyl-3-pyridazyl sulphone yielded p-*aminophenyl* 6-*methyl*-3-*pyridazyl sulphone* (IV; R = NH_2), isolated as the monohydrate. This sulphone exhibited no bacteriostatic activity *in vitro* against *Staphylococcus aureus*.

Few compounds of the sulphonamide class containing heterocyclic residues, described hitherto, possess a sulphanilyl residue attached to a nitrogen atom of the heterocyclic nucleus. One such compound is (V) prepared by Roblin *et al.* (*J. Amer. Chem. Soc.*, 1940, **62**, 2002). The attempt has now been made to prepare a similar derivative of a pyridazone.



(V.) (VI.) (VII.)

It has been shown (Homer, Gregory, and Wiggins, *J.*, 1948, 2191) that alkylation of 6-methyl-3-pyridazone (VI) gives rise to 2-alkyl derivatives, and, when (VI) was treated with *N*-acetylsulphanilyl chloride, a compound was obtained which by analogy with the 2-alkyl derivatives of pyridazone is termed p-*acetamidophenyl* 6-*methylpyridaz*-3-*on*-2-*yl sulphone* (VII; R = Ac). Hydrolysis of this with sodium hydroxide or hydrochloric acid solution resulted in rupture of the nitrogen–sulphur linkage and regeneration of 6-methyl-3-pyridazone (VI). Consequently a more suitable residue with which to mask the amino-group in sulphanilyl chloride was sought, so that after the condensation the group protecting the amino-residue could be removed without use of either acid or alkaline reagents. The carbobenzyloxy-group appeared to answer these requirements since it can be removed from an amino-residue by catalytic hydrogenation under mild conditions.

Sodium N-*carbobenzyloxysulphanilate* was prepared by treating sodium sulphanilate in

aqueous solution with benzyl chloroformate and sodium hydrogen carbonate. Hydrogenation at room temperature in the presence of palladium resulted in cleavage of the carbobenzyloxy-residue and the formation of sodium sulphanilate. When dry sodium *N*-carbobenzyloxysulphanilate was intimately mixed with phosphorus pentachloride at room temperature it afforded crystalline N-*carbobenzyloxysulphanilyl chloride* which was converted into N-*carbobenzyloxysulphanilamide* on treatment with ammonia. Dohrn and Diedrich have previously (U.S.P. 2,411,495) prepared this compound by the condensation of sulphanilamide with benzyl chloroformate and record m. p. 192—192·5°. Whilst it was not possible to raise the m. p. of our compound above 189—190°, the similarity of these constants indicates that the compounds, although prepared in different ways, are identical. Hydrogenation of *N*-carbobenzyloxysulphanilamide was readily accomplished and sulphanilamide isolated. Treatment of 6-methyl-3-pyridazone (VI) with *N*-carbobenzyloxysulphanilyl chloride gave crystalline p-O-*benzylurethanophenyl* 6-*methylpyridaz*-3-*on*-2-*yl sulphone* (VII; R = $CH_2Ph{\cdot}O{\cdot}CO{\cdot}$). Hydrogenation of this in the conditions which were applied to *N*-carbobenzyloxysulphanilamide did not lead to the formation of the desired sulphone (VII; R = H); only sulphanilamide and *N*-carbobenzyloxysulphanilamide were isolated.

In bacteriostatic tests against *Staphylococcus aureus*, aqueous solutions of the acetyl derivative (VII; R = Ac) showed some inhibitory effect at a concentration of 1 : 500.

Experimental.

Di-(6-*methyl*-3-*pyridazyl*) *Disulphide.*—A solution of 3-mercapto-6-methylpyridazine (1 g.; *J.*, 1948, 2199) in a mixture of ethyl alcohol (50 c.c.) and 5N-aqueous ammonia (30 c.c.) was kept at room temperature for several days. The solution was then evaporated to dryness under reduced pressure, and the residue recrystallised from water, giving shining flakes of *di-*(6-*methyl*-3-*pyridazyl*) *disulphide*, (0·6 g.), m. p. 148° (Found: C, 47·9; H, 4·05; N, 22·4. $C_{10}H_{10}N_4S_2$ requires C, 48·0; H, 4·0; N, 22·4%). The compound was warmed in dilute sodium hydroxide solution, cooled, and acidified; 3-mercapto-6-methylpyridazine separated which, recrystallised from ethyl alcohol, had m. p. 203—205°.

Oxidation of 3-*Ethylthio*-6-*methylpyridazine.*—(*a*) To 3-ethylthio-6-methylpyridazine (0·77 g.; *J.*, 1948, 2199), dissolved in chloroform (10 c.c.), were added ice and 5N-sulphuric acid (10 c.c.). The mixture was cooled to 0° and potassium permanganate (0·63 g.) added slowly in portions. When the addition was complete, the mixture was allowed to reach room temperature, made alkaline, decolorised with sulphur dioxide, and extracted with chloroform. The dried ($MgSO_4$) chloroform extract was evaporated to dryness, and the residue recrystallised several times from benzene–light petroleum (b. p. 40—60°), giving 6-*methyl*-3-*pyridazyl ethyl sulphone* (0·35 g.), m. p. 107—108° (Found: C, 45·4; H, 5·5. $C_7H_{10}O_2N_2S$ requires C, 45·2; H, 5·4%).

(*b*) A solution of 3-ethylthio-6-methylpyridazine (0·77 g.) in acetic acid (5 c.c.) and hydrogen peroxide (30%; 5 g.) was set aside at room temperature for 3 days. The solution was diluted with water, neutralised (sodium hydroxide), and extracted with chloroform. The chloroform extract was washed with water, dried ($MgSO_4$), and evaporated to dryness. The syrupy residue crystallised on trituration with ether and, recrystallised from benzene–light petroleum (b. p. 40—60°), gave the sulphone (0·3 g.), m. p. 107—108°, alone or in admixture with the compound obtained as above.

Attempted Condensation of 3-*Mercapto*-6-*methylpyridazine with Iodobenzene.*—3-Mercapto-6-methylpyridazine (1·0 g.), iodobenzene (1·62 g.), and sodium hydroxide (0·32 g.) in ethyl alcohol (12 c.c.) were heated at 150—160° for 5 hours. The reaction mixture was evaporated to dryness under reduced pressure, and the unchanged iodobenzene was extracted with ether. The residue, recrystallised from water, afforded di-(6-methyl-3-pyridazyl) disulphide (0·3 g.), m. p. 148°, alone or in admixture with that previously prepared. The aqueous mother-liquors were acidified (hydrochloric acid), whereupon yellow needles of 3-mercapto-6-methylpyridazine (0·5 g.), m. p. 200—202°, were obtained.

3-p-*Nitrophenylthio*-6-*methylpyridazine.*—To 3-mercapto-6-methylpyridazine (3·25 g.) dissolved in dry ethyl alcohol was added a dry ethanolic solution of sodium methoxide (1·47 g.), followed by *p*-bromonitrobenzene (5·0 g.), and the mixture was heated on a water-bath for 5 hours. The concentrated solution deposited crystals (4·2 g.) on cooling. The mother-liquors were evaporated to dryness, the unchanged *p*-bromonitrobenzene was removed by steam-distillation, and the residue and the first crop of crystals were recrystallised several times from aqueous alcohol. The product, 3-p-*nitrophenylthio*-6-*methylpyridazine* (6·25 g.) had m. p. 142° (Found: C, 53·3; H, 3·80; N, 16·8. $C_{11}H_9O_2N_3S$ requires C, 53·4; H, 3·64; N, 17·0%).

Oxidation of 3-p-*Nitrophenylthio*-6-*methylpyridazine.*—(a) *By hydrogen peroxide.* 3-*p*-Nitrophenylthio-6-methylpyridazine (1·24 g.) was dissolved in acetic acid, and hydrogen peroxide (2·5 g.; 30%) was added. The solution was kept at room temperature for three days and then diluted with water, and sodium hydroxide solution was added until faint alkalinity was obtained. A yellow solid (1·2 g.) which separated was collected and after repeated crystallisation from 90% ethyl alcohol had m. p. 121—123°. It was p-*nitrophenyl* 6-*methyl*-3-*pyridazyl sulphoxide* (Found: C, 50·3; H, 3·53; N, 15·5. $C_{11}H_9O_3N_3S$ requires C, 50·2; H, 3·4; N, 16·0%).

(b) *By potassium permanganate.* (i) 3-*p*-Nitrophenylthio-6-methylpyridazine (1·24 g.) was dissolved in glacial acetic acid (25 c.c.), and a 5% solution of potassium permanganate (0·63 g.) was added slowly with shaking. Immediate oxidation occurred. When the addition was complete, the reaction mixture was heated to boiling, cooled, decolorised with sodium hydrogen sulphite, and extracted with chloroform. The chloroform extract was dried ($MgSO_4$) and evaporated to dryness. The residue, recrystallised five times from 90% ethyl alcohol, gave *p*-nitrophenyl 6-methyl-3-pyridazyl sulphoxide (0·7 g.), m. p. 121—123°. (ii) The above experiment was repeated with 3-*p*-nitrophenylthio-6-methylpyridazine

(1·38 g.) and potassium permanganate (1·83 g.). On decolorisation with sodium hydrogen sulphite, pale yellow crystals of p-*nitrophenyl* 6-*methyl*-3-*pyridazyl sulphone* separated which, recrystallised from ethyl alcohol, formed nearly colourless needles (0·32 g.), m. p. 175°. Extraction of the mother-liquors with chloroform gave a further quantity (0·07 g.), m. p. 175° (Found : C, 47·7; H, 3·3; N, 14·7. $C_{11}H_9O_4N_3S$ requires C, 47·3; H, 3·2; N, 15·0%). Oxidation of *p*-nitrophenyl 6-methyl-3-pyridazyl sulphoxide with potassium permanganate in glacial acetic acid by the method described above also gave the sulphone, m. p. 175°, in 52% yield.

Reduction of p-*Nitrophenyl* 6-*Methyl*-3-*pyridazyl Sulphone.*—*p*-Nitrophenyl 6-methyl-3-pyridazyl sulphone (0·42 g.), suspended in ethyl alcohol (40 c.c.), was hydrogenated at room temperature with use of palladium on activated charcoal as a catalyst. Absorption of hydrogen ceased when the theoretical amount of hydrogen necessary for reduction to an amino-group had been absorbed. The mixture was filtered, and the solution evaporated to a syrup which, on trituration with alcohol, rapidly crystallised. p-*Aminophenyl* 6-*methyl*-3-*pyridazyl sulphone monohydrate* crystallised from water in fine colourless needles (0·28 g.), m. p. 120—121° (Found : C, 49·5; H, 4·9; N, 15·7. $C_{11}H_{11}O_2N_3S,H_2O$ requires C, 49·5; N, 4·8; N, 15·7%). Attempts to remove the water of crystallisation at 65° *in vacuo* were unsuccessful, and the use of higher temperatures resulted in decomposition of the compound.

p-*Acetamidophenyl* 6-*Methylpyridaz*-3-*on*-2-*yl Sulphone.*—Anhydrous 6-methyl-3-pyridazone (1 mol., 1·06 g.) was dissolved in dry pyridine (10 c.c.), and a solution of *N*-acetylsulphanilyl chloride (1·1 mol., 2·12 g.) in pyridine (10 c.c.) was added. The mixture was warmed to 45° for 1 hour and then poured into water (50 c.c.) containing sodium hydroxide (1 mol.; 0·39 g.). Concentration of the solution and removal of the pyridine afforded an oil which slowly crystallised. p-*Acetamidophenyl* 3-*methylpyridaz*-6-*on*-1-*yl sulphone monohydrate* crystallised from ethyl alcohol–water in shining white needles which gradually became pink when kept; m. p. 96—97°; yield, 1·16 g. (Found : C, 48·3; H, 5·1; N, 13·3. $C_{13}H_{13}O_4N_3S,H_2O$ requires C, 48·0; H, 4·6; N, 12·9%). Attempts to deacetylate this substance by warming it with dilute sodium hydroxide or with hydrochloric acid resulted in hydrolysis and the recovery of 6-methyl-3-pyridazone.

Sodium N-*Carbobenzyloxysulphanilate.*—To a solution of sodium sulphanilate (1·40 g.) in water (20 c.c.), sodium hydrogen carbonate (2 mols., 1·25 g.) and benzyl chloroformate (1 mol., 1·26 g.) were added. The mixture was shaken, whereupon a solid *sodium* salt separated. This was collected and recrystallised from alcohol–water from which it formed shining white triangular plates (48%), m. p. 250° (with darkening) (Found : C, 49·7; H, 3·7; N, 4·1. $C_{14}H_{12}O_5NSNa,\frac{1}{2}H_2O$ requires C, 49·7; H, 3·8; N, 4·1%). The compound (0·40 g.) in aqueous solution (20·0 c.c.) was hydrogenated at room temperature in the presence of palladium on activated charcoal. Slow absorption of hydrogen occurred and at the end of the reaction toluene was detected in the solution. The filtered solution was evaporated to dryness. The residue was recrystallised from water and identified as sodium sulphanilate (m. p. >200°) by conversion into sulphanilic acid (m. p. >300°).

N-*Carbobenzyloxysulphanilyl Chloride.*—Dry sodium *N*-carbobenzyloxysulphanilate (7·0 g.) and phosphorus pentachloride (7 g.) were ground together until a semi-liquid mass was obtained. The mixture was set aside *in vacuo* at room temperature for 4 hours and then mixed with ice. The solid which separated was collected and dried *in vacuo* over phosphoric oxide. The dry solid was extracted with boiling benzene, and the cooled, filtered extract evaporated. The residue, N-*carbobenzyloxysulphanilyl chloride*, crystallised from benzene in colourless needles (1·70 g.; 26·4%), m. p. 109—110° (Found : C, 52·0; H, 3·9; S, 9·2. $C_{14}H_{12}O_4NClS$ requires C, 51·7; H, 3·7; S, 9·8%).

N-*Carbobenzyloxysulphanilamide.*—*N*-Carbobenzyloxysulphanilyl chloride (0·2 g.) was suspended in dilute aqueous ammonia (5 c.c.), the suspension saturated 0° with gaseous ammonia, and the mixture kept at 0° for 10 days. The solid *N*-carbobenzyloxysulphanilamide (0·15 g.) was collected and had m. p. 169—172°. After this product had been crystallised six times from methyl alcohol, the m. p. was raised to 189—190°, the last three crystallisations not having affected the m. p. (Found : C, 54·3; H, 4·5. Calc. for $C_{14}H_{14}O_4N_2S$: C, 54·9; H, 4·6%).

Hydrogenation of N-*Carbobenzyloxysulphanilamide.*—*N*-Carbobenzyloxysulphanilamide (0·15 g.), suspended in water (5 c.c.), was hydrogenated at room temperature in the presence of palladium–charcoal. Slow absorption of hydrogen occurred. At the end of the reaction the solution was warmed and then filtered. Concentration of the filtrate yielded a solid, which, recrystallised from alcohol–water, formed colourless needles, m. p. 163° alone or in admixture with sulphanilamide.

p-O-*Benzylurethanophenyl* 6-*Methylpyridaz*-3-*on*-2-*yl Sulphone.*—A solution of *N*-carbobenzyloxysulphanilyl chloride (1·1 mol., 1·43 g.) in anhydrous pyridine (10 c.c.) was added to anhydrous 6-methyl-3-pyridazone (0·44 g.) in pyridine (5 c.c.). The mixture was set aside at room temperature overnight and was then poured into water. An oil separated which crystallised when kept. p-O-*Benzylurethanophenyl* 6-*methylpyridaz*-3-*on*-2-*yl sulphone* crystallised from alcohol–water in colourless needles, m. p. 146—147°; yield, 1·0 g. (57%) (Found : C, 56·9; H, 4·4; N, 10·6. $C_{19}H_{17}O_5N_3S$ requires C, 57·1; H, 4·2; N, 10·5%).

Hydrogenation of p-O-*Benzylurethanophenyl* 6-*Methylpyridaz*-3-*on*-2-*yl Sulphone.*—The sulphone (0·6 g.) in alcohol–water (50 c.c.) was hydrogenated at room temperature over palladium–charcoal. From the filtered concentrated solution a brown oil (0·20 g.) separated, but this could not be induced to crystallise and was not identified. The aqueous solution remaining was evaporated to a syrup which partly crystallised on nucleation with *N*-carbobenzyloxysulphanilamide. These crystals were collected and washed with water, and then had m. p. 168—171°, alone or in admixture with *N*-carbobenzyloxysulphanilamide (yield, 0·02 g.). The remainder of the syrup crystallised overnight and after recrystallisation from ethyl alcohol was shown to be identical with sulphanilamide, m. p. 163° (yield, 0·13 g.).

The authors gratefully acknowledge the support of the Colonial Products Research Council during this investigation.

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