446. *The Conversion of Sucrose into Pyridazine Derivatives. Part V. Experiments on the Synthesis of 3-Amino-6-methylpyridazine and of its Sulphanilamido-derivative.*

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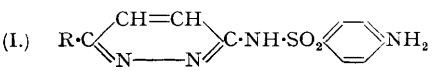
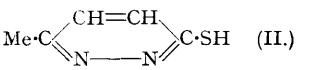
The preparation of 3-mercapto-6-methylpyridazine from both 6-methyl-3-pyridazone and 3-chloro-6-methylpyridazine is described. 6-Methyl-3-pyridazone is found to undergo the Bucherer reaction.

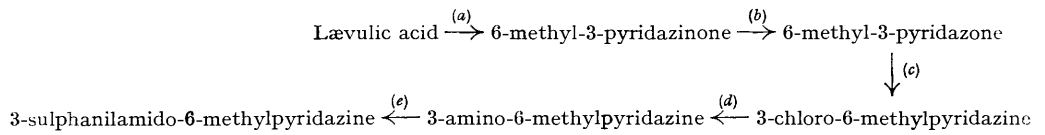
Two sulphanilamidopyridazines have been prepared from lævulic acid and were described in Parts I and IV of this series. These substances were 3-sulphanilamido-6-methylpyridazine (I; R = Me) and 3-sulphanilamidopyridazine (I; R = H). The former compound has been found to have pronounced bacteriostatic power and to possess favourable solubility properties.

(I.) 



(II.)

Its synthesis was achieved through the following steps :

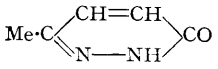
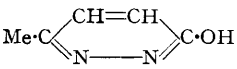


Each of the steps (*a*), (*b*), and (*c*) was readily carried out in > 95% yield. The conversion of 3-chloro-6-methylpyridazine into the corresponding amine was difficult, as would be expected from the aromatic character of the pyridazine ring. The yields usually obtained were of the order of 60%. The final stage in the synthesis was accomplished by the condensation of 3-amino-6-methylpyridazine with *p*-acetamidobenzenesulphonyl chloride followed by hydrolysis of the product. These reactions [step (*e*)], proceeded satisfactorily. Some effort has been made now to improve step (*d*), and, although these efforts have not been successful, some interesting aspects of the chemistry of pyridazone have emerged.

One way in which to improve step (*d*) would be to convert 3-chloro-6-methylpyridazine directly into 3-(*p*-acetamidobenzenesulphonamido)-6-methylpyridazine. Thus, attempts have been made to condense 3-chloro-6-methylpyridazine with *p*-acetamidobenzenesulphonamide. This entirely failed when the reagents were heated in pyridine solution at 150°, but some condensation was effected when the two substances were fused together in the presence of potassium carbonate, although the yield of condensation product was only 10%. It might be envisaged that if 3-*mercapto*-6-*methylpyridazine* (II) could be obtained, the mercapto-group might be more easily replaced than the chlorine atom. Crystalline 3-mercapto-6-methylpyridazine was obtained by heating 3-chloro-6-methylpyridazine with sodium hydrogen sulphide in alcohol at 150°. Alternatively, 6-methyl-3-pyridazone, on treatment with phosphorus pentasulphide, was converted into (II) though in poor (20%) yield. It was also obtained, although in an even smaller yield, when 6-methyl-3-pyridazone was passed over heated aluminium sulphide in a vacuum. The replacement of the mercapto-group by an amino-residue was effected by treatment with methyl-alcoholic ammonia, but 3-amino-6-methylpyridazine was obtained in only very small yield. The replacement did take place, however, at a lower temperature than that obtaining in the case of the 3-chloro-6-methylpyridazine. It was found also that this introduction of an amino-group was as difficult to effect when an ethylthio-group replaced the mercapto-group. 3-*Ethylthio*-6-*methylpyridazine* was obtained on ethylation of the corresponding 3-mercapto-compound with ethyl iodide and sodium hydroxide. Treatment of

this with methyl-alcoholic ammonia gave 3-amino-6-methylpyridazine (18% yield) together with unchanged starting material (80% by weight).

Since 6-methyl-3-pyridazone (III) must exist in equilibrium with its lactim form (IV) there is the possibility that it might undergo the Bucherer reaction, by means of which certain phenolic

(III.)   (IV.)

compounds, particularly naphthols, can be converted into amines. On heating 6-methyl-3-pyridazone with sodium sulphite and ammonia at 240° under pressure, there was isolated, besides unchanged 6-methyl-3-pyridazone, a little 3-amino-6-methylpyridazine. This shows that this pyridazone derivative (IV) does undergo the Bucherer reaction, although the low yield prohibited the attachment of any preparative value to this fact.

Experimental.

3-Mercapto-6-methylpyridazine.—(*a*) 3-Chloro-6-methylpyridazine (2 g.) was heated in a sealed tube at 150° for 3 hours with ethyl alcohol (20 c.c.) saturated with sodium hydrogen sulphide. Crystalline material separated on cooling. This was filtered off and washed with water. Yellow needles remained which, recrystallised from ethyl alcohol–water, formed long yellow needles (1·0 g.; 52·6%) of *3-mercapto-6-methylpyridazine*, m. p. 203·5—205° (decomp.). They exhibited a greenish fluorescence in ultra-violet light (Found: C, 47·8; H, 5·1. $C_5H_6N_2S$ requires C, 47·6; H, 4·8%).

(*b*) 6-Methyl-3-pyridazone (2·5 g.) and phosphorus pentasulphide (6·2 g.) were boiled under reflux in xylene for 3 hours. The hot xylene solution was filtered, and the crystalline solid which separated collected. This, recrystallised from ethyl alcohol–water, formed long yellow needles (0·55 g.; 19·6%), m. p. 203·5—204·5° (decomp.) alone or in admixture with 3-mercapto-6-methylpyridazine.

(*c*) 6-Methyl-3-pyridazone (5·0 g.) was distilled in high vacuum (0·005 mm.) and the vapour was passed over heated aluminium sulphide. A yellow distillate was collected (1·01 g.). This was extracted with hot water. The aqueous extract deposited slightly yellow needles (0·5 g.) which had m. p. 123—125° alone or in admixture with 6-methyl-3-pyridazone monohydrate. The residue, recrystallised from ethyl alcohol–water, formed yellow needles (0·2 g.), m. p. 203—205° (decomp.) alone or in admixture with 3-mercapto-6-methylpyridazine.

Treatment of 3-Mercapto-6-methylpyridazine with Ammonia.—(*a*) The material (0·647 g.) was heated with aqueous ammonia in a sealed tube at 100° for a day. The solution was then evaporated to dryness and the residue extracted with water. The water-insoluble material was unchanged starting material (0·33 g.). The aqueous extract was evaporated to dryness, and then extracted with chloroform. This extract was evaporated, and the residue washed with water to remove last traces of 3-mercapto-6-methylpyridazine. The aqueous extract was evaporated to dryness; the residual solid, recrystallised from water, had m. p. 224° alone or in admixture with 3-amino-6-methylpyridazine. Yield 0·08 g.

3-Ethylthio-6-methylpyridazine.—To 3-mercapto-6-methylpyridazine (1·26 g.) in ethyl alcohol (30 c.c.) was added sodium hydroxide (0·4 g.) in alcohol (5 c.c.), and ethyl iodide (1·56 g.; 1 equiv.) in ethyl alcohol (10 c.c.). The solution was then heated under reflux for 2 hours, and the solvent evaporated under reduced pressure. The residue was extracted with ether; evaporation of the ethereal extract gave a yellow oil which rapidly crystallised. Careful recrystallisation from ether gave colourless needles of *3-ethylthio-6-methylpyridazine*, m. p. 41° (Found: C, 54·4; H, 6·4. $C_7H_{10}N_2S$ requires C, 54·6; H, 6·2%).

Treatment of 3-Ethylthio-6-methylpyridazine with Ammonia.—The compound (1·0 g.) was heated with methyl-alcoholic ammonia (saturated at 0°) in a sealed tube at 160° for 3 days. Evaporation of the solvent gave a semi-crystalline residue. To this, water was added; the oil which separated was extracted with ether, and the residual aqueous portion evaporated to dryness under reduced pressure. Recrystallisation of the residue gave 3-amino-6-methylpyridazine (0·12 g.; 18%), m. p. 222—224° alone or in admixture with an authentic specimen. Evaporation of the ethereal extract gave a yellow oil (0·8 g.) which crystallised and was found to be unchanged starting material.

6-Methyl-3-pyridazone in the Bucherer Reaction.—Sodium sulphite (10·66 g.) was dissolved in water (50 c.c.), 6-methyl-3-pyridazone monohydrate (7·3 g.) added, and the solution made up to 700 c.c. with aqueous ammonia (*d* 0·88). This solution was heated at 240° for 3 days in an autoclave, filtered, and evaporated to dryness. The residue was extracted with acetone, giving an extract (*A*) and a residue (*B*). The extract (*A*) was evaporated to dryness; the residue recrystallised from water (charcoal) in colourless plates (1·0 g.) of 6-methyl-3-pyridazone monohydrate, m. p. 123—124°. The residue (*B*) was heated with sodium hydroxide for an hour and then acidified with hydrochloric acid and evaporated to dryness. The solid residue was dried thoroughly and was then extracted first with chloroform [extract (*C*)] and then ethyl alcohol [extract (*D*)]. On removal of the solvent from extract (*C*) a residue was obtained which, recrystallised from water (charcoal), formed colourless needles (0·204 g.), m. p. 123—125° alone or in admixture with 6-methyl-3-pyridazone monohydrate. The extract (*D*) was evaporated to dryness, the residue dissolved in the minimum of water, and a concentrated solution of sodium hydroxide added. Crystals separated which, recrystallised from water, formed colourless rhombs (0·2 g.), m. p. 224° alone or in admixture with 3-amino-6-methylpyridazine.

Attempted Condensation of 3-Chloro-6-methylpyridazine with p-Acetamidobenzenesulphonamide.—(*a*) 3-Chloro-6-methylpyridazine (0·75 g.) and *p*-acetamidobenzenesulphonamide (1·0 g.) were dissolved in dry pyridine (200 c.c.), and the solution heated at 150° in an autoclave for 4 hours. Thereafter the product was concentrated to 20 c.c. and poured into water containing sodium hydroxide (0·23 g.), and unchanged *p*-acetamidobenzenesulphonamide, m. p. 218°, separated. No condensation product could be isolated.

(*b*) 3-Chloro-6-methylpyridazine (0·133 g.), *p*-acetamidobenzenesulphonamide (0·128 g.), and dry potassium carbonate (0·13 g.) were fused together. After being cooled, the mixture was treated with water and the undissolved portion collected. After recrystallisation from acetic acid–water, this product (0·026 g.; 10%) had m. p. 246—247° alone or in admixture with 3-(*p*-acetamidobenzenesulphonamido)-6-methylpyridazine.

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