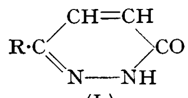
271. *The Conversion of Sucrose into Pyridazine Derivatives. Part VI. The Behaviour of Pyridaz-3-one and its Derivatives towards Aldehydes.*

By Hilda Gregory, Joan Hills, and L. F. Wiggins.

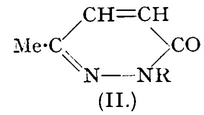
Neither pyridaz-3-one nor 6-methylpyridaz-3-one gives Mannich bases when treated with formaldehyde and dimethylamine. Instead, a hydroxymethyl group is attached to position 2 of the pyridazone nucleus. Condensation of pyridaz-3-one and of 6-methylpyridaz-3-one with benzaldehyde results in the formation of *phenylbis(pyridaz-3-on-2-yl)methane* and *phenylbis(6-methylpyridaz-3-on-2-yl)methane*, respectively. Experiments which indicate the structure of these compounds are described.

In an attempt to prepare Mannich bases from 6-methylpyridaz-3-one (I; R = Me) obtained from lævulic acid (Overend and Wiggins, *J.*, 1947, 239), the compound was treated with formaldehyde and dimethylamine hydrochloride according to Mannich and Kather's procedure (*Arch. Pharm.*, 1919, **257**, 18) for the preparation of Mannich bases from antipyrine. A crystalline compound was isolated, which was not a Mannich base since it did not contain a dimethylamine residue. Moreover, it was very unstable and readily liberated formaldehyde when heated alone or boiled with water. That dimethylamine was not involved in the reaction was proved by the fact that the same compound was isolated when piperidine was used instead of dimethylamine. In fact, it was later found that the presence of a secondary base was not essential to the reaction, since 6-methylpyridaz-3-one and aqueous formaldehyde gave the same compound, on being heated together. Owing to the instability of the compound, a molecular-weight determination by ebulloscopic methods was impracticable. By the *X*-ray method, however, a value of either 254 or 127 was obtained, and application of Barger's method for the determination of molecular weight indicated the latter as the correct value. This and ultimate analysis showed the compound to be a hydroxymethyl derivative of 6-methylpyridaz-3-one.

That the methyl group at position 6 was not involved in the reaction was indicated by the fact that a very similar compound was isolated when pyridaz-3-one (I; R = H) itself was heated with formaldehyde solution. The hydroxymethyl group may therefore be attached to the nitrogen atom at position 2 of the pyridazone nucleus (II; R = $CH_2\cdot OH$) or be combined with the hydroxyl group of the enolic form of (I; R = Me) in hemi-acetal formation as shown by (III; R = $O\cdot CH_2\cdot OH$). Formulæ (IV) and (V) are also possible but very improbable because a hydroxymethyl group attached to the pyridazone nucleus by a carbon to carbon bond is very unlikely to be removed by warming with water.



(I.)



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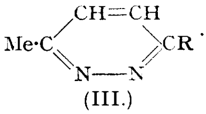
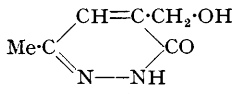


(III.)



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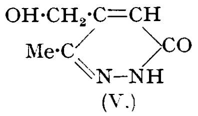
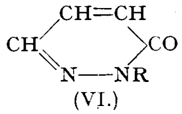


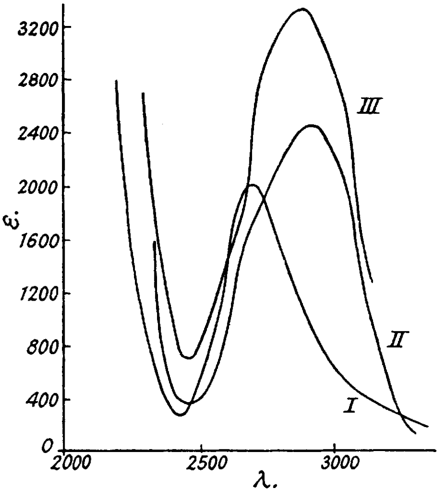
(V.)



(VI.)

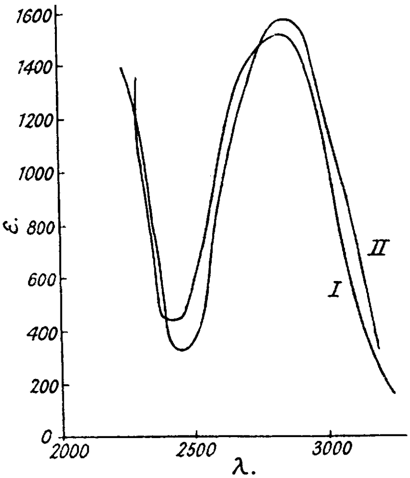
Hence, there are two possible formulæ for the hydroxymethyl derivative obtained from 6-methylpyridaz-3-one, namely (II; R = $CH_2\cdot OH$) and (III; R = $O\cdot CH_2\cdot OH$). A decision between these two possibilities has been made by a study of the absorption spectra of the condensation product and related pyridazone derivatives. 6-Methylpyridaz-3-one can be alkylated at position 2 with methyl iodide and sodium methoxide, and the constitution of this as 2 : 6-dimethylpyridaz-3-one (II; R = Me) has been proved by synthesis (Overend and Wiggins, forthcoming publication).

FIG. 1.



I. 3-*Methoxy*-6-*methylpyridazine.*
II. 2 : 6-*Dimethylpyridaz*-3-*one.*
III. 6-*Methyl*-2-*hydroxymethylpyridaz*-3-*one.*

FIG. 2.



I. 2-*Hydroxymethylpyridaz*-3-*one.*
II. 2-*Methylpyridaz*-3-*one.*

On the other hand, when 3-chloro-6-methylpyridazine (III; R = Cl) is treated with sodium methoxide, an isomeric compound with entirely different properties is obtained. This, by its method of preparation, must be 3-methoxy-6-methylpyridazine (III; R = OMe).

2 : 6-Dimethylpyridaz-3-one shows selective absorption of light in the ultra-violet at λ 2940 A. ($\varepsilon_{max.}$ 2460), whereas 3-methoxy-6-methylpyridazine shows absorption at λ 2710 A. ($\varepsilon_{max.}$ 2000) (see Fig. 1). Now the hydroxymethyl derivative of 6-methylpyridaz-3-one shows a very similar absorption spectrum to that of 2 : 6-dimethylpyridaz-3-one with optimum absorption at λ 2890 A. ($\varepsilon_{max.}$ 3340). Hence it would appear that the compound, m. p. 131°, is 6-*methyl*-2-*hydroxymethylpyridaz*-3-*one* (II; R = $CH_2\cdot OH$).

A similar conclusion is reached when the hydroxymethyl derivative of 3-pyridazone itself is studied. Its absorption spectrum shows a band very similar to that of its homologue described above, but the absorption peak is displaced a little towards the ultraviolet (λ 2820 A.). A comparison of its spectrum with that of 2-methylpyridaz-3-one (VI; R = Me) (λ 2860 A.), obtained by alkylation of pyridaz-3-one with methyl iodide and sodium methoxide, indicates that the two compounds have essentially the same structure (see Fig. 2). In addition, comparison of the spectra of 2 : 6-dimethyl- and 2-methyl-pyridaz-3-one with those of the hydroxymethyl derivatives of 6-methylpyridaz-3-one and pyridaz-3-one shows that removal of the methyl group at position 6 of the pyridazone nucleus results in a displacement of the absorption peak towards the ultra-violet of 70—80 A. Hence, the hydroxymethyl derivative of pyridaz-3-one is *2-hydroxymethylpyridaz-3-one* (VI; R = CH_2·OH). The ultra-violet absorption data are summarised in the following table.

Compound.	λ, A.	$\varepsilon_{max.}$	Concn. in EtOH, mg. per 100 c.c.
3-Benzyloxy-6-methylpyridazine	2730	1480	8·4
2-Benzyl-6-methylpyridaz-3-one	3010	1618	8·5
Phenyldi-(6-methylpyridaz-3-on-2-yl)methane	2980	4759	6·7
Phenyldi-(pyridaz-3-on-2-yl)methane	2930	5364	1·43
3-Methoxy-6-methylpyridazine	2710	2000	4·5
2 : 6-Dimethylpyridaz-3-one	2940	2460	7·48
6-Methyl-2-hydroxymethylpyridaz-3-one	2890	3340	4·2
2-Hydroxymethylpyridaz-3-one	2820	1512	6·15
2-Methylpyridaz-3-one	2860	1538	9·37

Additional evidence for the structures (II; R = CH_2·OH) and (VI; R = CH_2·OH) for these derivatives may be adduced from the fact that secondary amines are known readily to form *N*-hydroxymethyl derivatives (Walker, "Formaldehyde," Reinhold Publishing Corporation, New York, 1944, p. 199).

It was envisaged that pyridazone derivatives might form Mannich bases if the reaction were effected with a derivative in which the hydrogen atom at position 2 of the pyridazone nucleus were replaced by an alkyl residue. Accordingly, 2 : 6-dimethylpyridaz-3-one was treated with formaldehyde and dimethylamine hydrochloride, but no reaction occurred.

When 6-methylpyridaz-3-one was condensed with formaldehyde in the presence of acetic anhydride no definite product could be isolated, but when it was treated with benzaldehyde in boiling acetic anhydride a crystalline compound (m. p. 207°) was obtained. Since Poppenberg (*Ber.*, 1901, **34**, 3257) condensed benzaldehyde and 6-methylpyridazine to form 6-styrylpyridazine, the product obtained in this case might be 6-styrylpyridaz-3-one (VII). If this were so, then pyridaz-3-one itself would not be expected to yield a condensation product under similar conditions; however, it did condense with benzaldehyde under exactly the same conditions as were used for the condensation of the 6-methyl derivative and a crystalline compound (m. p. 239°) was isolated. Moreover, the absorption spectra of these two compounds so closely resembled one another as to suggest that they possessed similar structures (see Fig. 3). An attempt was also made to effect the condensation of pyridaz-3-one-6-carboxylic acid (Homer, Gregory, Overend, and Wiggins, *J.*, 1948, 2195) with benzaldehyde, but decarboxylation occurred and the same compound as was obtained from pyridaz-3-one was isolated.

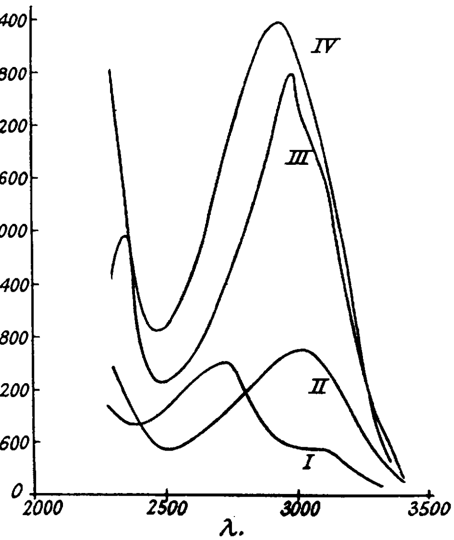
Determination of the molecular weight of these two condensation products showed them both to contain two pyridazone residues and one phenyl group, and ultimate analysis showed that benzaldehyde had condensed with two molecules of each pyridazone with elimination of one molecule of water.

Since the condensation does not involve the methyl group of 6-methylpyridaz-3-one it must take place through the attachment of the benzylidene group to either C_4 or C_5, to the nitrogen atom at position 2, or to the hydroxyl group at C_3 of the enolic form of the pyridazone nucleus. The compound, however, is not very stable, for it is readily decomposed by aqueous acids with the liberation of benzaldehyde. This would indicate that structures of the type (VIII) are unlikely, as it would be expected that if C–C bonds were involved in the linkage of benzaldehyde and 6-methylpyridaz-3-one then they would be resistant to these conditions of hydrolysis. Moreover, attachment of the benzylidene group at C_4 or C_5 would leave the pyridazone residues liable to *N*-alkylation at position 2. This does not occur. In addition, condensation does not occur with benzaldehyde when position 2 is alkylated. For instance, 2 : 6-dimethylpyridaz-3-one does not condense with benzaldehyde under the same conditions.

Hence, two possible structures remain for these condensation products, *i.e.*, (IX) and (X), where R = Me or H. In fact, the structure phenyldi-(6-methylpyridaz-3-on-2-yl)methane

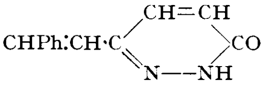
(X; R = Me) has been assigned to the condensation product of benzaldehyde and 6-methylpyridaz-3-one by a comparison of its absorption spectrum with those of compounds having the type of structure shown by (IX) and (X) (R = Me). The two compounds showing most resemblance to (IX) and (X) and with which a comparison could justly be made were 2-benzyl-6-methylpyridaz-3-one, obtained by Homer and Wiggins (forthcoming publication), and 3-*benzyloxy*-6-*methylpyridazine*, prepared by the treatment of 3-chloro-6-methylpyridazine with sodium benzyloxide.

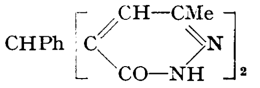
FIG. 3.

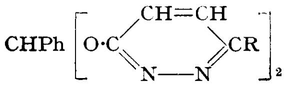


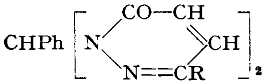
I. 3-*Benzyloxy*-6-*methylpyridazine*.
II. *Benzyl*-6-*methylpyridaz*-3-*one*.
III. *Phenyldi*-(6-*methylpyridaz*-3-*on*-2-*yl*)*methane*.
IV. *Phenyldi*(*pyridaz*-3-*on*-2-*yl*)*methane*.

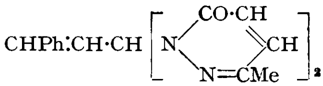
The condensation product of 6-methylpyridaz-3-one with benzaldehyde showed maximum absorption at λ 2980 A. ($\varepsilon_{\max.}$ 4759), whereas 2-benzyl-6-methylpyridaz-3-one showed maximum absorption at approximately the same wave-length (λ 3010 A.) but with a much lower intensity ($\varepsilon_{\max.}$ 1618). On the other hand, 3-benzyloxy-6-methylpyridazine showed absorption at λ 2730 A. ($\varepsilon_{\max.}$ 1480) (see Fig. 3). Hence structure (X; R = Me) is assigned to the product of m. p. 207°.


(VII.)


(VIII.)


(IX.)


(X.)


(XI.)

The condensation product of benzaldehyde with pyridaz-3-one itself is considered to have an analogous structure and to be *phenyldi*(*pyridaz*-3-*on*-2-*yl*)*methane* (X; R = H) on account of the similarity of its absorption spectrum with that of the analogous condensation product from 6-methylpyridaz-3-one (see Fig. 3). The absence of the 6-methyl group in (X; R = H) results in the expected shift of the head of the absorption band towards the ultra-violet by 50 A. (see table).

A similar compound was obtained when cinnamaldehyde was condensed with 6-methylpyridaz-3-one, and by analogy with the foregoing compounds it is believed to be *styryldi*-(6-*methylpyridaz*-3-*on*-2-*yl*)*methane* (XI).

EXPERIMENTAL.

Condensation of 6-*Methylpyridaz*-3-*one with Formaldehyde*.—(*a*) *In presence of dimethylamine hydrochloride*. The procedure used was that of Mannich and Kather (*loc. cit.*). 6-Methylpyridaz-3-one (1·5 g.), dimethylamine hydrochloride (1·2 g.; 1 mol.), 40% formalin solution (1·2 c.c.; 1 mol.), and water (10 c.c.) were shaken together for 24 hours. The crystals which had separated were filtered off; m. p. 125—128° (yield, 0·7 g.). The product readily lost formaldehyde when heated alone or in solvents, thus rendering recrystallisation difficult. It was finally recrystallised from 40% formalin solution; m. p. 131°. It was 6-*methyl*-2-*hydroxymethylpyridaz*-3-*one* (Found: C, 51·3; H, 5·8; N, 20·4; CH_2O, 21·8. $C_6H_8O_2N_2$ requires C, 51·4; H, 5·7; N, 20·0; CH_2O, 21·4%). The product (0·3 g.) in water (1·0 c.c.) was heated under reflux for one hour. Formaldehyde was evolved, and on cooling crystals (0·19 g.) separated which after being collected had m. p. 122—123°, alone or in admixture with 6-methylpyridaz-3-one.

(*b*) 6-Methylpyridaz-3-one (1·5 g.), paraformaldehyde (0·62 g.; 1·5 mols.), dimethylamine hydrochloride (1·2 g.; 1 mol.), concentrated hydrochloric acid (1 drop), and absolute alcohol (3 c.c.) were heated under reflux for one hour; paraformaldehyde (0·42 g.; 1 mol.) was then added, and the mixture heated for a further 2 hours. Crystals (1·5 g.) separated on cooling; m. p. 131°, alone or in admixture with 6-methyl-2-hydroxymethylpyridaz-3-one.

(*c*) *In presence of dimethylamine*. 6-Methylpyridaz-3-one (1·1 g.), aqueous dimethylamine solution (25%; 2 c.c.), and 40% formalin solution (2·0 c.c.) were heated together on a boiling water-bath for 3 hours. On cooling, the crystals (1·13 g.) which separated were filtered off and had m. p. 126—128°. After being recrystallised from 40% formalin solution, the product had m. p. 131°, alone or in admixture with 6-methyl-2-hydroxymethylpyridaz-3-one.

(*d*) *In presence of piperidine*. The experiment was repeated but with a few drops of piperidine instead of dimethylamine. 6-Methyl-2-hydroxymethylpyridazone was isolated in 60% yield.

(*e*) *Without a catalyst*. 6-Methylpyridaz-3-one (1·0 g.) and 40% formalin solution (4·0 c.c.) were heated together on a boiling water-bath for 3 hours. After being kept overnight, crystals (0·8 g.) separated which had m. p. 131° and were identical with 6-methyl-2-hydroxymethylpyridaz-3-one.

Treatment of Pyridaz-3-*one with Formaldehyde and Dimethylamine*.—Pyridaz-3-one (2·0 g.), 26% aqueous dimethylamine solution (4·4 c.c.; 1·1 mols.), and 40% formalin solution (10 c.c.) were heated together on a water-bath for 3 hours. On cooling, colourless crystals separated (1·95 g.); m. p. 142°. This 2-*hydroxymethylpyridaz*-3-*one* readily lost formaldehyde when heated alone or in solvents. It was recrystallised from 40% formalin solution but this recrystallisation did not raise the m. p. (Found: C, 47·9; H, 4·98; N, 22·8; CH_2O, 24·4. $C_5H_6O_2N_2$ requires C, 47·6; H, 4·76; N, 22·2; CH_2O, 23·8%). The product (0·1 g.) was heated gently; formaldehyde was evolved and the residue distilled as a colourless liquid which immediately solidified in long needles of pyridaz-3-one, m. p. 103°, alone or in admixture with an authentic specimen.

X-*Ray Examination of* 2-*Hydroxymethylpyridaz*-3-*one*.—By means of single-crystal rotation and oscillation photographs the following cell dimensions were obtained: $a = 13·6$, $b = 11·35$, $c = 7·39$ A.; space group *pcab*. From the observed density, 1·478 g./c.c., the molecular weight was calculated to be $1016/n$, where n may be either 4 or 8; an approximate molecular-weight determination by Barger's method (*J.*, 1904, **85**, 286) indicated the lower molecular weight, whence $n = 8$, and the appropriate molecular weight of 2-hydroxymethyl-3-pyridazone is therefore 127 (Calc.: 126).

2-*Methylpyridaz*-3-*one*.—To pyridaz-3-one (4·0 g.) dissolved in dry methyl alcohol were added methyl iodide (4·0 c.c.) dissolved in the same solvent and then a dry methyl-alcoholic solution of sodium methoxide (4·5 g.). The mixture was heated under reflux for 2 hours and then evaporated almost to dryness. Water was added, and the solution extracted with benzene. The dried extract was evaporated, and the residual oil distilled at 220° (bath temp.)/10 mm. The product solidified immediately and was 2-methylpyridaz-3-one (2·1 g.; 46%), m. p. 38—39°, in agreement with that recorded by Evans and Wiselogle (*J. Amer. Chem. Soc.*, 1945, **67**, 60).

Condensation of 6-*Methylpyridaz*-3-*one with Benzaldehyde*.—Anhydrous 6-methylpyridaz-3-one (5·0 g.), benzaldehyde (7 c.c., freshly distilled), and acetic anhydride (5 c.c., redistilled) were heated together under reflux for 16 hours. Excess of benzaldehyde was removed by steam-distillation, the viscous brown oil which separated was washed with a little alcohol and then triturated with ether, whereby a semi-crystalline mass was obtained. The crude product, recrystallised from aqueous alcohol, had m. p. 207° (1·9 g., 27%) and was *phenyldi*-(6-*methylpyridaz*-3-*on*-2-*yl*)*methane* (Found: C, 66·1; H, 5·3; N, 17·6. $C_{17}H_{16}O_2N_4$ requires C, 66·2; H, 5·2; N, 18·1%). The compound (0·5 g.) was kept overnight with fuming nitric acid (2 c.c.). The mixture was then poured into ice-water, and a white solid separated. This, collected and recrystallised from ethyl alcohol, had m. p. 121—122°, alone or in admixture with 6-methylpyridaz-3-one monohydrate. Benzaldehyde was detected in the acidic mother-liquors.

Non-methylation of Phenyldi-(6-*methylpyridaz*-3-*on*-2-*yl*)*methane*.—To the condensation product (1·0 g.) in dry methyl alcohol, were added a solution of sodium methoxide (0·2 g.; 1 mol.) in dry methyl alcohol and then methyl iodide (1·7 g.; 1·5 mols.), and the mixture was heated under reflux for one hour. The solution was evaporated nearly to dryness under reduced pressure, a little water added, and the aqueous solution extracted with benzene. The extract was dried ($MgSO_4$), evaporated to dryness, and the residue recrystallised from aqueous alcohol; m. p. 207° alone or in admixture with the starting material (yield, 0·9 g.).

Condensation of Pyridaz-3-*one with Benzaldehyde*.—Anhydrous pyridaz-3-one (3·0 g.), benzaldehyde (3 c.c., freshly distilled), and acetic anhydride (3 c.c.) were heated together under reflux for 20 hours. Thereafter, the mixture was cooled, alcohol and water added to the syrup, and the crystalline mass obtained was filtered off. Recrystallised from alcohol, it formed colourless needles of *phenyldi*(*pyridaz*-3-*on*-2-*yl*)*methane*, m. p. 239° (2·0 g.) (Found: C, 64·3; H, 4·3; N, 20·0. $C_{15}H_{12}O_2N_4$ requires C, 64·3; H, 4·3; N, 20·0%).

Condensation of Pyridaz-3-*one*-6-*carboxylic Acid with Benzaldehyde*.—Anhydrous pyridaz-3-one-6-

carboxylic acid (2·0 g.), benzaldehyde (4 c.c.), and acetic anhydride (2·5 c.c.) were heated together under reflux for 20 hours. Excess of benzaldehyde was removed by steam-distillation, and the solid which separated was collected and recrystallised from aqueous alcohol; m. p. 239° alone or in admixture with the phenyldi(pyridaz-3-on-2-yl)methane obtained as above.

Oxidation of Phenyldi-(6-*methylpyridaz*-3-*on*-2-*yl*)*methane*.—The substance (1·8 g.) was dissolved in concentrated sulphuric acid (18 c.c.). The solution was mechanically stirred and the temperature kept at *ca.* 20° whilst finely ground potassium dichromate (1·1 mols.) was added slowly in portions. When the addition was complete, stirring was continued for another hour, the resulting green mixture was poured on ice, and the mixture set aside for several hours. A white solid separated (0·3 g.), which was filtered off and recrystallised from water. It had m. p. 257°, alone or in admixture with pyridaz-3-one-6-carboxylic acid. Benzaldehyde was detected in the acidic mother-liquors.

Condensation of 6-*Methylpyridaz*-3-*one with Cinnamaldehyde*.—Anhydrous 6-methylpyridaz-3-one (11·0 g.), cinnamaldehyde (7 c.c.), and acetic anhydride (7 c.c.) were heated together on an oil-bath under reflux for 12 hours. The mixture was cooled and made alkaline with sodium hydroxide; a white solid separated, which was filtered off and recrystallised from aqueous alcohol (yield, 2·1 g.). It had m. p. 239° and was *styryldi*-(6-*methylpyridaz*-3-*on*-2-*yl*)*methane* (Found: C, 68·6; H, 5·34; N, 16·8. $C_{19}H_{18}O_2N_4$ requires C, 68·3; H, 5·39; N, 16·8%). The compound (0·3 g.) was kept at room temperature for 2 hours with fuming nitric acid. The mixture was then poured into ice–water; no solid separated, but cinnamaldehyde was detected in the acid solution, indicating that decomposition had occurred.

3-*Benzyloxy*-6-*methylpyridazine*.—A mixture of 3-chloro-6-methylpyridazine (5·0 g.), benzyl alcohol (4·1 c.c.), and sodium (0·9 g.) in dry benzene (100 c.c.) was heated under reflux for 3 hours. The dark brown reaction mixture was filtered, and the solvent evaporated to give a viscous syrup which partly crystallised. The product was then pressed on a porous tile, and the solid obtained recrystallised first from alcohol–light petroleum (b. p. 40—60°) and then from ether–light petroleum. The colourless needles of 3-*benzyloxy*-6-*methylpyridazine* had m. p. 105° (Found: C, 71·8; H, 6·17; N, 13·4. $C_{12}H_{12}ON_2$ requires C, 72·0; H, 6·0; N, 14·0%).

Our thanks are due to the Colonial Products Research Council for supporting this investigation, and to Drs. R. W. H. Small and J. C. Tranter for carrying out the molecular-weight determinations on 2-hydroxymethylpyridaz-3-one.

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[*Received, November 25th*, 1948.]