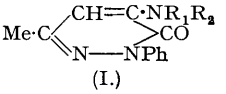
536. *The Conversion of Sucrose into Pyridazine Derivatives. Part VIII. Some Basic Derivatives of 2-Phenyl-6-methyl-3-pyridazone.*

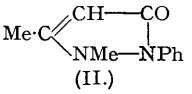
By Hilda Gregory and L. F. Wiggins.

Amongst the several basic derivatives of 2-phenyl-6-methyl-3-pyridazone described herein, 4-*dimethylamino*-2-*phenyl*-6-*methyl*-3-*pyridazone* is found to have analgesic potency somewhat greater than that of phenazone.

In the course of studies on the pyridazine and pyridazone derivatives obtained from lævulic acid, the pharmacological properties of many compounds described in Parts I—VII of this series have been investigated. This work indicated that 4-amino-2-phenyl-6-methyl-3-pyridazone (I; $R_1 = R_2 = H$) exhibited marked analgesic activity when compared with phenazone (II).



(I.)



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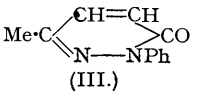


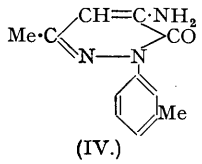
(III.)

Replacement of the amino-group in (I; $R_1 = R_2 = H$) by chloro-, ethoxy-, or hydroxy- nullified the activity, whereas replacement by hydrogen to give 2-phenyl-6-methyl-3-pyridazone (III) reduced the duration of the action. It appears therefore that the presence of a basic group in the pyridazone nucleus exerts a powerful and important contribution towards the analgesic

activity of this type of compound. In view of these findings efforts have now been directed towards introducing other basic groups into the pyridazone nucleus of 2-phenyl-6-methyl-3-pyridazone.

Replacement of the amino-group in (I; $R_1 = R_2 = H$) by a morpholine or piperidine residue was accomplished by heating 4-chloro-2-phenyl-6-methyl-3-pyridazone with a methyl-alcoholic solution of the appropriate base, 4-*morpholino-* and 4-*piperidino*-2-*phenyl*-6-*methyl*-3-*pyridazone* being thus formed. These compounds had, however, no analgesic power. Heating the 4-chloro-compound with methyl-alcoholic methylamine or dimethylamine gave 4-*methylamino-* (I; $R_1 = Me$, $R_2 = H$) and 4-*dimethylamino*-2-*phenyl*-6-*methyl*-3-*pyridazone* (I; $R_1 = R_2 = Me$), respectively, as well-defined crystalline compounds. These, together with the 4-amino-derivative, enable a comparison to be made of the effect of a primary, secondary, and tertiary amino-group on the analgesic activity of the pyridazone (III). In addition, 4-*diethylamino*-2-*phenyl*-6-*methyl*-3-*pyridazone* (I; $R_1 = R_2 = Et$) was prepared by the same procedure; this was a liquid, but was characterised as a crystalline *monopicrate*. Comparative tests showed that, whereas the presence of the 4-methylamino-residue in 2-phenyl-6-methyl-3-pyridazone eliminated the analgesic potency, the introduction of the 4-dimethylamino-group greatly increased its activity. It is, however, anomalous that 4-diethylamino-2-phenyl-6-methyl-3-pyridazone had very little activity.

It has been possible to study the pharmacological effect of varying several other aspects of the 4-amino-2-phenyl-6-methyl-3-pyridazone molecule. Thus, introduction of a *p*-nitro-group into the phenyl residue, to give 4-amino-2-*p*-nitrophenyl-6-methyl-3-pyridazone (Part II of this series) destroyed the activity. The effect of replacing the phenyl by a *m*-tolyl group, involving the synthesis of 4-*amino*-2-m-*tolyl*-6-*methyl*-3-*pyridazone* (IV), has now been investigated.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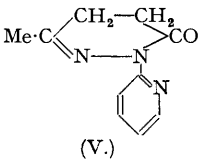
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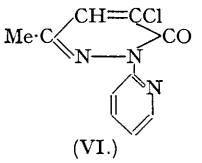
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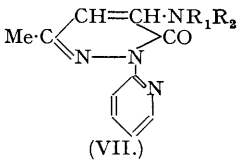
(VII.)

Lævulic acid *m*-tolylhydrazone was cyclised to 2-m-*tolyl*-6-*methyl*-3-*pyridazinone*, which with phosphorus pentachloride furnished 4-*chloro*-2-m-*tolyl*-6-*methyl*-3-*pyridazone*. Since it was proved by Ach (*Annalen*, 1889, **253**, 44) that the treatment of 2-phenyl-6-methyl-3-pyridazinone with phosphorus pentachloride effected dehydrogenation, as well as chlorination of the heterocyclic residue at position 4, it is reasonable to assume that in this case also the halogenation of the diazine molecule has occurred at $C_{(4)}$. The 4-amino-2-*m*-tolyl-6-methyl-3-pyridazone obtained on treatment of the 4-chloro-derivative with ammonia possessed, however, very little analgesic power. The effect of replacing the 2-phenyl group by pyridine in 4-amino- and 4-dimethylamino-2-phenyl-6-methyl-3-pyridazone has also been studied, especially as it was expected that this change would improve the rather low solubility of 4-amino-2-phenyl-6-methyl-3-pyridazone in water. *Lævulic acid 2-pyridylhydrazone* was readily prepared in crystalline form, and, in contrast to lævulic acid phenylhydrazone, was stable for many months at room temperature. Cyclisation to the pyridazinone was not so easily achieved as with the phenylhydrazone and was accompanied by a greater amount of decomposition. On treating the resultant 2-2′-*pyridyl*-6-*methyl*-3-*pyridazinone* (V) with phosphorus pentachloride a monochloro-derivative was obtained, which, by analogy, is described as 4-*chloro*-2-2′-*pyridyl*-6-*methyl*-3-*pyridazone* (VI). Treatment with ammonia or dimethylamine then gave 4-*amino-* (VII; $R_1 = R_2 = H$) and 4-*dimethylamino*-2-2′-*pyridyl*-6-*methyl*-3-*pyridazone* (VII; $R_1 = R_2 =$ Me), respectively. The analgesic activity of both of these compounds was less than that of the corresponding 2-phenyl derivative, but comparable with that of phenazone. The relative analgesic activities of compounds mentioned in this paper are indicated in the following table.

Comparative analgesic activities of certain 3-pyridazone derivatives.

Substituents.	Analgesic activity.	Substituents.	Analgesic activity.
(Phenazone)	3+	4-Amino-2-*p*-nitrophenyl-6-methyl- ...	—
4-Amino-2-phenyl-6-methyl-	3+	4-Amino-2-*m*-tolyl-6-methyl-	2+
4-Methylamino-2-phenyl-6-methyl- ...	—	4-Amino-2-2′-pyridyl-6-methyl-	2+
4-Diethylamino-2-phenyl-6-methyl- ...	+	4-Dimethylamino-2-2′-pyridyl-6-methyl-	3+
4-Dimethylamino-2-phenyl-6-methyl-...	6+	2-Phenyl-6-methyl-	3+

A detailed account of the results of the pharmacological investigation will be published elsewhere.

Experimental.

4-Methylamino-2-phenyl-6-methyl-3-pyridazone.—4-Chloro-2-phenyl-6-methyl-3-pyridazone (5·0 g.) was heated in an autoclave at 130° for 3 days with ethyl alcohol (200 c.c.) containing methylamine (16·0 g.). After cooling, the mixture was filtered and the reddish-brown solution evaporated to dryness under reduced pressure. The solid residue was heated with barium hydroxide (7·5 g.; hydrated) in water (150 c.c.) for 1 hour at 80° in an atmosphere of nitrogen, and the mixture was then evaporated to dryness. The dry residue was extracted exhaustively with hot chloroform, the extract dried ($MgSO_4$), and the chloroform removed by distillation. The product, recrystallised from ethyl alcohol, formed colourless prisms, m. p. 148—149° (3·85 g., 81%) (Found: C, 67·1; H, 6·1; N, 20·0. $C_{12}H_{13}ON_3$ requires C, 67·0; H, 6·05; N, 19·5%).

4-Dimethylamino-2-phenyl-6-methyl-3-pyridazone.—4-Chloro-2-phenyl-6-methyl-3-pyridazone (10·0 g.) was heated in an autoclave at 140° for 3 days with ethyl-alcoholic dimethylamine (8%; 700 c.c.). After cooling, the mixture was filtered and the solution evaporated to dryness. The syrupy residue was hydrolysed by heating with barium hydroxide (15 g.; hydrated) in water (300 c.c.) for 1 hour at 80° in an atmosphere of nitrogen. The mixture was then evaporated to dryness under reduced pressure, the dry residue extracted several times with hot chloroform, and the extract evaporated to a viscous brown syrup. After decolorisation with charcoal in alcohol, a solid residue of the tertiary *amine* was obtained, which recrystallised from light petroleum (b. p. 40—60°), containing a trace of methyl alcohol, in long colourless needles, m. p. 61° (5·35 g., 52%) (Found: C, 68·6; H, 6·4; N, 18·1. $C_{13}H_{15}ON_3$ requires C, 68·2; H, 6·55; N, 18·3%).

4-Diethylamino-2-phenyl-6-methyl-3-pyridazone.—4-Chloro-2-phenyl-6-methyl-3-pyridazone (10·0 g.) was heated in an autoclave at 150° for 3 days with diethylamine (150 c.c.) and ethyl alcohol (850 c.c.). From the resulting solution the *diethylaminopyridazone* was obtained in a manner similar to that described for the corresponding dimethylamino-derivative. It was isolated as a dark brown, viscous syrup which distilled at 196—198°/0·01 mm. to give a thick yellow oil, n_D^{21} 1·6053 (8·60 g., 74%) (Found: C, 69·5; H, 7·7; N, 16·4. $C_{15}H_{19}ON_3$ requires C, 70·0; H, 7·4; N, 16·3%). This compound (0·1 g.) on being treated with picric acid (0·1 g.) in ethyl alcohol gave a *monopicrate* which, recrystallised from aqueous alcohol, formed rosettes of needles, m. p. 107—108° (Found: C, 52·2; H, 4·75; N, 17·6. $C_{21}H_{22}O_8N_6$ requires C, 51·9; H, 4·53; N, 17·3%).

Lævulic Acid m-*Tolylhydrazone.*—The acid (1·16 g.) was dissolved in water (2·0 c.c.), and *m*-tolylhydrazine (1·2 g.; 1 mol.), dissolved in glacial acetic acid (2·0 c.c.), added. An immediate reaction occurred, heat was developed, and crystals separated which were collected and recrystallised from aqueous alcohol in nearly colourless prisms, m. p. 133° in agreement with that given by Sah (*Science Repts. Natl. Tsing Hua Univ.*, 1936, *A*, **3**, 403) (yield, 1·91 g., 87%). When kept under anhydrous conditions the hydrazone slowly decomposed.

2-m-*Tolyl*-6-*methyl*-3-*pyridazinone.*—Lævulic acid *m*-tolylhydrazone (3·0 g.) was heated at 155—160° for 1·5 hours. After cooling, the syrupy 2-m-*tolyl*-6-*methyl*-3-*pyridazinone* crystallised on trituration with ethyl alcohol and recrystallised from light petroleum (b. p. 40—60°) in colourless prisms, m. p. 68° (1·9 g., 69%) Found: C, 71·3; H, 6·93; N, 13·4. $C_{12}H_{14}ON_2$ requires C, 71·3; H, 6·93; N, 13·9%).

Chlorination of 2-m-*Tolyl*-6-*methyl*-3-*pyridazinone.*—The pyridazinone (5·0 g.) and phosphorus pentachloride (25·0 g.) were intimately mixed, phosphoryl chloride (8 c.c.) was added, and the mixture heated at 110—112° for 0·5 hour. Some of the excess of phosphoryl chloride was evaporated off under reduced pressure, the mixture was then cooled to 0°, and ice-water added to decompose the excess of phosphorus chlorides. After being kept for a few hours, the crystals which separated were collected and, recrystallised from aqueous alcohol, formed colourless feathery needles of 4-*chloro*-2-m-*tolyl*-6-*methyl*-3-*pyridazone*, m. p. 109° (3·05 g.) (Found: C, 61·2; H, 4·6; N, 12·0. $C_{12}H_{11}ON_2Cl$ requires C, 61·4; H, 4·7; N, 11·9%). The mother-liquors were then made alkaline with potassium hydroxide and extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated to dryness. The residue, recrystallised from aqueous alcohol, had m. p. 109° and was identical with the chloro-compound already isolated; yield, 0·5 g.; total yield, 61%.

4-*Amino*-2-m-*tolyl*-6-*methyl*-3-*pyridazone.*—4-Chloro-2-*m*-tolyl-6-methyl-3-pyridazone (10·0 g.) was heated in an autoclave at 150° for 3 days with methyl alcohol, saturated with ammonia at 0°. After cooling, the mixture was filtered and evaporated to dryness. The solid residue was hydrolysed by heating it with hydrated barium hydroxide (15 g.) in water (300 c.c.) for 1 hour at 80° in an atmosphere of nitrogen, and the product, after being evaporated to dryness, was extracted with boiling chloroform. The extract, after being dried ($MgSO_4$), was evaporated to a dark brown syrup which crystallised on trituration with ethyl alcohol. Recrystallisation, first from ethyl alcohol–water and then from acetone, gave colourless prisms of 4-*amino*-2-m-*tolyl*-6-*methyl*-3-*pyridazone*, m. p. 153° (5·1 g., 56%) (Found: C, 67·1; H, 6·0; N, 19·5. $C_{12}H_{13}ON_3$ requires C, 67·0; H, 6·05; N, 19·5%).

This amine (0·3 g.), freshly fused sodium acetate (0·3 g.), and acetic anhydride (5 c.c.) were heated together under reflux for 0·5 hour. After cooling, the mixture was poured into water and the precipitated 4-*acetamido*-compound filtered off; it recrystallised from ethyl alcohol in colourless needles, m. p. 237° (yield, quantitative) (Found: C, 65·6; H, 5·9; N, 16·3. $C_{14}H_{15}O_2N_3$ requires C, 65·4; H, 5·8; N, 16·3%).

2-*Pyridylhydrazine.*—2-Bromopyridine (18·0 g.), obtained from 2-aminopyridine by the method of Craig (*J. Amer. Chem. Soc.*, 1934, **56**, 232), and hydrazine hydrate (50 c.c.) were heated together under reflux for 5 hours. After cooling, the mixture was extracted with ether, and the extract dried ($MgSO_4$) and evaporated to dryness, whereby colourless needles (8·0 g.) were obtained having m. p. 43—45°, raised to 48° by recrystallisation from light petroleum (b. p. 40—60°). The solution, after extraction with ether, was evaporated under reduced pressure and the residue treated with concentrated potassium hydroxide solution. This solution was then extracted with ether. The ethereal extract was dried ($MgSO_4$) and evaporated to dryness, giving a further 1·9 g. of 2-pyridylhydrazine. Total yield: 9·9 g., 80%. The compound decomposed rapidly on exposure to air.

Lævulic Acid 2-*Pyridylhydrazone.*—To lævulic acid (4·0 g.), dissolved in water (4 c.c.), was added

pyridylhydrazine (3·75 g.) dissolved in the minimum volume of ethyl alcohol. Heat was evolved and crystals separated immediately; these were collected and the *hydrazone*, recrystallised from ethyl alcohol, formed colourless flakes, m. p. 190—191° (6·1 g., 81%) (Found: C, 58·1; H, 6·3; N, 19·8. $C_{10}H_{13}O_2N_3$ requires C, 58·0; H, 6·3; N, 20·3%).

2-2′-*Pyridyl*-6-*methyl*-3-*pyridazinone*.—Lævulic acid 2-pyridylhydrazone (10·0 g.) was heated to 170° and maintained thereat for 2 hours, whereafter the elimination of water appeared to have ceased. The dark brown liquid was then distilled at 240—250°/12—15 mm., giving a yellow distillate which solidified almost completely. This was triturated with alcohol and ether and filtered off; 2-2′-*pyridyl*-6-*methyl*-3-*pyridazinone*, recrystallised from ethyl alcohol, formed large plates, m. p. 128° (5·2 g.) (Found: C, 63·6; H, 6·0; N, 22·0. $C_{10}H_{11}ON_3$ requires C, 63·5; H, 5·8; N, 22·2%).

In subsequent experiments the lævulic acid pyridylhydrazone was not isolated. The reaction mixture was heated at 140° for 2 hours to remove water and ethyl alcohol and then at 170° for 1 hour to effect the cyclisation, and finally distilled.

4-*Chloro*-2-2′-*pyridyl*-6-*methyl*-3-*pyridazone*.—2-2′-Pyridyl-6-methyl-3-pyridazinone (5·0 g.), phosphorus pentachloride (25·0 g.), and phosphoryl chloride (8·0 g.) were heated at 120° for 0·75 hour. The bulk of the excess of phosphoryl chloride was removed by evaporation under reduced pressure; the mixture was then cooled to 0° and ice-water added. The dark brown solution was made alkaline with potassium hydroxide solution, and the brown syrup which separated was extracted with chloroform. The chloroform extract was dried ($MgSO_4$) and evaporated to a semi-solid mass, which was triturated with alcohol and ether. The 4-*chloro*-2-2′-*pyridyl*-6-*methyl*-3-*pyridazone* was then filtered off and recrystallised from ethyl alcohol in colourless prisms, m. p. 123° (3·0 g.) (Found: C, 54·1; H, 3·8; N, 19·4. $C_{10}H_8ON_3Cl$ requires C, 54·2; H, 3·6; N, 19·0%).

4-*Amino*-2-2′-*pyridyl*-6-*methyl*-3-*pyridazone*.—4-Chloro-2-2′-pyridyl-6-methyl-3-pyridazone (5·0 g.) was heated with methyl-alcoholic ammonia (saturated at 0°) at 150° in an autoclave for 3 days. After cooling, the mixture was filtered and evaporated to dryness. The residue was heated with barium hydroxide (5·0 g.) in water (150 c.c.) at 80° for 1 hour in an atmosphere of nitrogen. The mixture was then evaporated to dryness and extracted exhaustively with chloroform. The chloroform extract was dried ($MgSO_4$) and evaporated to a semi-solid residue. This was triturated with ethyl alcohol and light petroleum (b. p. 40—60°), and the solid filtered off. The *product* was recrystallised from ethyl alcohol and had m. p. 172° (yield, 2·4 g.) (Found: C, 59·3; H, 4·9; N, 27·9. $C_{10}H_{10}ON_4$ requires C, 59·4; H, 4·95; N, 27·7%). The compound was sensitive to light and became pink on exposure.

The crude amine (0·2 g.), fused sodium acetate (0·5 g.), and acetic anhydride (5·0 c.c.) were heated under reflux for 0·5 hour. The mixture was then poured into water, and the solid which separated was filtered off and recrystallised from ethyl alcohol. The *acetyl* derivative had m. p. 216° (yield, 0·14 g.) (Found: C, 59·1; H, 4·8; N, 22·7. $C_{12}H_{12}O_2N_4$ requires C, 59·0; H, 4·9; N, 22·9%).

4-*Dimethylamino*-2-2′-*pyridyl*-6-*methyl*-3-*pyridazone*.—4-Chloro-2-2′-pyridyl-6-methyl-3-pyridazone (3·5 g.) was heated with 6% ethyl-alcoholic dimethylamine (500 c.c.) at 140° in an autoclave for 3 days. The solution was then evaporated to dryness under pressure. The 4-*dimethylamino*-compound was isolated exactly as described for the corresponding amino-compound. Recrystallised from light petroleum (b. p. 40—60°) containing a little methyl alcohol, it formed colourless prisms, m. p. 94° (2·0 g.) (Found: C, 62·3; H, 6·2; N, 24·5. $C_{12}H_{14}ON_4$ requires C, 62·6; H, 6·1; N, 24·35%).

4-*Piperidino*-2-*phenyl*-6-*methyl*-3-*pyridazone* (with S. Dixon).—4-Chloro-2-phenyl-6-methyl-3-pyridazone (2 g.) was mixed with a solution of piperidine (2 g.) in dry methyl alcohol (50 c.c.). The mixture was heated in a sealed tube for 3 days at 208°. The dark brown solution was evaporated under reduced pressure, and a semi-solid residue obtained. The mixture was dissolved in hot alcohol–water, filtered (charcoal), and allowed to cool; 4-*piperidino*-2-*phenyl*-6-*methyl*-3-*pyridazone* separated in colourless needles, m. p. 80° (1·5 g., 63%) (Found: C, 71·0; H, 7·05; N, 15·6. $C_{16}H_{19}ON_3$ requires C, 71·4; H, 7·05; N, 15·6%).

4-*Morpholino*-2-*phenyl*-6-*methyl*-3-*pyridazone*.—4-Chloro-2-phenyl-6-methyl-3-pyridazone (2 g.) was mixed with morpholine (2 g.) and dry methyl alcohol (50 c.c.). The mixture was heated for 3 days at 200° under pressure. The dark solution was evaporated under reduced pressure and the 4-*morpholino*-2-*phenyl*-6-*methyl*-3-*pyridazone* recrystallised from alcohol–water in white plates, m. p. 132° (2·0 g., 83%) (Found: C, 66·4; H, 6·45; N, 16·0. $C_{15}H_{17}O_2N_3$ requires C, 66·4; H, 6·3; N, 15·5%).

The pharmacological studies of these compounds were carried out in the Department of Pharmacology, University of Birmingham, by Dr. M. R. A. Chance and Mrs. I. Wajda. We are greatly indebted to the Colonial Products Research Council for supporting this investigation.

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