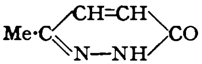
631. *The Conversion of Sucrose into Pyridazine Derivatives. Part IX. The Nitration of Pyridazine Derivatives.*

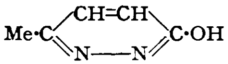
By S. Dixon and L. F. Wiggins.

Attempts have been made to nitrate pyridazine and several of its derivatives but, as in the isomeric pyrimidines and pyrazines, the diazine ring is resistant to such a reaction. A nitration product from 3-amino-6-methylpyridazine was, however, obtained but this was a nitramino-derivative. A similar compound was isolated by the nitration of 3-aminopyridazine. Both nitramines react with benzylamine, elimination of nitrous oxide taking place to form the corresponding 3-benzylaminopyridazine derivatives.

A study of the reactions of pyrimidine, pyrazine, and their derivatives reveals that these substances show a remarkable stability towards nitrating agents. With pyrazine, in no recorded instance does nitration proceed in the ring itself. With pyrimidine, nitration of the heterocylic nucleus does occur but is only possible when activating groups such as NH_2, OH, or SH are present in the molecule.

(I.)

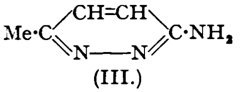




(II.)

In this paper experiments concerned with the action of nitrating agents on pyridazine derivatives are described. Such reagents as fuming nitric acid and concentrated sulphuric acid–potassium nitrate were used but in no case was nuclear nitration effected. Pyridazine, prepared by a slight modification of the method of Evans and Wiselogle (*J. Amer. Chem. Soc.*, 1945, **67**, 60), was treated with concentrated sulphuric acid and potassium nitrate at room temperature but, despite the production of some carbonaceous decomposition product, the pyridazine was recovered unchanged in 80% yield. 6-Methylpyridaz-3-one behaves as an equilibrium mixture of (I) and the enol (II) and can therefore be considered to contain a group (OH) which might activate the heterocyclic ring towards nitrating agents. However, when it was treated at room temperature with concentrated nitric acid no reaction took place. On the other hand, treatment of (I) with hot dilute nitric acid caused oxidation of the 6-methyl group with formation of 1 : 6-dihydro-6-ketopyridazine-3-carboxylic acid (Homer, Gregory, Overend, and Wiggins, *J.*, 1948, 2195). Similarly, pyridaz-3-one was recovered unchanged after being treated with concentrated sulphuric acid and potassium nitrate, with fuming nitric and fuming sulphuric acids, or fuming nitric acid at a higher temperature. Thus, although the presence of an activating group is possible in the pyridazones by virtue of the enolisation referred to above, the effect is insufficient to promote nitration of the heterocyclic nucleus.

Another substituent which might be expected to activate the heterocylcic nucleus to an extent sufficient to allow nitration to occur is the amino-group. When 3-amino-6-methylpyridazine (III) (Overend and Wiggins, *J.*, 1947, 239) was treated with fuming nitric acid at room temperature, and the mixture poured on ice, a crystalline mononitro-derivative was



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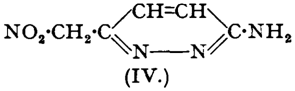

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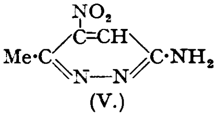

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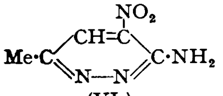

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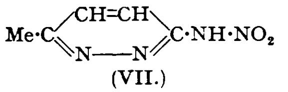

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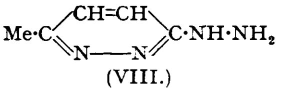
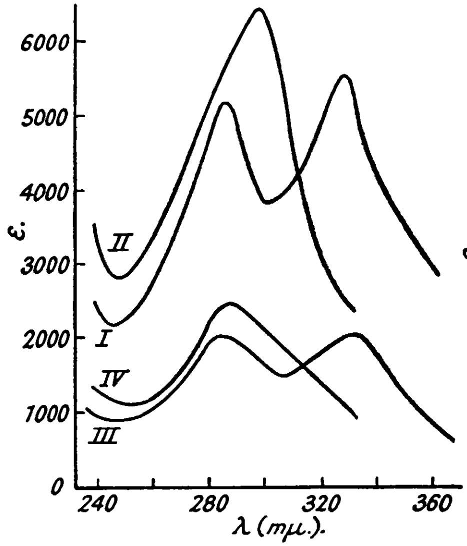


(VIII.)

isolated. This procedure sometimes led to serious decomposition of the material and it was found more expedient to use concentrated sulphuric acid and potassium nitrate as the nitrating agent. The nitro-group could be attached to the pyridazine (III) at any one of a number of positions, and structures (IV)—(VII) are all theoretically possible.

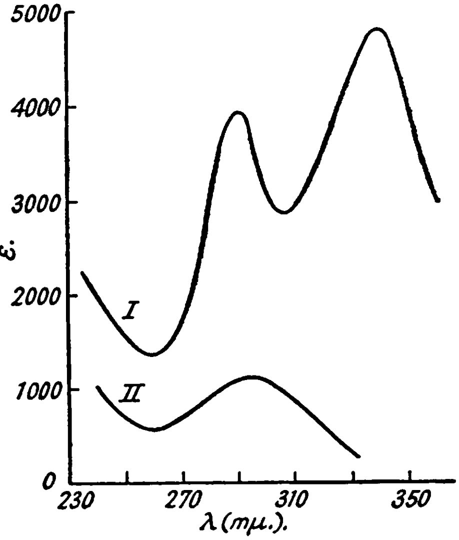
Reduction might be expected to lead to formation of a diamine if structure (IV), (V), or (VI) were correct. Extreme decomposition followed hydrogenation with Raney nickel and hydrogen or reduction with zinc in acetic acid or sodium hydroxide solution. Sodium hydrosulphite (dithionite) had no action on the nitro-compound. Hydrogen, in the presence of palladium on charcoal, however, not only effected reduction of the nitro-group but also brought about its complete removal to produce 3-amino-6-methylpyridazine in 80% yield. Deamination of the nitro-compound, if it were represented by (IV), (V), or (VI), would be expected to give a nitropyridazine or nitropyridazone. When, in fact, it was treated with sodium nitrite and hydrochloric acid, simultaneous removal of the nitro-group on deamination occurred and 6-methylpyridaz-3-one was isolated. Hydrochloric acid alone had no action on the nitro-compound. This evidence precludes structures (IV), (V), and (VI) and it would appear that the nitration product from 3-amino-6-methylpyridazine is the nitramine (VII).

FIG. 1.



I. 3-*Nitramino*-6-*methylpyridazine.*
II. Potassium salt of I.
III. 3-*Nitraminopyridazine.*
IV. Potassium salt of III.

FIG. 2.

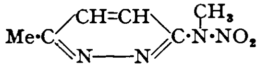


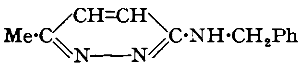
I. 3-*Methylnitramino*-6-*methylpyridazine.*
II. Solution of I with a few drops of added alkali. Subsequent neutralisation and acidification produce no change.

(*Measurements in ethyl-alcoholic solution.*)

Although catalytic hydrogenation of the nitramine did not yield the hydrazine (VIII), this compound was nevertheless synthesised by treating 3-chloro-6-methylpyridazine with hydrazine hydrate. It gave a characteristic hydrazone with lævulic acid.

Conclusive evidence was that the nitro-compound gave a colourless crystalline potassium salt which, with methyl iodide, gave an *N*-methyl derivative (IX), a behaviour characteristic of nitramines. Moreover, it reacted with benzylamine, elimination of nitrous oxide leading to 3-benzylamino-6-methylpyridazine (X), which was also obtained directly, although in

(IX.)

$$\mathrm{Me{\cdot}C}\begin{smallmatrix}\diagup\mathrm{CH{=}CH}\diagdown\\ \diagdown\mathrm{N{-\!-}N}\diagup\end{smallmatrix}\mathrm{C{\cdot}\overset{CH_3}{N}{\cdot}NO_2}$$


$$\mathrm{Me{\cdot}C}\begin{smallmatrix}\diagup\mathrm{CH{=}CH}\diagdown\\ \diagdown\mathrm{N{-\!-}N}\diagup\end{smallmatrix}\mathrm{C{\cdot}NH{\cdot}CH_2Ph}$$
(X.)

much smaller yield, by the action of benzylamine on 3-chloro-6-methylpyridazine. A similar series of reactions was carried out with 3-aminopyridazine. Nitration led to the formation of 3-nitraminopyridazine which formed a colourless potassium salt. This, with methyl iodide, gave an *N*-methyl derivative. Treatment of 3-nitraminopyridazine with benzylamine gave 3-benzylaminopyridazine in high yield, identical with the material obtained directly from 3-chloropyridazine and benzylamine.

The absorption spectra of the nitramines and their derivatives are of interest (see Figs. 1 and 2) though the explanation of the movement, in alkaline solution, of the absorption peak (especially in the case of the methylated derivatives) is not obvious.

Examination of the formulæ of pyrazine and pyridazine together with the resonance forms which might contribute to these structures shows that all the carbon atoms in both diazines are the seat of a fractional positive charge and hence any reaction with the nitrating ion, NO_2^+, would be hindered. In the case of pyrimidine, all the carbon atoms, except that at $C_{(5)}$, possess a similar fractional positive charge and hence nitration is difficult. Only in the case of position 5, where the positive charge is of an inductive nature, does reaction with nitrating agents occur.

EXPERIMENTAL.

3-*Nitramino*-6-*methylpyridazine*.—(i) *Action of fuming nitric acid.* 3-Amino-6-methylpyridazine (1·0 g.) was treated dropwise with fuming nitric acid (10 c.c.) at 0°. After the initial vigorous reaction had subsided the clear solution was kept at room temperature for 24 hours and then poured into ice-water. A crystalline precipitate of 3-*nitramino*-6-*methylpyridazine* separated. Recrystallised (charcoal) from boiling water, it formed needles or plates, m. p. 178° (decomp.) (0·8 g., 57%) (Found : C, 38·7; H, 4·1; N, 36·1. $C_5H_6O_2N_4$ requires C, 38·9; H, 3·9; N, 36·4%); $\varepsilon_{max.}$ = 5020 at 2800 A.; $\varepsilon_{max.}$ = 5780 at 3290 A.

(ii) *Action of concentrated sulphuric acid and potassium nitrate.* The material (1·0 g.) was dissolved, with cooling, in concentrated sulphuric acid (10 c.c.). Finely powdered potassium nitrate (2·0 g.) was slowly added and, after being well stirred, the solution was kept at room temperature for 4 hours. Thereafter it was poured into ice-water, and ammonia gas was carefully passed into it. A precipitate separated which, recrystallised (charcoal) from hot water, formed needles or plates, m. p. 178° (decomp.) (1·0 g., 71%). The product was identical with that obtained above.

Reduction with hydrogen in the presence of palladium. 3-Nitramino-6-methylpyridazine (0·25 g.) was treated as a suspension in dry methanol (40 c.c.) with hydrogen in the presence of a catalyst prepared by reduction of palladous chloride (0·9 g.) on activated charcoal (2·5 g.) under a slight pressure of hydrogen. The hydrogenation was stopped after the theoretical amount (110 c.c.) of hydrogen necessary for the reduction of the nitro-group had been absorbed. The catalyst was separated, and the pale pink solution concentrated. The residue, recrystallised from acetone–light petroleum, formed needles (0·14 g., 79%), m. p. 225° alone or in admixture with an authentic specimen of 3-amino-6-methylpyridazine.

Attempted hydrolysis. 3-Nitramino-6-methylpyridazine (0·3 g.) was dissolved in hot 2N-hydrochloric acid (20 c.c.), and the solution heated under reflux for 3 hours. After cooling, crystals of unchanged starting material separated (0·1 g.). The filtrate was evaporated to dryness, and the residue, recrystallised from water, had m. p. 178° alone or in admixture with an authentic specimen of 3-nitramino-6-methylpyridazine (0·19 g.); the total recovery was 0·29 g. (97%).

Treatment with sodium nitrite. 3-Nitramino-6-methylpyridazine (0·8 g.) was dissolved in concentrated hydrochloric acid (15 c.c.), and an equal volume of water added. Sodium nitrite (0·5 g.) was added, and the solution boiled for 5 minutes, then poured into water and neutralised with aqueous ammonia. Thereafter it was evaporated to dryness, and the residue extracted several times with hot chloroform. Evaporation of the extracts yielded a solid which, recrystallised from water, gave plates (0·4 g., 60%) of m. p. 120—123° alone or on admixture with an authentic specimen of 6-methylpyridaz-3-one monohydrate.

Potassium salt. 3-Nitramino-6-methylpyridazine (0·5 g.) was warmed with an alcoholic potassium hydroxide solution (19·8 c.c., 0·164N.) until complete dissolution was achieved. The solution was cooled, and on the addition of a few drops of light petroleum a white crystalline precipitate appeared. This was separated and, recrystallised from alcohol–light petroleum, formed plates, m. p. 188° (0·45 g., 72%). It was the *potassium* salt of 3-nitramino-6-methylpyridazine (Found : C, 30·9; H, 2·65; N, 29·0. $C_5H_5O_2N_4K$ requires C, 31·2; H, 2·6; N, 29·2%); $\varepsilon_{max.}$ = 6320 at 2910 A.

3-N-*Methylnitramino*-6-*methylpyridazine*.—The above potassium salt (0·35 g.) was dissolved in a small volume of dry methyl alcohol and treated with methyl iodide (0·3 g.). The solution was heated under reflux for 3 hours and then allowed to cool. The solvent was evaporated off, and the residual solid extracted several times with hot chloroform. Evaporation of the extract yielded a dark brown solid which was heated with alcohol containing charcoal, filtered, and evaporated. The residual pale yellow powder recrystallised from alcohol–light petroleum in long needles (0·1 g., 33%) and was 3-N-*methylnitramino*-6-*methylpyridazine*, m. p. 148° (Found : C, 43·1; H, 4·4; N, 33·2. $C_6H_8O_2N_4$ requires C, 42·9; H, 4·8; N, 33·4%); $\varepsilon_{max.}$ = 3925 at 2910 A.; $\varepsilon_{max.}$ = 4840 at 3420 A.; after alkali treatment, $\varepsilon_{max.}$ = 1190 at 2970 A.

Nitration of 3-*Aminopyridazine*. 3-*Nitraminopyridazine*.—3-Aminopyridazine (0·5 g.) was dissolved, with cooling, in concentrated sulphuric acid (6 c.c.), and finely powdered potassium nitrate (0·5 g.) slowly added with stirring. Thereafter the solution was kept at room temperature for 4 hours and then poured into ice-water. Pale yellow 3-*nitraminopyridazine* separated and was collected. Recrystallised (charcoal) from hot water, it gave pale yellow needles, m. p. 184° (decomp.) (0·53 g., 72%) (Found : C, 34·5; H, 2·9; N, 39·8. $C_4H_4O_2N_4$ requires C, 34·3; H, 2·9; N, 40·0%); $\varepsilon_{max.}$ = 1930 at 2820 A.; $\varepsilon_{max.}$ = 2040 at 3250 A. The substance was readily soluble in alkali.

Potassium salt. 3-Nitraminopyridazine (0·6 g.) was dissolved in the theoretical amount of alcoholic potassium hydroxide solution (27·4 c.c.; 0·156N.) under reflux. The solution was allowed to cool, and light petroleum (b. p. 100—120°) added dropwise until a faint permanent turbidity was produced. The colourless crystalline *potassium* salt of 3-nitraminopyridazine slowly separated. Recrystallised from dry methyl alcohol–ether–light petroleum, it formed needles, m. p. 175° (decomp.) (0·67 g., 88%). The salt was extremely hygroscopic and decomposed completely when kept in air for 6 hours (Found : C, 27·0; H, 1·75; N, 31·6. $C_4H_3O_2N_4K$ requires C, 27·0; H, 1·7; N, 31·5%).

3-N-*Methylnitraminopyridazine.*—The foregoing potssium salt (0·5 g.) was heated under reflux in dry methyl-alcoholic solution together with methyl iodide (0·2 c.c.). A brown colour rapidly developed; after 3 hours all solvent was evaporated off, and the solid residue extracted several times with hot chloroform. Evaporation of the extract yielded a dark brown solid which, recrystallised (charcoal) from dry ethyl alcohol, formed pale yellow needles (0·2 g., 46%) of 3-N-*methylnitraminopyridazine*, m. p. 98° (Found : C, 38·9; H, 4·0; N, 36·8. $C_5H_6O_2N_4$ requires C, 38·95; H, 3·9; N, 36·4%).

3-*Benzylaminopyridazine.*—3-Nitraminopyridazine (0·75 g.) was treated with a solution of benzylamine (1·5 c.c.) in dry xylene (8 c.c.). The mixture was heated gently and a clear solution was rapidly produced. Heating was continued and after about 2 minutes a gas was evolved. When evolution of the gas had ceased the solution was allowed to cool. A solid separated which, recrystallised from benzene–light petroleum, formed fine colourless needles (0·8 g., 81%) of 3-*benzylaminopyridazine*, m. p. 110° (Found : C, 71·1; H, 5·95; N, 23·0. $C_{11}H_{11}N_3$ requires C, 71·4; H, 5·95; N, 22·7%). A *picrate* was prepared by dissolving a little of the amine in alcohol–water and adding a cold concentrated aqueous solution of picric acid. The yellow solid which separated, recrystallised from alcohol–water, formed needles, m. p. 169—170° (Found : C, 49·3; H, 3·5; N, 20·1. $C_{17}H_{14}O_7N_6$ requires C, 49·3; H, 3·4; N, 20·3%).

3-*Benzylamino*-6-*methylpyridazine.*—(i) 3-Nitramino-6-methylpyridazine (0·95 g.) was warmed in the presence of a solution of benzylamine (3 c.c.) in dry xylene (20 c.c.). A rapid evolution of gas occurred. Heating was continued for 30 minutes, and the solution was then allowed to cool. 3-*Benzylamino*-6-*methylpyridazine* separated and recrystallised from alcohol–water in needles, m. p. 138° (1·1 g., 90%) (Found : C, 72·5; H, 6·4; N, 21·7. $C_{12}H_{13}N_3$ requires C, 72·4; H, 6·5; N, 21·2%).

(ii) A solution of 3-chloro-6-methylpyridazine (2·0 g.) in dry benzylamine (20 c.c.) was heated under reflux for 6 hours. The excess of benzylamine was removed by distillation under reduced pressure, and the oily residue allowed to cool. After solidifying, it was recrystallised from acetone–light petroleum, forming plates, m. p. 133° (0·9 g., 29·3%). These, recrystallised from water, gave colourless plates of 3-benzylamino-6-methylpyridazine, m. p. 138° alone or mixed with the product obtained as in (i). A *picrate* was prepared by dissolving a small quantity of the base in dilute alcohol and adding dropwise a cold saturated solution of picric acid in alcohol–water. The precipitate was washed with warm water and, recrystallised from alcohol–water, formed plates, m. p. 165° (Found : C, 50·7; H, 3·9. $C_{18}H_{16}O_7N_6$ requires C, 50·45; H, 3·7%).

6-*Methyl*-3-*pyridazylhydrazine.*—3-Chloro-6-methylpyridazine (10·0 g.) and hydrazine hydrate (50 c.c.) were heated together under reflux for 5 hours. After being cooled, the mixture was extracted several times with ether, and the extract dried ($MgSO_4$). Evaporation of the solvent afforded a solid residue, m. p. 70—72° (1·8 g.). Crystals (3·8 g.) which separated when the aqueous layer was kept were collected and found to have m. p. 67—70°. The filtrate was then evaporated under reduced pressure to a thin syrup, concentrated aqueous potassium hydroxide added, and the solution extracted exhaustively with ether, and the extract dried ($MgSO_4$). Evaporation of the ether gave a further 2·1 g. of 6-*methyl*-3-*pyridazylhydrazine*. The crude product recrystallised from ether in long needles of the monohydrate, m. p. 71—72° (7·7 g., 80%) (Found : C, 42·5; H, 7·15; H_2O, 12·5. $C_5H_8N_4,H_2O$ requires C, 42·3; H, 7·0; H_2O, 12·7%). The hydrazine (1·0 g.), dissolved in ethyl alcohol, was added to lævulic acid (0·94 g.), dissolved in water, and the mixture heated for a few minutes. After being kept overnight at room temperature the solution was evaporated to dryness, and the solid residue, recrystallised from ethyl alcohol, had m. p. 175°. It was the 6-*methyl*-3-*pyridazinylhydrazone* of lævulic acid (1·2 g., 67%) (Found : C, 53·7; H, 6·1; N, 25·3. $C_{10}H_{14}O_2N_4$ requires C, 54·0; H, 6·3; N, 25·2%).

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