HETEROCYCLIC COMPOUNDS

Part XIV.* Synthetic Experiments in the Pyrido-(1, 2 a)-Pyrimidone Series

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The formation of a pyrido-(1, 2 a)-pyrimidone from ethyl acetoacetate and 2-amino-pyridine was studied by several workers\(^1\) under different conditions. The product was first formulated as 4-methyl-2H-pyrido-(1, 2 a)-pyrimidin-2-one (I) and later as 2-methyl-4H-pyrido-(1, 2 a)-pyrimidin-4-one (II). The latter structure was confirmed by Adams et al.\(^2\) by the studies of ultraviolet absorption curves of several pyrido-(1, 2 a)-pyrimidones and by providing unequivocal chemical evidence. The synthesis of the isomer (I) has not yet been effected.

\[ \begin{align*}
\text{N} & \quad \text{O} \\
\text{CH} & \quad \text{CH} \\
\text{I} & \\
\text{II} & \\
\end{align*} \]

In continuation of work already reported from this laboratory,\(^3\) it was proposed to synthesise the compound (I) or its 3, 4-dihydro derivative by the reaction of homologues of acrylic ester or \(\beta\)-bromo-propionic ester with 2-amino-pyridine and other methyl-substituted 2-amino-pyridines. The condensation of 2-amino-pyridine or methyl-2-amino-pyridine with ethyl \(\beta\)-bromo-butyrate or \(\beta\)-bromo-butyric acid was attempted according to the

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Addition of ethyl crotonate (or crotonic acid) to 2-amino-pyridine (and methyl-2-amino-pyridines) to form the cyclised base (I) was also attempted by Adams' method. In each case, no reaction took place and most of the reactants were recovered unchanged.

2-Amino-pyridine was condensed with α-methylmethacrylate by heating the reactants on the water-bath in the presence of little tertiary-butyl catechol as the polymerisation inhibitor. The expected base, 3-methyl-3, 4-dihydro-2H-pyrido-(1, 2 a)-pyrimidine-2-one (III) was obtained in fairly good yields.

The hydrobromide (IV) of the above base was also obtained by heating 2-amino-pyridine with methyl β-bromo-isobutyrate in absolute chloroform for twenty-five hours. The ultraviolet spectrum of (IV) was compared with the known pyrido-(1, 2 a)-pyrimidin-2-ones (see Fig. 1). The similarity of the spectrum to that of the known compounds lends additional evidence to the structure.

However, when the reaction was applied to methyl-substituted 2-amino-pyridines, the expected condensation products could not be obtained. When the reactants were refluxed for eight hours in chloroform, the hydrobromides of the pyridine-amines were precipitated. This action is in sharp contrast to simple 2-amino-pyridine which showed little tendency to act as a dehalogenating agent. Drake and McElvain observed differences in the nature of the reactivity of bromo-esters towards piperidine, the difference being related to the position of the bromine atom. In this investigation it is found that the same bromo-ester reacts differently when passing from 2-amino-pyridine to methyl 2-amino-pyridines.
The difference in behaviour now reported between 2-amino-pyridine and four methyl-substituted 2-amino-pyridines towards β-bromo-isobutyric ester is probably due to greater basicity of methyl-substituted 2-amino-pyridines. Brown et al. and Bruehlman and co-workers have reported similar observations. It is known that the basicity of pyridine molecule is increased by the introduction of methyl group, the inductive as well as hyper-conjugative effect of the methyl group being responsible.

**EXPERIMENTAL**

*Condensation of ethyl β-bromo-butyr ate and 2-amino-pyridine*

Ethyl β-bromo-butyr ate was prepared according to the method of Johanson. 2-amino-pyridine (1.8 gm.) and ethyl β-bromo-butyr ate (3.9 gm.) were refluxed for twenty-four hours in 20 ml. of chloroform. No solid separated.

The chloroform layer was successively extracted with water. The base, obtained on evaporation of aqueous extract, was characterised as 2-amino-pyridine by conversion into the picrate, m.p. 216–17°. Most of the above ester was recovered from the chloroform layer.

The substitution of β-bromo-butyr ic acid instead of the ester did not effect the condensation. Methyl-2-amino-pyridines also did not condense with the above acid or ester.
Condensation of ethyl crotonate and 2-amino-pyridine

Ethyl crotonate (2·8 gm.), 2-amino-pyridine (2·3 gm.) and of tertiary-butyl catechol (0·05 gm.) were heated on the water-bath for twelve hours. Working up the product in the same way as above, it was found that the reaction did not take place at all.

3-methyl-3, 4-dihydro-2H-pyrido-(1, 2 a)-pyrimidin-2-one

2-amino-pyridine (4·7 gm.), a-Methylmethacrylate (5 gm.) and of tertiary-butyl catechol (0·1 gm.) were heated on the water-bath for twelve hours without any solvent. The dark solution was kept in the ice-chest for two days. Small flowery crystals separated. It was triturated with 10 ml. of benzene and filtered. The solid was dissolved in 10 ml. of chloroform, boiled with charcoal and filtered. The solution upon dilution with light petrol (40–60°) yielded white powdery substance of m.p. 195–96°. Repeated crystallisation from chloroform-petrol mixture raised the m.p. to 199–200°.

Found: C, 66·25; H, 6·05; Calculated for C₉H₁₀N₂O. C, 66·67; H, 6·17.

The picrate of the base was prepared in the usual manner. The yellow picrate was crystallised from ethanol, m.p. 181–82°.

Found: C, 46·36; H, 3·6; Calculated for C₉H₁₀N₂O.C₆H₅N₃O₇. C, 46·04; H, 3·33.

It was observed that the mother liquor, after removal of the crude base, when kept in the ice-chest for a long time deposited crystals which were identified as 2-amino-pyridine.

The hydrobromide of 3-methyl-3, 4-dihydro-2H-pyrido-(1, 2 a)-pyrimidin-2-one

Methyl β-bromo-isobutyrate was prepared by the method of Clemo and Melrose.⁸ A solution of 2-amino-pyridine (1·98 gm.) and β-bromo-isobutyric ester (3·6 gm.) in 30 ml. of dry chloroform was heated under reflux for twenty-four hours. Solid separated after 12 hours of refluxing. The solid was filtered and dissolved in minimum amount of absolute ethanol and completely precipitated by the addition of absolute ether. 2·4 gm. of the hydrobromide of m.p. 293–95° was obtained. An analytical sample after two recrystallisations from ethanol-ether mixture melted at 300° (decomp.).

Found: C, 44·42; H, 4·7; N, 11·1; Calculated for C₉H₁₆N₂O.HBr. C, 44·42; H, 4·5; N, 11·5. The u.v. spectrum was taken in 95% ethanol.
3-methyl-3, 4-dihydro-2H-pyrido-(1, 2 a)-pyrimidin-2-one hydrobromide ....
3, 4-dihydro-2H-pyrido-(1, 2 a)-pyrimidin-2-one hydroiodide ......
6-methyl-3, 4-dihydro-2H-pyrido-(1, 2 a)-pyrimidin-2-one hydroiodide ..

The picrate prepared from the hydrobromide had m.p. 181-82° undepressed by authentic specimen prepared from the base. The free base, obtained from the hydrobromide, had m.p. 195-97°.

Condensation of 5-methyl-2-amino-pyridine and methyl β-bromo-isobutyrate

5-methyl-2-amino-pyridine (2·1 gm.) and methyl β-bromo-isobutyrate (3·6 gm.) were refluxed for 12 hours in 25 ml. of chloroform. A strong odour of α-methylmethacrylate was noticed after six hours. The precipitated solid (3 gm.) was crystallised from absolute methanol-ether mixture, m.p. 170-72°. Two more recrystallisations from the same solvent increased the m.p. to 175-76°.

Found: C, 38·2; H, 5·2; C₈H₆N₂HBr requires C, 38·05% and H, 4·7%.

The picrate of 5-methyl-2-amino-pyridine was prepared in the usual manner. On crystallisation from isopropyl alcohol, it separated as yellow fluffy mass, m.p. 249-50°.

Found: N, 20·75; Calculated for C₈H₆N₂.C₆H₃N₂.O₂. N, 20·77. The picrate from the hydrobromide melted at 249° and the mixed m.p. of the two picrates remained constant.

Condensation of 4-methyl-2-amino-pyridine (2·1 gm.) and methyl β-bromo-isobutyrate (3·6 gm.) in the same manner yielded 3 gm. of the hydrobromide. The hydrobromide though it melted sharply at 162-63°, was hygroscopic and could not be obtained analytically pure. The m.p. of yellow picrate (from acetic acid) was 227° and remained constant upon admixture with pure sample.

In the case of 3-methyl-2-amino-pyridine, the hydrobromide obtained melted at 153-55°, but was also too hygroscopic to work with. The picrate
from the salt melted at 229° (yellow prisms from alcohol). The mixed m.p. of the picrates remained the same.

3·5 gm. of the hydrobromide was obtained from the condensation 2·1 gm. of 6-methyl-2-amino-pyridine and 3·6 gm. of methyl β-bromo-isobutyrate. The HBr salt had m.p. 142°. After three recrystallisations from ethanol-ether mixture, it melted at 149°. The reported m.p. in the literature9 is 149–50°. The picrate melted at 202° and was identical with pure specimen.

Summary
Synthesis of 3-methyl-3, 4-dihydro-2H-pyrido-(1, 2 a)-pyrimidin-2-one is reported. Methyl β-bromo-isobutyrate on reacting with methyl-substituted 2-amino-pyridines underwent dehalogenation with the production of unsaturated compound.

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Literature Cited

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