Short Communications

A New Procedure for the Preparation of Isonicotinic Acid Hydrazide

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A well-known preparative method for aliphatic amides consists in the thermal decomposition of the ammonium salts of the acids. A simple example is the formation of acetamide from ammonium acetate by heating. Similarly the hydrazone salts of the acids on heating give rise to the hydrazides. The preparation of acyl hydrazides by this method, though less well-known has been reported in the literature¹.

The reactions may be represented as follows:

If R is aromatic the reaction generally fails and the hydrazide can only be prepared via the corresponding ester, acid chloride or the anhydride. This involves an extra step in the process and it was, therefore, considered worthwhile to investigate the possibility of a direct conversion of the hydrazone salt to the acid hydrazide.

In the last few years, isonicotinic acid hydrazide has come into prominence as a valuable remedy against tuberculosis. The hydrazide is usually manufactured by the condensation of the ethyl ester of isonicotinic acid or the acid chloride with hydrazine hydrate^{2,3}.

During the study undertaken in our laboratory, it was realised that the reaction

could be made to proceed to the right if the water formed in the reaction is constantly and almost completely removed.

Such a dehydration may be performed by azeotropic distillation with the help of a suitable water entrainer. Many such media are available but the choice is restricted as a certain temperature is also required to obtain a workable rate of reaction. It has been found that immiscible water entrainers having boiling points above 120° are most suitable, e.g. amyl alcohol, hexyl alcohol, or octyl alcohol, and hydrocarbons, e.g. toluene, xylene or mesitylene. It has thus been described how maleic anhydride can be prepared from the acid by an azeotropic removal of water by the use of xylene⁴.

It is likely that the reaction mechanism is not as simple as represented above but perhaps passes through an ester stage where an alcohol is used as water entrainer or through the anhydride where a hydrocarbon is used. The experimental procedures finally worked out are described in the experimental section.

Experimental. Procedure 1. Normal amyl alcohol (60 ml) was added to a solution of isonicotinic acid (30 g) in 60 % hydrazine hydrate (27 ml). The reaction mixture was slowly distilled when a mixture of amyl alcohol and dilute solution of hydrazine hydrate distilled over. A further quantity of dry amyl alcohol (40 ml) was added and the distillation continued till water ceased to appear in the distillate. The mixture was then refluxed for 3 h, the water formed at this stage removed by distillation, and the refluxing continued for another 3.5 h. The reaction product was cooled to 0° when crude isonicotinic acid hydrazide crystallised out. The product was purified by recrystallisation from a small amount of ethyl alcohol yielding isonicotinic acid hydrazide, m.p. 170–172°, and a purity of 98.5–99.0 %, when assayed by the B.P. procedure. Yield 24 g.

The amyl alcoholic mother liquor was acidified with hydrochloric acid to a pH 3.5 when the unreacted isonicotinic acid (4–5 g) precipitated. Taking into consideration the recovered material, an yield of 86.5 % was obtained.

The mother liquor, after the precipitation of isonicotinic acid, in the previous step, con-

tained some dissolved hydrazide besides other condensation products formed by side reactions. Further quantity of the acid was recovered by hydrolysing these products. The mother liquor was boiled under reflux with an excess of sodium hydroxide, acidified to a pH 3.5 and the precipitated acid collected by filtration. The total yield of the hydrazide, taking into consideration the recovered *isonicotinic* acid in both the steps amounted to over 90 % of the theory.

Procedure 2. To a solution of *isonicotinic* acid (30 g) in 60 % hydrazine hydrate (27 ml), xylene (100 ml) was added and the mixture was heated in an oil bath at 170°. A mixture of xylene and hydrazine hydrate distilled over slowly during the first 2 h. The temperature of the oil bath was now lowered to 150° and maintained at this point for the next 4 h. During this period the last traces of xylene and a strong solution of hydrazine hydrate distilled over. The reaction product was cooled somewhat, water (20 ml) was added and the resulting solution filtered at a temperature between 70–75°. The filtrate was cooled to –3° when crude *isonicotinic* acid hydrazide crystallised out; yield 24–25 g.

Recovery of *isonicotinic* acid was carried out as described under procedure 1.

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A New Synthesis of 4-*O*-Methyl-D-Glucose

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The unambiguous synthetic routes leading to 4-*O*-methyl-D-glucose¹⁻³ are rather tedious and give low yields. As we required this substance and its methyl β -pyranoside we sought for other methods

of preparing them. Bearing in mind the ease with which acyl migration takes place from the 4- to the 6-position, we investigated the direct methylation of the easily available methyl 2,3,4-tri-*O*-acetyl- β -D-glucopyranoside with methyl iodide and silver oxide. The alkalinity of the silver oxide we believed would probably be sufficient to effectively catalyse the acyl migration. This reaction has already been investigated in the α -series by Haworth, Hirst and Teece⁴. They found that methylation took place in the 2-position. On the other hand, Helferich and Lang⁵ prepared methyl 2,3,6-tri-*O*-acetyl 4-*O*-methyl- β -D-glucopyranoside by the Purdie methylation of methyl 2,3,6-tri-*O*-acetyl- β -D-glucopyranoside. These results show that acyl migration is rather unpredictable and may proceed by several paths.

By methylation of methyl 2,3,4-tri-*O*-acetyl- β -D-glucopyranoside with methyl iodide and silver oxide in dimethylformamide, according to the method of Kuhn *et al.*⁶, we have now obtained crystalline methyl 2,3,6-tri-*O*-acetyl-4-*O*-methyl- β -D-glucopyranoside in a yield of 45 %. A hydrolysate of the mother liquors contained 4-*O*-methyl-D-glucose as the main product, contaminated by glucose and by some methyl glucoses. 2-*O*-Methyl-D-glucose, which has almost the same electrophoretic mobility as 4-*O*-methyl-D-glucose but a higher R_F -value, was only present in traces. The pure, acetylated glucoside was converted by standard procedures to the crystalline methyl 4-*O*-methyl- β -D-glucopyranoside and to the amorphous 4-*O*-methyl-D-glucose. Paper chromatographic and paper electrophoretic examination of this latter product showed it to be indistinguishable from an authentic sample of 4-*O*-methyl-D-glucose but to be readily distinguishable from the other mono-*O*-methyl-D-glucoses. The values of the m.p. and optical rotations of the crystalline products were in good agreement with those previously recorded^{1,2}. As comparatively few steps are needed, and as the yields are fairly good, this is probably the most convenient synthesis of 4-*O*-methyl-D-glucose and of its methyl- β -pyranoside.

Experimental. Methyl 2,3,6-tri-*O*-acetyl-4-*O*-methyl- β -D-glucopyranoside. Methyl 2,3,4-tri-*O*-acetyl- β -D-glucopyranoside (4.0 g) was dissolved in dimethylformamide (50 ml) and to this solution methyl iodide (12 ml) was added. Silver oxide (8.0 g) was added in four portions during 30 min under vigorous stirring and