THE SYNTHESIS AND REDUCTION OF 3-INDOLYLACETONITRILE

By B. MATKOVICS, L. FERENCZY* and S. FÖLDEÁK
Institute of Organic Chemistry, The University, Szeged

(Received March 30, 1960)

The important plant growth hormone, indolylacetonitrile was succesfully prepared by the authors in various ways. Reduction by lithium aluminium hydride of the compound gave tryptamine, an important intermediate of tryptophane metabolism.

The activity of indolylacetic acid as a plant growth hormone was demonstrated first by KÖGL et al. [1].

Later, plant growth promoting effect was experienced also with other compounds having the indole skeleton. Thus, *e. g.*, in 1952 a group of English researchers [2], [3] succeeded in isolating indolylacetonitrile from pumpkin by means of chromatographic methods.

The present paper deals with the methods tried by us in synthesising indolylacetonitrile and for the reduction of this compound to the corresponding amine:

1. The first authors reporting about natural 3-indolylacetonitrile gave also a method for its synthesis which was accomplished by route I, described in the experimental part.

2. A second route was found in quaternerizing the corresponding MANNICH base, isolating the quaternary salt and boiling the product with potassium cyanide; this method, however, gave but moderate yields (Route II) [4].

3. Condensation with formaldehyde and potassium cyanide may also become a practical way of synthesis (Route III) [5].

4. The work of several authors revealed another possibility for the preparation of indole-3-acetonitrile (Route IV); in comparison with the rest of the methods, this synthesis appears to be the best [6].

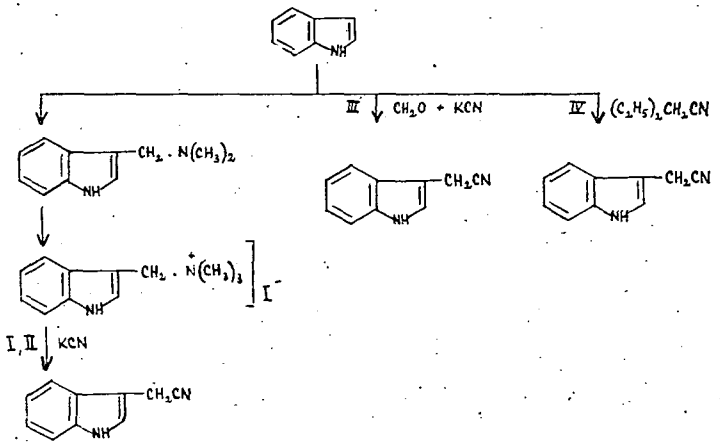
A consideration of these syntheses clearly reveal that yields are always lower in the processes where the nitrilo-group is formed in several steps than in the cases where this reaction consists of one single step. The only difference between route I and II is that the quaternary product is not isolated in the latter case. The synthesis according to route III could be realized only with a poor yield.

On the other hand, indole-3-acetonitrile could be prepared in a good yield according to route IV, when proper temperature control was applied.

Freshly distilled indole-3-acetonitrile gave tryptamine on reduction with lithium aluminium hydride or with sodium borohydride.

* Institute of Plant Physiology, The University, Szeged

The above routes of synthesis may be outlined as follows:



Experimental

The materials used were of the following grade and origin:

Indole, „rein", „Gesellschaft für Teerverwertung" m. b. H. Duisburg—Meiderich.

Formaldehyde, pro anal., 35%aqueous solution, Fine Chemicals Factory, Reanal, Budapest.

Diethylamine aqueous solution, Fine Chemicals Factory, Reanal, Budapest.

Potassium cyanide „Kalium cynatum, Ph. H. IV" material was used.

Diethylaminoacetonitrile was prepared as described in Organic Syntheses [7].

The synthesis of indolylacetonitrile in various ways, and the reduction of this product are described in detail below. It should be noted that the synthesis according to route III is suitable primarily for the preparation of the potassium salt of indolylacetic acid.

The starting material of the synthesis according to route II was gramine or ethylgramine [8]. In both cases trimethyl or diethylmethyl skatyl ammonium methylsulphate had to be synthezised first, from which compounds the quaternary iodides were made [9].

Diethylmethylskatylammoniummethylsulphate was a new compound of this series; it was prepared from diethylgramine by means of dimethyl sulphate in anhydrous tetrahydrofuran [9]. The product was recrystallized from anhydrous ethanol, m. p. 156—157°C.

Analysis: Calculated for $(C_{14}H_{21}N_2) . (CH_3O_4S)$ (328,4): C 51,19; H 7,35%. Found: C 51,62; H 7,49%.

When an aqueous solution of this compound was treated with potassium iodide, the quaternary iodide was obtained, which gave recrystallization from methanol-ether (1:1) a material of m. p. 170—172° C.

$(C_{14}H_{21}N_2)I$(340,2) requires I 37,30%. Found I 38,00%.

0,1 mol of the isolated quaternary iodide was refluxed in aqueous solution for 10 hours with 0,1 mol of KCN. The product was extracted with five 100 ml portions of ether, the ethereal layer was washed with water, dilute sulphuric acid and sodium carbonate solution, finally it was dried over anhydrous sodium sulphate. The ether was evaporated, and the remaining nitrile was distilled in good vacuum. B. p. 165—169° C at 0,5 mm.

$C_{10}H_8N_2$ (157,19) requires C 76,9; H 5,15%. Found C 77,1; H 5,50%.

The picrate was precipitated by treatment with a calculated amount of 5% picric acid solution in ethanol, m. p. 120° C. $C_{16}H_{11}O_7N_5$ (385,29) requires N 18,19%. Found 18,75%.

It should be noted that indole could be recovered at the end of the distillation; it was isolated in the form of its picrate, m. p. 181° C. $C_{14}H_{10}O_7N_4$ (346,25) requires N 16,18%. Found N 16,40%.

According to route I, indolylacetonitrile could be prepared without isolating the quaternary salt [3].

The synthesis according to route IV, developed in 1953 [6] should be described more detailed, since this method was proved to be the simplest way of preparing indolylacetonitrile.

0,1 mol indole and 0,2 mol of diethylaminoacetonitrile was refluxed under nitrogen atmosphere for 6 hours at 170° C (measured in the mixture). The condensation took place, and after a time the indolylacetonitrile could be isolated in a good yield. Proper control of temperature is absolutely necessary during this reaction.

Then the excess diethylaminoacetonitrile was evaporated in the vacuum of a water-pump, then the residue was distilled at 0,2 mm, b. p. 160—165° C.

The product was converted into the corresponding picrate for the purpose of identification.

The fore-run of the distillation gave indole and another crystalline material having m. p. 150° C. This material gave the following analysis: C 82,49; H 6,32; N 12,0%.

Treatment with an alcoholic solution of picric acid gave the picrate of the unknown material, m. p. 158—159° C. Found: N 20,94%.

It follows from these results that the unknown compound must be of the indole structure, containing some unsaturated side chain. The elucidation of its structure would afford valuable support concerning the detailed mechanism of the reaction.

The indolylacetonitrile was converted to tryptamine in anhydrous ether solution by reduction with $LiAlH_4$ [10]. The tryptamine was then isolated in the form of its hydrochloric acid salt, m. p. 246—247° C. The base had m. p. 116° C.

The reduction could be carried out in a similar way in aqueous medium with sodium borohydride. The isolation and purification of the final product was again possible in the form of the hydrochloride.

References

[1] *Kögl, Erxleben, Haagen-Smit:* Z. physiol. Chem. **228**, 90 (1934).
[2] *Henbest, H. B., E. R. Jones, G. F. Smith:* Nature, **169**, 485 (1952).
[3] *Henbest, H. B., E. R. Jones, G. F. Smith:* J. Chem. Soc. **1953**, 3796.
[4] *Thesing J., F. Schulde :* Ber. **85** 324 (1952).
[5] *Melnyikov, N. N.:* Khimia gerbicidov i stimulatorov. Goskhimizdat, Mocsow, 1954.

[6] *Eliel, E. L., N. J. Murphy:* J. Am. Chem. Soc. **75**, 3589 (1953).
[7] *Allen, C. F. H., I. A. Van Allan:* Org. Synth. **20** (1947).
[8] *Butenandt, A., H. Hellmann:* Z. physiol. Chem. **284**, 168 (1949).
[9] *Schöpf, C., J. Thesing:* Angew. Chem. **63**, 377 (1951).
[10] *Nógrády, Th.:* Monatshefte **88**, 768 (1957).

СИНТЕЗ И РЕДУКЦИЯ 3-ИНДОЛИЛАЦЕТОНИТРИЛА

Б. Маткович, Л. Ференци и Ш. Фельдеак

Применением различных методов удалось получить важнейший растительный гормон роста — индолацетонитрил. Восстановление его алюминиевым гидридом лития привело к триптамину, являющемуся важным промежуточным продуктом обмена веществ триптофана.