[CONTRIBUTION FROM THE MERCK RESEARCH LABORATORIES]

Improved Syntheses of Indole-3-aldehyde

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Indole-3-aldehyde, an intermediate in several of the recorded syntheses for *dl*-tryptophan, has been prepared from indole by the application of the Reimer–Tiemann reaction[2] and by converting indole to the magnesium derivative followed by reaction with ethyl formate.[3] Boyd and Robson,[4] in an extended investigation of methods for preparing indole-3-aldehyde, developed an improved process based on the application of the Gattermann aldehyde synthesis to 2-carbethoxyindole. The resulting 2-carbethoxy-3-aldehyde was hydrolyzed to the free acid, converted to the anil, 3-(phenyliminomethyl)-2-indolecarboxylic acid, and decarboxylated in 40–50% yield by heating in liquid paraffin at 220°. More recently Elks, Elliot and Hems[5] reported an improved synthesis of indole-3-aldehyde wherein indole was first converted to indole-3-glyoxylic acid by treatment with oxalic ester. On treatment with aniline the glyoxylic acid was transformed to the anil which was decarboxylated and hydrolyzed to indole-3-aldehyde. Although this approach has certain advantages, the over-all yield is quite low (38%).

We should like to record improvements made on the Boyd and Robson synthesis as well as a direct synthesis of the 3-aldehyde from indole.

2-Carbethoxyindole-3-aldehyde was prepared from 2-carbethoxyindole in quantitative yield by a modification of the N-methyl formanilide synthesis of aldehydes which was first introduced by Vilmeier and Haak[6] and extended by others.[7]

Conversion of the aldehyde ester to the anil was accomplished by the method of Boyd and Robson.[4] Attempts to decarboxylate this material in liquid petrolatum in the manner described by these authors gave poor results. The use of tetralin and quinoline, with a copper catalyst, was of no advantage. Excellent yields were obtained, however, by refluxing the anil with dimethylaniline. Steam distillation of the decarboxylation mixture resulted in the simultaneous removal of dimethylaniline and hydrolysis of the decarboxylated anil. The yield of pure indole-3-aldehyde from the anil of 2-carboxyindole was 75–80%. The aldehyde was identified by conversion to the known 3-indolalhydantoin.

The excellent results obtained with N-methylformanilide in the synthesis of 2-carbethoxyindole-3-aldehyde suggested its application to indole. Various attempts to effect the desired reaction at 0 to 25° resulted in yields of 19 to 37%. However, when the reactants were dissolved in ethylene dichloride and heated to reflux for thirty minutes in the presence of finely divided calcium carbonate, a 53.5% yield of indole-3-aldehyde was obtained.

Experimental

2-Carbethoxyindole-3-aldehyde.—A mixture of 15.6 g. of N-methylformanilide and 17.7 g. of phosphoryl chloride protected from atmospheric moisture, was stirred for fifteen minutes. To the mixture was added 75 g. of ethylene dichloride followed by 18.9 g. of 2-carbethoxyindole.[4] After refluxing the mixture for one hour, it was poured into a solution of 75 g. of sodium acetate and 150 cc. of ice water, whereupon the product separated. The 2-carbethoxyindole-3-aldehyde was filtered, washed with water and then ether and dried at 80°; yield 21.6 g., 99.5%; m. p. 190.5–192°, mixed m. p. with an authentic sample 190–192°.

3-(Phenyliminomethyl)-2-indolecarboxylic Acid.—To a suspension of 21.6 g. of 2-carbethoxyindole-3-aldehyde in 362 cc. of 95% ethanol was added a solution of 6.1 g. of sodium hydroxide in 226 cc. of water. After refluxing the mixture for fifteen minutes, 10.1 g. of aniline was added. The hot solution was diluted with 900 cc. of water, cooled to 0° and acidified to congo paper with *N* hydrochloric acid. The precipitated product was filtered, washed with water and dried; yield 24.7 g. (93.6%); m. p. 243–243.5°, mixed melting point with an authentic sample 243–243.5°.

Indole-3-aldehyde.—In a 125-cc., round-bottom flask, equipped with a condenser and mechanical stirrer, were placed 10.0 g. of 2-carboxyindole-3-aldehyde anil and 100 cc. of dimethylaniline. The stirred mixture was slowly heated to reflux (193°) and held at this temperature until the evolution of carbon dioxide ceased (about twenty minutes). To the cooled solution was added 500 cc. of water and the mixture was steam distilled until all the dimethylaniline was removed. The boiling solution was treated with 2 g. of Norite, filtered and slowly cooled to 0°. After standing for twenty-four hours at 0°, the product was filtered and washed with water; yield 4.16 g., 76%; m. p. 194–196°, mixed melting point with an authentic sample 194–196°.

Indole-3-aldehyde from Indole.—N-Methylformanilide (15.6 g.) and phosphoryl chloride (17.8 g.) were mixed in a flask protected from atmospheric moisture and provided with a mechanical stirrer. After standing at room temperature for fifteen minutes, 75 g. of ethylene dichloride was added and the solution cooled in an ice-bath. When the internal temperature reached 0°, 6.0 g. of indole was added in small portions at such a rate that the temperature did not rise above 10°. Finally, 20 g. of finely divided calcium carbonate was added and the ice-bath removed. The mixture was rapdily heated to reflux, with stirring, and maintained at this temperature for thirty minutes. During this time hydrogen chloride was evolved.

The reaction mixture was cooled and poured into a solution of 75 g. of sodium acetate in 75 cc. of water containing 15 g. of ice. The ethylene dichloride was removed by steam distillation and the residual solution diluted with water to a volume of 1200 cc. After heating to reflux, treating with Norite and filtering through a preheated funnel, the solution was allowed to cool to room temperature and then placed in the refrigerator overnight. The

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(2) Ellinger, *Ber.*, **39**, 2520 (1906).

(3) Majima and Kotake, *ibid.*, **55**, 3859 (1922).

(4) Boyd and Robson, *Biochem. J.*, **29**, 555 (1935).

(5) Elks, Elliot and Hems, *J. Chem. Soc.*, 629 (1944).

(6) Vilmeier and Haak, *Ber.*, **60**, 118 (1927).

(7) Wood and Bost, THIS JOURNAL, **59**, 1722 (1937); Vollmann Becker, Corell and Streeck, *Ann.*, **531**, 1 (1937); Fieser and Hershberg, THIS JOURNAL, **60**, 2547 (1938); Fieser and Hartwell, *ibid.*, **60**, 2556 (1938).

product was filtered and washed with water; yield 4.0 g., 53.5%; m. p. 193–195°, mixed melting point with an authentic sample 193–195°.

3-Indolalhydantoin.—In a 100-cc. round-bottom flask equipped with a mechanical stirrer were placed 6.0 g. of indole-3-aldehyde, 5.0 g. of hydantoin and 18.5 cc. of piperidine. The mixture was heated rapidly to boiling and refluxed for ten to fifteen minutes until a solid cake was formed. The solid was cooled to room temperature, slurried with 500 cc. of distilled water and acidified to litmus paper with glacial acetic acid. The yellow precipitated product was filtered and washed three times with 50-cc. portions of water; wt. 8.5 g., 90.7%; m. p. 325°, mixed melting point with an authentic sample 325°.

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Summary

Two improved methods for preparing indole-3-aldehyde are described. The first method starting with 2-carbethoxyindole is a modification of a recorded synthesis. The second procedure is a direct conversion of indole to indole-3-aldehyde. In both methods N-methylformanilide is utilized in formylating the indole nucleus.

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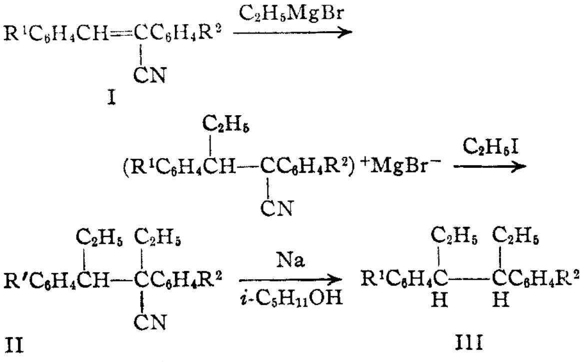
Applications of the 1,4-Addition of Grignard Reagents to α,β-Unsaturated Acid Derivatives. I. Synthesis of Compounds Related to Hexestrol

BY STANLEY WAWZONEK

Methods available for the synthesis of hexestrol and related compounds may be divided into four types[1]: reduction of diethylstilbestrol, thermal decomposition of azomethanes, Wurtz-type reactions on anethole hydrobromide or hydrochloride, and formation of free radicals followed by coupling. Reactions carried out by Kohler[2] and summarized below (Ia-IIIa) suggested another possible method for such compounds.



$$R^1C_6H_4CH{=}\underset{\substack{|\\ CN}}{C}C_6H_4R^2 \xrightarrow{C_2H_5MgBr}$$

I

$$(R^1C_6H_4\overset{\substack{C_2H_5\\ |}}{C}H{-}\underset{\substack{|\\ CN}}{C}C_6H_4R^2)^{+}MgBr^{-} \xrightarrow{C_2H_5I}$$

$$R'C_6H_4\overset{\substack{C_2H_5\\ |}}{C}H{-}\overset{\substack{C_2H_5\\ |}}{\underset{\substack{|\\ CN}}{C}}C_6H_4R^2 \xrightarrow[i\text{-}C_5H_{11}OH]{Na} R^1C_6H_4\overset{\substack{C_2H_5\\ |}}{\underset{H}{C}}{-}\overset{\substack{C_2H_5\\ |}}{\underset{H}{C}}C_6H_4R^2$$

II III

(a) $R^1 = R^2 = H$
(b) $R^1 = p\text{-}CH_3O$; $R^2 = H$
(c) $R^1 = R^2 = p\text{-}CH_3O$

This method which has the advantage of allowing variations in the alkyl and the aryl groups, has been carried out successfully with α-phenyl-p-methoxycinnamonitrile (Ib) and α-(p-methoxyphenyl)-p-methoxycinnamonitrile (Ic).

Both cinnamonitriles (I) when added to ethylmagnesium bromide in ether behaved in a similar manner to that observed by Kohler[2] with α-phenyl cinnamonitrile (Ia). Treatment of these solutions with a slight excess of ethyl iodide gave an 86% yield of oily nitriles (II) which could be separated into a solid and a liquid isomer. This behavior is different from the 98% yield of one solid isomer reported by Kohler[2] with α-phenylcinnamonitrile. Reinvestigation of Kohler's work gave only a 90% yield of a solid which by fractional crystallization and mechanical picking could be separated into two isomeric nitriles (IIa). The structure of the new isomer thus obtained, was proved by its reduction with sodium and isoamyl alcohol to 3,4-diphenylhexane (IIIa). Varying the conditions by using an excess of ethylmagnesium bromide instead of the theoretical amount, had no effect on the composition of the final product, but increased the yield slightly and greatly reduced the time necessary for the reaction.

The oily mixture of α-ethyl-α-phenyl-β-(p-methoxyphenyl)-valeronitriles (IIa) when treated with a fifteen fold excess of sodium in boiling isoamyl alcohol gave a 76% yield of a mixture of isomeric 3-(p-methoxylphenyl)-4-phenylhexane (IIb) in approximately equal amounts. α-Ethyl-α,β-di-(p-methoxyphenyl)-valeronitrile (IIc) upon similar treatment gave an 80% yield of a mixture of hexestrol dimethyl ethers (IIc). From this mixture a 33% yield of the higher melting isomer could be separated. The pure valeronitriles (II) upon similar treatment gave mixtures of the isomeric hexanes.

Further study of the applications of the 1,4-addition of Grignard reagents to α,β-unsaturated acid derivatives is now in progress.

Experimental[3]

p-Methoxybenzyl Cyanide.[4]—p-Methoxybenzyl cyanide was prepared from p-nitrobenzyl cyanide[5] according to

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(1) (a) Jones, "Annual Reports on the Progress of Chemistry," 1943, p. 137; (b) Kharasch, McBay and Urey, *J. Org. Chem.*, **10**, 401 (1945).

(2) Kohler, *Am. Chem. J.*, **35**, 386 (1906).

(3) Melting points and boiling points are not corrected.

(4) For a better and more recent method, see Shriner and Hull, *J. Org. Chem.*, **10**, 228 (1945).

(5) "Organic Syntheses," Coll. Vol. I, 2nd ed., p. 396.