LXIV. THE SYNTHESIS OF INDOLE-3-ALDEHYDE AND ITS HOMOLOGUES.

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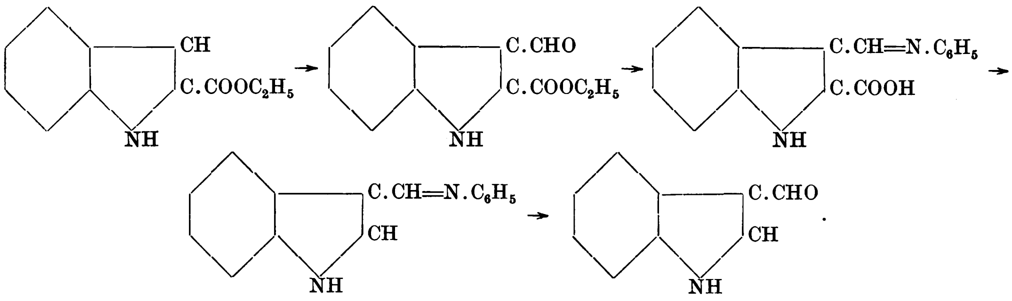
ONE of the many major difficulties encountered in the synthesis of tryptophan is that connected with the preparation of the parent substance, indole-3-aldehyde. Despite the exceedingly poor yields which Ellinger [1906] and Ellinger and Flamand [1908] obtained on synthesising this latter compound from indole, surprisingly few attempts have been made either to improve the yield or to evolve new methods of making it. The only one, indeed, worthy of mention is that of Majima and Kotake [1922] who employed a modified Grignard reaction on indole, using anisole instead of the customary ether as a solvent. The method, whilst it gives a primary yield of aldehyde higher than that obtained by Ellinger, suffers from the drawback that it is not applicable [Robson, 1924] with the same success to other derivatives of indole.

Preliminary experiments having already indicated that the modifications which may be successfully introduced into the Wheeler-Hoffman hydantoin synthesis of phenylalanine and tyrosine [Boyd and Robson, 1935, 1, 2] are applicable with even greater advantage to the synthesis of tryptophan from indole-3-aldehyde, it was decided to re-examine the problem of the preparation of the latter compound and its homologues with the view of making them more readily available.

The investigation followed two lines. The first had for its basis the modification of Ellinger's original method. On repeating the synthesis of indole-3-aldehyde according to that author it was noticeable that at the end of the reaction the resulting mixture still smelled strongly of chloroform. This fact in conjunction with the knowledge that Ellinger recovered unchanged half of the initial indole led to an examination of the quantities of the reacting substances used in the synthesis. It was at once evident that a much better yield of the aldehyde was to be expected if the quantity of hydroxide employed were considerably increased. An actual experiment proved this to be the case, the yield of aldehyde immediately obtainable being raised from the original figure of 9 % to one of 31 % of the figure demanded by theory. In addition, whilst 3-chloroquinoline is present as before in the steam distillate from the reaction mixture, it is accompanied by only insignificant amounts of unchanged indole. The same procedure applied to 2-methylindole and 5-methylindole gave the corresponding aldehydes in yields higher than those previously obtained by Ellinger's method.

In describing the synthesis of 7-methylindole-3-aldehyde, which has not been previously reported, mention must be made of the preparation of 7-methylindole. The first attempt to obtain this compound was made by Raschen [1887] along the lines of Fischer's classical method. For some reason, not apparent from his paper, Raschen did not succeed in decarboxylating the 7-methylindole-2-carboxylic acid. Following much the same procedure as Raschen, Kruber [1926] was able to isolate a small quantity of 7-methylindole and, moreover, evolved a method of isolating it from coal tar. In repeating Kruber's synthesis, the present writers have introduced modifications at certain stages. It has been found, for example, that ring closure is best effected by dissolving the pyruvic acid-*p*-tolylhydrazone in cold alcohol saturated with hydrochloric acid. When the same reaction is attempted with a hot alcoholic solution a second compound in addition to ethyl 7-methylindole-2-carboxylate is formed. Analysis of this substance indicates that it possesses the formula $C_{25}H_{20}O_7N_3$. It contains an amide grouping, the corresponding acid having the formula $C_{25}H_{19}O_8N_2$. Its structure is being further investigated. Kruber's method has been further improved in the last stage. Here, as has been reported previously in other cases, a much higher yield of the indole is obtained by heating the ammonium salt instead of the free carboxylic acid.

The second part of the investigation included several attempts to synthesise indole-3-aldehyde and its homologues on entirely new lines. Of these, only one merits description at the present stage. 2-Carbethoxyindole, by means of the modification of the well-known Gatterman hydrogen cyanide method introduced by Adams and Levine [1923], gave the corresponding 3-aldehyde in excellent yield. The ester aldehyde so obtained was hydrolysed without difficulty to the acid, the sodium salt of which in hot aqueous solution reacted with aniline, the anil thus formed being precipitated on carefully neutralising the cold solution.



Decarboxylation of the latter compound should yield the anil of indole-3-aldehyde. Attempts, however, to carry out this reaction were not altogether satisfactory owing to formation of tar. The best yields were obtained by heating the substance in liquid paraffin at 220° and precipitating the decarboxylated anil from solution therein by the addition of light petroleum. The compound thus obtained gave the required aldehyde on warming with water acidulated with a few drops of acetic acid. In the case of indole-3-aldehyde the yield approximated to 40–50 % but in the case of the 5-methyl and the 7-methyl homologues it was exceedingly poor.

During the course of this part of the investigation an attempt was made to synthesise 2-methylindole-3-aldehyde from 2-methylindole by the Adams-Levine method referred to above. It has already been shown by Barger and Ewins [1917] that on submitting 2-methylindole to the original Gattermann technique, the aldehyde is obtained in very good yield. On applying the method of Adams and Levine, however, we found that the product obtained was by no means homogeneous, but that it consisted of two fractions, one being easily soluble in hot alcohol whilst the other was practically insoluble in that medium. Further examination showed that the soluble fraction consisted of the required 2-methylindole-3-aldehyde and that the insoluble compound was the tri(2-methylindolyl)-

methane, originally obtained by Fischer and Pisbor [1923] by heating a mixture of 2-methylindole and 2-methylindole-3-aldehyde with alcoholic potash.

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EXPERIMENTAL.

Indole-3-aldehyde. Indole (20 g.) was dissolved in a mixture of chloroform (150 ml.) and 96 % alcohol (400 ml.) contained in a 2 l. flask fitted with a rubber stopper carrying a reflux condenser, a stirrer and a dropping funnel. The mixture was kept gently boiling over an electric hot plate and stirred while a solution of potassium hydroxide (250 g.) in water (300 ml.) was gradually dropped in over a period of 4–5 hours. The mixture was boiled for 30 minutes after the last addition of potassium hydroxide. When the contents of the flask had cooled, the potassium chloride was collected on a Büchner funnel and washed with alcohol. The combined filtrate and washings were then steam-distilled, the receiver being changed when the chloroform and most of the alcohol had passed over. The distillation was continued for 30 minutes after the distillate was no longer turbid owing to the presence of 3-chloroquinoline.

The hot aqueous liquid in the flask was decanted from the tarry residue and set aside to cool. The tarry material remaining was dissolved in the minimum quantity of hot alcohol, the alcoholic solution poured into a litre of hot water, the whole again boiled until the tarry globules had coalesced (an action which can be hastened by the addition of a little sodium chloride to the solution) and then filtered through a hot fluted filter-paper. The tar remaining on the filter was extracted yet another time in the same way. Aldehyde separated from all three aqueous solutions. This was filtered off and the combined filtrates amounting to some 2·5–3·0 litres were concentrated to about 300 ml. This concentrated solution on cooling yielded a further crop of aldehyde. The total yield of aldehyde thus obtained amounted to 7·5 g. (31 % of theory). The crude material melted at 194° and after recrystallisation from water at 198° (*cf.* Ellinger and Flamand, 195°). It contained 9·57 % N. C_9H_7NO requires N 9·66 %.

2-Methylindole-3-aldehyde. 2-Methylindole (13 g.) gave, by the above method 8 g. of 2-methylindole-3-aldehyde (51 % of theory).

5-Methylindole-3-aldehyde. By the same procedure, 20 g. of 5-methylindole yielded 6·5 g. of 5-methylindole-3-aldehyde (27 % of theory).

*Pyruvic acid-*o*-tolylhydrazone.* *o*-Toluidine (107 g.) was slowly added to a litre of hydrochloric acid (sp. gr. 1·16), cooled to 0°. A semi-crystalline mass of the hydrochloride separated out. Sodium nitrite (69 g.) dissolved in 150 ml. of water was slowly added, the temperature being maintained at zero by means of a freezing mixture. Stannous chloride (580 g.) dissolved in 500 ml. of hydrochloric acid and cooled to zero was next added. A white precipitate separated out. The mixture was left overnight in a cool place and next day the white precipitate was filtered off and well pressed. It was then shaken with 600 ml. of 25 % sodium hydroxide solution and 800 ml. of ether, and the ethereal layer was separated. The extraction with ether was repeated three times and the combined extracts were washed with water and then shaken with a slight excess of 1 % hydrochloric acid. The aqueous layer was separated and the ether was again washed twice with 100 ml. of dilute acid. To the combined acid solutions a solution of pyruvic acid in water equivalent to the *o*-tolylhydrazine present was added slowly with stirring. The yellow crystalline hydrazone began to separate at once and finally the mixture became semi-solid. It was filtered by suction on a Büchner funnel, and the solid was washed with a little water, air-dried and crystallised from hot 80 % alcohol. It melted at 157° (Raschen gives 158°). Yield 82·2 % of the theoretical.

2-Carbethoxy-7-methylindole. The pyruvic acid-*o*-tolylhydrazone (60 g.) was dissolved in cold absolute alcohol (500 ml.) which had been previously saturated with dry hydrogen chloride. The solution was kept at room temperature overnight and then poured into 5 litres of cold water. After standing overnight the precipitated material had become hard and was collected and dried at 100°. The brown amorphous product weighed 58 g. It was distilled at atmospheric pressure in a current of superheated steam and yielded 27 g. of light yellow 2-carbethoxy-7-methylindole which was somewhat impure as it melted below 100°. After crystallisation from hot 80 % alcohol it gave 15 g. of pure ester (M.P. 128°). The material in the mother-liquor was precipitated by the addition of water, collected, dried and extracted with hot light petroleum. In this way a further 3 g. of pure ester was obtained. The yield of pure ester from 60 g. of the pyruvic acid-*o*-tolylhydrazone was thus 18g. or 28 % of the theoretical yield. On decarboxylation of the impure uncrystallisable material, however, pure 7-methylindole corresponding to a further 8 % was obtained, making the total yield of ester 36 % of the theoretical value.

When the ester of the pyruvic acid-*o*-tolylhydrazone was used instead of the acid, no improvement in yield or purity of 2-carbethoxy-7-methylindole was found. The hydrazone ester was prepared by dissolving 50 g. of the hydrazone acid in 500 ml. of absolute alcohol, adding 25 ml. of concentrated sulphuric acid and heating the mixture under reflux for 30 minutes. The mixture was then poured into several litres of water, the precipitate which formed was collected and crystallised from 80 % alcohol. The yield was practically theoretical. The product melted at 61° (Raschen gives 61°, Kruber 62°).

When the solution of the pyruvic acid-*o*-tolylhydrazone in absolute alcohol previously saturated with hydrogen chloride was kept overnight and then heated on the water-bath for an hour before being poured into water, no improvement in yield or purity was obtained.

When pyruvic acid-*o*-tolylhydrazone was dissolved in absolute alcohol and the solution was then saturated with dry hydrogen chloride the yield was much less, and another crystalline substance was formed in considerable quantity. This appears to be an amide of high molecular weight. It was formed under the following conditions. *o*-Tolylhydrazone of pyruvic acid (80 g.) was dissolved in absolute alcohol (500 ml.) and dry hydrogen chloride was passed in. After a time the flask was cooled to prevent the alcohol from boiling away, and the saturation of the alcohol was completed. The solution was kept at room temperature overnight, and next day a white crystalline deposit was found at the bottom of the flask. This substance, of which about 5 g. were present, was very insoluble in ether, benzene, petroleum, cold alcohol and cold water. It was recrystallised from hot water and then melted with decomposition at 283° and evolved ammonia on being warmed with dilute sodium hydroxide. On acidifying the alkaline solution with hydrochloric or sulphuric acid, an acidic substance was precipitated which melted after recrystallisation from water at 235°. It was more soluble in water than the parent substance and dissolved in sodium bicarbonate solution with evolution of carbon dioxide.

Elementary analysis of these substances showed them to be an amide and the corresponding acid of compositions corresponding respectively to the formulae $C_{25}H_{20}O_7N_3$ and $C_{25}H_{19}O_8N_2$. (Found for amide: C, 63·9; H, 4·0; N, 8·83 %. For acid: C, 63·6; H, 4·0; N, 5·9, 6·0 %.)

The substances did not give a coloration with Ehrlich's reagent or with glyoxylic acid and concentrated sulphuric acid.

7-Methylindole-2-carboxylic acid. The corresponding ester was hydrolysed by boiling under a reflux with 6 % alcoholic KOH for 30 minutes. The alcoholic solution was then poured into water, the alcohol distilled off and the solution acidified. The 7-methylindole-2-carboxylic acid which separated was filtered off and recrystallised from dilute alcohol. It formed fine needles melting at 173°. Raschen gives 171° and Kruber 170°. The yield was quantitative. The substance contained 7·94 %N. $C_{10}H_9O_2N$ requires N 8·00 %.

7-Methylindole. Although Raschen failed originally to obtain the indole by melting 7-methylindole-2-carboxylic acid, Kruber obtained it in this way. In the present case the ammonium salt was used. The acid was dissolved in dilute ammonium hydroxide and the solution evaporated to dryness on the water-bath. The dry ammonium salt was transferred to a small distilling flask and carefully heated in a metal-bath to 240° at which temperature it melted and evolved ammonium carbonate which condensed in the side tube of the flask and was expelled by warming. On further heating the indole distilled as a water-clear liquid which solidified to a white mass. The yield was 62 % of the theoretical. Crystallisation of the indole from alcohol gave white plates melting at 78°. After recrystallisation from light petroleum, it melted at 82°. Since Kruber has reported a melting-point of 85°, the product was twice recrystallised from light petroleum and the melting-point redetermined. It was still 82°. After careful sublimation of the product in a test-tube, it was still the same. Commercial 7-methylindole from coal-tar also melted at 82° before and after recrystallisation from light petroleum. A mixture of the synthetic and coal-tar products also melted at 82°. (Found: C, 82·54; H, 6·98 %. C_9H_9N requires C, 82·39; H, 6·92 %.)

The picrate, prepared by adding aqueous picric acid solution to a hot saturated aqueous solution of the indole, separated as the solution cooled as a crimson precipitate. It crystallised from light petroleum in fine needles, which melted at 172° (*cf.* Kruber, 175°).

In working up impure 7-methylindole-2-carboxylic ester which could not be purified by crystallisation it was found convenient to convert it into crude ammonium salt and to decarboxylate it as already described. The indole was then readily recovered reasonably pure by steam distillation. It melted at 78° on recrystallisation from alcohol.

7-Methylindole-3-aldehyde. This substance was prepared in exactly the same way as indole-3-aldehyde. The yield from 20 g. of 7-methylindole was 7–8 g. It crystallised in gritty prisms of a sandy colour or in plates and melted at 202°. It contained 8·89 % N. $C_{10}H_9ON$ requires N 8·81 %.

3-Chloro-8-methylquinoline. This substance, which has not been described hitherto, was obtained in the steam distillate of the reaction mixture obtained in the Tiemann-Reimer preparation of 7-methylindole-3-aldehyde. Since there was little unchanged 7-methylindole present, the chloromethylquinoline crystallised out from the aqueous distillate. The yield from 20 g. of 7-methylindole was 5·0 g. It crystallised in long needles from dilute alcohol melting at 55°. Found 19·79 % Cl. $C_{10}H_8NCl$ requires Cl 20·00 %.

2-Carbethoxyindole-3-aldehyde. 2-Carbethoxyindole (19 g.), zinc cyanide (17 g.) and 300 ml. of ether which had been distilled over sodium were placed in a flask fitted with (*a*) an inlet tube dipping below the surface of the ether, (*b*) an outlet tube connected through a sulphuric acid trap to the outside air and (*c*) an efficient stirrer. Dry hydrogen chloride was passed into the ether for

3 hours, the reaction flask being kept cold by an ice-bath. After 2 hours, the ice-bath was removed and one of warm water substituted so that the ether just boiled. After a further 30 minutes the reaction was considered complete. The 2-carbethoxyindoleiminochloride was deposited as a yellowish white substance on the sides of the flask. Next morning the ether was decanted off, and the inside of the flask and its solid contents were washed with ether. The imino-compound was then boiled with water and the aldehyde which separated was filtered off and crystallised from dilute alcohol. 15 g. of pure product melting at 187° (188–189° after recrystallisation from chloroform) were obtained. A further crop of 3 g. of crude product was isolated from the mother-liquor. 3·5 g. of unchanged carbethoxyindole were recovered from the ether. The 2-carbethoxyindole-3-aldehyde contained 6·49 % N. $C_{12}H_{11}O_3N$ requires N 6·45 %.

2-Carboxyindole-3-aldehyde anil. 3·0 g. of indole-3-aldehyde-2-carboxylic ester were warmed with 1·5 equiv. of dilute alcoholic sodium hydroxide for 15 minutes. 1·4 g. of aniline were added to the hot solution with stirring. The liquid was cooled and carefully neutralised to Congo red with dilute hydrochloric acid, whereupon the acid anil was precipitated. The yield of anil was practically quantitative. It melted at 239° (raised to 244–245° on recrystallisation from dilute alcohol). It crystallised in yellow needles and contained 10·52 % N. $C_{16}H_{12}O_2N_2$ requires N 10·61 %.

Indole-3-aldehyde anil. 1·5 g. of indolealdehyde-2-carboxylic acid anil were suspended in 15 ml. of medicinal paraffin and heated to 210°. Gas was evolved and the substance gradually passed into solution. After evolution of gas had ceased, the addition of light petroleum to the solution precipitated the decarboxylated product. This was filtered off, washed with light petroleum and recrystallised from chloroform and finally from light petroleum. It melted at 123° and contained 12·61 % N. $C_{15}H_{12}N_2$ requires N 12·73 %. A certain amount of tar was formed, but the yield was estimated at approximately 50 % of the theoretical.

0·5 g. of ordinary indole-3-aldehyde was heated with 0·7 g. of aniline in a test-tube. The product was crystallised from alcohol and recrystallised from 50 % alcohol. It melted at 122·5°. Majima and Kotake [1925] quote 126–127° as the melting-point of the product made by a different method.

Treatment of the anil with a very slight excess of dilute acetic acid sufficed to liberate the aldehyde.

2-Carbethoxy-7-methylindole-3-aldehyde. The preparation of this substance from 2-carbethoxy-7-methylindole followed exactly the preparation of 2-carbethoxyindole-3-aldehyde as described above. The yield was similar, but a small quantity of another product was obtained which was less soluble in alcohol. This has not been further investigated. After recrystallisation from alcohol the product melted at 189°, and contained 6·09 % N. $C_{13}H_{13}O_3N$ requires N 6·04 %.

2-Carboxy-7-methylindole-3-aldehyde anil. This substance was prepared from the ester-aldehyde (or from the acid-aldehyde) as described for the anil of 2-carboxyindole-3-aldehyde. It melted at 255° with decomposition. The yield was reduced by the formation of an insoluble yellow compound which melted at 245°, and could not be decomposed with acid to regenerate the aldehyde.

7-Methylindole-3-aldehyde anil. The preparation of this substance from the preceding compound by decarboxylation followed closely that of the anil of indole-3-aldehyde. It was also formed by fusing 7-methylindole-3-aldehyde and aniline together as described for the lower homologue. Both preparations melted at 128° and gave the aldehyde on treatment with very slight excess of acetic acid. The anil contained 11·82 % N. $C_{16}H_{14}N_2$ requires N 11·97 %.

2-Methylindole-3-aldehyde (*by the modified Gattermann method*). A mixture of 2-methylindole (15 g.), zinc cyanide (17 g.) and 150 ml. of dry ether was treated with dry hydrochloric acid gas (*cf.* the preparation of 2-carbethoxyindole-3-aldehyde above) first for 2·5 hours at 0° and finally for 30 minutes at 40°. The highly pigmented mass which had separated during the reaction was filtered off, washed several times with ether and then warmed with hot water. Gradually an almost colourless crystalline mass began to separate. After standing some time, this was filtered off and washed several times with water and dried. The dry product was triturated with hot alcohol which dissolved only a fraction of it. While still hot, the mixture was filtered and water was added to the filtrate until crystallisation commenced. When the mixture was cold, the crystals were filtered off and dried. They weighed 3·5 g. They had M.P. 201° (Barger and Ewins give 202–203°) and contained 8·9 % N. This fraction of the product was therefore 2-methylindole-3-aldehyde.

For purposes of purification, the alcohol-insoluble fraction of the product was dissolved in pyridine and reprecipitated with benzene, and was thus obtained almost colourless. M.P. 319°. It contained 10·62 % N. $C_{28}H_{25}N_3$ requires N 10·4 %. These characteristics showed that this fraction was undoubtedly the tri-(methylindolyl)methane obtained originally by Fischer and Pisbor [1923]. Approximately 10 g. of it were obtained by the above procedure.

SUMMARY.

Ellinger's original method of synthesising indole-3-aldehyde has been modified so that an increased yield of the product is obtained in one operation and the necessity of recovering unchanged indole is avoided. Similarly improved yields of 2-methylindole- and 5-methylindole-3-aldehyde have also been obtained by the modified method. Modification of the synthesis of 7-methylindole has led to increased yields of that substance; moreover, the synthesis of 7-methyl-3-aldehyde, which has not been recorded previously, is described. Details are given of an alternative method of synthesising indole-3-aldehyde.

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