142. *Preparation of Certain 3-Substituted Indoles.*

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Indole and indole-2-carboxylic acid are converted by methanolic sodium methoxide at 210—220° into skatole, which may be conveniently prepared in this way.

The scope of these methods of 3-alkylation has been investigated. The carboxylic acid may be used with aliphatic primary alcohols, with benzyl alcohol, and γ-phenylpropyl alcohol, and their sodio-derivatives. β-Phenylethyl alcohol gave a complex mixture from which no pure substance could be isolated and β-ethoxyethyl alcohol and ethylene glycol gave 3-ethylindole. No tryptamine or ketotetrahydro-carboline was obtained from indole-2-carboxylic acid, ethanolamine, and its sodio-derivative under the usual conditions.

Indole-2-carboxylic acid could not be alkylated by means of secondary alcohols and their sodio-derivatives. On the other hand, indole could be converted into 3-*iso*propylindole, and 7-methylindole was transformed into 3-cyclo*hexyl-7-methylindole*.

SKATOLE finds application in the perfumery industry, but none of the numerous methods hitherto available for its preparation is satisfactory from the technical point of view.

Having improved Reissert's synthesis of indole-2-carboxylic acid (*Ber.*, 1897, **30**, 1030) and the decarboxylation of the latter with formation of indole, it occurred to us that skatole (or its carboxylic acid) might be obtainable by a process of direct methylation of these intermediates.

The *C*-methylation of ethyl *o*-nitrophenylpyruvate (Kermack, Perkin, and Robinson, J., 1921, **119**, 1609) was found unpromising on account of the formation of by-products.

When indole-2-carboxylic acid was heated under pressure with methanolic hydrogen chloride, the products were the methyl ester and tar.

In the pyrrole series much use has been made of methylation by means of hot methanolic sodium methoxide (cf., *e.g.*, Fischer and Bartholomäus, *Z. physiol. Chem.*, 1912, **80**, 10, for the conversion of hæmopyrrolecarboxylic acid into phyllopyrrolecarboxylic acid) whereby methyl groups may be introduced in the 2- or the 3-position of the nucleus. The only examples of the application of this method in the indole series are recorded by Oddo and Alberti (*Gazzetta*, 1933, **63**, 236), who made a variety of 3-substituted 2-methylindoles in this way. These authors state that indole itself does not undergo the reaction (methylation) and is recovered unchanged, but do not record the conditions of their experiment in specific terms. Our work was fortunately carried out before this communication was noted and under the conditions we used the yield of skatole from indole was 71%.

We find that indole-2-carboxylic acid is also converted into skatole by methanolic sodium methoxide at 210—220°. The yield is slightly lower in this case, but if indole is made by way of the 2-carboxylic acid, the overall yield of skatole would be considerably improved by taking advantage of the combined methylation and decarboxylation. For this reason we have paid more attention to indole-2-carboxylic acid as the starting point and have obtained in this way : skatole, 3-ethylindole, 3-*propylindole*, 3-n-*butylindole*, 3-n-heptylindole, 3-*benzylindole*, and 3-γ-*phenylpropylindole*. When *iso*propyl alcohol was used, the indole-2-carboxylic acid was recovered unchanged and this indicates that decarboxylation does not precede alkylation in the case of primary alcohols. For if decarboxylation were the first process, there appears to be no reason why it should not occur in *iso*propyl-alcoholic solution, and, if it did occur, the indole would be alkylated. Apparently the 3-substituted indole-2-carboxylic acids should be much more readily decarboxylated than indole-2-carboxylic acid itself. This is not what would be anticipated on theoretical grounds, because the elimination is a cationoid reaction of the sodium salt of the carboxylic acid and alkyl substitution should not facilitate it. A small specimen of 3-methylindole-2-carboxylic acid (Kermack, Perkin, and Robinson, J., 1921, 1634) was available and this was recovered unchanged after being heated in a sealed tube with methanolic sodium methoxide at 210° ; the production of skatole could only be recognised by smell and by the Ehrlich reaction.

An alternative hypothesis is that alkylation and decarboxylation occur simultaneously or nearly so. On this basis one would expect the product to be a 2-substituted indole produced by displacement, and the formation of the 3-derivative can only be explained by the assumption of intramolecular electronic displacements (p. 681),

which as usual are assumed to alternate * until the processes are completed. This is a simplification based on an admittedly erroneous representation of the function of R'ONa. It is presented merely to illustrate the possibility of virtual migration. Probably the aldehyde or ketone corresponding to the alcohol is liberated in a reactive form from the alkoxy-ion and the product of condensation of this with the indole derivative is

Forward stages — *Recovery stages* — (*A.*)
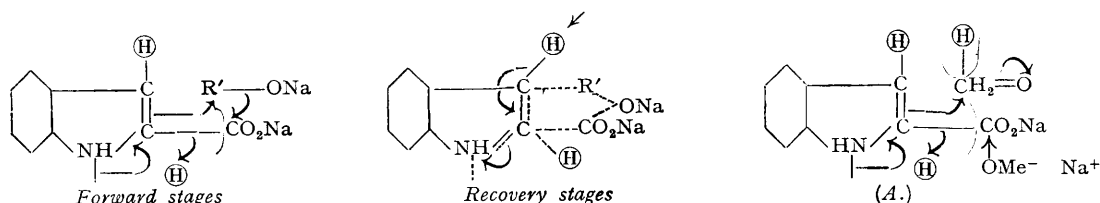
later reduced (cf. the following paper). Thus in the case of methylation the first hypothetical stages can be expressed more accurately by scheme (*A*). Although it is possible to formulate such a process, the elimination and substitution reactions are seen to be distinct and do not collaborate in so far as the displacements are concerned. There may be a general activation of the molecule which exerts a trigger action. A decision between the two hypotheses (*a*) alkylation, followed by decarboxylation, and (*b*) alkylation with virtually simultaneous decarboxylation, cannot yet be made. Included in (*b*) would be the possibility that an intermediate in the process is especially readily decarboxylated.

The methylation of indole itself to skatole shows that there is no tendency for the 2-position to be attacked. Similarly, 7-methylindole afforded 3 : 7-dimethylindole.

Indole, sodium *iso*propoxide and *iso*propyl alcohol reacted with formation of 3-*iso*propylindole and 3-*cyclo*hexyl-7-methylindole was prepared from 7-methylindole, *cyclo*hexanol, and its sodio-derivative. Indole was recovered unchanged after being heated at 210—220° with *tert.*-butyl alcohol and its sodio-derivative.

EXPERIMENTAL.

Indole-2-carboxylic Acid.—*o*-Nitrophenylpyruvic acid was prepared according to Mayer and Balle (*Annalen*, 1914, **403**, 1188). Sodium hydrosulphite (about 230 g.; the amount needed varies with quality) was added to a cold, stirred solution of *o*-nitrophenylpyruvic acid (90 g.) in aqueous sodium hydroxide (20 g. in 700 c.c.) until a test portion no longer became red on the addition of excess of sodium hydroxide; the temperature rose to 40—45°. The cooled solution was acidified with hydrochloric acid (160 c.c., *d* 1·16) and then heated on the steam-bath to expel sulphur dioxide. · The product (45 g. or 64·9%; m. p. 200—202°) was collected by means of ether and so separated from insoluble solid material.

General Method.—Except when stated otherwise, the indole, or derivative, (10 g.) was heated in an autoclave with the alcoholic sodium alkyloxide (from 12 g. of sodium in 150 c.c.) for 12 hours at 210—220°. Where variations are mentioned, the other conditions remained unaltered.

Skatole.—(a) *From indole-2-carboxylic acid.* The solvent was removed by distillation and steam-distillation. Continued steam-distillation gave 5·2 g. (63%) of skatole, m. p. 93° alone or mixed with an authentic specimen. The Ehrlich reaction was identical with that shown by an authentic specimen.

(b) *From indole.* The product was isolated in the same way (8 g., 71%), m. p. 93°.

3-Ethylindole.—Indole-2-carboxylic acid and ethyl alcohol (210 c.c.) were used. The mixture was steam-distilled, and the distillate collected after removal of the alcohol. It was saturated with sodium chloride; the product, isolated by means of ether, had b. p. 150—156°/20 mm. and crystallised in large plates, m. p. 37° (5·6 g., 62%) (Found : C, 82·6; H, 7·6; N, 9·5. Calc. for $C_{10}H_{11}N$: C, 82·8; H, 7·6; N, 9·6%). The Ehrlich reaction (2 g. of *p*-dimethylaminobenzaldehyde in 100 c.c. of alcohol and 25 c.c. of hydrochloric acid, *d* 1·16) was a blood-red coloration in the cold and reddish-purple on boiling. The colours may be alternated by heating and cooling. On continued heating the colour becomes bluer and duller.

The picrate crystallised from benzene–light petroleum (b. p. 60—80°) in red needles, m. p. 121°, and, in agreement with von Braun and Bayer (*Ber.*, 1925, **58**, 391), the same m. p. was found for the picrate of the cyclisation product of *n*-butaldehydephenylhydrazone by means of zinc chloride; a mixture of the specimens had m. p. 121° (Found : N, 14·8%).

On the other hand, Pictet and Duparc (*Ber.*, 1887, **20**, 3416) (reaction of aniline with lactic acid in the presence of zinc chloride) give m. p. 143°; Oddo (*Gazzetta*, 1911, **41**, 232) (ethyl iodide on indolymagnesium iodide) gives m. p. 144·5°; Korczynski, Brydowna, and Kiersck (*ibid.*, 1926, **56**, 905) (Fischer method using nickel chloride) give m. p. 143—144°; Alberti (*ibid.*, 1937, **67**, 238) (sodium ethoxide on 3-acetylindole) gives m. p. 143—144°; all for the picrate of 3-ethylindole. A specimen was prepared by the addition of saturated alcoholic picric acid to a slight excess of pure 3-ethylindole The red needles were collected, washed with light petroleum, and dried in a vacuum, m. p. 120—121° (Found : C, 51·1; H, 4·0. $C_{10}H_{11}N,C_6H_3O_7N_3$ requires C, 51·3; H, 3·7; N, 15·0%). This experiment was performed so as to avoid dissociation by recrystallisation and in order to use a different solvent. It would appear that the substance may exist in two modifications, but we have only encountered that of the lower m. p.

3-n-Propylindole.—This *substance* is mentioned, without any details, in G.P. 38,784 and the same applies to 3-*n*-butyl- and 3-benzyl-indoles. It was obtained from indole-2-carboxylic acid and propyl alcohol (250 c.c.). The product, isolated as in the preceding case, was an almost colourless oil (6·3 g., 64%), b. p. 162—164°/20 mm. (Found : C, 82·8; H, 8·3; N, 8·5. $C_{11}H_{13}N$ requires C, 83·0; H, 8·2; N, 8·8%). The picrate crystallised in red needles, m. p. 113—114°, from benzene–light petroleum (b. p. 60—80°). The Ehrlich reaction was the same as that shown by 3-ethylindole.

3-isoPropylindole.—Under the usual conditions with *iso*propyl alcohol, indole-2-carboxylic acid was recovered unchanged. Indole (5 g.), *iso*propyl alcohol (130 c.c.), and sodium (6 g.) were used. The product was a colourless oil

* I do not concur with Ingold and Hughes (J., 1941, 608), for whom chronology in electronic displacements has ceased to have any meaning. In particular, the argument derived from the " uncertainty " principle is not valid, because it refers to a time-scale altogether finer graded than that applicable to displacements represented by the symbols ⟶ and ⤵. These are assumed to be tangible processes and the conditions resulting from them exist for a definite, though doubtless often very small, period of time. They are the statistical averages of a number of single displacements, to each of which the uncertainty principle can properly be applied. R. R.

(4·3 g., 63%), b. p. 155—160°/20 mm. (Found : C, 82·8; H, 8·4; N, 8·7%). The picrate crystallised in red needles, m. p. 102—103°, and the Ehrlich reaction was normal, but the blood-red colour made its appearance very much more slowly than with 3-propylindole. For comparison 5 c.c. of the reagent were added to one drop of the indole derivative. The substance has previously been prepared from *iso*valeraldehydephenylhydrazone (Trenkler, *Annalen*, 1888, **248**, 106) and the m. p. 98—99° assigned to the picrate.

3-n-*Butylindole*.—Indole-2-carboxylic acid and n-butyl alcohol (250 c.c.) were used. The *product* was a colourless oil (6·6 g., 62%) (Found : C, 82·8; H, 8·7; N, 8·1. $C_{12}H_{15}N$ requires C, 83·2; H, 8·7; N, 8·1%). The picrate crystallised from benzene–light petroleum (b. p. 60—80°) in red needles, m. p. 114°, and the Ehrlich reaction was normal; there was no perceptible slowness of appearance of the coloration as compared with 3-ethylindole.

3-n-*Heptylindole*.—Indole-2-carboxylic acid and n-heptyl alcohol (210 c.c.) were used. The isolated neutral products on distillation afforded unchanged heptyl alcohol (120 g.), a fraction (12 g.), b. p. 165—185°/15 mm., which solidified to a wax (cf. Guerbet, *Compt. rend.*, 1901, **132**, 207, for the products of condensation of heptyl alcohol in the presence of sodium heptoxide at 220°), a fraction (A) (14 g.), b. p. 145—175°/0·3 mm., a fraction, b. p. 175—195°/0·3 mm., and residue. (A) on redistillation gave 6 g., b. p. 155—165°, which solidified. The substance, after two crystallisations from light petroleum (b. p. 60—80°), was obtained in colourless needles, m. p. 60° (Found : C, 83·3; H, 9·8; N, 6·8. Calc. for $C_{15}H_{21}N$: C, 83·7; H, 9·8; N, 6·5%). The Ehrlich reaction was first blood-red and then bluish cherry-red in the cold; on heating, the colour became deeper and similar to that obtained in the preceding cases. The orange picrate dissociated when an attempt was made to crystallise it. 3-n-Heptylindole has been made by Korczynski *et al.* (*loc. cit.*) by the Fischer reaction using nickel chloride as catalyst. It is described as a reddish oil, b. p. 179—182°/3 mm.

3-*Benzylindole*.—Indole-2-carboxylic acid and benzyl alcohol (200 c.c.) were used. Steam-distillation was continued until the oil came over slowly and partly crystallised. The neutral oil remaining in the flask was isolated by means of ether and then solidified. The *substance* crystallised from light petroleum (b. p. 80—100°) in colourless, prismatic needles (8·5 g.; 66%), m. p. 103°. Recrystallisation from the same solvent and then from aqueous alcohol raised the m. p. to 111° (Found : C, 87·0; H, 6·5; N, 6·7. $C_{15}H_{13}N$ requires C, 87·0; H, 6·3; N, 6·6%). With the Ehrlich reagent the coloration appeared very slowly in the cold; on heating, the purplish colour was a shade bluer than with 3-ethylindole. The picrate crystallised from benzene–light petroleum (b. p. 60—80°) in red needles, m. p. 115°. About 40 g. of benzoic acid were produced in the formation process and the odour of benzaldehyde was observed.

3-γ-*Phenylpropylindole*.—Indole-2-carboxylic acid and γ-phenylpropyl alcohol (180 c.c.) were used (time, 14 hours). The neutral products were isolated by means of ether and on distillation gave unchanged phenylpropyl alcohol (60 g.), 35 g. of material, b. p. 160—175°/0·2 mm., and 3·4 g., b. p. 175—180°/0·2 mm. The last solidified and after three re-crystallisations from light petroleum (b. p. 40—60° and later b. p. 60—80°), the *substance* was obtained in colourless needles, m. p. 73° (Found : C, 86·5; H, 7·4; N, 5·9. $C_{17}H_{17}N$ requires C, 86·8; H, 7·2; N, 6·0%). A further 3 g. was obtained by refractionation of the large second fraction. The Ehrlich reaction was normal, but when the hot solution was cooled the colour faded to a bluish-red and not to the original blood-red. The picrate separated from benzene–light petroleum (b. p. 60—80°) in dark red, flat needles, m. p. 116°. β-Phenylpropionic acid (30 g.) was isolated from the aqueous alkaline solution and other products were formed but not further investigated.

3 : 7-*Dimethylindole*.—This was prepared from 7-methylindole, and the product (8 g.; 75%) isolated as in the case of skatole. It crystallised from light petroleum (b. p. 40—60°) in colourless plates, m. p. 56° (Found : C, 82·7; H, 7·7; N, 9·6. Calc. for $C_{10}H_{11}N$: C, 82·8; H, 7·6; N, 9·6%). The Ehrlich reaction was a cherry-red coloration in the cold, greatly intensified on heating, and the picrate crystallised from light petroleum (b. p. 60—80°) in red needles, m. p. 164°. Mendlik and Wibaut (*Rec. Trav. chim.*, 1911, **50**, 109) prepared the substance by the Fischer reaction but describe it as an oil, picrate, m. p. 142—143°.

3-*cycloHexyl-7-methylindole*.—7-Methylindole (5 g.), sodium (6 g.), and *cyclo*hexanol (200 c.c.) were used. The mixture was steam-distilled to remove *cyclo*hexanol; on cooling, the residual oil in the flask partly crystallised. It was taken up in methyl alcohol; on keeping, 3-cyclo*hexyl-7-methylindole* separated in colourless, rhombic plates (5·6 g.; 82%), m. p. 115° (Found : C, 84·7; H, 9·2; N, 6·6. $C_{15}H_{19}N$ requires C, 84·5; H, 8·9; N, 6·6%). The picrate dissociated, even in non-hydroxylic solvents. The Ehrlich reaction was a brownish-red coloration in the cold that made its appearance slowly; on heating, the colour changed to deep reddish-purple.

Miscellaneous Reactions.—Indole-2-carboxylic acid and ethylene glycol (200 c.c.) afforded 4 g. of 3-ethylindole. With the same quantity of β-ethoxyethanol the yield of 3-ethylindole was 5·9 g. Similarly, ethanolamine (200 c.c.) gave rise to the formation of 1·4 g. of basic material, b. p. 180—200°/0·67 mm., but this could not be purified. No better result was obtained with β-diethylaminoethanol. Benzylidenebis-2-methylindole and methyl alcohol (10 hours at 220—230°) furnished 2 : 3-dimethylindole (5·5 g.), separated by steam-distillation. The neutral substances remaining in the flask were isolated by means of ether and after crystallisation from light petroleum (b. p. 60—80°) and from alcohol, furnished stout, colourless prisms, m. p. 119—120° (yield, about 1 g.) (Found : N, 6·6. Calc. for $C_{16}H_{15}N$: N, 6·3%). The substance is evidently 3-benzyl-2-methylindole (Kuroda, *J. Pharm. Soc. Japan*, 1923, **493**, 131; Hushino, *Annalen*, 1932, **500**, 40). The Ehrlich reaction was negative in the cold; on heating, the solution became brownish-green and then dichroic (red and bluish-green); on cooling, the colour faded to pale yellowish-brown. The yield of 2 : 3-dimethylindole was greater than that which could have resulted from a simple fission into benzylmethylindole and methylindole. Therefore both indole nuclei must have been a source of this substance. In confirmation the yield of benzylmethylindole was low.