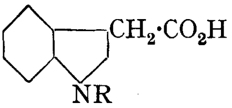
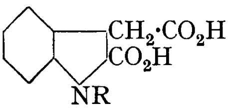
418. *Synthesis of Indoleacetic Acids.*

By Frederick E. King and Philibert L'Ecuyer.

The following experiments were made in connexion with a problem in alkaloid chemistry, and the substances to which the title especially refers are indole-3-acetic acid (I, R = H), synthesised by Ellinger (*Ber.*, 1904, **37**, 1801), its homologue (I, R = Me) (Piccinini, *Chem. Centr.*, 1899, i, 1073), and the corresponding, but unknown, indole-2-acetic acids. For the particular object in view all four compounds are equally suitable, and the choice between them is entirely dependent on their relative ease of preparation. The recorded syntheses being hardly satisfactory, more productive means of obtaining compounds of type (I) had to be found. The most promising of these appeared to be the selective decarboxylation of dibasic acids such as (II, R = H) (cf., *e.g.*, Barrett, Perkin, and Robinson, J., 1929, 2942).


(I.)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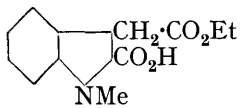
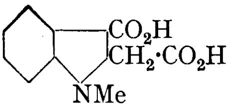

(III.)

The diethyl ester of (II, R = H) was obtained by an application of Fischer's indole synthesis, the requisite hydrazone being made from benzenediazonium chloride and ethyl α-acetylglutarate (Japp–Klingemann reaction). The iodopropionic ester used in preparing the latter was rapidly obtained from ethyl β-chloropropionate and sodium iodide in boiling acetone, whereas Henry (*Compt. rend.*, 1885, **100**, 115) has stated that in alcoholic solution there is no reaction (contrast, however, Baker, J., 1933, 216).

Hydrolysis of the diethyl ester gave an alcohol-insoluble sodium salt and thence the free dibasic acid (II, R = H). This, heated alone or in the presence of a solvent, invariably yielded skatole, but by collecting the carbon dioxide and interrupting the experiment after 1 mol. had been expelled, a small amount of the desired compound (I, R = H) was isolable from the residue of unchanged dicarboxylic acid.

2-*Carboxy*-1-*methylindole*-3-*acetic acid* (II, R = Me) was directly obtained from phenylmethylhydrazine and α-ketoglutaric acid. It was converted at its melting point into 1 : 3-dimethylindole, but cautious heating in quinoline until gas evolution slackened gave an appreciable amount of a compound with the properties recorded by Piccinini (*loc. cit.*) for 1-methylindole-3-acetic acid (I, R = Me). A far better synthesis was discovered, however, during an attempt to esterify the acid (II, R = Me) with alcoholic hydrogen chloride, a sparingly soluble half ester separating. This was identified as *ethyl* 2-*carboxy*-1-*methylindole*-3-*acetate* (III), because on heating above its melting point to expel carbon dioxide, there remained a liquid (*ethyl* 1-*methylindole*-3-*acetate*) which when hydrolysed afforded the acid (I, R = Me). Had the half esterification of (II, R = Me) proceeded in the alternative direction, the product of these reactions would have been the quite different 1 : 3-dimethylindole-2-carboxylic acid already described by Kermack, Perkin, and Robinson (J., 1921, **119**, 1611). Since all the processes involved in the formation of (I, R = Me) give very satisfactory yields, this acid with its interesting synthetical possibilities is now readily available.

Although the immediate problem was thus solved, it was yet considered of interest to study the decarboxylation of 3-*carboxy*-1-*methylindole*-2-*acetic acid* (IV). This was obtained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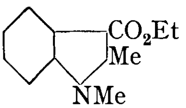
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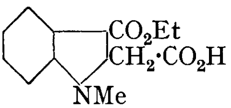
(VI.)

from the phenylmethylhydrazone of ethyl acetonedicarboxylate, which when cyclised with alcoholic hydrogen chloride yielded (IV) as the *diethyl* ester. From this ester, according to the nature of the acid used in isolating the hydrolysis product, either the free acid (IV) or an acid potassium salt was obtained, but from neither substance was it possible to proceed to a monocarboxylic acid.

Under other conditions of hydrolysis a half ester of (IV) was obtained, and by its thermal decomposition to ethyl 1 : 2-dimethylindole-3-carboxylate (V) (Degen, *Annalen*, 1886, **236**, 157) this was shown to be 3-*carbethoxy*-1-*methylindole*-2-*acetic acid* (VI). Owing to a considerable disparity between the melting point of the acid derived from (V) and that recorded for 1 : 2-dimethylindole-3-carboxylic acid, the preparation due to Degen (*loc. cit.*) was repeated by an improved method. The ester and the acid thus obtained were found to be identical with the specimens derived from the new compound (VI).

EXPERIMENTAL.

Ethyl β-*Iodopropionate.*—Acetone (250 c.c.), ethyl β-chloropropionate (50 g.), and anhydrous sodium iodide (70 g.) were heated on a steam-bath, at first for 2 hours under reflux, and then to expel the solvent. From the residue, washed with aqueous sodium thiosulphate, ethyl β-iodopropionate (yields, 80—90%) was isolated by distillation (b. p. 85°/13 mm.).

Ethyl 2-*Carbethoxyindole*-3-*acetate.*—Ethyl α-acetylglutarate (48 g.), prepared from the iodopropionic ester and ethyl sodioacetoacetate (Perkin and Simonsen, J., 1907, **91**, 1740), was dissolved in alcohol (200 c.c.) and aqueous sodium hydroxide (150 c.c. of 20%) below 0°. A solution of benzenediazonium chloride, prepared from aniline (19·5 g.), concentrated hydrochloric acid (61 c.c.), water (105 c.c.), and sodium nitrite (14·2 g.), was immediately added, and the red oil which separated and then solidified on acidification with dilute acid, was collected. After drying over concentrated sulphuric acid, the crude hydrazone (38 g.) was dissolved in absolute alcohol (80 c.c.), and the solution saturated with hydrogen chloride and heated under reflux on a steam-bath for 45 minutes. Water (200 c.c.) precipitated an oil which rapidly solidified, and two crystallisations from small amounts of alcohol (20—25 c.c.) gave ethyl 2-carbethoxyindole-3-acetate (Keimatsu and Sugasawa, *J. Pharm. Soc. Japan*, 1928, **48**, 101) of m. p. 82—84°. The pure indole ester crystallised in long rectangular plates, m. p. 85° (Found : C, 65·2; H, 6·1. Calc. for $C_{15}H_{17}O_4N$: C, 65·4; H, 6·2%).

2-*Carboxyindole*-3-*acetic Acid* (II, R = H) (see Kermack, Perkin, and Robinson, *loc. cit.*, p. 1622).—Sodium hydroxide (9 g.) in water (6 c.c.) and alcohol (40 c.c.) was added to the indole-ester (16 g.) dissolved in alcohol (40 c.c.), and the solution heated under reflux on a steam-bath. Almost immediately a thick white paste of the disodium salt formed, which after 10 minutes was cooled and collected. The crystalline salt, dissolved in water (30 c.c.) and treated with a slight excess of hydrochloric acid, yielded 2-carboxyindole-3-acetic acid (12·5 g.), m. p. 230—235°. Recrystallisation from aqueous alcohol gave colourless, pointed stout prisms, m. p. 236° with loss of carbon dioxide (Found : C, 60·1; H, 4·2. Calc. for $C_{11}H_9O_4N$: C, 60·3; H, 4·1%).

Indole-3-*acetic Acid.*—By careful heating (oil-bath) at its m. p., 2-carboxyindole-3-acetic acid was completely degraded to skatole. Even when solvents (*e.g.*, diphenylamine and quinoline) were used and carbon dioxide was evolved at 195—200°, the result was similar, and so the following procedure was adopted. The acid (1 g.), dissolved in quinoline (5 g.) containing a trace of copper powder, was heated in an oil-bath at 195° until 1 mol. of gas (102 c.c., collected over carbon tetrachloride) had been evolved (1½ hours). The cooled product, dissolved in ether, was shaken with aqueous sodium hydroxide, and the alkaline solution acidified and extracted twice with hot ethyl acetate. The extract was evaporated to dryness, and the crystalline residue boiled with small quantities of benzene (total, 15—20 c.c.), which removed the crude monocarboxylic acid (0·11 g.), m. p. 159—162°, from the unchanged compound (II, R = H) (0·5 g.). Recrystallisation from water (charcoal) and benzene gave indole-3-acetic acid, m. p. 164—165°, in colourless hexagonal plates (Found : C, 68·5; H, 5·1. Calc. for $C_{10}H_9O_2N$: C, 68·6; H, 5·1%).

2-*Carboxy*-1-*methylindole*-3-*acetic Acid* (II, R = Me).—A cooled solution of phenylmethylhydrazine (24 g.) and α-ketoglutaric acid (30 g.) in water (120 c.c.) and acetic acid (30 c.c.) slowly deposited a cream-coloured solid (90% yield), m. p. *ca.* 95° (decomp.). When, however, this mixture was heated on a steam-bath for 30 minutes, darkening occurred, and by cooling and dilution with water (100 c.c.), 2-*carboxy*-1-*methylindole*-3-*acetic acid* (31 g., some accidental loss) was obtained, which crystallised from a moderate volume of acetic acid in colourless prisms, m. p. 234° with loss of carbon dioxide (Found : C, 61·5; H, 4·7; N, 6·1. $C_{12}H_{11}O_4N$ requires C, 61·8; H, 4·7; N, 6·0%). The dicarboxylic acid dissolves but sparingly, being most soluble in alcohol and acetic acid. With boiling alcoholic *p*-dimethylaminobenzaldehyde and concentrated hydrochloric acid (Ehrlich's reagent) it slowly gives a reddish-purple colour, which fades in the cold but is restored by heating, thus recalling the behaviour of the indole (II, R = H) (Kermack, Perkin, and Robinson, *loc. cit.*).

Decarboxylation of 2-*Carboxy*-1-*methylindole*-3-*acetic Acid* (II, R = Me).—(i) When the acid (II, R = Me) was heated at its m. p. under diminished pressure, 1 : 3-dimethylindole (b. p. 130°/12 mm.) distilled (Found : C, 82·8; H, 7·6. Calc. for $C_{10}H_{11}N$: C, 82·8; H, 7·6%). With Ehrlich's reagent this gave the deep colour characteristic of 1 : 3-dialkylated indoles (cf. J., 1933, 271).

(ii) The dicarboxylic acid (1 g.), in quinoline (5 g.) containing a trace of copper powder, was heated in an oil-bath at 195—200° for 1¼ hours. Evolution of carbon dioxide had then slackened, and the solution was cooled and shaken with aqueous sodium hydroxide and ether. The aqueous layer when acidified deposited a reddish solid, which after crystallisation from aqueous alcohol (charcoal) and then petroleum (b. p. 100—120°) gave 1-methylindole-3-acetic acid (0·4 g.), in colourless prisms, m. p. *ca.* 128° (Found : C, 69·7; H, 5·9. Calc. for $C_{11}H_{11}O_2N$: C, 69·8; H, 5·8%). The acid is freely soluble in organic solvents except petroleum, and gives with Ehrlich's reagent only the feeble reaction of the parent dicarboxylic acid (II, R = Me).

Ethyl 2-*Carboxy*-1-*methylindole*-3-*acetate* (III).—A solution of 2-carboxy-1-methylindole-3-acetic acid (21 g.) in absolute alcohol (50 c.c.) was heated on a steam-bath during saturation with hydrogen chloride. Within 15 minutes crystals appeared, the solution rapidly became pasty with the precipitated monoethyl ester, and after 20 minutes water was added. *Ethyl* 2-*carboxy*-1-*methylindole*-3-*acetate* crystallised from a moderate volume of boiling alcohol in voluminous aggregates of colourless slender prisms (18 g.), m. p. 184° with slight effervescence (Found : C, 64·4; H, 5·7. $C_{14}H_{15}O_4N$ requires C, 64·4; H, 5·7%). It dissolves readily in warm aqueous sodium bicarbonate, and is soluble in all the common organic solvents except light petroleum.

Ethyl 1-*Methylindole*-3-*acetate*.—The foregoing dicarboxyindole mono-ester (18 g.) was heated in an open flask by an oil-bath at 190—200°. Evolution of carbon dioxide proceeded smoothly with comparatively little darkening, and pure *ethyl* 1-*methylindole*-3-*acetate* (11·5 g.) was readily obtained as a straw-coloured liquid, b. p. 165°/1 mm., by a single distillation (Found : C, 72·0; H, 6·9. $C_{13}H_{15}O_2N$ requires C, 71·9; H, 6·9%).

1-*Methylindole*-3-*acetic Acid* (I, R = Me).—The ester (2 g.) was hydrolysed by potassium hydroxide (1·2 g.), dissolved in water (2 c.c.) and alcohol (10 c.c.), heated under reflux at 100° for 20 minutes. The solution was then concentrated, and the 1-methylindole-3-acetic acid (1·6 g.) liberated by acidification with dilute acetic acid. When recrystallised, it had m. p. 128°, alone or mixed with a specimen obtained from the acid (II, R = Me).

Ethyl 3-*Carbethoxy*-1-*methylindole*-2-*acetate*.—Phenylmethylhydrazine (5 g.) reacted mildly with acetonedicarboxylic ester (8·7 g.) in an evacuated desiccator, giving a syrupy hydrazone. On passing hydrogen chloride into a solution of this product in alcohol (20 c.c.), a sudden rise of temperature occurred and ammonium chloride separated. When the solution was saturated, water was added, and the precipitated solid (9—10 g.) was dried and crystallised from petroleum (b. p. 60—80°). The *indoledicarboxylic ester* was obtained in magnificent colourless needles, m. p. 90° (Found : C, 66·3; H, 6·8; N, 5·0. $C_{16}H_{19}O_4N$ requires C, 66·4; H, 6·6; N, 4·8%).

3-*Carboxy*-1-*methylindole*-2-*acetic Acid* (IV).—A solution of the foregoing ester (3 g.) in alcohol (22 c.c.) containing potassium hydroxide (2·4 g.) and water (2·5 c.c.), which had been refluxed at 100° for 15 minutes, was concentrated, cooled, and acidified with the minimum amount of dilute hydrochloric acid. The moist, freshly precipitated acid tended to acquire a pink colour, and to avoid such decomposition, the product was at once filtered, washed, and crystallised from aqueous alcohol (80%). The *dicarboxylic acid* was thus obtained in colourless prisms, m. p. 262° with loss of carbon dioxide (Found : C, 61·3; H, 4·7. $C_{12}H_{11}O_4N$ requires C, 61·8; H, 4·7%). With Ehrlich's reagent a persistent deep crimson colour was produced. This exactly matched the colour reaction of 1 : 2-dimethylindole (m. p. 55°), which was obtained on heating the dicarboxylic acid to its m. p. Dissolved in quinoline, the acid lost carbon dioxide at temperatures as low as 130—140°, but even when the heating was stopped after the evolution of 1 mol. of gas, no monocarboxylic acid could be isolated from the product.

By using acetic acid to acidify the solution obtained after hydrolysis of the ester, a white solid was obtained which crystallised from aqueous alcohol (75%) in colourless, long, rectangular leaflets, charring at 320°. This compound, which contained potassium, dissolved in water, giving a solution acid to litmus, and was probably an acid potassium salt. No new acid was obtained by heating this salt under the various conditions already described, and attempts to convert it into a half ester were also unsuccessful.

3-*Carbethoxy*-1-*methylindole*-2-*acetic Acid* (VI).—The dissolution at room temperature of ethyl 3-carbethoxy-1-methylindole-2-acetate (4 g.) in alcohol (30 c.c.) containing potassium hydroxide (3·2 g.) in water (2 c.c.) was rapidly followed by the formation of a white paste of crystals. After an hour, water and a slight excess of hydrochloric acid were added; the solid product (3·5 g.) crystallised from aqueous alcohol in colourless long needles of 3-*carbethoxy*-1-*methylindole*-2-*acetic acid*, m. p. 170° with loss of carbon dioxide (Found : C, 64·1; H, 5·7. $C_{14}H_{15}O_4N$ requires C, 64·4; H, 5·7%).

1 : 2-*Dimethylindole*-3-*carboxylic Acid*.—(i) The foregoing half ester (2·2 g.) was maintained at 180—190° (oil-bath) until carbon dioxide ceased to be evolved. The residue (1·8 g.) immediately solidified on cooling, and by crystallisation from alcohol the compound (V) was obtained

in colourless plates, m. p. 96°. Hydrolysis of this ester by refluxing with a solution of potassium hydroxide (1·5 g.) in water (1·5 c.c.) and alcohol (10 c.c.) occupied at least 30 minutes. 1 : 2-Dimethylindole-3-carboxylic acid was then isolated in the usual way, and when crystallised from moderate volumes of ethyl acetate, separated first in micro-crystalline flocks which later changed to compact square tablets, m. p. 217° with loss of carbon dioxide (Found : C, 69·8; H, 5·8. Calc. for $C_{11}H_{11}O_2N$: C, 69·8; H, 5·9%). Degen (*loc. cit.*) and Angeli and Alessandri (*Chem. Centr.*, 1915, i, 609) give m. p. 185°. Tested with Ehrlich's reagent, the acid gave the deep scarlet colour reminiscent of 1 : 2-dimethylindole.

(ii) A mixture of phenylmethylhydrazine (5 g.) and ethyl acetoacetate (5 g.), after 10 minutes at 100°, was dissolved in alcohol and saturated with hydrogen chloride (cf. Degen's use of zinc chloride). Ammonium chloride then appeared, and, following short heating under reflux, the product was poured into water. The precipitated solid (3·5—4 g.) crystallised from alcohol in colourless plates, m. p. 96°, which on hydrolysis yielded 1 : 2-dimethylindole-3-carboxylic acid, m. p. 217°.

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