1,3,4,5-Tetrahydrobenz[*cd*]indoles and Related Compounds. Part I. A New Synthesis of 3,4-Dihydrobenz[*cd*]indol-5(1*H*)-one (Uhle's Ketone)

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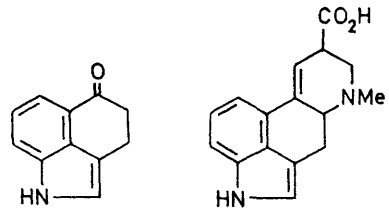
New syntheses of 4-carboxyindole-3-propionic acid (9) starting from 3-amino-4-chlorobenzoic acid are described. A process involving thermal decarboxylation of 2,4-dicarboxyindole-3-propionic acid (8) in aqueous alkali is shown to be suitable for the large-scale preparation of the diacid (9) and thence Uhle's ketone (1).

3,4-DIHYDROBENZ[*cd*]INDOL-5(1*H*)-ONE (1), first obtained by Uhle [1] in 1949 as the result of an eight-stage synthesis from 6-chloro-2-nitrotoluene, contains much of the lysergic acid (2) skeleton and is thus of interest as an intermediate for the preparation of pharmacologically active substances; in addition, as Uhle pointed out, it represents an attractive starting point for the synthesis of lysergic acid itself.

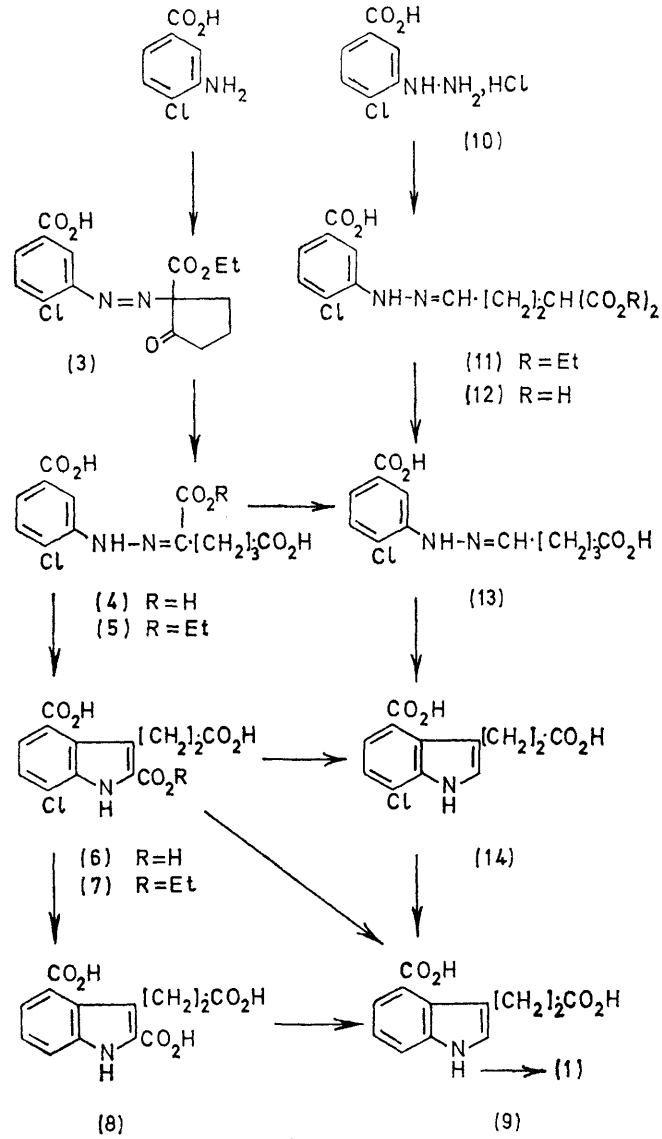


(1) (2)

Although satisfactory for the preparation of small quantities of the ketone (1), the original process and another reported later by Grob *et al.*[2,3] contain at least one stage which would present difficulties on the multi-kilogram scale; more recently Jansen *et al.*[4] have reported its preparation from the readily available corresponding indoline [5] by oxidation with manganese dioxide.

The preliminary stages of the synthesis followed closely some earlier work of Koelsch,[6] except that we started from the appropriate chloroanthranilic acid in order to obtain a single indole isomer on Fischer cyclisation. Thus condensation of 5-carboxy-2-chlorobenzenediazonium chloride with ethyl 2-oxocyclopentanecarboxylate (improved preparation) yielded the azo-compound (3) which could be hydrolysed directly without purification to the hydrazono-triacid (4) or its monoester (5). Both hydrazones furnished in good yield the corresponding indole (6) or (7), from which the chloro-substituent was removed by catalytic reduction in the presence of sodium hydroxide, to give 2,4-dicarboxyindole-3-propionic acid (8). In the laboratory, decarboxylation of the latter proceeded smoothly in boiling 4-methylquinoline to give the required diacid (9), but on a larger scale this reaction proved both unpleasant and capricious and had to be abandoned.

We next attempted to overcome this difficulty by effecting decarboxylation prior to indolisation, and found that the phenylhydrazono-triacid (4) lost carbon dioxide in refluxing dimethylacetamide to yield the



hydrazono-diacid (13) in high yield; the latter was also prepared by condensation of 4-chloro-3-hydrazinobenzoic

[1] F. C. Uhle, *J. Amer. Chem. Soc.*, 1949, **71**, 761.
[2] C. A. Grob and J. Voltz, *Helv. Chim. Acta*, 1950, **33**, 1796.
[3] C. A. Grob and B. Hofer, *Helv. Chim. Acta*, 1952, **35**, 2095.
[4] A. B. A. Jansen, J. M. Johnson, and J. R. Surtees, *J. Chem. Soc.*, 1964, 5573.
[5] E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, and R. B. Woodward, *J. Amer. Chem. Soc.*, 1956, **78**, 3087.
[6] C. F. Koelsch, *J. Org. Chem.*, 1943, **8**, 295.

acid hydrochloride (10) and diethyl (3,3-diethoxypropyl)-malonate in aqueous media to give the diester (11), which was submitted to hydrolysis and decarboxylation in the usual manner.

After a number of experiments, Fischer cyclisation of the hydrazono-diacid (13) to give the chloroindole diacid (14) was achieved by refluxing with dilute sulphuric acid, but again all attempts to carry out this reaction on a larger scale were unsuccessful.

It was not until we discovered that indole-2-carboxylic acids could be smoothly decarboxylated in high yield by heating with aqueous alkali under pressure at 200—240°[7] that this problem could be solved. With the aid of this technique, the most readily accessible intermediate, the indole diacid monoester (7) could be converted in an overall yield of 67% into the required 4-carboxyindole-3-propionic acid (9) in a ' one-pot ' procedure involving firstly, hydrolysis and hydrogenolysis in alkaline solution to remove halogen, followed, after removal of catalyst, by decarboxylation at 240°. An advantage of this route is that the products at each of the three stages of the synthesis separate in a high state of purity and may be used directly without further purification. Conversion of the indole diacid (9) into Uhle's ketone proceeded in reasonable yield.[1]

EXPERIMENTAL

Ethyl 2-Oxocyclopentanecarboxylate.—Absolute ethanol (600 ml) was added slowly to a stirred mixture of sodium hydride (50% oil dispersion; 500 g), toluene (5 l), and dimethylformamide (750 ml). When reaction was complete, the mixture was heated to 80° and diethyl adipate (2·02 kg) was added during 1 h. During and after the addition, ethanol produced was removed as its azeotrope with toluene (b.p. 77°) by distillation through a fractionating column until the vapour temperature rose to 90°. The resulting solution was cooled to 30° and added with stirring to aqueous acetic acid (15%; 6 l). The organic layer was washed with water and distilled to give the keto-ester (1280 g, 82%) as an oil, b.p. 126—130° at 25 mmHg.

Ethyl 1-(5-Carboxy-2-chlorophenylazo)-2-oxocyclopentanecarboxylate (3).—3-Amino-4-chlorobenzoic acid was diazotised and treated with ethyl 2-oxocyclopentanecarboxylate as described by Koelsch [6] to give the *azo-ester* (90%) as yellow plates (from benzene–light petroleum), m.p. 138—139° (Found: C, 53·5; H, 4·5; N, 8·3. $C_{15}H_{15}ClN_2O_5$ requires C, 53·2; H, 4·5; N, 8·3%).

2-Oxohexanedioic Acid (5-Carboxy-2-chlorophenyl)hydrazone (4).—The preceding azo-compound (8·78 g) was added to 2N-sodium hydroxide (55 ml); the mixture was boiled for 2 h, treated with charcoal, and acidified to give the *hydrazone* (8·2 g), which formed cream prisms, m.p. 217—218° (decomp.) (from ethanol) (Found: C, 47·8; H, 4·0; N, 8·4. $C_{13}H_{13}ClN_2O_6$ requires C, 47·5; H, 4·0; N, 8·5%).

1-Ethyl Hydrogen 2-Oxohexanedioate (5-Carboxy-2-chlorophenyl)hydrazone (5).—Water (12 l) and crushed ice (12 kg) were added to a suspension of 3-amino-4-chlorobenzoic acid (5·0 kg) in concentrated hydrochloric acid (6 l) with stirring, and a solution of sodium nitrite (2·05 kg) in water (3 l) was added below the surface during 1 h, with the temperature kept at 0—2° by further addition of ice. Stirring was continued at this temperature for a further 1 h whereupon hydrated sodium acetate (5 kg) was added, followed by ethyl 2-oxocyclopentanecarboxylate (4·55 kg). An oil soon separated which gradually hardened and some 30 min later was removed by filtration. The resulting orange solid was washed with ice–water and added to aqueous acetic acid (80%; 30 l), and the mixture was heated with stirring to 95—100° for 1 h. After cooling, the product (6·6 kg, 63%), m.p. 215—217°, which was sufficiently pure for subsequent experiments, was obtained by filtration and drying. A sample crystallised from aqueous–ethanol (1 : 1) as yellow prismatic *needles*, m.p. 217—218° (Found: C, 50·7; H, 4·4; N, 7·8. $C_{15}H_{17}ClN_2O_6$ requires C, 50·5; H, 4·8; N, 7·9%).

Smaller scale runs gave yields of 80—85%.

2,4-Dicarboxy-7-chloroindole-3-propionic Acid (6).—A stirred suspension of the hydrazone (4) (410 g) in glacial acetic acid (2 l) was heated to reflux temperature and a solution of concentrated sulphuric acid (168 ml) in glacial acetic acid was (350 ml) was added dropwise during 45 min. The mixture refluxed for a further 2 h, cooled, and filtered. The residue was washed with acetic acid (2 × 350 ml) and water (3 × 300 ml) and dried to give the *triacid* (245 g), m.p. 290—294°. A sample crystallised from ethanol had m.p. 297° (Found: C, 49·8; H, 3·3; N, 4·5. $C_{13}H_{10}ClNO_6$ requires C, 50·1; H, 3·2; N, 4·5%).

The triacid was also obtained by alkaline hydrolysis of its monoethyl ester (7).

4-Carboxy-7-chloro-2-ethoxycarbonylindole-3-propionic Acid (7).—Boron trifluoride–acetic acid complex (4·5 l) was added to a suspension of the hydrazone (5) (6·6 kg) in glacial acetic acid (25 l) and the mixture was heated with stirring to 90°, whereupon a vigorous reaction set in, necessitating removal of external heating. When spontaneous refluxing stopped, external heating was applied and the mixture was boiled under reflux for 4 h during which some of the product crystallised out. The cooled mixture was filtered and the solid product was washed with water and dried to give the *indole ester* (5·1 kg, 81%), which crystallised from glacial acetic acid as pale yellow laths, m.p. 259—260° (Found: C, 53·1; H, 4·3; N, 4·3. $C_{15}H_{14}ClNO_6$ requires C, 53·0; H, 4·2; N, 4·1%).

2,4-Dicarboxyindole-3-propionic Acid (8).—A solution of the diacid ester (7) (30 g) in 2N-sodium hydroxide (250 ml) was refluxed for 1 h, cooled and, after addition of 10% palladium–carbon (3 g), shaken in hydrogen at atmospheric pressure until uptake of gas ceased (1960 ml). The mixture was heated to 90°, then filtered, and the partially cooled filtrate (50°) was acidified with 2N-hydrochloric acid (250 ml). Filtration yielded the *indole triacid* (21 g), m.p. 259°, which crystallised from dimethylformamide–water (1 : 8) as a hemihydrate, m.p. 260—261° (Found: C, 54·8; H, 4·6; N, 5·1. $C_{13}H_{11}NO_6,0{\cdot}5H_2O$ requires C, 54·6; H, 4·2; N, 4·9%).

4-Carboxyindole-3-propionic Acid (9).—A solution of the triacid (8) (212 g) in 4-methylquinoline (1 l) was heated to its b.p. during 45 min, kept at that temperature for 1 h, and allowed to cool to room temperature. After dilution with chloroform (1 l), the mixture was extracted succesively with 2N-sodium hydroxide (850 ml) and water (500 ml). Acidification of the combined aqueous extracts followed by extraction with ethyl acetate and evaporation of the organic extract to dryness gave the crude diacid. Crystallisation from water gave a still impure product (131 g), m.p. 172—

[7] R. E. Bowman and P. J. Islip, *Chem. and Ind.*, 1971, 154.

178°. A further crystallisation from water yielded the pure diacid as needles, m.p. 180—181° (lit., 179—181°) (Found: C, 61·6; H, 4·2; N, 6·3. Calc. for $C_{12}H_{11}NO_4$: C, 61·8; H, 4·8; N, 6·0%).

The *diethyl ester*, prepared by the azeotropic method, formed needles (from light petroleum), m.p. 78—79° (Found: C, 66·7; H, 6·5; N, 4·8. $C_{16}H_{19}NO_4$ requires C, 66·4; H, 6·6; N, 4·8%).

4-Chloro-3-hydrazinobenzoic Acid Hydrochloride (10).—The procedure used was exactly as described for the dechloro-compound.[8] The *hydrochloride monohydrate* formed yellow needles (from 6N-hydrochloric acid), m.p. 252° (Found: C, 35·2; H, 4·1; N, 11·8. $C_7H_7ClN_2O_2$, HCl,H_2O requires C, 34·9; H, 4·2; N, 11·6%).

Diethyl (2-Formylethyl)malonate (*5-Carboxy-2-chlorophenyl)hydrazone* (11).—To a solution of the preceding hydrochloride (10 g) in water (150 ml) at 90° was added diethyl (3,3-diethoxypropyl)malonate [9] (9·0 g) with stirring. The mixture was kept at 90° for 10 min. and cooled; the oil which had separated then solidified (11·4 g). The *hydrazone* formed pale yellow cubes (from benzene–light petroleum), m.p. 117—119° (Found: C, 52·9; H, 5·3; N, 7·3. $C_{17}H_{21}ClN_2O_6$ requires C, 53·1; H, 5·5; N, 7·3%).

Glutaraldehydic Acid (*5-Carboxy-2-chlorophenyl)hydrazone* (13).—(a) *From the ester* (11). Hydrolysis with excess of aqueous ethanolic sodium hydroxide and acidification yielded the *malonic acid* (12), pale orange prisms (from aqueous ethanol), m.p. 180° (decomp.) (Found: C, 47·5; H, 4·2; N, 8·8. $C_{13}H_{13}ClN_2O_6$ requires C, 47·5; H, 4·0; N, 8·5%). A solution of the latter (2·5 g) in anhydrous pyridine (25 ml) was refluxed for 1·5 h and evaporated to dryness *in vacuo*. Treatment with excess of 2N-hydrochloric acid furnished the *hydrazono-acid* (1·6 g), pale orange plates (from ethyl acetate), m.p. 174—176° (Found: C, 50·4; H, 4·5; N, 10·0. $C_{12}H_{13}ClN_2O_4$ requires C, 50·6; H, 4·6; N, 9·8%).

(b) *From the hydrazone* (4).—A solution of the triacid (39 g) in dimethylacetamide (300 ml) was refluxed under nitrogen until no further carbon dioxide was evolved (1·5 h) and concentrated to half volume *in vacuo*, the diacid (21 g) then slowly crystallised; m.p. and mixed m.p. 174—176°.

4-Carboxy-7-chloroindole-3-propionic Acid (14).—(*a*) (With P. J. Islip). The hydrazone (13) (46 g) was added to 4·5N-sulphuric acid (700 ml) at 80° with vigorous stirring under nitrogen; the mixture was brought rapidly to reflux temperature and kept at that temperature for 3 h. During the early stages of the reaction (*ca.* 8 min) the orange solid dissolved to give a clear solution; this soon deposited an oil which gradually solidified. The cooled mixture was extracted with ethyl acetate (2 × 200 ml) and the organic extract was washed with water, dried (Na_2SO_4), and concentrated to a small volume. The *chloro-diacid* (18·1 g) separated as needles, m.p. 186—188° (Found: C, 53·6; H, 3·7; N, 5·2. $C_{12}H_{10}ClNO_4$ requires C, 53·8; H, 3·8; N, 5·2%). It formed a *diethyl ester*, needles (from benzene–light petroleum), m.p. 85° (Found: C, 59·2; H, 5·6; Cl, 10·9; N, 4·4. $C_{16}H_{18}ClNO_4$ requires C, 59·4; H, 5·6; Cl, 11·0; N, 4·3%), and on reductive dehalogenation in alkaline media as previously furnished 4-carboxyindole-3-propionic acid (9) in quantitative yield.

(*b*) A solution of the chloro-triacid (6) (8·0 g) in water (200 ml) containing potassium hydroxide (85%; 7·2 g) was heated in a stainless steel autoclave under nitrogen to 240° during 5 h, maintained at the same temperature for 3 h, and allowed to cool overnight. Acidification of the almost colourless solution yielded the same material (6·2 g, 90%), m.p. 185—187°.

4-Carboxyindole-3-propionic Acid (9) (*Preferred Process*).—A solution of the ester diacid (7) (680 g) in water (2·5 l) containing potassium hydroxide (535 g) was refluxed for 2 h. *All* ethanol produced was then removed by distillation. The hot mixture was filtered (charcoal) and the filtrate was shaken in an autoclave in the presence of 10% palladium–carbon (10 g) under 30 atm of hydrogen until uptake of gas ceased. Catalyst was then removed by filtration and the filtrate was heated in a stainless steel autoclave (4 l), after purging with nitrogen, as rapidly as possible to 240° and kept at that temperature for 2 h. The product was allowed to cool overnight. Acidification yielded an oil which solidified rapidly; crystallisation from boiling water furnished the indole diacid (310 g), m.p. 180°.

Uhle's Ketone (1).—A mixture of 4-carboxyindole-3-propionic acid (310 g), acetic anhydride (2·5 l), and anhydrous sodium acetate (13 g) was refluxed for 24 h in the absence of light and then evaporated to dryness *in vacuo*. The brown residual oil was then extracted with hot xylene (1·5 l) and the mixture was filtered through Kieselguhr to remove tar. The filtrate was evaporated to dryness under reduced pressure, and the resulting *N*-acetyl derivative was dissolved in hot ethanol (1 l). 2N-Sodium hydroxide (1200 ml) was added to the cooled solution at such a rate as to maintain the temperature of the reactants at 40°. The mixture was then set aside for 15 min and ethanol was removed *in vacuo*. Filtration yielded the ketone as a yellow-brown solid (124 g), m.p. 161—163°. This material was sufficiently pure for subsequent use but could be purified by crystallisation from boiling toluene or by passage in benzene solution (5%) through a column of alumina; [2] it was obtained either as orange rhombs or pale yellow needles, or as a mixture of both forms,[3] m.p. and mixed m.p.[2] 162—164° (Found: C, 77·2; H, 5·1; N, 8·2. Calc. for $C_{11}H_9NO$: C, 77·2; H, 5·3; N, 8·2%), $\lambda_{max.}$ (EtOH) 205 (ε 21,600), 223 (14,400), 245 (15,600), 325 (4400), and 365 (4500) nm, $\nu_{max.}$ (Nujol) 3185 (NH), 1645 (C=O), and 1610, 1596, and 1491 cm^{-1} (C=C ring system); $\nu_{max.}$ ($CHCl_3$) 3394 and 3233 (NH), 1656 (C=O), 1612, 1598, and 1489 cm^{-1}.

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[8] E. M. F. Stephenson, *Org. Synth.*, 1955, Coll. Vol. III, p. 495.
[9] D. T. Warner and O. A. Moe, *J. Amer. Chem. Soc.*, 1948, **70**, 3470.