SYNTHESSES IN THE CHAULMOOGRIC ACID SERIES

Part III. Synthesis of dl-Hydnocarpic Acid

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In Part I of this series Bokil and Nargund (1937) described a new synthesis of dihydrohydnocarpic acid, requiring fewer steps than those involved in the method of Noller and Adams (1926). On the lines of the methods developed for the syntheses of dihydro derivatives, Noller and Adams (1926) attempted the synthesis of dl-hydnocarpic acid; thus starting with \( \Delta^2 \)-cyclopentene chloride they had prepared the hydroxy compound

\[
\text{CHOH(CH}_2)_5\text{COOCH}_2\text{CHCH}_2
\]

It appears, however, that they did not succeed in eliminating the hydroxy group when they finally declared the subject to have been abandoned (Arvin and Adams, 1928) due to the prior synthesis of dl-chaulmoogric acid by Perkins and Cruz (1927). Finally by converting hydnocarpic acid into chaulmoogric acid, Stanley and Adams (1929) indirectly proved the structure of hydnocarpic acid. In spite of these syntheses, however, the direct synthesis of hydnocarpic acid by a more suitable method was thought to be a sufficiently inviting problem, especially in view of the fact that the excellent methods of syntheses in this series, developed by Adams and his co-workers, seemed to have proved unworkable for its synthesis. Moreover, the above methods, and the method of Perkins and Cruz (loc. cit.) involved the use of a substance (cyclopentadiene) of most uncommon occurrence and—to put it in the words of the latter authors “a substance (\( \Delta^2 \)-cyclopentenyl chloride) of extraordinary reactivity which renders unusual precautions necessary in its preparation and handling,” although it may form an excellent starting material.

The new method for the synthesis of hydnocarpic acid and its homologues, indicated by the present authors in Part I (loc. cit.)—though it depends upon the availability of the required halogen substitution products of fatty acids, as is also the case in Perkins and Cruz’s synthesis—has the added advantage that it avoids the use of \( \Delta^2 \)-cyclopentenyl chloride. The first member of the series—\( \Delta^2 \)-cyclopentenyl carboxylic acid—was synthesised
according to the methods suggested in Part I, and has already been reported in Part II by Bokil and Nargund (1940). It was at first thought possible to synthesise dl-hydnocarpic acid from cyclopentanone-2-ω-undecylic acid or its ester, by similar methods in accordance with the following scheme:

\[
\begin{align*}
&\text{I} \\
&\text{CO} \quad \text{CHCOOR} \\
&\rightarrow \\
&\text{IV} \\
&\text{CHOH} \quad \text{CH(CH}_2\text{)}_{10}\text{COOH}
\end{align*}
\]

Diagram No. 1

The free acid (III) was treated with sodium and alcohol according to the method used by R. Hirst (cf. Rapson and Robinson, 1935) for the reduction of cyclopentanone-2-β-propionic acid. Treatment with phosphorus pentoxide of the resulting product—which could not be purified—gave, however, negative results. A modification of the above method was then tried in which the possibility of the formation of the isomeric product (V) could be avoided, and the double bond could be fixed in the required position in accordance with the following scheme:

\[
\begin{align*}
&\text{II} \\
&\text{CO} \quad \text{C-(CH}_2\text{)}_{10}\text{COOR} \\
&\rightarrow \\
&\text{VII} \\
&\text{CHOH} \quad \text{CH(CH}_2\text{)}_{10}\text{COOH}
\end{align*}
\]

Diagram No. 2

Ethyl cyclopentane-2-one-1-carbethoxy-1-ω-undecylate (II) was treated with large excess of sodium amalgam in aqueous alcoholic solution. As in the first case, the extent of reduction could not be determined because of the nondistillability of the product; hence it was directly treated with phosphorus pentoxide in benzene. From the resulting product, only the keto acid (III—semicarbazone reaction), and a small quantity of a tribasic acid (m.p. 89–90°) were isolated, the latter being identified later, as α-α'-δ-tricarboxy-n-tetradecane (IX). It was, therefore, evident that the keto acid was not reduced to any appreciable extent, it being merely decomposed during subsequent treatment.
The object, however, was finally achieved by a further modification of the above method. The keto ester (II) was decomposed by alcoholic potash (containing the phase \(\text{C}_2\text{H}_5\text{OK}\)) into a tricarboxylic acid—\(\text{a-a'}-\delta\)-tricarboxy-\(n\)-tetradecane (IX), m.p. 92–93°—and the ester of this was cyclised into ethyl cyclopentane-2-one-I-carbethoxy-3-\(\omega\)-undecylate (X—cf. Dieckmann, 1901). This keto ester was reduced with a very large quantity of sodium amalgam in aqueous alcoholic solution, till it gave no bluish violet colour with alcoholic ferric chloride solution. The hydroxy ester (XI) could not be purified; it was hydrolysed and the resulting hydroxy dibasic acid was boiled with acetic anhydride. This yielded, in addition to a small quantity of the tribasic acid (IX), a mixture of unsaturated dibasic acid (XII), and an unsaturated monobasic acid—\(dl\)-hydnocarpic acid (VI), by the simultaneous decarboxylation of the above dicarboxylic acid (cf. Wallach, 1907):

\[
\begin{align*}
\text{COOR} & \quad \text{COOR} \\
\text{C} - \quad \text{(CH}_2\text{)}_{10} \text{COOH} & \quad \text{(CH}_2\text{)}_3 - \text{CH} - \text{(CH}_2\text{)}_{10} \text{COOH} \\
\text{CH CO} & \quad \text{CH(COOR)} \\
\text{COOR} & \quad \text{COOR} \\
\text{CH CH} & \quad \text{CH CH} \\
\text{CH}_2\text{)}_{10} & \quad \text{CH}_2\text{)}_{10}
\end{align*}
\]

Diagram No. 3

The separation of the two unsaturated acids was conveniently effected through their barium salts—the salt of the monobasic acid being soluble in hot alcohol. Power and Barrowcliff (1905) took advantage of the same method in separating active hydnocarpic acid from the rest of the acids. The monobasic acid thus obtained melted at 46–47°. It was at first purified from 80 per cent. alcohol at 0° (m.p. 53–54°) and then recrystallised several times from light petroleum at 10–15°. It now melted at 58–59°, and was identified by the melting point of its mixture with an authentic sample (m.p. 58.5–59.5°—prepared from the "ethyl hydnocarpate oil" of B.D.H quality) which did not change. The amides were also prepared from both the synthetic and the natural active hydnocarpic acids, according to the method of Hinegardner (1933), and identified by mixed melting point. This is in agreement with the observation of Hinegardner (loc. cit.) who racemised active hydnocarpic acid and showed that the \(dl\)-acid (melting point same as that of the active acid) and the active acid do not show a depression in their melting point when mixed together. Their amides also showed the same behaviour.
Ethyl cyclopentane-2-one-1-carbethoxy-1-ω-undecylate (II) was prepared as described in Part I (loc. cit.).

Preparation of the tribasic acid.—α-α′-δ-Tricarboxy-n-tetradecane (IX):—
The above keto ester (35 gm.) was mixed with an alcoholic solution of caustic potash (16 gm. in 10 c.c. water made up to 50 c.c. by absolute alcohol); heat was evolved and the mixture solidified within a minute. It was then heated on water-bath for two hours, alcohol distilled off and the residue evaporated to dryness. A concentrated solution of this in water was extracted with ether and acidified carefully with concentrated hydrochloric acid under cooling; the white precipitate was filtered at the pump and dried without washing. The substance was soluble in water and was found to be an acid potassium salt. For purposes of analysis it was purified by precipitating it from its concentrated solution in water by alcohol. (0.7362 gm. gave 0.1751 gm. K₂SO₄; K = 10.7 per cent. C₁₇H₃₀O₆ K requires K = 10.6 per cent.)

Complete decomposition of the above salt gave a solid acid (yield 25 gm.) which was insoluble in benzene, petroleum ether and chloroform, and soluble in ether, alcohol and ethyl acetate. It separated in the form of white powder from a mixture of ether and petrol—m.p. 92–93° (sintering at 90°). It also crystallises from dilute ethyl alcohol (about 30 per cent. strength) in the form of fine short silky needles—m.p. 92–93°. (Found: C, 61.5; H, 9.1 per cent.; Equit. wt., 110.5; C₁₇H₃₀O₆ requires C, 61.9; H, 9.1 per cent.; Equit. wt., 110.)

Preparation of the triester.—The usual Fischer Speier method of esterification gave a low yield of the triester; it was therefore, prepared by the silver salt method—a thick colourless liquid which distilled between 250–60°/5 mm. Comparatively a large amount of the ester gets decomposed during distillation; 37 gm. of the acid yielded 28 gm. of the purified ester, i.e., 65 per cent. of the theory. (Found: C, 66.3; H, 10.4 per cent.; C₂₃H₄₂O₆ requires C, 66.7; H, 10.1 per cent.)

Cyclisation of the above triester—formation of ethyl cyclopentane-2-one-1-carbethoxy-3-ω-undecylate (X).—Finely powdered sodium (2.6 gm.) was placed in 100 c.c. dry benzene in a flask fitted with a reflux condenser; the triester (41.4 gm.) was added and the mixture heated on a boiling water bath for an hour and a half, when a yellowish-red, transparent jelly-like mass of the sodium salt separated. To complete the reaction the mixture was heated further for five hours, cooled and decomposed by ice-cold 10 per cent. hydrochloric acid solution. Benzene layer was washed, dried
and the solvent removed—yield 36.5 gms. It gave an intense bluish-violet colouration with alcoholic ferric chloride. It could not be distilled even at very low pressure (2 mm.); only low boiling portions were distilled off up to 200°. The dark red liquid in the flask was taken up with ether to remove some sediment collected at the bottom, and ether removed—yield 26 gm. It gave a semicarbazone crystallising from alcohol in white flocculent powder—m.p. 146-47° (clear at 150°). (0.2123 gm. gave 17.1 c.c. of \( \text{N}_2 \) at 30° and 758 mm. pressure. Found: N, 10.1 per cent.; \( \text{C}_{22}\text{H}_{39}\text{O}_{5}\text{N}_{3} \) requires N, 9.9 per cent.)

_Reduction of the above ester._—The ester in lots of 5 gm. each in 60 c.c. of alcohol and 15 c.c. of water, was treated with 225 gm. of 4 per cent. sodium amalgam in a strong current of carbon dioxide during 24 hours; then it gave no colouration when tested with alcoholic ferric chloride. Alcohol was then removed and the substance recovered; yield 18 gm. from 25 gm. of the keto ester. It could not be purified by distillation even under reduced pressure.

_Hydrolysis of the hydroxy ester_ by methyl alcoholic potassium hydroxide was carried out in the usual manner. The acid recovered (yield 14 gm.) was used for dehydration without further purification.

_Dehydration of the above hydroxy dibasic acid._—The acid (13 gm.) was mixed with acetic anhydride (22 c.c.) and the mixture gently boiled on a sand-bath for three hours. Water was then added, steam-distilled to remove acetic acid and the substance recovered by ether—yield 12 gm., a thick dark brown liquid which quickly decolourised bromine in chloroform. Titration of the crude product (equivalent weight = 175) indicated that the original crude acid mixture may contain about 25 per cent. of dl-hydnocarpic acid. The crude acid mixture was dissolved in alcohol (100 c.c.) and neutralised by a saturated solution of barium hydroxide (litmus reaction). This was heated on water-bath and the insoluble salt separated (A). The alcoholic solution was concentrated on water-bath to 50 c.c. and the flocculent precipitate obtained on cooling was separated and dried (B). 10.5 gm. of the dehydrated product yielded 5 gm. of soluble salt (B), and 11.5 gm. of the insoluble salt (A).

_Isolation of the dl-hydnocarpic acid from B (VI)._—The acid recovered in the usual way by decomposing the barium salt (5 gm.) was a pale yellow sticky solid, m.p. 46-47°—yield 3.5 gm. It was first treated with light petroleum to remove the slight quantity of unsaturated dibasic acid it contained—the dibasic acid is insoluble in petrol. The recovered acid was converted into methyl ester and distilled, b.p. 175-80° at 8-9 mm. Shriner
and Adams (1925) give the boiling point of methyl dextro hydnocarpate as 182-83° at 10 mm. The ester was hydrolysed and the acid recovered was crystallised first from 80 per cent. alcohol at 0° (keeping overnight) when it melted at 53–54°. It was then twice recrystallised from light petroleum (b.p. 40-60°) at 10–15° when it had m.p. 58–59°. (Found: C, 76.5; H, 11.0 per cent.; Equit. wt., 251.4; Calculated for C\textsubscript{16}H\textsubscript{28}O\textsubscript{2}, C, 76.2; H, 11.1 per cent.; Equit. wt., 252. Found: iodine number (Hanus) = 99.1; Theoretical value = 100.7.)

The amide of the above acid—prepared by the method of Hinegardner (1933)—was crystallised from petrol and melted at 109–110°.

Isolation of (3-carboxy-Δ²-cyclopentenyl-1-)ω-undecylic acid (XII).—The insoluble barium salt (11.5 gm.) was decomposed with hydrochloric acid and the acid recovered in the usual manner, when it was obtained as a brown sticky solid (5 gm.). Its equivalent weight indicated it to be a mixture. It was soluble in alcohol, ether, acetic acid and ethyl acetate, but insoluble in benzene and petrol. It gave turbid solution in chloroform. The whole of it was treated with chloroform and filtered from a small amount of insoluble substance which was identified as a-a'-δ-tricarboxy-n-tetradecane by mixed m.p. The substance recovered from chloroform was converted into the ethyl ester and distilled—b.p. 240–70° at 6–7 mm., D\textsubscript{4}\textsuperscript{26} = 0.9897 N\textsubscript{D}\textsuperscript{26} = 1.45247. The acid obtained by hydrolysing the above ester crystallised in colourless granules from a mixture of petrol and ether, m.p. 82–83° (sintering at 79°). It did not decolourise Br\textsubscript{2} in CHCl\textsubscript{3}. (Found: C, 68.6; H, 9.5 per cent.; Equit. wt., 147.2; C\textsubscript{17}H\textsubscript{28}O\textsubscript{4} requires C, 68.9; H, 9.4 per cent.; Equit. wt., 148.)

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Summary

1. Synthesis of dl-hydnocarpic acid has been effected for the first time and described.

2. The method developed for its synthesis is a simple one and capable of being used as a general method for the synthesis of compounds containing Δ\textsuperscript{2}-cyclic groups.
## Syntheses in the Chaulmoogric Acid Series—III

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