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SYNTHESIS OF 1,3-DIMETHYL-1,3-DICARBOXYCYCLOHEXANE-2-ACETIC ACID

AN ISOMER OF THE DEGRADATION PRODUCT OF ABIETIC ACID[1]

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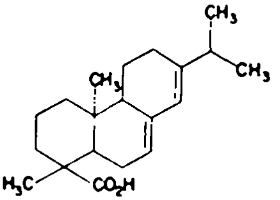
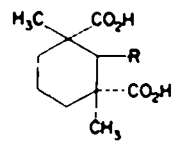
Abstract—A synthesis of 1,3-dimethyl-1,3-dicarboxycyclohexane-2-acetic acid has been described, and proved to be an isomer of the C_{12}-acid—an oxidative degradation product of abietic acid.

Abietic acid (I) yields two optically inactive homologous tricarboxylic acids,[2-5] $C_{11}H_{16}O_6$ (II) and $C_{12}H_{18}O_6$ (III), on energetic oxidation with potassium permanganate or vigorous ozonolysis[6,7] and oxidation with nitric acid.[8] The stereochemistry of the C_{11}- and C_{12}-acids has played a very important part in determining the configuration of ring A and B of abietic acid (I) and related resin acids. Barton and Schmeidler[5] assigned the *trans-meso* configuration to these acids (II and III) on the basis of the thermodynamic dissociation constant and optical inactivity.[9]



I



II, R = CO_2H
III, R = CH_2CO_2H

Although various attempts to synthesize the C_{12}-acid have been recorded,[10,11] final confirmation of its structure by synthesis still remains to be achieved. The

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[1] Abstracted from the Ph.D. Thesis (Utkal, 1957) of S. N. Mahapatra and presented at the Golden Jubilee Symposium on Terpenoids held at the Indian Institute of Science, Bangalore, October (1959).
[2] L. Ruzicka and H. Waldmann, *Helv. Chim. Acta* **16**, 842 (1933).
[3] F. Vocke, *Liebigs Ann.* **497**, 247 (1932).
[4] H. N. Rydon, *J. Chem. Soc.* 257 (1937).
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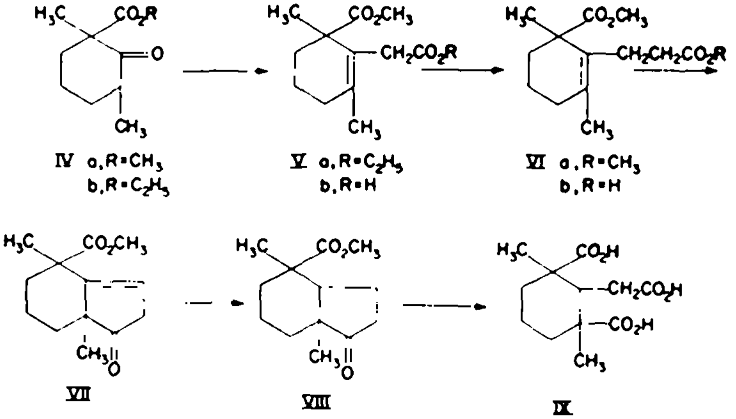
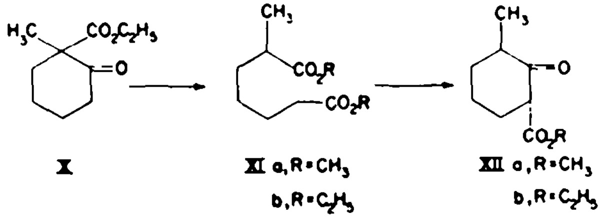
[6] L. Ruzicka, J. Meyer and M. Pfeiffer, *Helv. Chim. Acta* **8**, 637 (1925).
[7] L. Ruzicka, M. W. Goldberg, H. W. Huyser and C. F. Seidel, *Helv. Chim. Acta* **14**, 545 (1931).
[8] P. Levy, *Ber. Dtsch. Chem. Ges.* **62**, 2497 (1929).
[9] L. Ruzicka and L. Sternbach, *Helv. Chim. Acta* **21**, 565 (1938).
[10] S. M. Mukherjee, *J. Ind. Chem. Soc.* **24**, 495 (1947).
[11] P. N. Rao and P. Bagchi, *Sci. & Cult.* **19**, 507 (1954); *J. Org. Chem.* **23**, 169 (1958).



present paper deals with an investigation on the synthesis of the C_{12}-acid by the method outlined below.

Methyl 2,6-dimethylcyclohexanone-2-carboxylate (IVa) was employed as the starting material. The corresponding ethyl ester (IVb) was first prepared by Ruzicka *et al.*[12] and later by Haworth and Barker[13] by methylation of ethyl 6-methylcyclo-



hexanone-2-carboxylate (XIIb), the latter being prepared by the method of Kotz *et al.*[14] In the present investigation a different procedure, as outlined below, was adopted for the preparation of XIIa. Ethyl 2-methylcyclohexanone-2-carboxylate[15] (X) on treatment with sodium ethoxide yielded diethyl α-methylpimelate[16] (XIb), contaminated with presumably the β-keto ester (XIIb) giving colour with alcoholic ferric chloride. As it was not possible to separate the two by fractional distillation, the crude product was treated with 10 per cent aqueous methanolic potassium hydroxide with the expectation that, besides saponification, the contaminating β-keto ester would undergo ketonic fission by this treatment. The resulting acidic material was esterified to yield the pure dimethyl α-methylpimelate (XIa) in 60 per cent overall yield. Dieckmann cyclization of XIa, using sodium dust, furnished methyl 6-methylcyclohexanon-2-carboxylate (XIIa) in 45 per cent yield; the use of sodium hydride increased the yield to 90 per cent. The β-keto ester (XIIa) was methylated with sodium dust and methyl iodide in benzene to give methyl 2,6-dimethylcyclohexanone-2-carboxylate (IVa) in 95 per cent yield.

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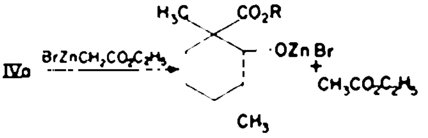
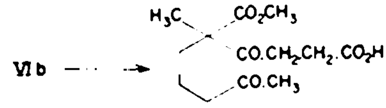
[16] W. Dieckmann, *Ber. Dtsch. Chem. Ges.* **33**, 2670 (1900).

The keto ester (IVa) was subjected to Reformatsky reaction using equivalent quantities of ethyl bromoacetate and zinc wool in presence of a crystal of iodine. After decomposition of the resulting complex the crude condensation product was obtained in 30 per cent yield, and 60 per cent of the keto ester (IVa) was recovered. Use of larger quantities[17] of ethyl bromoacetate and zinc did not have any appreciable effect on the yield. This was probably due to the simultaneous formation of an enolate complex (XIII), analogous to the observation of Newman[18]. Hence, it was found expedient to use equimolecular proportions of the reactants and repeat the experiment several times with the recovered keto ester. The crude condensation product was dehydrated using thionyl chloride and pyridine to yield ethyl 2,6-dimethyl-6-carbomethoxycyclohexene-1-acetate (Va) in 68 per cent yield. The dehydrated product consisted mainly of the β,γ-isomer (Va), indicated by the absence of the characteristic ultra-violet absorption maximum of the acrylic ester system.[19] The unsaturated diester (Va) was partially saponified by treatment with one equivalent of 10 per cent aqueous methanolic potassium hydroxide to yield 2,6-dimethyl-6-carbomethoxycyclohexene-1-acetic acid (Vb). The acid chloride, obtained from Vb by treatment with oxalyl chloride,[20] was converted into methyl 2,6-dimethyl-6-carbomethoxycyclohexene-1-β-propionate (VIa) in 50 per cent yield by treatment with diazomethane[21] followed by Wolff rearrangement[22] of the crude diazoketone. The diester (VIa), thus obtained, was partially saponified to give 2,6-dimethyl-6-carbomethoxycyclohexene-1-β-propionic acid (VIb). Evidence for the γ,δ-ethylenic linkage in 2,6-dimethyl-6-carbomethoxycyclohexane-1-β-propionic acid (VIb) was provided by ozonolysis[23] of VIb-which yielded a diketo acid (XIV) identified through its bis-2,4-dinitrophenylhydra, zone. In this reaction no neutral aldehydic or ketoester could be detected indicating the absence of β,γ- or α,β-ethylenic linkage. Cyclization of the homologous ester acid (VIb) was carried out with phosphorus pentoxide[24] in refluxing benzene to yield 4,8-dimethyl-4-carbomethoxy-Δ^3-hydrindene-1-one (VII) in 40 per cent yield. The unsaturated keto ester (VII) did not show any ultra-violet absorption maximum



XIII



XIV

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characteristic of Δ^2-cyclopentenone derivative[25] and hence was assigned the structure VII. Catalytic reduction of VII yielded 4,8-dimethyl-4-carbomethoxy-hydrindane-1-one (VIII) as a colourless mobile oil. Barton[26] had shown that among 1,2,2,6,6-pentasubstituted derivatives of cyclohexanes the axial substituent at C_1 is less hindered than the equatorial substituent, and assuming that the heavier carbomethoxyl group was equatorial and the methyl group axial we considered that the hydrogen might approach from the less hindered[27] axial side giving a *trans*-hydrindanone derivative. On the other hand, on account of hindrance due to the axial methyl groups,[28] the hydrogen might approach from the equatorial side leading to a *cis*-hydrindanone ring system. Consequently, the triacid (IX), obtainable by oxidation of the reduced keto ester (VIII), could be either *trans–meso* or *cis–meso* or a mixture of the two depending on the mode of hydrogenation of the unsaturated keto ester (VII). The saturated keto ester (VIII) was condensed with ethyl formate to yield the corresponding hydroxymethylene derivative which was oxidized[29] in the crude state with hydrogen peroxide to yield 1,3-dimethyl-1-carbomethoxy-3-carboxycyclohexane-2-acetic acid, and this was directly saponified[30] with 25 per cent aqueous methanolic potassium hydroxide to give 1,3-dimethyl-1,3-dicarboxycyclohexane-2-acetic acid (IX) as a solid. It was crystallized from acetone to give clusters of very fine needles, m.p. 212–213°(d). The mixed melting point, however, was depressed by 8° on admixture with the C_{12}-acid, m.p. 212–213°, obtained by the degradation of abietic acid,[5,8] thus indicating the synthetic acid to be a stereoisomer having, presumably, a *cis–meso* configuration. Rao and Bagchi[11] also obtained an isomer melting at the same temperature, which is in all probability identical with our product.

EXPERIMENTAL*

Dimethyl α-methylpimelate (XIa). Ethyl 2-methylcyclohexanone-2-carboxylate[15] (X, 184 g) and a solution of sodium ethoxide, prepared from sodium (4·6 g) and ethanol (58 ml), were heated for 4 hr on a steam bath. To the reaction mixture, which gave ferric chloride colouration, was added 10% aqueous methanolic KOH (2 l.) and the mixture was refluxed for 5 hr. The methanol was removed under reduced press and the aqueous solution of the residue, after one extraction with ether, was acidified with cold dil HCl. The oily product was extracted with ether, and the ether extract was washed with water and dried (Na_2SO_4). After removal of the solvent, the crude acidic product was esterified by refluxing for 72 hr with methanol (900 ml) containing conc H_2SO_4 (90 ml). The cooled reaction mixture was poured into ice cold brine and worked up by extraction with ether in the usual way. Removal of the solvent and distillation of the residue *in vacuo* furnished XIa (120 g, 60%), b.p. 98–100° (1 mm), n_D^{27} 1·4320. (Found: C, 59·30; H, 8·83. $C_{10}H_{18}O_4$ requires: C, 59·40; H 8·91%).

Methyl 6-methylcyclohexanone-2-carboxylate (XIIa). A small portion (ca. 10 g) of dimethyl α-methylpimelate (XIa, 107 g) was added to refluxing benzene (500 ml) suspension of sodium hydride (23 g) in an atmosphere of nitrogen. After the reaction started (ca. 30 min), the rest of the diester was slowly added and the refluxing continued for 4 hr. The cooled reaction mixture was decomposed with an excess of cold dil HCl under nitrogen. The organic layer was separated and washed

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* All m.ps and b.ps are uncorrected, and all ultra-violet measurements were taken in 95% ethanol with a Beckmann Quartz Ultra-violet Spectrophotometer, Model DU.

[25] W. M. Schubert and W. A. Sweeny, *J. Amer. Chem. Soc.* 77, 2297 (1955).

[26] D. H. R. Barton, *Chem. & Ind.* 664 (1953); *J. Chem. Soc.* 1027 (1953).

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[30] F. E. King, T. J. King and J. G. Topliss, *Chem. & Ind.* 113 (1956).

successively with water, ice cold aqueous $NaHCO_3$, and water. The solvent was removed and the residue distilled to give XIIa (82 g, 90%), b.p. 65–68° (1 mm), n_D^{28} 1·4768. (Found: C, 63·51; H, 8·35. $C_9H_{14}O_3$ requires: C, 63·53; H, 8·23%).

When the aforementioned reaction was carried out using sodium dust the β-keto ester (XIIa) was obtained in 45% yield.

Methyl 2,6-dimethylcyclohexanone-2-carboxylate (IVa). Methyl 6-methylcyclohexanone-2-carboxylate (XIIa, 162 g) was slowly added to an ice cold suspension of sodium dust (23·06 g) in dry benzene (1 l.) and allowed to stand overnight. To the sodio derivative thus formed was added methyl iodide (150 ml), and the mixture was refluxed till it did not give any colour with alcoholic ferric chloride (ca. 6 hr). It was poured into water and the benzene layer was separated. The aqueous layer was extracted with ether and the combined ether–benzene mixture was washed with water and dried (Na_2SO_4). The solvent was removed and the residue distilled to yield IVa (165 g, 95%), b.p. 81–82° (1 mm), n_D^{24} 1·4571. (Found: C, 65·25; H, 8·59. $C_{10}H_{16}O_3$ requires: C, 65·22; H, 8·69%).

Ethyl 2,6-dimethyl-6-carbomethoxycyclohexene-1-acetate (Va). A solution of methyl 2,6-dimethylcyclohexanone-2-carboxylate (IVa, 60 g) and ethyl bromoacetate (56 g) in thiophene-free dry benzene (200 ml) was slowly distilled until about 30 ml of benzene was collected to remove the last traces of moisture. This was cooled to the room temp with protection from moisture and zinc wool[21] (22 g) and a crystal of iodine were added. On heating the mixture on a steam bath an exothermic reaction ensued, and the vigour of the reaction was maintained as far as practicable by continuing the heating. Subsequently the reflux was continued for 4 hr. The cooled reaction mixture was decomposed with ice-cold dil H_2SO_4. The benzene solution was separated and the aqueous layer was extracted with ether benzene mixture. The combined ether-benzene extract was washed successively with water, ice-cold dil NH_4OH and finally with water. After drying (Na_2SO_4) the solvent was removed. The residue was distilled to recover the starting keto ester (IVa, 43 g), and the crude condensation product weighed 20 g. The aforementioned Reformatsky reaction was repeated 3 times using the recovered keto ester from each experiment, thus yielding a total quantity of 36 g of the crude condensation product. To a vigorously stirred, cooled (0°) solution of the aforementioned condensation product and pyridine (21 g) in dry ether (100 ml) was added thionyl chloride (10 ml) over a period of 1 hr, the temp being kept below 5°. The reaction mixture was left overnight at room temp. The ethereal layer was decanted off and the dark residue after repeated washing with dry ether was diluted with a large volume of water, filtered from the slimy residue, and worked up by extraction with ether in the usual manner. The solvent was removed on a steam bath and finally under reduced press. The residue was taken up in dry benzene (100 ml) and refluxed for 5 hr with freshly precipitated copper to remove the contaminating sulphur. After removal of the benzene from the filtered solution, the residue was distilled to yield Va (23 g, 68%), b.p. 115–118° (1 mm), n_D^{26} 1·4753. (Found: C, 66·08; H, 8·63. $C_{14}H_{22}O_4$ requires: C, 66·15; H, 8·68%).

2,6-*Dimethyl-6-carbomethoxycyclohexene-1-acetic acid* (Vb). Ethyl 2,6-dimethyl-6-carbomethoxycyclohexene-1-acetate (Va, 13 g) was refluxed for 4 hr with aqueous methanolic KOH (31 ml, 1·624 N). The methanol was removed under reduced press and the residue was dissolved in water. The aqueous solution, after one extraction with ether, was acidified with cold dil HCl. The oily product was extracted with ether and the extract washed with water and dried (Na_2SO_4). After removal of the solvent, the product was distilled, b.p. 155–160° (0·5 mm), to yield an oil which subsequently solidified. It was crystallized from acetone to furnish Vb (8 g, 69%), m.p. 123–124·5° (Found: C, 63·66; H, 7·95. $C_{12}H_{18}O_4$ requires: C, 63·72; H, 7·96%).

The *S-benzylthiuronium salt* of Vb crystallized from dil ethanol, m.p. 129–130° (Found: N, 7·20. $C_{20}H_{28}N_2O_4S$ requires: N, 7·14%).

Methyl 2,6-dimethyl-6-carbomethoxycyclohexene-1-β-propionate (VIa). To an ice-cold solution of 2,6-dimethyl-6-carbomethoxycyclohexene-1-acetic acid (Vb, 10 g) in dry benzene was added oxalyl chloride[22] (9 ml). After keeping at room temp for 4 hr, the mixture was warmed for 10 min at 45°. The benzene along with excess of oxalyl chloride were removed under reduced press. Fresh dry benzene (10 ml) was added and distilled off under *vacuo* to remove the last traces of oxalyl chloride. A solution of the crude acid chloride (10 g) in dry ether (50 ml) was added to a cold (0°) anhydrous ethereal solution of CH_2N_2, prepared from nitrosomethyl urea[23] (23 g), with stirring over a period of

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[22] H. Staudinger, *Ber. Dtsch. Chem. Ges.* **41**, 3558 (1908).

[23] F. Arndt, *Org. Syntheses* Vol. II, p. 165 (1950).

1 hr, when the evolution of nitrogen stopped. The solvent and excess of CH_2N_2 were removed under reduced press at room temp to yield the oily diazo ketone (12 g).

To a warm (50°), stirred solution of the crude diazo ketone (12 g) in absolute methanol (300 ml) was added in 3 lots a slurry of silver oxide in methanol, obtained from 10% aqueous $AgNO_3$ (50 ml). The mixture was refluxed for 2 hr, and after boiling with norite was filtered. The alcohol was removed under reduced press and the residue was distilled to yield VIa (5 g, 50%), b.p. 125–130° (1 mm), n_D^{22} 1·4820. (Found: C, 66·36; H, 8·66. $C_{14}H_{22}O_4$ requires: C, 66·15; H, 8·68%).

2,6-*Dimethyl-6-carbomethoxycyclohexene*-1-*β-propionic acid* (VIb). Methyl 2,6-dimethyl-6-carbomethoxycyclohexene-1-β-propionate (VIa, 8 g) was partially saponified as before by refluxing with 10% aqueous methanolic KOH (18 ml, 1·624 N) for 4 hr and worked up as usual to yield VIb (5 g, 76%). It was crystallized from acetone, m.p. 143 144·5°. (Found: C, 64·98; H, 8·23. $C_{13}H_{20}O_4$ requires: 65·00; H, 8·33%).

The S-*benzylthiuronium salt* of VIb crystallized from dil ethanol, m.p. 141–142°. (Found: N, 7·03. $C_{21}H_{30}N_2O_4S$ requires: N, 6·89%).

Ozonolysis of 2,6-*dimethyl-6-carbomethoxycyclohexene*-1-*β-propionic acid* (VIb). To a cooled (0°) solution of the unsaturated ester acid (VIb, 0·2 g) in carbon tetrachloride (50 ml) was passed a current of ozonized oxygen for 30 min. The solvent was removed and the residue was heated for 15 min on a steam bath with a mixture of zinc dust (0·4 g), water (15 ml), and acetic acid (0·7 ml). The reaction mixture was extracted with ether and the ethereal solution was extracted thoroughly with 5% ice-cold NaOH. The acidic material was isolated as an oil by acidification of the alkaline extract followed by extraction with ether and was converted to the *bis*-2,4-*dinitrophenylhydrazone* of 5-carbomethoxy-4,9-dioxo-5-methyldecanoic acid (XIV) by the usual method. It was crystallized from alcohol, m.p. 185–186°. (Found: N, 17·70. $C_{25}H_{28}N_8O_{12}$ requires: N, 17·72%).

On removal of the ether from the neutral fraction no product could be isolated.

4,8-*Dimethyl-4-carbomethoxy-Δ^8-hydrindene*-1-*one* (VII). To a vigorously stirred, refluxing solution of P_2O_5 (20 g) in benzene (100 ml) was added a solution of 2,6-dimethyl-6-carbomethoxycyclohexene-1-β-propionic acid (VIb, 3 g) in dry benzene (80 ml) over a period of 30 min, and the refluxing was continued for 3 hr. The reaction mixture was cooled and the benzene was decanted off. The dark residue after repeated washing with benzene, was decomposed with powdered ice, diluted with a large volume of water, filtered from the slimy residue, and extracted with ether. The combined ether benzene extract was washed successively with water, 10% aqueous NaOH, water, and dried (Na_2SO_4). The solvent was removed and the residue distilled to furnish VII (1·2 g, 43%), b.p. 100–105° (0·6 mm), n_D^{22} 1·4830. (Found: C, 70·70; H, 8·40. $C_{13}H_{18}O_3$ requires: C, 70·26; H, 8·10%).

4,8-*Dimethyl-4-carbomethoxyhydrindane*-1-*one* (VIII). A solution of the aforementioned unsaturated keto ester (VII, 1·2 g) in ethanol (15 ml) was hydrogenated with prereduced platinum oxide catalyst (0·1 g). After absorption of the calculated quantity of hydrogen (ca. 24 hr) the catalyst was removed by filtration followed by the removal of the solvent. The residue was purified by shortpath distillation to yield VIII (1 g, 83%), 110 115° (bath temp) (1 mm), n_D^{22} 1·4685. (Found: C, 69·60; H, 8·99. $C_{13}H_{20}O_3$ requires: C, 69·65; H, 8·93%).

1,3-*Dimethyl*-1,3-*dicarboxycyclohexane-2-acetic acid* (IX). To a vigorously stirred ice-cold suspension of sodium ethoxide in dry benzene, prepared from sodium (0·2 g) and absolute ethanol (0·4 g), was added ethyl formate (1 g) under nitrogen. After 30 min a solution of the saturated ketone (VIII, 1 g) in dry benzene (10 ml) was added, and the mixture was left overnight at room temp. After adding ice-cold water to the cooled reaction mixture, the aqueous layer was separated and the benzene layer was thoroughly extracted with 2% ice-cold aqueous NaOH. The combined aqueous solution, after one extraction with ether, was acidified with ice-cold dil HCl. The resulting oily suspension was extracted with ether and the crude hydroxymethylene ketone (0·8 g), obtained after removal of the solvent, gave violet colour with alcoholic ferric chloride.

To a solution of the aforementioned crude hydroxymethylene ketone (0·8 g) in ethanol (2 ml) and 2 N NaOH (30 ml) was added 30% hydrogen peroxide (9 ml), and the mixture was allowed to stand at the room temp for 1 hr. It was next heated under reflux for 2 hr followed by two more similar treatments with hydrogen peroxide. The solvent was removed under reduced press, and the aqueous solution of the residue, after one extraction with ether, was acidified with cold dil HCl. The oily product was worked up by extraction with ether. After removal of the solvent, the crude ester diacid (0·4 g) was saponified by refluxing for 5 hr at 150° with 25% aqueous methanolic KOH (8 ml). The methanol was removed under reduced press and the aqueous solution of the residue, after one extraction with ether, was acidified with cold dil HCl. The resulting oily suspension was worked up by extraction with ether. While removing the solvent, the triacid crystallized out as a white solid IX (0·1 g, 10%). It was crystallized from acetone, m.p. 212–213° (d). (Found: C, 56·01; H, 7·07. $C_{11}H_{16}O_6$ requires: C, 55·82; H, 7·09%).

Acknowledgements—We wish to record our thanks to Messrs. B. R. Seetharamia and D. P. Bose for the microanalyses and to the Government of Orissa and the Government of India for the award of a scholarship to one of us (S. N. M.).