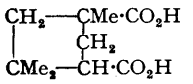
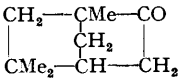
44. *Terpene Compounds. Part IV. A Synthesis of* cis- *and* trans-(±)-iso*Fenchocamphoric Acid.*

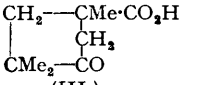
By R. Swaminathan, (Miss) Debi Mukherji, and J. C. Bardhan.

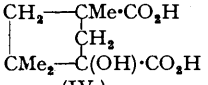
Ethyl 2 : 2 : 4-*trimethyl*cyclo*hexan*-1-*one*-4-*carboxylate*, the preparation of which is now described, affords, on bromination followed by treatment with barium hydroxide, 1-*hydroxy*-3 : 5 : 5-*trimethyl*cyclo*pentane*-1 : 3-*dicarboxylic acid*. The reaction involves molecular rearrangement of the type previously observed by Wallach, Simonsen, and their co-workers. The product is probably the *trans*-modification of Aschan's α-hydroxy*iso*fenchocamphoric acid, since, on dehydration with phosphorus oxychloride and pyridine, it gives 3 : 5 : 5-trimethyl-*cyclo*pent-1-ene-1 : 3-dicarboxylic acid (dehydro*iso*fenchocamphoric acid). This on catalytic reduction gives (±)-*cis*-*iso*fenchocamphoric acid, which establishes the correctness of Semmler–Wallach formula for this acid. A direct synthesis of dehydro*iso*fenchocamphoric acid from ethyl 2 : 2 : 4-trimethyl*cyclo*pentan-1-one-4-carboxylate (Bardhan and Ganguli, *J.*, 1936, 1852) by the action of hydrogen cyanide followed by dehydration and hydrolysis is also described.

*iso*Fenchocamphoric acid was first prepared by the oxidation of *iso*fenchone by Wallach (*Annalen*, 1907, **357**, 49; 1908, **362**, 19; **363**, 5) who represented it as (I) on the assumption that Semmler's formula (II) for *iso*fenchone ("Die Ätherischen Öle", 1906, III, 549) was correct. This view was fully substantiated by the later work of Aschan (*Annalen*, 1912, **387**, 1) on the degradation of (±)-*iso*fenchocamphoric acid. The acid was, moreover, found to exist in six possible stereoisomeric modifications (cf. Wallach, *loc. cit.*; Aschan, *loc. cit.*; Sandelin, *Annalen*, 1913, **396**, 287) as, indeed, the Semmler–Wallach formulation for *iso*fenchocamphoric acid demanded.


(I.)

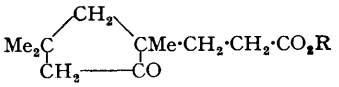

(II.)

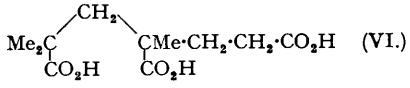

(III.)


(IV.)

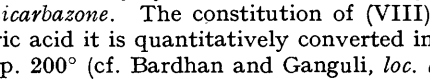
A synthesis of *iso*fenchononic acid (III) has been described (Bardhan and Ganguli, *J.*, 1936, 1853), and it was hoped that it might be possible to convert it into *iso*fenchocamphoric acid. We first tried unsuccessfully to prepare 1-*hydroxy*-3 : 5 : 5-*trimethyl*cyclo*pentane*-1 : 3-*dicarboxylic acid* (IV) from (III) *via* the cyanohydrin. The following successful synthesis of (IV) is, however, in complete accord with the structure (I) for *iso*fenchocamphoric acid.

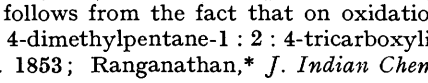
2 : 4 : 4-Trimethyl*cyclo*pentanone, prepared by the Clemmensen reduction of dimethyldihydroresorcinol (Dey and Linstead, *J.*, 1935, 1063; Khuda, *Nature*, 1933, **132**, 210), was converted by sodamide in ethereal solution into the sodio-derivative, which condensed with ethyl β-chloropropionate to give *ethyl* 2 : 4 : 4-*trimethyl*cyclo*pentan*-1-*one*-2-β-*propionate* (V; R = Et). This on hydrolysis with hydrochloric acid yielded the corresponding *acid* which was characterised by the preparation of the *semicarbazone*.

(V.) 


(VI.)

The *keto-acid* (V; R = H) on oxidation with nitric acid gave an excellent yield of 3 : 5-*dimethylhexane*-1 : 3 : 5-*tricarboxylic acid* (VI). The corresponding *triethyl* ester, prepared according to the alcohol-vapour method, on sodium condensation furnished *ethyl* 2 : 2 : 4-*trimethyl*cyclo*hexan*-1-*one*-4 : 6-*dicarboxylate* (VII). This on hydrolysis with hydrochloric acid afforded 2 : 2 : 4-*trimethyl*cyclo*hexan*-1-*one*-4-*carboxylic acid* (VIII), which was purified through the *semicarbazone*. The constitution of (VIII) also follows from the fact that on oxidation with nitric acid it is quantitatively converted into 2 : 4-dimethylpentane-1 : 2 : 4-tricarboxylic acid, m. p. 200° (cf. Bardhan and Ganguli, *loc. cit.*, p. 1853; Ranganathan,* *J. Indian Chem. Soc.*,

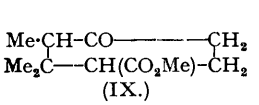
(VII.) 

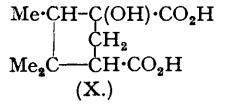

(VIII.)

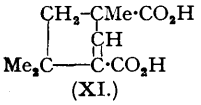
1937, **14**, 266, gives m. p. 185—186°). The *methyl* ester (as VIII) on bromination in ice-cold acetic acid solution furnished a semi-solid product which was directly hydrolysed with a solution

* Mr. Swaminathan who has repeated the action of potassium cyanide on the lactone of ethyl β-hydroxy-ββδ-trimethyladipate under the conditions prescribed by Ranganathan (*loc. cit.*) reports that there is no evidence of the formation of 2 : 4-dimethylpentane-1 : 2 : 4-tricarboxylic acid as asserted by Ranganathan.

of barium hydroxide to give 1-*hydroxy*-3 : 5 : 5-*trimethyl*cyclo*pentane*-1 : 3-*dicarboxylic acid* (IV). This acid, which was characterised by the preparation of an *acetyl* derivative, proved to be different from α-hydroxy*iso*fenchocamphoric acid described by Aschan (*loc. cit.*, p. 71), since, unlike the latter, it could not be converted into the characteristic lactonic acid, m. p. 177°. There can be little doubt that the new acid is correctly represented by the structure (IV), since, on oxidation with potassium permanganate in presence of sulphuric acid it is smoothly converted into *iso*fenchononic acid previously prepared by Bardhan and Ganguli. It seems to us probable that the new acid must be the *trans*-modification of Aschan's α-hydroxy*iso*fenchocamphoric acid. Evidently its formation involves molecular rearrangement and recalls the conversion of methyl 2 : 2 : 3-trimethyl*cyclo*hexan-4-one-1-carboxylate (IX) into *trans*-1-hydroxy-4 : 4 : 5-trimethyl*cyclo*pentane-1 : 3-dicarboxylic acid (X) (Bhagavat and Simonsen, *J.*, 1927, 79; Wallach, *Annalen*, 1918, **414**, 296).


(IX.)


(X.)


(XI.)

(IV) is readily converted into the *ethyl* ester; this on dehydration with phosphoryl chloride and pyridine followed by hydrolysis of the resulting product furnished 3 : 5 : 5-trimethyl*cyclo*pent-1-ene-1 : 3-dicarboxylic acid (XI), identical with (±)-dehydro*iso*fenchocamphoric acid (Toivonen, *Annalen*, 1919, **419**, p. 198). On reduction with hydrogen in presence of Adams's platinum oxide catalyst in acetic acid solution it gave the corresponding saturated acid, which proved to be *cis*-(±)-*iso*fenchocamphoric acid (I). The identity was established by direct comparison with an authentic specimen of the acid kindly supplied by Prof. Gustav Komppa of Helsingfors to whom we wish to express our indebtedness. The synthetic acid on treatment with acetyl chloride gave the characteristic anhydride, which on hydration gave the original *cis*-acid. Finally, the synthetic *cis*-acid on heating with hydrochloric acid gave the *trans*-acid (cf., *e.g.*, Aschan, *loc. cit.*, p. 57; Sandelin, *loc. cit.*, p. 332).

When this work was completed it seemed of interest to attempt once more the preparation of the cyanohydrin of ethyl 2 : 2 : 4-trimethyl*cyclo*pentan-1-one-4-carboxylate. Although the keto-ester could not be induced to react with hydrogen cyanide at 0°, combination took place readily at −5°; the resulting product on treatment with phosphorus oxychloride and pyridine followed by hydrolysis with hydrochloric acid gave a good yield of a crystalline acid, identical with dehydro*iso*fenchocamphoric acid (XI) described above.

Experimental.

2 : 4 : 4-*Trimethyl*cyclo*pentan*-1-*one*-2-β-*propionic Acid* (V; R = H).—2 : 4 : 4-Trimethyl*cyclo*pentanone was conveniently prepared by the Clemmensen reduction of dimethyldihydroresorcinol (Dey and Linstead, *loc. cit.*). The yield was greatly improved by carrying out the reduction in a flask fitted with a short column, and thus allowing the volatile products to distil as fast as they were produced. 165 G. of dimethyldihydroresorcinol yielded 81·5 g. of an almost pure ketone, b. p. 160—164°. The semicarbazone, after two crystallisations from aqueous alcohol, had m. p. 168—169°.

Powdered sodamide (15 g.) and anhydrous ether (400 c.c.) were gently boiled in a reflux apparatus; 2 : 4 : 4-trimethyl*cyclo*pentanone (47 g.) was then added drop by drop and the whole heated for 6 hours. The flask was cooled in ice, ethyl β-chloropropionate (52 g.) slowly added with shaking, and the mixture left in the cold overnight. The mixture was heated as before for 7½ hours under reflux, cooled, and diluted with water, and the ethereal layer separated, dried, and evaporated. The residue on rectification under reduced pressure yielded the keto-ester as a colourless oil (47 g.), b. p. 127°/5 mm. The crude keto-ester (23 g.) was refluxed on the water-bath with potassium hydroxide (8 g.) dissolved in water (16 c.c.) and alcohol (64 c.c.) for 1¼ hours. The excess of alcohol was evaporated as completely as possible, and the residue cooled and acidified with hydrochloric acid. The oil was extracted with ether, the ether removed, and the residue distilled under reduced pressure, giving the keto-acid (18·5 g.), b. p. 150°/4 mm., from which the *semicarbazone*, m. p. 187—188°, was readily prepared in good yield. This on recrystallisation twice from dilute alcohol formed minute prisms, m. p. 197° (Found: C, 56·7; H, 8·3. $C_{12}H_{21}O_3N_3$ requires C, 56·5; H, 8·2%). 2 : 4 : 4-*Trimethyl*cyclo*pentan*-1-*one*-2-β-*propionic acid* regenerated from the semicarbazone (5 g.) was obtained as an oil, and on distillation under reduced pressure formed a colourless, somewhat viscous liquid (3·4 g.), b. p. 150°/4 mm., which on standing solidified to a hard mass, and on recrystallisation from light petroleum (b. p. 40—60°) formed minute prisms, m. p. 55° (Found: C, 67·1; H, 9·3. $C_{11}H_{18}O_3$ requires C, 66·7; H, 9·1%). It formed a semicarbazone identical with that prepared from the crude acid (see above).

3 : 5-*Dimethylhexane*-1 : 3 : 5-*tricarboxylic Acid* (VI).—The liquid keto-acid (above) (18 g.) was placed in an all-glass apparatus fitted with a condenser, mixed with nitric acid (450 c.c.; *d* 1·2), and heated on the water-bath. A vigorous reaction started after a few minutes, and was kept under control by cooling the flask in running water. The mixture was again heated on the water-bath for 4½ hours and then gently boiled on a sand-bath for 4 hours. Excess of nitric acid was removed by evaporating the clear solution on the water-bath with frequent addition of water, and the solution concentrated to a small

volume and left overnight. The crystals which separated were collected, washed with a little ice-cold water, and dried (18·3 g.). On recrystallisation from concentrated hydrochloric acid, 3 : 5-*dimethylhexane*-1 : 3 : 5-*tricarboxylic acid* formed glistening prisms, m. p. 162° [Found : C, 53·7; H, 7·4; equiv. (by titration), 81·0. $C_{11}H_{18}O_6$ (tribasic) requires C, 53·6; H, 7·3%; equiv., 82·0]. The *triethyl* ester was readily prepared by heating (VI) (57·5 g.), absolute alcohol (120 c.c.), and concentrated sulphuric acid (12 c.c.) at 110° in an oil-bath, and passing the vapour of alcohol (6 l.) through the mixture for 17 hours; it formed an almost colourless oil (72 g.; 94%), b. p. 160°/5 mm. (Found : C, 61·6; H, 9·3. $C_{17}H_{30}O_6$ requires C, 61·8; H, 9·1%).

Ethyl 2 : 2 : 4-*Trimethylcyclohexan*-1-*one*-4 : 6-*dicarboxylate* (VII).—Ethyl 3 : 5-dimethylhexane-1 : 3 : 5-tricarboxylate (11 g.) was added to a suspension of finely divided sodium (0·92 g.) in dry benzene (22 c.c.) and heated on the water-bath under reflux. After an hour, when all the sodium had gone into solution, the clear brown liquid was cooled in ice, acidified with ice-cold concentrated hydrochloric acid (5 c.c.), and extracted with ether. The ether–benzene layer was separated, washed successively with water, sodium carbonate solution, and water, and evaporated. *Ethyl* 2 : 2 : 4-*trimethylcyclohexan*-1-*one*-4 : 6-*dicarboxylate* formed a colourless, viscous liquid (6·6 g.; 66%), b. p. 146°/4 mm. (Found : C, 63·8; H, 8·6. $C_{15}H_{24}O_5$ requires C, 63·4; H, 8·4%). It gave an intense violet colouration with alcoholic ferric chloride.

2 : 2 : 4-*Trimethylcyclohexan*-1-*one*-4-*carboxylic Acid* (VIII).—The foregoing keto-ester (6·6 g.) was hydrolysed by boiling it with a mixture of concentrated hydrochloric acid (20 c.c.) and water (53 c.c.) for 16 hours on a sand-bath. On cooling, the *keto-acid* separated in crystals (3·3 g.; 70%), m. p. 109—110°. On recrystallisation from hot water it formed colourless needles, m. p. 110—111° (Found : C, 65·5; H, 8·8. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7%). The *semicarbazone*, on repeated crystallisation from rectified spirit, formed minute prisms, m. p. 211° (Found : C, 55·0; H, 8·1. $C_{11}H_{19}O_3N_3$ requires C, 54·8; H, 7·9%). The *methyl* ester, prepared by boiling the acid with methanolic hydrogen chloride, formed a colourless, viscous liquid, b. p. 98°/4 mm. (Found : C, 66·4; H, 9·3. $C_{11}H_{18}O_3$ requires C, 66·7; H, 9·1%).

2 : 4-*Dimethylpentane*-1 : 2 : 4-*tricarboxylic Acid*.—The keto-acid (VIII) (0·5 g.) was heated with nitric acid (7·8 c.c.; *d* 1·4) and water (4·7 c.c.) on the water-bath in an all-glass apparatus for 4 hours. On keeping overnight, crystals (m. p. 193°) separated which on recrystallisation from concentrated hydrochloric acid had m. p. 200° alone or mixed with an authentic specimen (Bardhan and Ganguli, *loc. cit.*) (Found : C, 51·6; H, 7·0. Calc. for $C_{10}H_{16}O_6$: C, 51·7; H, 6·9%).

1-*Hydroxy*-3 : 5 : 5-*trimethylcyclopentane*-1 : 3-*dicarboxylic Acid* (IV).—The keto-ester (4 g.) was dissolved in glacial acetic acid (4 c.c.), and the solution cooled in ice and treated dropwise with bromine (2·2 c.c.) diluted with an equal volume of glacial acetic acid. On standing, the colour of the bromine was nearly discharged, and the solution was then poured on ice, and the viscous semi-solid product collected in ether. The ethereal solution was washed with water, then with a dilute solution of sodium carbonate, and dried ($CaCl_2$), and the solvent evaporated at the ordinary temperature. The residual brown oil was mixed with a hot solution of crystallised barium hydroxide (22·5 g.) in water (75 c.c.), and the whole heated under reflux on the sand-bath with mechanical stirring. After about 20 minutes a vigorous reaction started, and the sparingly soluble barium salt of the hydroxy-acid gradually began to separate. At the end of 1½ hours the heating was discontinued and the product left overnight. The next day the mixture was slightly warmed and treated with hydrochloric acid (7 c.c.; *d* 1·2) till it was only just alkaline to phenolphthalein. The solution was boiled, and the first crop of crystals was collected, washed with a little hot water, and dried in air (3·2 g.). The mother liquor on concentration gave a further quantity (0·70 g.) of the barium salt. The finely powdered, dry barium salt (3·2 g.) was boiled with the calculated quantity of anhydrous sodium carbonate (0·89 g.) dissolved in water (50 c.c.) for 1½ hours, water being frequently added to wash down the solid on the sides and to maintain the volume. The solution was filtered hot, the precipitate repeatedly washed with warm water, and the filtrate concentrated to a small volume, cooled, and acidified with hydrochloric acid. 1-*Hydroxy*-3 : 5 : 5-*trimethylcyclopentane*-1 : 3-*dicarboxylic acid* on recrystallisation from water formed microscopic prisms, m. p. 185—186° [Found : C, 55·5; H, 7·5; equiv. (by titration), 107·0. $C_{10}H_{16}O_5$ (dibasic) requires C, 55·5; H, 7·4%; equiv., 108].

The *acetyl* derivative was prepared by heating (IV) (0·5 g.) with freshly distilled acetic anhydride (10 c.c.) for 2 hours under reflux on the sand-bath. The product was diluted with water, and evaporated on the water-bath. The gummy residue on being rubbed with a few drops of water crystallised, and on purification from hot water formed stout prisms, m. p. 188—189° (Found : C, 51·7; H, 7·3. $C_{12}H_{18}O_6,H_2O$ requires C, 52·2; H, 7·2%). The *ethyl* ester was prepared by heating (IV) (4·7 g.) with absolute alcohol (20 c.c.) and concentrated sulphuric acid (1 c.c.) on the water-bath for 15—16 hours under a reflux condenser. The product was cooled, diluted with water, and extracted with ether. The ethereal solution was washed with dilute sodium carbonate solution, again washed with water, dried, and distilled. The ester formed a mobile, colourless oil (4·7 g.; 80%), b. p. 133°/6 mm. (Found : C, 61·6; H, 8·5. $C_{14}H_{24}O_5$ requires C, 61·7; H, 8·8%).

iso*Fenchononic Acid* (III).—The hydroxy-acid (1 g.) was dissolved in boiling N-sulphuric acid (100 c.c.) and quickly mixed with a solution of potassium permanganate (16 c.c. of 1%). The oxidation proceeded vigorously with much frothing, and the colour of permanganate was rapidly discharged. On cooling, the clear solution was repeatedly extracted with ether, and the ethereal solution was washed, dried, and evaporated. The residue completely solidified when kept in an evacuated desiccator, and on purification from light petroleum (b. p. 60—80°) was identified as *iso*fenchononic acid by its m. p. 70—71° and by analysis (Found : C, 63·6; H, 8·1. Calc. for $C_9H_{14}O_3$: C, 63·5; H, 8·2%). It formed a semicarbazone, m. p. 225—226° (decomp.) (cf. Bardhan and Ganguli, *loc. cit.*).

3 : 5 : 5-*Trimethylcyclopent*-1-*ene*-1 : 3-*dicarboxylic Acid* (*Dehydroisofenchocamphoric Acid*) (XI).—The ethyl ester of (IV) (1 g.), phosphorus oxychloride (3·5 c.c.), and dry pyridine (15 c.c.) were refluxed in an oil-bath at 145° for 1 hour. The product was cooled in ice, and ice-cold water added drop by drop in order to decompose any unchanged oxychloride. It was then strongly acidified with concentrated hydrochloric acid, and extracted several times with pure ether. The ethereal solution was washed with water, dried, and evaporated. The residual liquid was hydrolysed with alcoholic potassium hydroxide

[potassium hydroxide (2 g.), water (3 c.c.), alcohol (13 c.c.)] in a reflux apparatus for 1½ hours. Excess of alcohol was then removed, and the solution cooled, filtered from a little suspended impurity, and acidified with hydrochloric acid. The acid which separated as an oil rapidly solidified to a microcrystalline powder (0·51 g.). On recrystallisation from water containing a little acetic acid, dehydro*iso*fenchocamphoric acid formed a crystalline powder, m. p. 190—191° [Found : C, 60·5; H, 6·9; equiv. (by titration), 99·3. Calc. for $C_{10}H_{14}O_4$ (dibasic) : C, 60·6; H, 7·0%; equiv., 99·0]. Toivonen (*loc. cit.*, p. 198) gives m. p. 190—191°.

cis-(±)-iso*Fenchocamphoric Acid* (I).—Pure dehydro*iso*fenchocamphoric acid (1·31 g.) was dissolved in glacial acetic acid (25 c.c.) and shaken with the addition of Adams's platinum oxide catalyst (0·1 g.) in an atmosphere of hydrogen. Rapid absorption occurred, and in about ½ hour the calculated amount of hydrogen (190 c.c.) had been absorbed. The solution was filtered, excess of acetic acid distilled off at the water-pump, and the residue diluted with water. On standing, crystals began to separate; these were collected and recrystallised from hot water. *cis*-(±)-*iso*Fenchocamphoric acid formed minute, glistening prisms, m. p. 174—175° [Found : C, 60·0; H, 8·0; equiv. (by titration), 99·95. Calc. for $C_{10}H_{16}O_4$ (dibasic) : C, 60·0; H, 8·0%; equiv., 100] (cf. Aschan, *loc. cit.*, p. 51). The anhydride crystallised from light petroleum (b. p. 40—60°) in beautiful plates, m. p. 95—96° (Aschan, *loc. cit.*, gives m. p. 94—95°) (Found : C, 66·4; H, 7·6. Calc. for $C_{10}H_{14}O_3$: C, 65·9; H, 7·7%).

trans-(±)-iso*Fenchocamphoric Acid*.—0·8 G. of *cis*-(±)-*iso*fenchocamphoric acid was converted into a mixture of the *trans*-acid and the anhydride of the *cis*-acid by the method of Aschan (*loc. cit.*, p. 56). The *trans*-acid (0·35 g.) was recovered by extraction with boiling carbon disulphide, in which the anhydride alone was soluble (Sandelin, *loc. cit.*, p. 321). On recrystallisation (charcoal) from hot water containing a few drops of acetic acid it formed minute prisms, m. p. 173·5—174·5° (Found : C, 59·8; H, 8·1. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·0%). In admixture with the pure *cis*-acid, m. p. 174—175°, the mixture had m. p. 141—142° (slight softening at 138°).

Conversion of Ethyl 2 : 2 : 4-*Trimethyl*cyclo*pentan*-1-*one*-4-*carboxylate* (*as* III) *into* (±)-*Dehydro*iso*fenchocamphoric Acid* (XI).—Ethyl 2 : 2 : 4-trimethyl*cyclo*pentan-1-one-4-carboxylate (Bardhan and Ganguli, *loc. cit.*, p. 1853) (5 g.) was slowly added to hydrogen cyanide [from potassium cyanide (10 g.), sulphuric acid (10 c.c., *d* 1·84), and water (10 c.c.) (Wade and Panting, *J.*, 1873, **73**, 256)] cooled to −5°. After the addition of a drop of potassium cyanide solution, the mixture was kept at this temperature overnight, two drops of concentrated sulphuric acid added, and the excess of hydrogen cyanide removed at the water-pump. The residual oil was heated at 120—130° for an hour with pyridine (80 c.c.) and phosphorus oxychloride (21 c.c.). It was cooled in ice, treated with iced water drop by drop to decompose excess of phosphorus oxychloride, acidified with hydrochloric acid (40 c.c.), and extracted with ether. The ethereal extract was washed with dilute sulphuric acid, then with aqueous sodium hydroxide, and dried, and the solvent evaporated. The residual dark brown oil was digested on the sand-bath with concentrated hydrochloric acid (50 c.c.) for 25 hours. The crystals (3 g.) which separated on cooling were recrystallised (charcoal) from very dilute acetic acid, and then had m. p. 190—191° alone or admixed with a specimen of dehydro*iso*fenchocamphoric acid described above (Found : C, 60·8; H, 7·2%).

A considerable portion of this work was carried out during 1940—1941, and formed the basis of a thesis presented by one of us (R. S.) for the M.Sc. degree.

UNIVERSITY COLLEGE OF SCIENCE AND TECHNOLOGY, CALCUTTA. [*Received, March 8th*, 1948.]