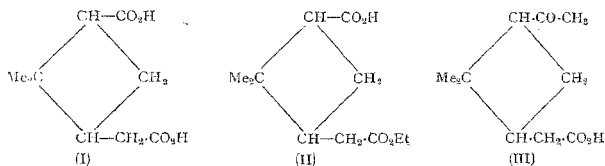


## SYNTHETICAL EXPERIMENTS IN THE PINANE GROUP.

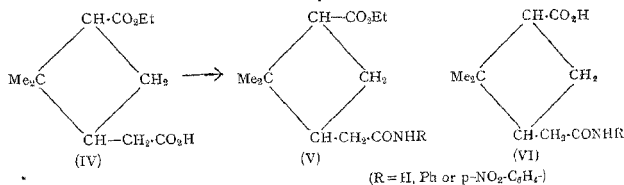
### Part VI. Further attempts to synthesise pinonic acid, nopinone and verbenone.

By P. C. Guha and P. L. Narasimha Rao.

In continuation of our experiments towards the synthesis of pinonic acid (III) from pinic acid (I) recorded in part IV of this series<sup>1</sup> we have now closely examined the possibility of improving the yield of the mono-ester (II) required for the desired synthesis, by partial esterification of (I).

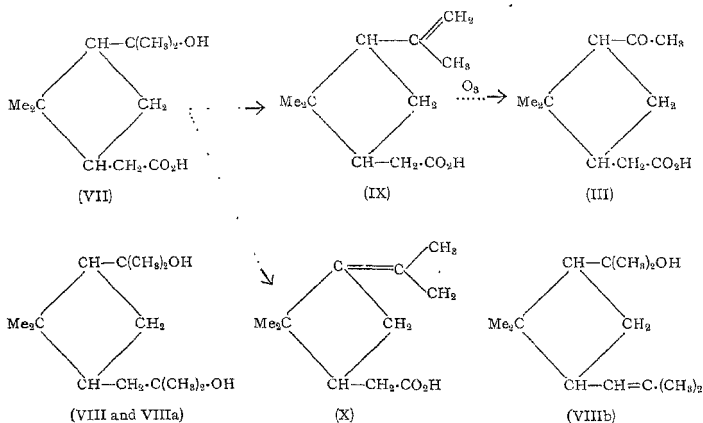


Next, attempts were made to prepare a suitable derivative of pinic acid (such as VI) with a view to applying Blaise's reaction for the synthesis of a pinonic acid derivative. Starting from the mono-ester (IV) formed in good yield on partial hydrolysis of diethyl pinate (part IV, *loc. cit.*), derivatives such as amido-, anilino- and *p*-nitroanilino etc. (V) were easily obtained, but hydrolysis of these compounds did not yield the required amido carboxylic acids (VI). The amido or arylamido groups get more easily hydrolysed than the ester grouping, giving rise to the mono-ester (IV) or pinic acid (I).



<sup>1</sup> For previous parts, see part I, *Ber.*, 1936, **69**, 1185; Part II, *ibid.*, 1937 **70**, 736; Part III, *ibid.*, 1937, **70**, 1505; Part IV, *ibid.*, 1938, **71**, 1591, Part V, *ibid.* 1938, **71**, 2663.

Attempts at a direct synthesis of pinonic acid from the mono-ester (IV) by controlled Grignard reaction with methyl magnesium iodide (viz., replacement of OEt by CH<sub>3</sub>) was not successful. The product consisted of the alcoholic acid (VII) besides some unchanged material. By using an excess of the reagent, the compound (VII) was obtained in excellent yields, together with a small quantity of a neutral product presumably *trans*-4,4,2,7-tetramethyl-2,7-dihydro-3,5-epimethylene octane<sup>2</sup> (VIII), a liquid with a characteristic odour.



With the object of preparing the unsaturated acid (IX) from (VII) by dehydration, and converting the former by ozonolysis into pinonic acid (III), dehydration experiments on (VII) and its ester under varying conditions and with different dehydrating agents were studied. No normal dehydration products like (IX and X) could, however, be isolated due perhaps to fission of the *cyclobutane* ring of (VII)<sup>3</sup>.

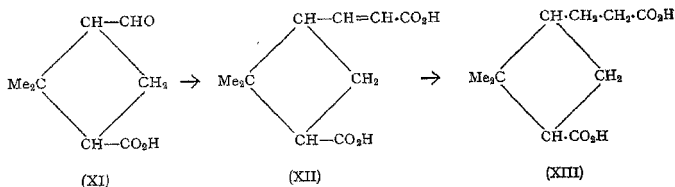
<sup>2</sup> cf. Grandperrin, *Annales der Chemie*, 1936, **6**, 26.

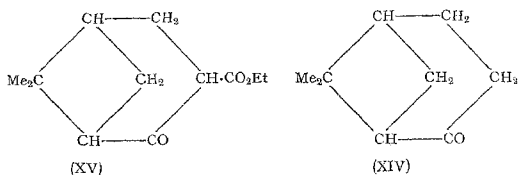
<sup>3</sup> cf. Ruzicka and Trebler, *Helv. Chim. Acta.*, 1920, **3**, 756; 1921, **4**, 666.

As the configurations of the compounds (VII, VIII, etc.) are *trans* being derived from *trans*-pinic acid, the preparation of the corresponding compounds of the *cis*-series (VIIa, VIIIa) have been attempted by the action of  $MgCH_3I$  upon ethyl *cis*-pinonate. The reaction, however, did not give a homogeneous product from which four compounds, (i) an acid probably *cis* form of (VII), (ii) a lactone, (iii) an unsaturated alcohol (VIIIb the position of the double bond being uncertain) and (iv) another compound probably the *cis*-form of (VIII) were isolated. The unsaturated alcohol (VIIIb) is formed evidently from the dialcohol (VIIIa) by the elimination of a molecule of water.

### On synthesis of nopinone.

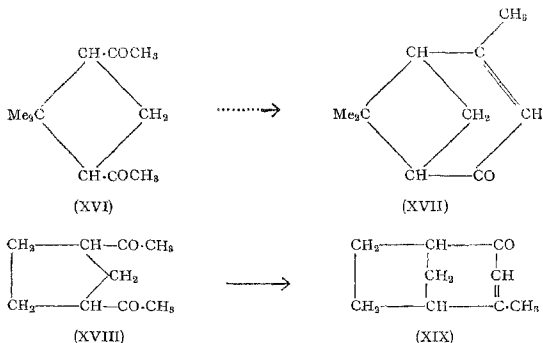
The scheme of synthesis of nopinone (XIV) indicated in part IV of this series (*loc. cit.*) has been tried with the following results. The difficultly-obtainable norpinic acid semialdehyde (XI) was condensed with malonic acid in presence of pyridine and a trace of piperidine to yield the acid (XII). Ethyl ester of (XII) was then reduced to unsymmetrical ethyl homopinate (XIII) by hydrogen in presence of Adam's catalyst. The ethyl ester of (XIII) could not be cyclised to (XV) by Dieckmannisation nor pyrolysis of the lead salt of (XIII) to (XIV) was successful. Although the reaction product in the former case gave a violet coloration with ferric chloride, and that in the latter gave a semicarbazone, no nopinone could, however, be isolated. It appears from these experiments that this new homopinic acid (a structural isomer of the one described in part II,<sup>1</sup> also possesses a *trans*-configuration.





### On synthesis of verbenone.

The diketonic compound obtained by the action of ZnMeI on norpinic diacid chloride (see part IV, *loc. cit.*) has been subjected to closer examination and proved to possess the diketonic structure (XVI). Peculiarly enough, it did not yield verbenone (XVII) on treatment with sodium ethoxide, though by analogy with the formation of the compound (XIX) from 1, 3-diacetyl-cyclopentane (XVIII)<sup>4</sup>, its formation was greatly to be expected.



### EXPERIMENTAL.

*Ethyl trans-2 : 2-dimethyl - cyclobutane-1-carboxy-3 - acetate* (II).—The experimental conditions recorded in part IV of this series (*loc. cit.*) were varied; thus altering the proportions of the reactants, quantities of the solvent and temperature had not materially affected the

<sup>4</sup> Mahunta and Roy, *J.C.S.*, 1934, 1328.

yield of the product. The purified substance was converted via, acid-chloride, to the amide which after purification by repeated crystallisations was found to be identical with the amide of the isomeric mono-ester (ethyl *trans*-2:2-dimethyl-cyclobutane-1-carbethoxy-3-acetic acid, IV), m.p. 97° (vide part IV). This showed that the product was not homogeneous but a mixture of the two mono-esters.

*Ethyl trans*-2:2-dimethyl-cyclobutane-1-carbethoxy-3-acetyl-*p*-nitranilide (V, R. = NO<sub>2</sub>.C<sub>6</sub>H<sub>4</sub>) was prepared from the acid chloride of the mono-ester (IV) and *p*-nitraniline in pyridine solution in the usual way. It crystallised readily from benzene or dilute alcohol in almost colourless, glistening crystals, m.p. 129-30° (Found: N, 8.22. C<sub>17</sub>H<sub>22</sub>O<sub>6</sub>N<sub>2</sub> requires N, 8.4 per cent.).

*Hydrolysis of the above amide.*—On subjecting to hydrolysis with varying amounts of 10% methyl alcoholic or aqueous potash solution at 0°, room or boiling temperatures during a period ranging from 8 to 24 hours, only *p*-nitraniline and picnic acid or the original mono-ester (IV) could be isolated, but not the required amido-compound. Hydrolysis with 10% barium hydroxide was very similar to that in the case of potash. Heating with water in an autoclave at 160-65° separated *p*-nitraniline almost quantitatively. In the product obtained by acid hydrolysis some *p*-nitraniline hydrochloride was isolated indicating that hydrolysis did not proceed in the desired manner.

The amide and the anilide of the ester (V, R = H or Ph) behaved similarly on hydrolysis.

*Action of MgMeI on compound IV: Formation of 2:2-dimethyl-cyclobutane-1-dimethylcarbinol-3-acetic acid (VII)*—Magnesium methyl iodide (prepared from 4.9 g. of Mg) was added under ice-cooling to the mono-ester (21.4 g.) under mechanical stirring and after standing for two hours, the reaction was completed by heating on the water-bath for half-an-hour and the product worked up as usual. The acidic portion of the product was esterified and the ester treated with semicarbazide hydrochloride and sodium acetate and steam-distilled after two days' standing. No pinonic ester semicarbazone

could be isolated from the residue. The distillate was then fractionated; the first fraction, b.p. 120-125°/5 mm. was pure diethyl pinate. The fraction b.p. 130-35°/5 mm. was ethyl *trans*-2 : 2-dimethyl-*cyclobutane*-3-acetate-1-dimethyl carbinol (ester of VII);  $d_4^{30}$ , 0.9764;  $n_D^{30}$ , 1.4492;  $R_{LD}$ , 63.1, calc. 62.5 (Found: C, 68.4; H, 10.43.  $C_{18}H_{24}O_3$  requires C, 68.4; H, 10.5 per cent.).

Hydrolysis of the above ester with 10 per cent. alc. potash, gave a thick gummy acid (VII) which did not crystallise even when kept in a vacuum desiccator for 7 days;  $d_4^{30}$ , 1.0228;  $n_D^{30}$ , 1.4642;  $R_{LD}$ , 54.8, calc. 54.1 (Found: Eq. Wt., 201.4;  $C_{11}H_{20}O_3$  requires Eq. Wt. 200).

The amide prepared via. acid chloride, was a thick gum which did not crystallise easily.

By using excess of Grignard reagent ( $3\frac{1}{2}$  mol.), the yield of the alcoholic ester was more than 80% of the theory. A small quantity of a neutral product, b.p.110-120°/5 mm.;  $d_4^{30}$ , 0.9579;  $n_D^{30}$ , 1.4614, was always formed and this may probably be *trans*-4,4,2,7-tetramethyl-2,7-dihydroxy-3,5-*epimethylene*-octane (VIII) (Found: C, 72.9; H, 12.18.  $C_{18}H_{26}O_2$  requires C, 72.9; H, 12.15 per cent.).

*Dehydration of the alcoholic acid* (VII).—When heated with potassium hydrogen sulphate at 180° for 1 hour it gave a *neutral* unsaturated product (60% yield), b.p.145-47°/14 mm.;  $d_4^{30}$ , 0.9327;  $n_D^{30}$ , 1.4582; absorbing bromine in  $CHCl_3$  with evolution of heat (Found: C, 69.63; H, 10.35.  $C_{22}H_{38}O_2$  requires C, 69.1; H, 9.95 per cent.).

*Dehydration of the ester of* (VII) was tried with the following reagents (i) formic acid (100%) at 100° and 120°; (ii) acetic anhydride under reflux; (iii) thionyl chloride and pyridine; (iv) phosphorus tribromide in chloroform at room temperature, and then on water-bath; and (v) potassium hydrogen sulphate at 180°.

In the case of the first two reagents, they did not appear to yield any unsaturated product. With thionyl chloride and phosphorus tribromide, the final products could be isolated only in poor yields; they gave tests for halogens and were-not further examined.

*Dehydration of (VII) with potassium hydrogen sulphate.*—A mixture of the ethyl ester of the compound (VII, 15 g.) and anhydrous  $\text{KHSO}_4$  (30 g.) was heated at  $180\text{--}200^\circ$  in a metal bath for one hour. Water was added after cooling when an oily liquid separated which was extracted out with ether, dried, ether removed and fractionated. The substance boiled at  $104\text{--}106^\circ/3$  mm.;  $d_4^{30}$ , 0.9855;  $n_D^{30}$ , 1.4542 (Found C, 68.80, 68.87; H, 9.92, 9.91 per cent.). The two analyses agree closely with the formula  $\text{C}_{22}\text{H}_{38}\text{O}_5$  (C, 69.1; H, 9.95 per cent.).

This compound absorbed bromine very readily and decolorised alkaline permanganate. From the products formed on oxidation of the substance with the latter reagent, oxalic acid has been isolated besides other gummy acids not investigated.

*Grignard reaction on ethyl pinonate.*—An ethereal solution of methyl magnesium iodide ( $\frac{1}{3}$  mol.) was added to an ethereal solution of the ethyl pinonate ( $\frac{1}{3}$  mol., 30 g.) under cooling and stirring; the reaction was completed by boiling on the water-bath during half-an-hour. The product after decomposition with dilute acid was extracted with ether, ether removed and the residual oil treated with semicarbazide hydrochloride and sodium acetate in alcoholic solution and distilled with steam after 24 hours standing. The residue yielded some ethyl-pinonate semi-carbazone. The distilled oil was then subjected to alkaline hydrolysis and the unsaponifiable product fractionated. The first fraction (4 g.) b.p.  $105\text{--}8/6$  mm.;  $d_4^{30}$ , 0.8972;  $n_D^{30}$ , 1.461;  $R_{L.D.}$ , 60.1; cal. for  $\text{C}_{13}\text{H}_{24}\text{O}$ , 60.0 (one double bond), appeared to be an unsaturated mono-alcohol (VIIIb) (Found: C, 79.8; H, 12.3.  $\text{C}_{13}\text{H}_{24}\text{O}$  requires C, 79.6; H, 12.2 per cent.). The second fraction (1.8 g.), b.p.  $115\text{--}120^\circ/5$  mm. was not further examined, but from its higher boiling point and from an analogy with the observations of Grandperrin<sup>2</sup>, it is likely to be the impure *cis*-diol (VIIIa). The alkaline solution on acidification gave an oily product from which acidic products were removed by means of sodium bicarbonate solution. The remaining lactonic fraction (0.8 g.) was purified by careful distillation, b.p.  $121\text{--}122^\circ/4$  mm.;  $d_4^{30}$ , 0.9681;  $n_D^{30}$ , 1.442. This was not further examined. The bicarbonate solution

on acidification gave acids and were separated by distillation into two fractions: (i) b.p. 135°/3 mm.;  $n_D^{22}$  1.472; (ii) b.p. 145-150°/3 mm.;  $n_D^{22}$ , 1.473. The first fraction (2 g.) appeared to be the pure *cis*-acid (VIIa) (Found: Eq. Wt. 201.2; calc. for  $C_{11}H_{20}O_3$  requires Eq. Wt. 200). The second fraction (5 g.) was not further examined.

*Norpinic semialdehyde* was prepared according to the method of Baeyer<sup>5</sup>.

*Ethyl 2 : 2-dimethyl-cyclobutane-3-carbethoxy-1-β-acrylate* (ethyl ester of XII).—A mixture of the crude norpinic semialdehyde (XI) (prepared from 10 g. of hydroxypinic acid, and dried in vacuum at 100° for 1 hour), malonic acid (12.5 g.), pyridine (40 c.c.) and piperidine (1.5 c.c.) was heated on the water-bath for 24 hours. After removal of pyridine under suction at 100°, the product was acidified by 10 % sulphuric acid, saturated with ammonium sulphate, and repeatedly extracted with ether. The ethereal solution after drying was evaporated, the gummy residue esterified and the resulting ester fractionated. It was a colorless oil possessing a mild pleasant smell; b.p. 123-25°/3.5 mm.;  $d_4^{30}$ , 1.0142;  $n_D^{30}$ , 1.4515, 1.452;  $R_{LD}$ , 67.56; calc. for  $C_{14}H_{22}O_4$ , 67.66 (one double bond). (Found: C, 66.21; H, 8.68.  $C_{14}H_{22}O_4$  requires C, 66.14; H, 8.6 per cent.). No crystalline product could be obtained by oxidising it with dilute permanganate.

*Ethyl 2 : 2-dimethyl-cyclobutane-1-carbethoxy-3-β-propionate* (XIII) was obtained by reducing the above ester (4 g.) in alcohol (20 c.c.) in presence of platinum oxide (0.1 g.) and hydrogen at 2.5 atmospheric pressure. The required theoretical quantity of hydrogen was absorbed within 2 hours but shaking was continued for 1 hour more. The reaction product was filtered, alcohol removed and the residual oil boiled at 130-32°/4 mm.; yield, 3.6 g;  $n_D^{30}$ , 1.4565 (Found: C, 65.70; H, 9.38.  $C_{14}H_{24}O_4$  requires C, 65.6; H, 9.4 per cent.).

<sup>5</sup> *Ber.*, 1896, **29**, 1907.



*Isolation of the acid* (XIII).—The substance on alkaline hydrolysis gave an acid which crystallised slowly, m.p. 55-60° (Found: Eq. Wt., 118.5.  $C_{10}H_{16}O_4$  requires Eq. Wt., 120).

*Cyclisation experiments*.—Dieckmannisation of the ester (5.1 g.) in benzene (25 c.c.) solution with sodium (0.71 g.) for 2 days or in xylene for 24 hours did not succeed. Although the product gave a violet coloration with ferric chloride, hydrolysis with barium hydroxide gave a gummy acidic product which on heating did not produce any nopinone.

Distillation of the lead salt of the acid (XIII, 3.2 g.) under conditions similar to those described by Komppa and Klami (*loc. cit.*) gave an oil (0.8 g.) from which a semicarbazone, m.p. 165-172° was obtained (less than 0.1 g.) which could not be further purified. The mixed m.p. of this sample with a genuine sample of nopinone semicarbazone (m.p. 185-86°), get depressed to about 150-55°.

2 : 2-Dimethyl-1 : 3-diacetyl-cyclobutane (XVI).—On close examination of the crystalline compound obtained by Blaise's reaction on norpinylic diacid chloride (see part I, Guha and Ganapathi, *Ber.*, 1936, **69**, 1194 ; part IV, *loc. cit.*) melted after careful purification at 104° (Found: C, 71.42 ; H, 9.52.  $C_{10}H_{16}O_2$  requires C, 71.4 ; H, 9.5 per cent.).

It gave a disemicarbazone, m.p. 233° (decomp.), which is difficultly crystallisable even from acetic acid. Three analyses of the compound gave values ranging from 27.5%, 27.9%, to 28.2%, for nitrogen which are below the required value for  $C_{12}H_{22}O_2N_6$  i.e., 29.8% nitrogen.

The ketone gave tests for  $CO.CH_3$  group (iodoform reaction). It is insoluble in 10% sodium hydroxide but gets slowly decomposed on prolonged boiling and decolorises alkaline permanganate only very slowly. Treatment with sodium ethoxide in alcoholic solution gave no verbenone but a white massy product which was not examined.

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