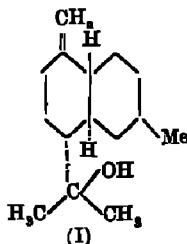


Terpenoids. Part XV. Synthesis of the Structure assigned to Veticadinol

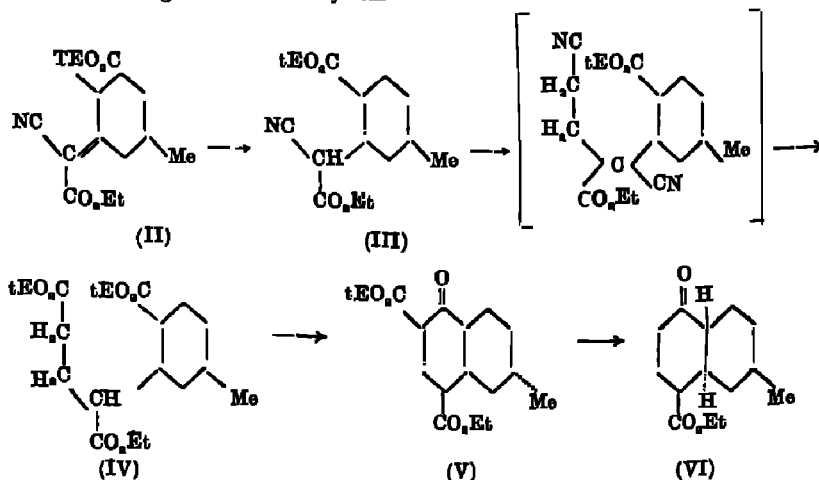
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By an application of the Wittig reaction with methyl-triphenylphosphonium iodide on 1-keto-4-ethoxy-carbonyl-6-methyldecalin and submitting the resulting 1-methylene-4-ethoxycarbonyl-6-methyldecalin to the Grignard reaction with methylmagnesium iodide, the synthesis of veticadinol has been achieved.

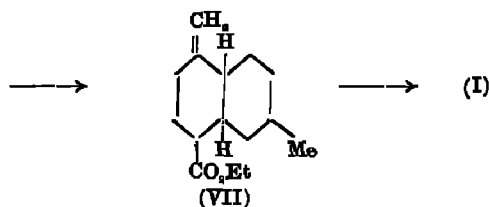
Veticadinol, the sesquiterpenoid monoethylenic tertiary alcohol, isolated from the oil of vetiver from Congo, has been assigned the expression (I) on the basis of chemical evidence.¹



The present investigations record a synthesis of the structure (I) with a *trans*-junction between the two rings in the decalin system:



1. Chiurdogiu and Deslomme, *Chem. Abs.*, 1961, 55, 18795; *Bull. Soc. Chim., Belg.*, 1961, 70, 5.



Ethyl 2-ethoxycarbonyl-5-methylcyclohexylidene-cyanoacetate (II), the starting material in this scheme, was obtained by condensing 2-ethoxycarbonyl-5-methylcyclohexanone² with ethyl cyanoacetate using ammonium acetate and glacial acetic acid.³ The unsaturated cyano-ester (II) was reduced with Pd-C catalyst (10%) under pressure. The addition of acrylonitrile to the afore-mentioned cyano-ester⁴ was carried out in presence of EtOH-KOH in dioxan and the resulting 2-ethoxycarbonyl-5-methyl-1-(α - γ -dicyano, α -ethoxycarbonylpropyl) cyclohexane (which was not isolated) was hydrolysed with dilute hydrochloric acid to provide tricarboxylic acid which was subsequently esterified to furnish 2-ethoxycarbonyl-5-methyl-(α - γ -diethoxycarbonylpropyl)cyclohexane (IV) in 64% overall yield.

Dieckmann cyclisation of the tri-ester (IV) afforded 1-keto-2,4-diethoxycarbonyl-6-methyldecalin (V) which was hydrolysed and decarboxylated by refluxing with dilute sulphuric acid and subsequently esterified with ethanol in presence of sulphuric acid to yield the keto-ester (VI). This keto-ester was heated with sodium ethoxide to convert the *cis* junction⁵ isomer in this compound (if present) to the *trans* one, the latter being more stable in the α -decalone system.⁷ This treatment further ensures the presence of the ethoxycarbonyl group at C₄ in the equatorial position which is more stable as compared to the axial one.

The keto-ester (VI) was characterised through its 2,4-dinitrophenylhydrazone and semicarbazone derivatives. Its IR absorption spectrum showed characteristic peaks⁸ at 1735 cm.⁻¹ (ester-C=O), 1720 cm.⁻¹ (-C=O), 1378 and 1460 cm.⁻¹ (-C-Me).

The ester (VI), when submitted to the Wittig reaction⁹ with methyltriphenylphosphonium iodide in the presence of methyl sulphanyl carbanion under nitrogen atmosphere, afforded *trans*-1-methylene-4-ethoxycarbonyl-6-methyldecalin (VII) in 66.72% yield. Its IR absorption spectrum showed peaks⁸ at 1735 cm.⁻¹ (-C=O), 1460 and 1360 cm.⁻¹ (-C-Me), 895 cm.⁻¹ ($\begin{matrix} R_1 \\ R_{11} \end{matrix} \text{C} = \text{CH}_2$).

The Grignard reaction on compound (VII) with methylmagnesium iodide afforded in 78.01% yield, *trans*-1-methylene-6-methyl-4-decalyldimethylcarbinol (I) in which the junction between the two rings of decalin is *trans* and the dimethylcarbinol group is in the equatorial position.

2. Kots and Hesse, *Annalen*, 1905, **342**, 306.

3. Banerjee and Shastri, *J. Amer. Chem. Soc.*, 1950, **72**, 1931.

4. Banerjee and Halwe, *this Journal*, 1960, **37**, 666.

5. Cross, "Introduction to Practical IR spectroscopy", Butterworth's Scientific Publications, London, 1960, pp. 59-63.

6. Nazarov et al., *Chem. Abs.*, 1953, **47**, 5366; *J. Gen. Chem. U.S.S.R.*, 1952, **22**, 449.

7. Bordwell, "Organic Chemistry", The Macmillan Co., New York, Collier Macmillan Ltd., London, 1963, p. 822.

8. Gipsenwald et al., *J. Org. Chem.*, 1962, **28**, 1188.

Compound (I) was characterised through its IR absorption spectrum which showed characteristic peaks⁵ at 3450, 1150 cm^{-1} ($-\text{OH}$), 1380 and 1460 cm^{-1} ($-\text{C}-\text{CH}_3$), 890 and 1650 cm^{-1} ($\begin{matrix} \text{R}_1 \\ \text{R}_{11} \end{matrix} \text{C}=\text{CH}_2$).

EXPERIMENTAL

Ethyl 2-Ethoxycarbonyl-5-methylcyclohexylidene-cyanoacetate (II).—A mixture of 2-ethoxycarbonyl-5-methylcyclohexanone (46 g.), ethyl cyanoacetate (28.5 g.), glacial acetic acid (12.0 ml.), ammonium acetate (4. g.), and benzene (300 ml.) was refluxed under a water separator till the water came over. The reaction mixture was cooled, ammonium acetate (2g.) was added, and the contents were refluxed for 3-4 hrs. Refluxing was again interrupted till a total of 8 g. of ammonium acetate had been added. Heating was continued for several hours after the last addition of the catalyst. The contents were cooled, washed with water ($\times 6$) and the organic substance was extracted with ether-benzene mixture. After removing the solvent, vacuum distillation of the product furnished the cyano-ester (II) as a colorless oil, b.p. 175-80°/15mm., yield 48.5 g. (69.5%), η_D^{20} 1.4830. (Found: N, 4.92. $\text{C}_{15}\text{H}_{21}\text{NO}_4$ requires N, 5.01%).

Wavenumber CM^{-1}

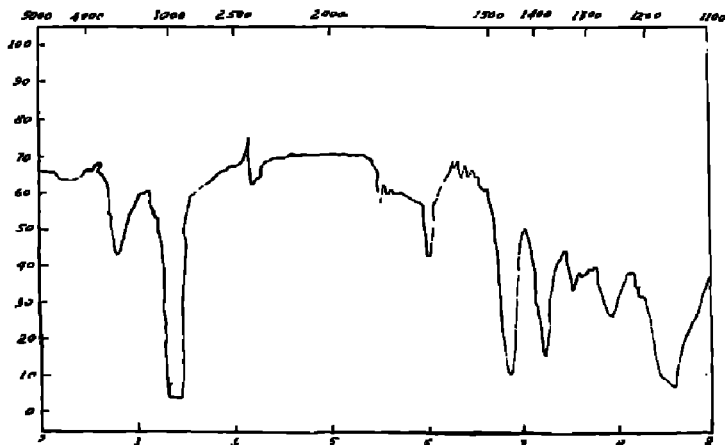


FIG. 1
Wavelength in Microns
IR Spectrum (Liquid film) of the structure assigned to Veticadinol.

Ethyl 2-Ethoxycarbonyl-5-methylcyclohexylcyanoacetate (III).—Hydrogenation of the unsaturated cyano-ester (II) (46.5 g.) was carried out at an initial pressure of 31 lb. in presence of palladised charcoal (10%, 1.5g.) in anhydrous ethanol (150 ml.). The reduction was completed in 30 hrs. The catalyst was filtered and the solvent removed. The residue was distilled to afford the ester (III) in 43.0g. (91.88%), yield, b.p. 155-60°/5 mm., η_D^{20} 1.4650. (Found: N, 5.01. $\text{C}_{11}\text{H}_{15}\text{NO}_4$ requires N, 4.98%).

*Melting points and boiling points are uncorrected. Microanalysis by Mr. B. N. Anand, Microanalyst, Panjab University, Chemistry Department, Chandigarh. IR spectra were recorded on Beckman IR 5 with sodium chloride optics using a thin liquid film.

2-Ethoxycarbonyl-5-methyl-1-(α,γ -diethoxycarbonylpropyl)-cyclohexane (IV).—To an ice-cold solution of the saturated cyano-ester (III) (40.1g.) and acrylonitrile (10.2 g.) in dry dioxan (40 ml.) was slowly added EtOH-KOH (10ml., 15%). The mixture was kept in an ice-bath for 1hr. with occasional shaking. The reaction mixture was left for 10 days at the room temperature when it turned deep brown. It was then taken up in benzene, washed thoroughly with HCl (dil.) and finally with water. The solvent was removed, leaving the crude product as a viscous oil, yield 41.75g. (87.5%). This product could not be distilled without decomposition and it was not analysed.

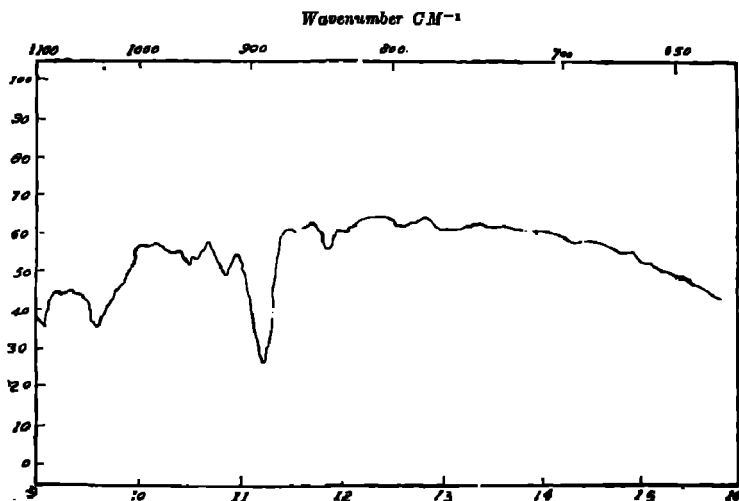


FIG. 2
IR Spectrum (Liquid film) of the structure assigned to Veticadinol.

The crude dicyano-ester (41.75g.) was refluxed for 50 hrs. with HCl (conc., 400 ml.). Excess of HCl was removed under reduced pressure and the residue was extracted with ether. The solvent was removed and the crude tricarboxylic acid was refluxed with a mixture of dry benzene (400 ml.), ethanol (150 ml.) and H_2SO_4 (conc., 10 ml.) in a flask fitted with a continuous water separator till no more water separated (40 hrs.) The contents were worked up in the usual manner to afford (IV), b.p. 185-88°/5-8 mm., yield 28.5 g. (84%) η_D^{25} 1.4870. (Found: C, 64.20; H, 9.19. $C_{10}H_{18}O_6$ requires C, 64.02; H, 9.05%).

Trans-1-Keto-4-ethoxycarbonyl-6-methyldecalin (VI).—To sodium dust (2.7g.) in dry benzene (50 ml.) was added the tri-ester (IV) (18.0g.) under an atmosphere of nitrogen. The reaction started immediately and the mixture was refluxed for 18 hrs. when the reaction mixture assumed a reddish-brown colour. The contents were cooled in an ice-bath and decomposed with HCl (dil.). The benzene layer was separated and washed with sodium bicarbonate solution and water. The residue obtained after removal of the solvent developed a violet colour with EtOH- $FeCl_3$. A small portion of the β -keto-ester (V) was purified by distillation at 165-70°/5 mm. for analysis. (Found: C, 65.99; H, 7.73. $C_{17}H_{26}O_3$ requires C, 66.21; H, 7.85%).

The β -keto-ester (V) was refluxed for 18 hr. with H_2SO_4 (15%, 60 ml.). The contents were cooled and extracted with ether. After removal of the solvent, the crude keto-acid was esterified with a mixture of ethanol (35 ml.), dry benzene (100 ml.) and H_2SO_4 (conc., 1 ml.) in a Dean and Stark apparatus till the water had ceased to separate (12 hrs.). The contents were worked up in the usual manner and the crude keto-ester was refluxed with sodium ethoxide (prepared from 0.77 g. of sodium and 10 ml. of ethanol) for 3 hrs. After the usual work-up, it provided *trans*-keto-4-ethoxycarbonyl-6-methyldecalin, b.p. 150-155°/6 mm., yield 5.0g. (41.6%), η_D^{25} 1.4750. (Found: C, 70.75; H, 9.42. $C_{14}H_{22}O_3$ requires C, 70.55; H, 9.31%).

The 2,4-*DNP*, prepared by the sulphuric acid method in cold and recrystallised from ethyl acetate afforded orange red needles, m.p. 134°. (Found: N, 13.20. $C_{20}H_{26}O_5N_4$ requires N, 13.30%).

The *semicarbazone*, prepared by the usual manner and recrystallised from dilute ethanol, melted at 208°. (Found: N, 14.14. $C_{12}H_{18}O_2N_3$ requires N, 14.23%).

Trans-1-Methylene-4-ethoxycarbonyl-6-methyldecalin (VII).—A solution of sodium methylsulphinyl carbanion was prepared under nitrogen atmosphere from sodium hydride (0.28g.) and dimethyl sulphoxide (5.5 ml.). The solution was cooled in a cold-water bath and stirred during addition of methyltriphenylphosphonium iodide (2.4 g.) in dimethyl sulphoxide (11.5 ml.) when the reddish colour of the methylene phosphorane was produced. After stirring at the room temperature for 15 min., the keto-ester (VI) (1.21g.) in THF (5 ml.) was added and stirring continued for 3 hrs. at 60°. The reaction mixture was cooled and poured on cold water. The organic layer was taken up in petroleum (40-60°) and washed thrice with cold water. After removal of the solvent, the residue was distilled under reduced pressure to afford (VII) (0.8 g.) in 66.72% yield, b.p. 110°C/7.8 mm., η_D^{20} 1.4750. (Found: C, 76.36; H, 10.10. $C_{15}H_{24}O_2$ requires C, 76.22; H, 10.24%).

Trans-1-Methylene-6-methyl-4-decalyldimethyl Carbinol (I).—To the Grignard reagent, prepared from magnesium (0.23 g.) and methyl iodide (1.4g.) in dry ether (10 ml.) was added dropwise a solution of the above compound (0.75 g.) in dry ether (15 ml.). After keeping overnight, the reaction mixture was refluxed for 7-8 hrs. on a water bath. It was then cooled and decomposed with a saturated solution of ammonium chloride and worked up in the usual manner. After evaporating the solvent, the residue was vacuum-distilled to provide compound (I) (0.55 g.) in 78.01% yield, b.p. 80°/4-5 mm., η_D^{25} 1.4940. (Found: C, 80.80; H, 11.59. $C_{15}H_{26}O$ requires C, 81.02; H, 11.79%).

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