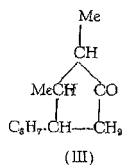
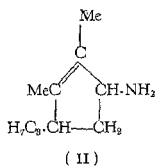
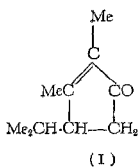


SYNTHETICAL INVESTIGATIONS IN THE THUJONE SERIES, PART VIII. SYNTHESIS OF IsoTHUJONE.

By P. C. Guha and A. Kuppusami.

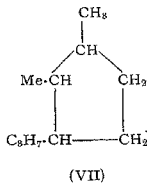
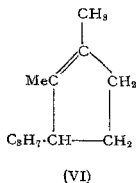
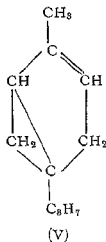
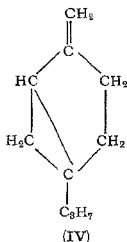
The rearrangement of the members of the thujane group into those containing cyclopentane ring is characteristically represented by the conversion of sabinol to *isothujone*¹ (I) on heating with aluminium *isopropylate*, of thujone into *isothujone* (i) on being heated with sodium¹ and also with ammonium hydrogen sulphide²; (ii) on distillation over copper or nickel³; (iii) by Sabatier and Senderen's process on reduction⁴; (iv) by concentrated sulphuric acid⁵. Other examples of this rearrangement are the reduction of thujone oxime (liquid) by sodium and alcohol to *isothujylamine* (II)⁶ and the conversion of thujone to thujamenthone (III) by hydrogen in presence of nickel⁶.



Richter, Wolff and Presting⁷ during their unsuccessful attempt to convert sabinene (IV) into the difficultly obtainable α -thujene (V)

1. Schmidt, *Ber.*, 1929, **62**, 573.
2. Agostenelli, *Gazz.*, 1914, **2**, 111.
3. Trieb and Schmidt, *Ber.*, 1927, **60**, 2338.
4. Godchot, *C.R.*, 1914, **158**, 1807; 1921, **172**, 688; 1927, **185**, 1807.
5. Bayer, *Ber.*, 1894, **27**, 1922; Wallach, *Annalen*, 1895, **286**, 101; 1902, **323**, 334; 1915, **408**, 163; *Ber.*, 1895, **28**, 1958; Haller, *C.R.*, 1905, **140**, 1728.
6. Wallach, *Annalen*, 1893, **272**, 99, 109; **275**, 179.
7. *Ber.*, 1931, **64**, 871.

under the influence of Pd black, analogously with rearrangement of β -pinene to α -pinene, found that sabinene is converted into 1:2-dimethyl-3-isopropyl-cyclo-pentene (VI; cf. Wallach⁸) (the position of the double bond being uncertain).



Formation of 1:2-dimethyl-3-isopropylcyclopentane (VII) has been observed from α -thujene⁹ on distillation over nickel in an atmosphere of hydrogen, from thujane¹⁰ by Sabatier and Senderen's process of hydrogenation, from sabinol¹¹ on catalytic hydrogenation with nickel, Pd and Pt, and from thujone¹² in the presence of Pd asbestos.

8. *Nach. K. Ges. Göttingen*, 1910, p. 544.

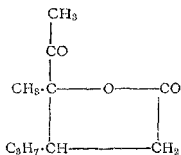
9. Zelinsky and Kasansky, *Ber.*, 1927, **16**, 1096.

10. Kishner, *J. Russ. Phy. Chem. Soc.*, 1912, **44**, 321.

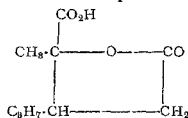
11. Henderson and Robertson, *J.C.S.*, 1923, **123**, 1715; 1926, 2761; Wallach, *Nach. Ges. Wis. Göttingen*, 1919, **44**, 759.

12. Kasansky, *Ber.*, 1929, **62**, 2205; Zelinsky and Kasansky, *Ber.*, **16**, 1096.

As the formation of *isothujone* from members of the *thujane* series (containing an 1:3-bridged *cyclohexane* skeleton) is associated with peculiar opening up of the *cyclohexane* ring involving rearrangement of bonds and as the structure assigned to *isothujone* is based on evidences (cf. Simonsen, *Terpenes*, Vol. II, p. 37) gathered from its degradation products having no *cyclopentane* skeleton present in them, *e.g.*, in the ketolactone (VIII), the lactonic acid (IX), *isopropyl laevulic acid* and *isopropyl succinic acid*; it seemed desirable to effect a direct synthesis and place its structure beyond all doubt and controversy.

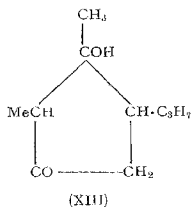
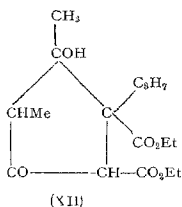
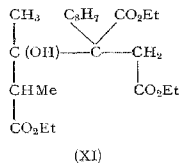
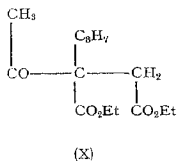


(VIII)



(IX)

For this synthesis, ethyl $\beta\beta$ -carbethoxy *isopropyl laevulate* (X), obtained from ethyl acetoacetate by successive replacement of its active hydrogen atoms by the groups ($-\text{C}_6\text{H}_7$) and ($-\text{CH}_2\text{CO}_2\text{Et}$), forms the starting material. β -Carbethoxy *isopropyl laevulinic ester* reacts with α -bromopropionic ester in presence of zinc to yield ethyl $\beta\beta$ -*isopropyl*: carbethoxy- $\gamma\gamma$ -hydroxy: methyl- δ -methyl adipate (XI). This on being subjected to the action of potassium in boiling xylene, yielded a mixture of two compounds of which one (XII) was soluble and the other (XIII) insoluble in alkali. The alkali insoluble portion, furnished 2:3-dimethyl-3-hydroxy-4-*isopropyl-cyclopentanone* (XIII). It is significant that the carbethoxy group attached to the carbon atom, linked with the *isopropyl* grouping, got replaced by an atom of hydrogen during Dieckmannisation. The hydroxy *cyclopentanone* compound (XIII) on dehydration with P_2O_5 yielded *isothujone* (I), b.p. 224-25°; oxime, 117.5°. The mixed melting point of the oxime (prepared from the synthetic product) taken with the oxime of a sample of *isothujone* prepared from *thujone* remained undepressed.



EXPERIMENTAL.

Ethyl ββ-carbethoxyisopropyl laevulate (X).—Sodium (15 g.) was dissolved in absolute alcohol (250 c.c.) and to the resulting sodium ethylate was added *isopropyl acetoacetic ester* (86 g.) prepared according to the method of Frankland and Duppa¹³. After allowing it to stand for about half-an-hour ethyl bromacetate (84 g.) was slowly added, taking care to maintain the reaction under control. After the initial reaction was over, the mixture was refluxed for about 10 to 12 hours on a water-bath. The excess of alcohol having been removed by distillation, the product was poured into water and neutralised with a little dilute acetic acid. The compound was extracted with ether, dried, ether removed by distillation and the residual liquid distilled under reduced pressure. The pure compound boils at 57°/20 mm.; yield 78 g. (Found: C, 59.58; H, 8.62. C₁₃H₂₂O₅ requires C, 60.48; H, 8.45 per cent.).

13. *Annalen*, **145**, 78.

Ethyl β:β-isopropyl:carbethoxy-γ:γ-hydroxy:methyl-δ-methyl adipate (XI).—The above ester (X, 50 g.), pure dry zinc (26.5 g.) and dry benzene (250 c.c.) were taken in a litre flask fitted with a reflux condenser and ethyl α-brom-propionate (35.3 g.) was slowly added. The vigorous reaction at the outset was kept under control by cooling the flask under tap. After the initial reaction was over, the contents of the flask were refluxed for about eight to ten hours on water-bath; and after cooling the reaction product was poured into water. In order to dissolve the basic zinc salt, the mixture was acidified with dilute hydrochloric acid and then extracted with benzene. After removal of benzene the residual oil was distilled under reduced pressure. The first fraction distilling between 57-75°/20 mm. was the unreacted original compound (X); the next two fractions distilled respectively between 100-115°/20 mm. and 148-180°/20 mm. From them on redistillation were obtained two fractions boiling respectively at 102-103°/25 mm. and 168°/23 mm. The former is the required hydroxy compound (XI); yield 20 g. (Found: C, 59.92; H, 9.1. C₁₈H₃₂O₇, requires C, 60.0; H, 8.89 per cent.).

The compound boiling at 168°/23 mm. weighed 14 g. (Found: C, 49.92; H, 5.1 per cent.) and has not been further examined.

Dieckmann reaction on compound (XI): Formation of compounds (XII) and (XIII).—The hydroxy compound (20 g.) was added slowly to molecular sodium (1.5 g.) in dry benzene and the mixture heated under reflux for 15 hours on a water-bath. It was then poured into a mixture of ice and dilute sulphuric acid. As no definite product could be isolated from this, the reaction was repeated using potassium in xylene medium.

The hydroxy compound (XI) was added slowly to molecular potassium (1.25 g.) in dry xylene. After the initial reaction was over, the contents of the flask were heated under reflux at 160° for about 30 hours. The solvent was then distilled off and the residue poured into ice-cold water and extracted with ether. The aqueous solution was acidified with dilute hydrochloric acid when an oily liquid separated out. This was extracted with ether, dried over anhydrous magnesium

sulphate, ether removed and the residual oil distilled, and the fraction coming over between 132-45°/12 mm. collected; yield 5 g. It gave a pink coloration with ferric chloride (Found: C, 60.97; H, 9.75. $C_{10}H_{16}O_6$ requires C, 61.15; H, 9.63 per cent.).

Isolation of 2:3-dimethyl-3-hydroxy-4-isopropyl-cyclopentanone (XIII) from the ether extract.—On removal of the ether and after distilling off the low boiling unreacted hydroxy compound (XI) under reduced pressure, a thick viscous liquid was left over. Placed in a vacuum desiccator, it was allowed to cool in a refrigerator during 7 days when a grey solid separated out. This recrystallised from a mixture of ether and petroleum ether in fine long colourless needles, m.p. 63-64°; yield, 0.5 g. (Found: C, 69.96; H, 10.92. $C_{10}H_{18}O_2$ requires C, 70.59; H, 10.59 per cent.).

Dehydration of compound (XIII): Formation of isothujone (I).—The compound (XIII, 3 g. collected from several experiments) was refluxed with phosphorus pentoxide (5 g.) in dry benzene during 10 to 12 hours and poured into water. After the removal of benzene the crude product was distilled under ordinary pressure and the fraction coming at 224-228° collected; yield 1.5 g. (Found: C, 78.68; H, 11.27. $C_{10}H_{16}O$ requires C, 78.84; H, 10.53 per cent.). The oxime melted at 116-117°.

Isothujone-oxime.—Isothujone was prepared by boiling thujone (25 g.) with 33 per cent. sulphuric acid (75 c.c.)⁵, b.p. 223-226°. The oxime melted at 117°.

Mixed m.p. of the above two samples of oximes remained undepressed.

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