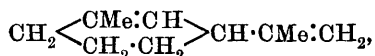


CLXXXVIII.—*Experiments on the Synthesis of the Terpenes. Part XIII. Synthesis of isoCarvestrene ($\Delta^{6:8(9)}$ -m-Menthadiene) and its Derivatives.*

By KENNETH FISHER and WILLIAM HENRY PERKIN, jun.

DURING last year (Perkin and Tattersall, *Trans.*, 1907, **91**, 480) an account was published of a series of experiments which resulted in the synthesis of carvestrene,

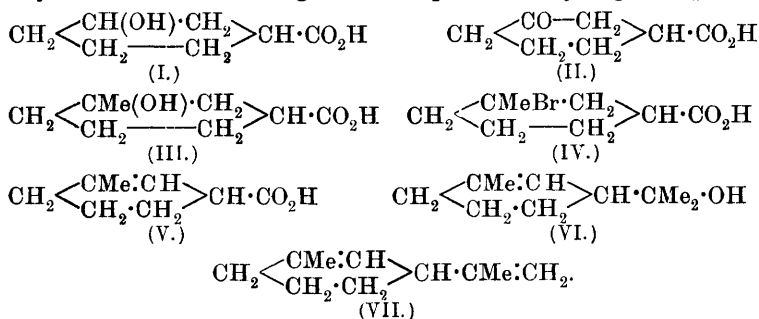


and several of its more important derivatives, and, as the methods employed during that research have a direct bearing on the present communication, the course of that synthesis may be briefly sketched in the following way. In the first place, *m*-hydroxybenzoic acid was reduced by sodium and alcohol to *cyclohexanol*-3-carboxylic acid (I), which, on oxidation with chromic acid, yielded *cyclohexanone*-3-carboxylic acid (II). By the action of magnesium methyl iodide on the ester of this acid, 1-methyl*cyclohexan*-1-ol-3-carboxylic acid (III)

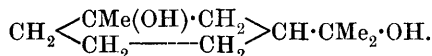
was obtained, and was next converted by treatment with hydrobromic acid into 1-bromo-1-methylcyclohexane-3-carboxylic acid (IV).

When this bromo-acid was digested with pyridine, it was decomposed with elimination of hydrogen bromide and formation of 1-methyl- Δ^1 -cyclohexene-3-carboxylic acid (V), the ester of which was converted into Δ^1 -*m*-menthenol(8) or dihydrocarvestrenol (VI) by the action of magnesium methyl iodide.

$\Delta^{1:8(9)}$ -*m*-Menthadiene or carvestrene (VII) was finally obtained when dihydrocarvestrenol was digested with potassium hydrogen sulphate.



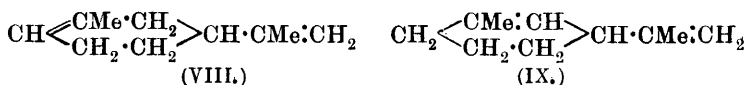
The properties of carvestrene which have a direct bearing on the present communication are the following. Carvestrene distils at 179°, gives a violet coloration when sulphuric acid is added to its solution in acetic anhydride, and combines with hydrogen chloride and hydrogen bromide to form carvestrene *trans*-dihydrochloride, $\text{C}_{10}\text{H}_{16}\cdot 2\text{HCl}$ (m. p. 52·5°), and *trans*-dihydrobromide, $\text{C}_{10}\text{H}_{16}\cdot 2\text{HBr}$ (m. p. 48—50°), respectively. Dihydrocarvestrenol, $\text{C}_{10}\text{H}_{17}\cdot\text{OH}$, distils at 105—108°/30 mm., and is converted by shaking with dilute sulphuric acid into *cis*-tetrahydrocarvestrenediol (m. p. 94°),



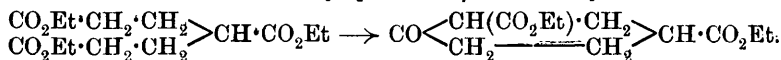
The corresponding *trans*-modification, obtained from *trans*-carvestrene dihydrobromide by treatment with silver acetate and subsequent hydrolysis, melts at 127°. A direct comparison of these synthetical products with the actual specimens of carvestrene and its derivatives prepared by Baeyer (*Ber.*, 1894, 27, 3486) during his classical researches on this hydrocarbon, proved conclusively that they were identical.

With the single exception of sylvestrene, the constitution of which still remains to be proved, the terpenes of the *m*-menthadiene series do not appear to occur in essential oils, and, as they possess many properties of great interest, it seemed important to attempt to prepare some, at all events, of the unknown members, by synthetical means. The present communication contains an account of the synthesis of

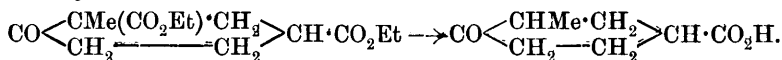
$\Delta^{6:9(9)}$ -*m*-menthadiene (VIII), for which, on account of its very close relationship to carvestrene (IX), we propose the name *isocarvestrene*:



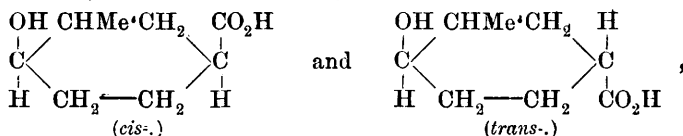
A short time since (Kay and Perkin, *Trans.*, 1906, **89**, 1647), it was shown that ethyl *cyclohexanone*-2:4-dicarboxylate is readily obtained when sodium reacts with ethyl pentane- $\alpha\gamma\epsilon$ -tricarboxylate:



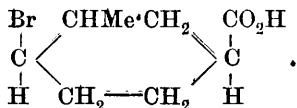
We now find that the sodium derivative of this ester is converted quantitatively by treatment with methyl iodide into *ethyl 1-methylcyclohexan-6-one-1:3-dicarboxylate*, and that this ester is decomposed on hydrolysis with formation of *1-methylcyclohexan-6-one-3-carboxylic acid*:



This new keto-acid melts at 94–96°, yields an *oxime* (m. p. 172°) and a *semicarbazone* (m. p. 200°), and, when reduced by sodium amalgam, is converted into a mixture of the *cis*- and *trans*-modifications of *1-methylcyclohexan-6-ol-3-carboxylic acid*:



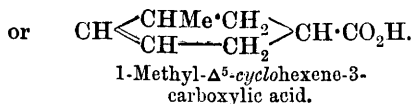
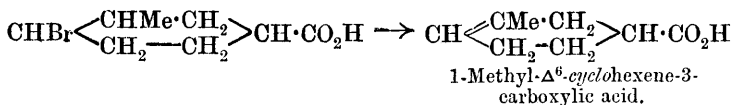
in which the latter greatly predominates. The *cis*-acid melts at 141°, yields a *lactone* (m. p. 46°), and, when treated with hydrobromic acid, is converted into *cis*-6-bromo-1-methylcyclohexane-3-carboxylic acid (m. p. 53°):



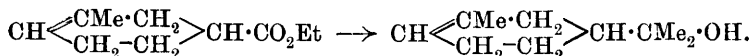
The *trans*-hydroxy-acid melts at 115–117°, and also reacts readily with hydrobromic acid, but the *trans*-6-bromo-1-methylcyclohexane-3-carboxylic acid thus produced is a syrup.

When the mixture of the *cis*- and *trans*-modifications of 6-bromo-1-methylcyclohexane-3-carboxylic acid, obtained by the action of hydrobromic acid on the product of the reduction of 1-methylcyclohexan-6-one-3-carboxylic acid, is esterified and digested with diethylaniline, hydrogen bromide is eliminated with the formation of *ethyl 1-methyl- Δ^6 -cyclohexene-3-carboxylate* (b. p. 146°/100 mm.), which on hydrolysis yields the free acid (b. p. 184°/100 mm.). The elimination of hydrogen

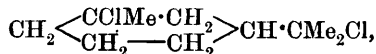
bromide from 6-bromo-1-methylcyclohexanecarboxylic acid may take place in the two following directions :



In order to decide between these two possibilities, a long series of oxidation experiments with ozone, permanganate, and nitric acid was undertaken, but the products in all these cases were syrups which we were unable to purify. We found, however, that the syrupy product obtained when the unsaturated acid was treated with ozone is a ketonic acid, and this is strong evidence in favour of the presence of the group $-\text{CH}:\text{CMe}-$. Fortunately, as the research developed, we were able to obtain indirect evidence which conclusively demonstrated that the product of the elimination of hydrogen bromide from 6-bromo-1-methylcyclohexane-3-carboxylic acid is 1-methyl- Δ^6 -cyclohexene-3-carboxylic acid. Furthermore, the fractional crystallisation and analysis of the calcium salt of the unsaturated acid (p. 1887) proved that it did not contain the other isomeride, even in small quantities. When ethyl 1-methyl- Δ^6 -cyclohexene-3-carboxylate is added to an ethereal solution of magnesium methyl iodide, it is quantitatively converted into dihydroisocarvestrenol or Δ^6 -m-menthenol(8) :

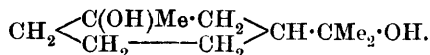


This interesting substance has the penetrating odour of peppermint and terpineol characteristic of its class; it distils at $106^\circ/20$ mm., and yields a *nitrosochloride*, melting at 125° . It reacts also with hydrogen chloride and bromide, yielding a *dihydrochloride*, $\text{C}_{10}\text{H}_{16}, 2\text{HCl}$, and a *dihydrobromide*, $\text{C}_{10}\text{H}_{16}, 2\text{HBr}$, which melt at 52.5° and $48-49^\circ$ respectively, and careful comparison has shown that these halogen derivatives are identical with carvestrene dihydrochloride,



and carvestrene dihydrobromide.

Furthermore, dihydroisocarvestrenol is converted by the prolonged action of dilute sulphuric acid into *cis-tetrahydrocarvestrendiol* (m. p. 94°)



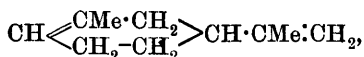
These important reactions prove in a striking manner the position

of the double linking, not only in dihydroisocarvestrenol, but also in 1-methyl- Δ^6 -cyclohexene-3-carboxylic acid.

Remarkable results were obtained during the investigation of the products of the elimination of water from dihydroisocarvestrenol.

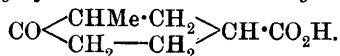
This elimination takes place very readily when the tertiary alcohol is left in contact with a large excess of magnesium methyl iodide at the ordinary temperature, and results in the formation of isocarvestrene (b. p. 176—177°/765 mm.) and a diterpene, $C_{20}H_{32}$, b. p. 188—190°/20 mm., which we have named *diisocarvestrene*.

isoCarvestrene has been very carefully investigated, and it is pointed out in the experimental part (p. 1891) that it exhibits quite unexpected properties both from a physical and chemical point of view. The determination of its refractive power has yielded results which are very high, and agree better with those characteristic of a terpene containing conjugated double linkings than with those of the hydrocarbon of the formula



which should result from the elimination of water from dihydroisocarvestrenol. Another remarkable point is the fact that, although dihydroisocarvestrenol reacts so readily with halogen acids to yield derivatives of carvestrene, these derivatives are not produced by the action of halogen acids on *isocarvestrene*. The hydrocarbon, on the contrary, appears to behave towards bromine and halogen acids in the way characteristic of a terpene containing conjugated double linkings (compare p. 1891).

1-Methylcyclohexan-6-one-3-carboxylic Acid,



The starting point in the synthesis of this keto-acid was ethyl cyclohexanone-2:4-dicarboxylate, which was prepared by the action of sodium on ethyl pentane- $\alpha\gamma\epsilon$ -tricarboxylate by the method described by Kay and Perkin (Trans., 1906, 89, 1647). This keto-ester (24 grams) was mixed with a solution of sodium (2.3 grams) in methyl alcohol, cooled well, and then methyl iodide (17 grams) gradually added. After remaining overnight, the product, which was quite neutral, was mixed with water, extracted with ether, the ethereal solution washed with water, evaporated, and the residual oil hydrolysed by boiling with dilute sulphuric acid (10 per cent.) for several hours and until the evolution of carbon dioxide had completely ceased. The product was saturated with ammonium sulphate, repeatedly extracted with ether, the ethereal solution dried and evaporated, when a syrup

remained which, especially when rubbed with a rod, rapidly crystallised. The mass was left in contact with porous porcelain until free from oil, and the colourless residue recrystallised from ether. A further quantity of solid was obtained by extracting the porous porcelain in a Soxhlet apparatus and fractionating the extract, when a quantity of oil distilled at 190—200°/20 mm. and crystallised on cooling:

0.1520 gave 0.3438 CO₂ and 0.1060 H₂O. C = 61.7; H = 7.7.

C₈H₁₂O₃ requires C = 61.5; H = 7.7 per cent.

1-Methylcyclohexan-6-one-3-carboxylic acid melts at 93—94°, and is sparingly soluble in dry ether or light petroleum; it dissolves readily in alcohol, benzene, chloroform, or hot water, but is much less soluble in cold water. It crystallises from ether in crusts, from a mixture of benzene and light petroleum in groups of irregular plates, and from water in hard, glistening, six-sided plates.

In order to determine whether the acid (like the parent substance, cyclohexanone-4-carboxylic acid: Trans., 1904, 85, 426) crystallises with water, a specimen was crystallised from water, and, after remaining in the air for several days, the analysis:

0.1453 gave 0.3279 CO₂ and 0.1038 H₂O. C = 61.5; H = 7.9 per cent.

showed that the acid was anhydrous. The basicity of the acid was determined by titration with decinormal sodium hydroxide, when 0.0775 neutralised 5.0 c.c., whereas this amount of a monobasic acid, C₈H₁₂O₃, should neutralise 4.97 c.c. The neutral solution of the ammonium salt of the acid showed the following behaviour with reagents. The addition of barium or calcium chlorides, or lead or copper acetates, gave no precipitate even on boiling, but, on the addition of silver nitrate, the *silver* salt separated as a crystalline precipitate, which is readily soluble in hot water, and separates, on cooling, as a satiny mass of crystals somewhat like silver acetate.

The *oxime*.—This derivative was prepared by dissolving the acid in excess of aqueous potassium hydroxide and adding hydroxylamine hydrochloride.

After two days, the solution was acidified with dilute hydrochloric acid, when a white, chalky precipitate separated, which was collected and crystallised from water:

0.1372 gave 9.5 c.c. N₂ at 16° and 762 mm. N = 8.1.

C₈H₁₃O₃N requires N = 8.2 per cent.

This oxime softens at about 165°, and melts at 171—172°; it is rather sparingly soluble in cold, but readily so in hot, water, and separates, when the solution is allowed to cool slowly, in glistening needles grouped in stars.

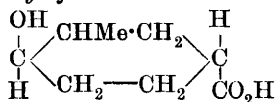
The *semicarbazone* separates at once as a granular precipitate when

the dilute aqueous solution of the acid is mixed with semicarbazide hydrochloride and sodium acetate. The precipitate was collected, washed, and recrystallised from much water, from which it is deposited in minute crystals; it may also be crystallised from alcohol, in which it is sparingly soluble. When rapidly heated, it softens at 195° and melts at about 200° with decomposition:

0.1626 gave 27.8 c.c. N_2 at 16° and 762 mm. $N = 20.0$.

$C_9H_{15}O_3N_3$ requires $N = 19.7$ per cent.

trans-1-Methylcyclohexan-6-ol-3-carboxylic Acid,



In preparing this acid, 1-methylcyclohexan-6-one-3-carboxylic acid is dissolved in as little sodium carbonate as possible, and treated, in a wide bottle fitted with a mechanical stirrer, with three times the theoretical amount of freshly-prepared sodium amalgam (3 per cent.).

The amalgam was added in about six portions during eight hours, and hydrochloric acid run in from time to time in order to neutralise most of the alkali as it was formed, but the solution was always kept distinctly alkaline. The product was acidified, extracted ten times with ether on the machine, the ethereal solution dried, evaporated, and the residual syrup again reduced in the same way.* After the second reduction and extraction, the syrupy acid generally became semi-solid, and, in contact with porous porcelain, a colourless mass was obtained, which, after crystallisation from ether, gave the following results on analysis:

0.1377 gave 0.3067 CO_2 and 0.1115 H_2O . $C = 60.7$; $H = 9.0$.

$C_8H_{14}O_3$ requires $C = 60.8$; $H = 8.8$ per cent.

This formula was controlled by titration with decinormal sodium hydroxide, when 0.0796 required 5.05 c.c. for neutralisation, whereas this amount of a monobasic acid, $C_8H_{14}O_3$, should neutralise 5.04 c.c.

trans-1-Methylcyclohexan-6-ol-3-carboxylic acid melts at $115-117^{\circ}$, is sparingly soluble in cold, but much more readily so in boiling, ether, and separates when the solution is concentrated and allowed to stand, in hard crusts. It appears to be more soluble in warm water than the *cis*-acid, and, unlike the latter, it usually takes several hours to crystallise, and then separates in stellate groups of flat needles. When the *trans*-hydroxy-acid (0.2 gram) is heated in a test-tube, it melts, and then distils without the least indication of

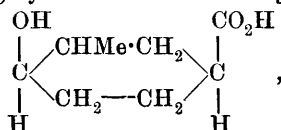
* If the amalgam employed is prepared from freshly-distilled mercury and clean sodium, this second reduction is often unnecessary.

elimination of water or charring. In contact with a speck of the crystalline hydroxy-acid, the colourless, syrupy distillate rapidly solidifies, melts directly at 108—113°, and consists of the almost pure *trans*-acid. This experiment shows that the *trans*-acid distils under the ordinary pressure without the formation apparently even of traces of the lactone of the *cis*-acid.

trans-6-Bromo-1-methylcyclohexane-3-carboxylic Acid.—The *trans*-hydroxy-acid dissolves readily in fuming aqueous hydrobromic acid (saturated at 0°), and the solution remains clear, but, when gradually heated on the water-bath, it clouds and an oil separates. Since this oil did not crystallise even on long standing, water was added, the bromo-acid extracted with ether, the ethereal solution dried and evaporated, when a syrup was obtained which contained about 34 per cent. of bromine, whereas the formula $C_8H_{13}O_2Br$ requires 36.2 per cent.

In this behaviour with hydrobromic acid, the *trans*-acid differs, in a striking manner, from the corresponding *cis*-acid (p. 1885).

cis-1-Methylcyclohexan-6-ol-3-carboxylic Acid,



and its Lactone.

It has already been mentioned (p. 1878) that the product of the reduction of 1-methylcyclohexan-6-one-3-carboxylic acid contains both the *cis*- and *trans*-modifications of 1-methylcyclohexanolcarboxylic acid, but that the *trans*-modification greatly predominates. The separation of the *cis*-acid proved, therefore, to be a matter of difficulty, and it was ultimately accomplished by the following indirect process.

The crude mixture of hydroxy-acids was dissolved in 5 volumes of hydrobromic acid (saturated at 0°), and then heated on the water-bath until the separation of the oily bromo-acids was complete. Water was then added, the bromo-acids extracted with ether, the ethereal solution washed, dried, evaporated, and the residue heated to boiling with 3 volumes of anhydrous pyridine for two hours. The product was acidified and distilled in steam, when an oil (*A*) passed over, and, as soon as this ceased to condense, the flask was changed and the distillation continued so long as a distinctly acid distillate (*B*) passed over. The residue in the distillation flask yielded, on extraction with ether, considerable quantities of the *trans*-hydroxy-acid. The distillate (*A*) was extracted with ether, the ethereal solution dried and evaporated, and the oily residue left in the ice-chest when,

after some days, a quantity of crystals of the lactone of the *cis*-acid had separated and were collected. The filtrate, which consisted largely of 1-methyl- Δ^6 -cyclohexene-3-carboxylic acid, was converted into the ester of the latter, and employed as such in the preparation of dihydroisocarvestrenol (p. 1887). The lactone of the *cis*-acid was left in contact with porous porcelain until quite free from oil, and then crystallised from light petroleum (b. p. 35—40°):

0.1745 gave 0.4393 CO₂ and 0.1342 H₂O. C = 68.8; H = 8.5.

C₈H₁₂O₂ requires C = 68.6; H = 8.6 per cent.

The lactone of *cis*-1-methylcyclohexan-6-ol-3-carboxylic acid melts at 46—47°, and is readily soluble in most organic solvents, but sparingly so in cold light petroleum. When boiled with water, it is hydrolysed only with great difficulty, and it is also only slowly attacked by dilute sodium carbonate. It dissolves readily in hot dilute potassium hydroxide, and, on acidifying and extracting with ether, a solid acid is obtained which, after recrystallisation from water, melts at 139—141° and consists of pure *cis*-1-methylcyclohexanolcarboxylic acid. The lactone dissolves in fuming hydrobromic acid (saturated at 0°), but decomposition takes place immediately; the solution clouds and an oil separates on the surface of the acid, which sometimes crystallises at once and always in a few hours, and the mass, after contact with porous porcelain, melts at about 53° and consists of *cis*-6-bromo-1-methylcyclohexane-3-carboxylic acid (compare p. 1885).

For the purpose of examination, some of the *cis*-methylcyclohexanolcarboxylic acid was obtained, as just explained, by the hydrolysis of the lactone, but the larger quantity was prepared from the steam distillate (*B*) (p. 1883). This was neutralised with sodium carbonate, evaporated to a small bulk, acidified, saturated with ammonium sulphate, and repeatedly extracted with much ether on the machine.

After drying thoroughly and concentrating considerably, the crystalline acid commenced to deposit from the boiling solution, and, on standing, hard crusts separated:

0.1705 gave 0.3789 CO₂ and 0.1342 H₂O. C = 60.6; H = 8.7.

C₈H₁₄O₃ requires C = 60.8; H = 8.8 per cent.

The basicity of the acid was determined by titration with decinormal sodium hydroxide, when 0.0930 required 5.87 c.c. for neutralisation, whereas this amount of a monobasic acid, C₈H₁₄O₃, should neutralise 5.89 c.c.

cis-1-Methylcyclohexan-6-ol-3-carboxylic acid melts at about 140—141°. It is comparatively sparingly soluble in cold water, but dissolves readily on warming, and separates, when the solution is allowed to cool slowly, in compact, stellate groups of needles.

When the *cis*-acid is gently heated in a test-tube, it effervesces

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owing to the escape of steam and an oil distils which, on cooling, crystallises and consists of the lactone, since, after contact with porous porcelain, it melts at about 40° and is insoluble in cold sodium carbonate.

A curious result was obtained in an attempt to prepare the ester of the *cis*-acid. The acid (6 grams) was digested with alcohol (32 grams) and sulphuric acid (8 grams) for several hours on the water-bath, the product extracted in the usual way and fractionated, when an oil distilled at about $152^{\circ}/100$ mm. and gave the following results on analysis :

0.1110 gave 0.2854 CO_2 and 0.0959 H_2O . $\text{C} = 70.1$; $\text{H} = 9.6$.

The ester of the *cis*-acid requires $\text{C} = 64.5$; $\text{H} = 9.7$ per cent., whereas the ester of 1-methyl- Δ^6 -cyclohexene-3-carboxylic acid (compare p. 1887) contains $\text{C} = 71.4$; $\text{H} = 9.6$ per cent., and distils at about $146^{\circ}/100$ mm. There can therefore be no doubt that the oil obtained by the esterification of the *cis*-acid, under the above conditions, consists essentially of ethyl methylcyclohexenecarboxylate, water having been eliminated during the preparation. For the sake of comparison, the *trans*-hydroxy-acid was esterified under exactly the same conditions, and found to yield an ester distilling at about 155 — $159^{\circ}/30$ mm.

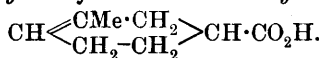
cis-6-Bromo-1-methylcyclohexane-3-carboxylic Acid.—This acid is most readily obtained from the lactone by the action of hydrobromic acid (p. 1884), but a considerable quantity was prepared directly from the *cis*-hydroxy-acid. This acid dissolves readily in fuming hydrobromic acid (saturated at 0°) ; the solution clouds almost immediately, and a syrup separates which sometimes crystallises at once, but usually only after several hours. The crystals were collected, and left in contact with porous porcelain over solid potassium hydroxide until quite dry :

0.1265 gave 0.1054 AgBr. $\text{Br} = 35.5$.

$\text{C}_8\text{H}_{13}\text{O}_2\text{Br}$ requires $\text{Br} = 36.2$ per cent.

cis-6-Bromo-1-methylcyclohexane-3-carboxylic acid melts at about 53° , and is readily soluble in most solvents ; it may be crystallised from formic acid, but with considerable loss.

1-Methyl- Δ^6 -cyclohexene-3-carboxylic Acid,



This acid is produced, together with the lactone of *cis*-1-methylcyclohexan-6-ol-3-carboxylic acid, when crude 6-bromo-1-methylcyclohexane-3-carboxylic acid is digested with pyridine (p. 1884), but it is most conveniently prepared by the following process.

The product of the action of hydrobromic acid on crude 1-methyl-*cyclohexanolcarboxylic acid*, obtained as described on p. 1883, is dissolved in three times its volume of 20 per cent. alcoholic sulphuric acid and allowed to remain for several days. After pouring into water and extracting with ether, the ethereal solution is well washed, dried and evaporated, and the residue distilled under reduced pressure, when a considerable fraction is obtained, boiling up to $175^{\circ}/100$ mm., which consists of ethyl bromomethyl*cyclohexanecarboxylate* containing some unsaturated ester. A higher fraction, distilling at about $155\text{--}175^{\circ}/30$ mm., is the crude hydroxy-ester, and is again treated with hydrobromic acid and converted into the bromo-ester.

The bromo-ester is digested with five times its volume of diethyl-aniline for five hours, the product mixed with excess of dilute hydrochloric acid, extracted with ether, the ethereal solution well washed with dilute hydrochloric acid, dried, evaporated, and the residue several times fractionated, being thus separated into a viscid oil, probably the hydroxy-ester, distilling at $155\text{--}165^{\circ}/30$ mm., and *ethyl 1-methyl- Δ^6 -cyclohexenecarboxylate*, boiling at about $146^{\circ}/100$ mm.:

0.2396 gave 0.6230 CO_2 and 0.2040 H_2O . C = 70.9; H = 9.5.

$\text{C}_{10}\text{H}_{16}\text{O}_2$ requires C = 71.4; H = 9.5 per cent.

This ester is readily hydrolysed by methyl-alcoholic potash in the cold, and, after remaining for twenty-four hours, the product is diluted with water, saturated with carbon dioxide, evaporated until free from methyl alcohol, acidified, and extracted with pure ether. After carefully drying and evaporating, the ethereal solution yields an oil which distils constantly at $184\text{--}186^{\circ}/100$ mm.:

0.2130 gave 0.5290 CO_2 and 0.1650 H_2O . C = 67.8; H = 8.6.

0.1704 „ 0.4264 CO_2 „ 0.1338 H_2O . C = 68.2; H = 8.7.

$\text{C}_8\text{H}_{12}\text{O}_2$ requires C = 68.5; H = 8.6 per cent.

1-Methyl- Δ^6 -cyclohexene-3-carboxylic acid is a viscid oil with an unpleasant odour, and reduces permanganate instantly in alkaline solution. It dissolves in fuming aqueous hydrobromic acid, but the solution clouds almost immediately, and the bromo-acid separates as a colourless, oily layer. When oxidised in sodium carbonate solution with ozone, it yields a syrupy ketonic acid, which gives an immediate precipitate with *p*-bromophenylhydrazine acetate and a separation of bromoform when mixed with potassium hypobromite.

The *calcium salt*.—This salt was made by heating the acid (40 grams) on the water-bath with much water and excess of freshly-precipitated calcium carbonate, and, after filtering, the solution was concentrated considerably and allowed to stand, when the *calcium salt* separated in slender needles radiating from the sides of the containing vessel, or in balls of needles radiating from a centre. The salt was collected, left

in contact with porous porcelain in the air for several days, and then analysed :

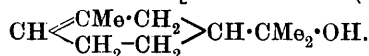
0.4108, heated at 130° until constant, lost 0.0850 H₂O and gave 0.1403 CaSO₄. H₂O = 20.7 ; Ca = 10.3.

(C₈H₁₁O₂)₂Ca, 4½ H₂O requires H₂O = 20.3 ; Ca = 10.0 per cent.

The mother liquor from this crystallisation was concentrated, and two other crops of calcium salt collected ; these were found to have exactly the same appearance as the first crop, and to contain 21.0 and 20.9 per cent. of water of crystallisation respectively.

The filtrate from the last crop was acidified, and the acid (9 grams), which distilled at 184—186°/100 mm., again converted into calcium salt, when exactly similar crystals were obtained, which contained 20.9 per cent. of water. We therefore conclude that the unsaturated acid, prepared by the above process, consists entirely of 1-methyl-Δ⁶-cyclohexene-3-carboxylic acid, and does not contain even traces of another isomeride.

Dihydroisocarvestrenol [Δ⁶-m-Menthenol(8)],



The ethyl 1-methyl-Δ⁶-cyclohexene-3-carboxylate required for this synthesis was prepared by dissolving the pure acid (20 grams) in 10 per cent. alcoholic sulphuric acid (150 c.c.) and allowing the solution to remain at the ordinary temperature for five days.

It was isolated in the usual manner, and distilled at 146°/100 mm.

This ester (27 grams) was added to an ethereal solution of magnesium methyl iodide (containing 12 grams Mg), when little evolution of heat was noticed at first, but, on standing, the temperature of the ether gradually rose to the boiling point. After four hours, the product was cautiously decomposed by water and dilute hydrochloric acid, the ethereal solution separated, washed with very dilute sulphurous acid to remove iodine, evaporated, and the residue mixed with potassium hydroxide (4 grams), dissolved in methyl alcohol, and allowed to stand for twelve hours in order to remove any unchanged ester which might be present.

Water was then added, the oil extracted with ether, the ethereal solution well washed, dried and evaporated, and the residue fractionated under reduced pressure :

0.1648 gave 0.4710 CO₂ and 0.1755 H₂O. C = 77.7 ; H = 11.8.

0.1452 „ 0.4125 CO₂ „ 0.1551 H₂O. C = 77.5 ; H = 11.9.

C₁₀H₁₈O requires C = 77.9 ; H = 11.7 per cent.

Dihydroisocarvestrenol boils at 106—107°/20 mm., and is a rather viscid oil with a pungent odour of terpeneol. When a drop of

sulphuric acid is added to its solution in acetic anhydride, a violet coloration is produced, which soon becomes an intense methylene-blue and, on longer standing, again violet.

Density: $d_{20^{\circ}/20^{\circ}} = 0.9376$; $d_{20^{\circ}/4^{\circ}} = 0.9359$.

Refractive power at 20° :

	μ .	$\frac{\mu-1}{d}$.	$\frac{\mu-1}{d} \cdot p$.	$\frac{\mu^2-1}{\mu^2+2} \cdot \frac{p}{d}$.
α	1.47751	0.51022	78.573	46.54
β	1.48711	0.52047	80.152	47.33
γ	1.49312	0.52688	81.139	47.83

Dispersion $\gamma - \alpha = 2.566$.

These physical constants agree closely with those of terpineol (Trans., 1906, 89, 851), namely, $d_{20^{\circ}/20^{\circ}} = 0.9385$.

Refractive power $\frac{\mu-1}{d} \cdot p$ at 18.4° : $\alpha = 78.885$; $\beta = 80.466$; $\gamma = 81.450$.

Dispersion $\gamma - \alpha = 2.565$.

$$\frac{\mu^2-1}{\mu^2+2} \cdot \frac{p}{d} = 46.68 \text{ for } \alpha.$$

The *nitrosochloride*, $C_{11}H_{18}O, NOCl$.—This derivative was prepared by dissolving dihydroisocarvestrenol (2 c.c.) in ethyl nitrite (10 c.c. of 10 per cent.), and gradually adding concentrated hydrochloric acid (2 c.c.) to the solution, cooled to -10° . After standing for an hour in ice and salt, a further quantity of ethyl nitrite (10 c.c.) and hydrochloric acid (2 c.c.) was added, and the mixture allowed to remain at the ordinary temperature, when the nitrosochloride soon began to crystallise. The crystals were collected, washed with methyl alcohol, and analysed:

0.1406 gave 8 c.c. N_2 at 18° and 741 mm. $N = 6.4$.

$C_{10}H_{18}O_2NCl$ requires $N = 6.4$ per cent.

Dihydroisocarvestrenol nitrosochloride melts, with decomposition, at 125° , and is sparingly soluble in alcohol, benzene, ethyl acetate, or methyl ethyl ketone.

Formation of Derivatives of Carvestrene from Dihydroisocarvestrenol.

Carvestrene dihydrochloride, $C_{10}H_{16}, 2HCl$, is obtained when dihydroisocarvestrenol is shaken in a stoppered bottle with five times its volume of concentrated hydrochloric acid. The crystals, which will have formed after about half an hour, are collected, washed, and left in contact with porous porcelain until quite free from oil.

The colourless mass is then crystallised from methyl alcohol, from which the hydrochloride separates in glistening needles:

0.1620 gave 0.2210 $AgCl$. $Cl = 33.8$.

$C_{10}H_{18}Cl_2$ requires $Cl = 33.9$ per cent.

This hydrochloride melted sharply at 52.5° , and, when mixed with a specimen of carvestrene dihydrochloride (Trans., 1907, **91**, 500), there was no alteration in melting point. When dihydroisocarvestrenol was shaken with eight volumes of hydrobromic acid (saturated at 0°) for two days, an oil still floated on the surface, but, on pouring into water and shaking vigorously, the heavy oil soon crystallised. The mass was well washed, left in contact with porous porcelain until quite colourless, and purified by crystallisation from methyl alcohol, from which the hydrobromide separated in hard, glistening, prismatic needles of melting point $48-49^{\circ}$:

0.2165 gave 0.2720 AgBr. Br = 53.5

$C_{10}H_{18}Br_2$ requires Br = 53.7 per cent.

That this substance is carvestrene dihydrobromide was proved by mixing it with a specimen of this substance which had been previously obtained (Trans., 1907, **91**, 500), when there was no alteration in melting point.

cis-Tetrahydrocarvestrenediol, $C_{10}H_{18}(OH)_2$.—This derivative of carvestrene was obtained by shaking dihydroisocarvestrenol (5 c.c.) with water (600 c.c.) and sulphuric acid (10 c.c.) on the machine.

The oil was almost insoluble at first, and was therefore only slowly attacked by the dilute sulphuric acid, but, after shaking for seven days, nearly all of it had passed into solution. The product was filtered, the clear filtrate saturated with ammonium sulphate, and the cloudy liquid repeatedly extracted with ether. The ethereal solution was dried and evaporated, when a viscid syrup remained, which soon commenced to crystallise and, especially when vigorously stirred, gradually became almost solid. The mass was left in contact with porous porcelain until quite hard, and then repeatedly crystallised from ether, from which woolly masses separated.

For analysis, the substance was dried over phosphoric oxide:

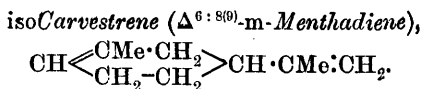
0.1223 gave 0.3120 CO_2 and 0.1280 H_2O . C = 69.6; H = 11.6.

$C_{10}H_{20}O_2$ requires C = 69.8; H = 11.6 per cent.

The melting point of the *cis*-tetrahydrocarvestrenediol obtained in this experiment was 94° , or rather higher than the melting point (about 90°) found for the original specimen (Trans., 1907, **91**, 501).

When, however, this original specimen was twice crystallised from ether, the melting point rose to $93-94^{\circ}$, and its identity with the substance, obtained as described above, was proved by the fact that there was no alteration in melting point when the two specimens were mixed. Careful examination of the ethereal mother liquors and of the porous porcelain used in the purification of the *cis*-tetrahydrocarvestrenediol failed to reveal even traces of the *trans*-modification,

and it was evident that the conversion of dihydroisocarvestrenol into *cis*-tetrahydrocarvestrenediol, under the above conditions, was almost quantitative.



The conversion of dihydroisocarvestrenol into *isocarvestrene* was carried out by gradually adding the former (21 grams) to an ethereal solution of magnesium methyl iodide (containing 15 grams of magnesium), and allowing the mixture to remain for four days. The product was then decomposed by water and dilute hydrochloric acid, the ethereal solution separated, washed with water containing a little sulphurous acid, and distilled under reduced pressure. The oil was thus readily separated into two fractions: (a) boiling below 140°/200 mm., and (b) boiling at 190—200°/20 mm. When the former was repeatedly distilled over sodium under the ordinary pressure, a large fraction (11 grams) was obtained, distilling constantly at 176—177°/765 mm.:

0.1118 gave 0.3610 CO₂ and 0.1190 H₂O. C = 88.1; H = 11.8.

0.1095 „ 0.3525 CO₂ „ 0.1143 H₂O. C = 88.0; H = 11.6.

C₁₀H₁₆ requires C = 88.2; H = 11.8 per cent.

isoCarvestrene has a very pungent odour of lemons, and is oxidised slowly in the air, since a small quantity, left in a tube over water, had absorbed one-fifth of the volume of air in seven days.

When a drop of sulphuric acid is added to its solution in acetic anhydride, a violet coloration is produced, which rapidly fades.

The density determinations gave:

$$d_{20^\circ/20} = 0.8496; d_{20^\circ/4^\circ} = 0.8481.$$

Refractive power at 20°:

	$\mu.$	$\frac{\mu-1}{d}.$	$\frac{\mu-1}{d}p.$	$\frac{\mu^2-1}{\mu^2+2} \cdot \frac{p}{d}$
α	1.47799	0.56360	76.649	45.39
β	1.49090	0.57881	78.718	46.43
γ	1.49893	0.58829	80.007	47.09

$$\text{Dispersion } \gamma - \alpha = 3.358.$$

These numbers, with the exception of the density, are distinctly higher than those found for dipentene (Trans., 1906, 89, 851), namely, $d_{20^\circ/20^\circ} = 0.8517$. Refractive power $\frac{\mu-1}{d}p$ at 14°: $\alpha = 75.602$; $\beta = 77.391$; $\gamma = 78.564$. Dispersion $\gamma - \alpha = 2.962$.

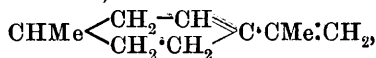
$$\frac{\mu^2-1}{\mu^2+2} \cdot \frac{p}{d} = 44.81 \text{ for } \alpha.$$

The most remarkable feature in connexion with the refraction

values for *isocarvestrene* is the fact that they are even higher than those of $dl\text{-}\Delta^{3:8(9)}\text{-}p\text{-menthadiene}$ (compare Trans., 1906, 89, 850), which has the values $\alpha = 76.31$; $\beta = 78.21$; $\gamma = 79.37$;

$$\frac{\mu^2 - 1}{\mu^2 + 2} \frac{p}{d} = 45.31.$$

But $dl\text{-}\Delta^{3:8(9)}\text{-}p\text{-menthadiene}$,



contains a conjugated system of two double linkings, and it has been shown (*loc. cit.*, p. 856) that this system causes a small, but distinct, rise in the values for the refraction above the normal:

	$\frac{\mu - 1}{d} p.$	Difference.
$dl\text{-}\Delta^{3:8(9)}\text{-}p\text{-Menthadiene}$	76.31	+ 0.71
Dipentene	75.60	

The comparison of *isocarvestrene* with dipentene:

	$\frac{\mu - 1}{d} p.$	Difference.
<i>iso</i> Carvestrene	76.65	+ 1.05
Dipentene	75.60	

yields an even greater difference, and, as it seems impossible that elimination of water from dihydro*isocarvestrenol* can lead to a hydrocarbon with conjugated double linkings, it is very difficult to understand the significance of these numbers. In connexion with this point, it has been shown (Perkin, Pickles, and Tattersall, Trans., 1905, 87, 641; also 1077 and 1101) that hydrocarbons containing a conjugated system of double linkings exhibit a characteristic behaviour when treated with bromine, hydrogen bromide, or hydrogen chloride. Thus, for example, $dl\text{-}\Delta^{3:8(9)}\text{-}p\text{-menthadiene}$ combines with one molecule of each of these, whereas dipentene, which does not contain conjugated double linkings, combines, as is well known, with two molecules in each case. It is very remarkable that *isocarvestrene* appears to behave in this matter in a similar way to $dl\text{-}\Delta^{3:8(9)}\text{-}p\text{-menthadiene}$. When *isocarvestrene* (1.25 grams), dissolved in three times its volume of dry chloroform and cooled to -10° , was titrated with bromine, a permanent straw-colour was produced when 1.7 grams of the halogen had been added, but the end point was not very sharp. This result agrees best with the formation of a dibromide, $\text{C}_{10}\text{H}_{16}\text{Br}_2$, which requires the addition of 1.47 grams of bromine, whereas the quantity required for the formation of a tetrabromide, $\text{C}_{10}\text{H}_{16}\text{Br}_4$, is 2.95 grams. *iso*-Carvestrene did not dissolve when it was shaken in a sealed tube with 5 volumes of a solution of hydrogen bromide in acetic acid (saturated at 0°); the solution became brown, but the hydrocarbon was not converted into a crystalline dihydrobromide, $\text{C}_{10}\text{H}_{16} \cdot 2\text{HBr}$.

When, after several days, the product was poured into water, a rather heavy oil separated, which showed no tendency to crystallise. *iso*-Carvestrene was then dissolved in dry ether, cooled to -10° , and saturated with hydrogen chloride; the solution soon became brown and then a deep claret, and yielded a resinous mass when it was washed with water and evaporated.

Again, when the hydrocarbon was shaken for ten days with ten times its volume of concentrated hydrochloric acid, no crystalline dihydrochloride separated. The product was poured into water, and the oil, after extraction with ether in the usual manner, analysed and found to contain 14.7 per cent. of chlorine, which is less even than that required for the mono-hydrochloride, $C_{10}H_{16}HCl$, namely, 20.6 per cent.

It has been pointed out on p. 1888 that dihydro*isocarvestrenol* readily combines with halogen acids to yield the carvestrene derivatives $C_{10}H_{16} \cdot 2HCl$ and $C_{10}H_{16} \cdot 2HBr$, and it is difficult to understand why *isocarvestrene* does not show the same behaviour, especially when it is remembered that carvestrene, under the same conditions, combines readily with halogen acids (compare Trans., 1907, 91, 500).

During the fractionation of the product of the action of magnesium methyl iodide on dihydro*isocarvestrenol* (p. 1890), a considerable quantity of an oil was obtained, distilling at $190-200^{\circ}/20$ mm.

When this was carefully fractionated over sodium, it boiled very constantly at $188-190^{\circ}/20$ mm., and yielded the following analysis:

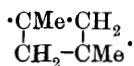
0.1560 gave 0.5050 CO_2 and 0.1620 H_2O . $C = 88.2$; $H = 11.6$.

$C_{20}H_{32}$ requires $C = 88.2$; $H = 11.8$.

The determination of the molecular weight by the cryoscopic method in benzene solution gave $M.W. = 254$, whereas the formula $C_{20}H_{32}$ requires $M.W. = 272$. This diterpene, for which we propose the name *diisocarvestrene*, is a viscid, colourless syrup, which has a faint odour of peppermint, and develops a pink coloration when a drop of sulphuric acid is added to its solution or suspension in acetic anhydride. If a drop of bromine is added to a solution of the diterpene in chloroform at -10° , a straw-colour is at once produced, and, on standing at the ordinary temperature, the solution soon becomes deep purple and, after twelve hours, an intense indigo-blue.

During the course of other investigations of this series, diterpenes similar to *diisocarvestrene* have been isolated, on several occasions, from the products of the dehydration of some of the corresponding alcohols. It seems possible that, during their formation, the characteristic group, $-CMe:CH_2$, of two molecules of the simple terpene

undergoes polymerisation with formation of a tetramethylene derivative containing the group [View Article Online](#)



We take this opportunity of thanking Mr. W. N. Haworth for valuable assistance during this difficult investigation, and we wish also to express our thanks to the Research Fund Committees of the Royal Society and Chemical Society for grants which have covered much of the expense involved.

THE SCHUNCK LABORATORY,
THE UNIVERSITY,
MANCHESTER.
