CLXIV.—*Experiments on the Synthesis of the Terpenes.*
Part XI. Synthesis of 4-isoPropylidenecyclohexanone
and its Derivatives.

By WILLIAM HENRY PERKIN, jun., and JOHN LIONEL SIMONSEN.

THE synthetical experiments which have been carried out in the terpene series have, so far, led only to the synthesis of those terpenes which, like dipentene, contain a single closed chain.

It is, however, characteristic of this series that some of its most important members belong to the bicyclic system, and, for a long time, we have been engaged on experiments instituted with the object of devising means for the synthesis of such terpenes. The problem appears to be one of unusual experimental difficulty, not only on account of the fact that there are very few methods available for the formation of bicyclic or bridged ring compounds, but also because the bridge in such terpenes as pinene,

is so unstable, especially towards acids, that the reagents available for synthetical work are more strictly limited than is usually the case. The present communication contains an account of an attempt to synthesise nopinone,

a ketone of great interest which Baeyer (*Ber.*, 1896, 29, 23, 25) first obtained during the course of his classical researches on the oxidation of oil of turpentine. It was thought that this ketone would probably react with magnesium methyl iodide to yield an alcohol (methylnopinol) which, when treated with dehydrating agents, would be decomposed with elimination of water and formation either of pinene or ψ -pinene:

We therefore prepared a quantity of nopinone and found that it reacted normally with magnesium methyl iodide, and the methylnopinol produced proved to be a crystalline substance melting at 58°.

While engaged in the investigation of the action of various dehydrating agents on this tertiary alcohol, Prof. O. Wallach informed us that he had, for some time, been studying this decomposition,* and we have therefore discontinued our work on this part of the subject. The experiments which we have carried out in our attempt to synthesise nopinone may be briefly summarised as follows.

The sodium derivative of ethyl α -acetylglutarate,

was treated, in alcoholic solution, with ethyl β -iodopropionate, when interaction rapidly took place with the formation of *ethyl γ -acetyl-pentane- $\alpha\gamma\epsilon$ -tricarboxylate*, $\text{CO}_2\text{Et} \cdot \text{CAc}(\text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{Et})_2$, and this ester, when digested with hydrochloric acid, was readily decomposed and converted into *γ -acetylpimelic acid*, $\text{CHAc}(\text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{H})_2$. When ethyl γ -acetylpimelate is treated with magnesium methyl iodide, it is converted into the lactone of *ethyl hydrogen γ -isopropenol-pimelate*,

and this lactone reacts readily with hydrobromic acid with formation of an oil which, on esterification, yields ethyl *γ -(bromoisopropyl) pimelate*, $\text{CMe}_2\text{Br} \cdot \text{CH}(\text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{Et})_2$.

When this bromo-ester is digested with pyridine, it is decomposed with elimination of hydrogen bromide and formation of ethyl *γ -isopropylidenepimelate*, $\text{CMe}_2 \cdot \text{C}(\text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{Et})_2$, which distils at 168° (13 mm.) and, on hydrolysis, yields *γ -isopropylidenepimelic acid* (m. p. 97°), the constitution of which is proved by the fact that,

* A preliminary account of these experiments has lately appeared in the *Nachr. k. Ges. Wiss. Göttingen*, 1907, p. 13; see also *Annalen*, 1907, 356, 239.

on oxidation with permanganate and then with chromic acid, it yields acetone and succinic acid. The solution of ethyl γ -isopropylidene-pimelate in toluene reacts readily with sodium and yields *ethyl 4-isopropylidenecyclohexanone-2-carboxylate*,

an oil which decomposes on distillation and the alcoholic solution of which gives an intense violet coloration with ferric chloride.

This ketonic ester is readily hydrolysed by alcoholic potash, and one of the products of hydrolysis is *4-isopropylidenecyclohexanone*,

which distils at 219—221°, yields a *semicarbazone* of melting point 201°, and is isomeric with nopinone (b. p. 210°), camphenilone (b. p. 195°), sabineneketone (b. p. 213°), and with other important ketones of the camphor and terpene series (compare p. 1746).

4-isopropylidenecyclohexanone combines readily with hydrogen bromide with formation of *4- β -bromoisopropylcyclohexanone*,* and if the formula of this substance is written side by side with that of nopinone,

it will be, at once, seen that these substances are related in the same way as dihydrocarvone hydrobromide to carone:

Now Baeyer (*Ber.*, 1894, **27**, 1919; 1896, **29**, 6) has shown that carone is formed when dihydrocarvone hydrobromide is left in contact with alcoholic potash at 0°, and, in order to bring about the similar conversion of *4- β -bromoisopropylcyclohexanone* into nopinone, we

* That this hydrobromide contains the grouping $\text{CMe}_2\text{Br}\cdot\text{CH}<$ and not $\text{CMe}_2\text{H}\cdot\text{CBr}<$ is proved by comparison with other analogous cases of the addition of hydrogen bromide to the grouping $\text{CMe}_2:\text{C}<$.

Terpinolene, $\text{CMe}_2:\text{C} \begin{array}{c} \text{CH}_2 \cdot \text{CH}_2 \\ \text{CH}_2 \text{---} \text{CH} \end{array} \text{C}\cdot\text{Me}$, for example, yields dipentene dihydrobromide, $\text{CMe}_2\text{Br}\cdot\text{CH} \begin{array}{c} \text{CH}_2 \cdot \text{CH}_2 \\ \text{CH}_2 \text{---} \text{CH}_2 \end{array} \text{CBrMe}$, when it is treated with hydrobromic acid.

caused this bromo-compound to react with alcoholic potash under a variety of conditions, but were unable to detect the formation even of traces of nopinone. In every case, the elimination of hydrogen bromide appeared to proceed principally in the direction :

giving rise to the formation of 4-isopropylidenecyclohexanone.

We next prepared the hydrogen bromide additive compound of ethyl 4-isopropylidenecyclohexanone-2-carboxylate (see p. 1745), a substance capable of yielding a sodium derivative which might reasonably be expected readily to undergo internal condensation with elimination of sodium bromide and formation of ethyl nopinonecarboxylate :

but, although elimination of sodium bromide did take place when the sodium derivative was digested in alcoholic solution, the product of the reaction, on hydrolysis with dilute alcoholic potash, did not furnish a trace of nopinone. In a previous communication (Trans., 1907, 85, 817), we had occasion to refer to the fact that the cyclopropane ring is not infrequently produced with much greater ease than the cyclobutane ring. Obviously the inability of the four-carbon chain to close under the highly favourable conditions presented in the case of the sodium derivative of ethyl 4-β-bromoisopropylcyclohexanone-2-carboxylate, whereas the formation of the cyclopropane ring takes place with such remarkable ease in the conversion of dihydrocarvone hydrobromide into carone, is strong evidence that, in a bicyclic system, the cyclopropane ring is more readily produced than the cyclobutane ring. Another example in illustration of this point is afforded by the behaviour of the hydrobromide of pulegone (I),

which, when treated with alcoholic potash, is reconverted into pulegone and does not yield a bicyclic ketone (II) of the type of nopinone.

Ethyl α-Acetylglutarate, $\text{CO}_2\text{Et}\cdot\text{CHAc}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$, and *Ethyl γ-Acetylpentane-αγε-tricarboxylate*, $\text{CO}_2\text{Et}\cdot\text{CAc}(\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{Et})_2$.

Ethyl α-acetylglutarate has already been described by Wolff (*Annalen*, 1883, 216, 129) and by Bentley and Perkin (*Trans.*, 1896, 69, 1511), and the following modified method was adopted as most convenient for the preparation of the large quantities of this ester which were required for the present research.

Sodium (11.6 grams) is dissolved in alcohol (150 grams), well cooled, and mixed with ethyl acetoacetate (65 grams), ethyl β-iodopropionate (114 grams) is then slowly added, care being taken that the temperature does not rise above 30° either during addition or for some hours afterwards. After twelve hours, the product is heated on the water-bath for half an hour, diluted with water, extracted with ether, and the ethereal solution washed thoroughly with water, dried over calcium chloride, and evaporated. On fractionation under reduced pressure (17 mm.), much ethyl acetoacetate passes over first, then nearly pure ethyl α-acetylglutarate (78 grams) distils at 158—165°, and almost the whole of the residue distils at 210—220° and consists of *ethyl γ-acetylpentane-αγε-tricarboxylate*.

The formation of the latter substance and the regeneration of a corresponding amount of ethyl acetoacetate is readily understood from the equation :

A large amount of this valuable ester was obtained in this way, and further large quantities were prepared by the following process.

Sodium (11.5 grams) is dissolved in alcohol (150 grams), mixed with ethyl α-acetylglutarate (115 grams), and ethyl β-iodopropionate (114 grams) gradually added, any rise of temperature above 30° being avoided by cooling under the tap. After standing for twelve hours, the product is heated on the water-bath for half an hour, diluted with water, and the oil extracted with ether, washed with water, and dried in the usual manner. With the exception of a considerable quantity of ethyl acrylate (formed by the elimination of hydrogen iodide from some of the ethyl β-iodopropionate employed), the product of the reaction distils almost constantly at 217° (15 mm.), and consists of *ethyl γ-acetylpentane-αγε-tricarboxylate* :

0.1483 gave 0.3156 CO_2 and 0.1055 H_2O . C = 58.0 ; H = 7.9.

$\text{C}_{16}\text{H}_{26}\text{O}_7$ requires C = 58.2 ; H = 7.9 per cent.

This ester, which does not appear to have previously been prepared, is a viscid, colourless oil and possesses only a faint odour.

γ-Acetylpimelic Acid, $\text{CHAc}(\text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{H})_2$.

This acid is readily obtained when ethyl γ -acetylpentane- $\alpha\gamma\epsilon$ -tricarboxylate is hydrolysed by hydrochloric acid. The ester (68 grams) is digested in a reflux apparatus with concentrated hydrochloric acid (136 grams) for eight hours, water (150 c.c.) is then added, and the boiling continued for a further eight hours. When the product is evaporated on the water-bath, γ -acetylpimelic acid remains as a thick syrup which (like so many derivatives of pimelic acid) shows no tendency to crystallise. A small quantity was purified by conversion into the semicarbazone (see below) and subsequent regeneration by decomposition with hydrochloric acid, and, after remaining over sulphuric acid in an evacuated desiccator, the almost colourless syrup gave the following approximate results on analysis :

0.1808 gave 0.3461 CO_2 and 0.1111 H_2O . $\text{C} = 52.2$; $\text{H} = 6.8$.

$\text{C}_9\text{H}_{14}\text{O}_5$ requires $\text{C} = 53.5$; $\text{H} = 6.9$ per cent.

The basicity of the acid was determined by titration with decinormal potassium hydroxide, when 0.1377 neutralised 0.0751 KOH, whereas this amount of a dibasic acid, $\text{C}_9\text{H}_{14}\text{O}_5$, requires 0.0763 KOH for neutralisation.

The *semicarbazone* is obtained when the acid is treated with semicarbazide hydrochloride and sodium acetate in the usual manner, and separates from hot water in plates which melt at 177° :

0.1961 gave 26.2 c.c. of nitrogen at 14° and 767 mm. $\text{N} = 15.9$.

$\text{C}_{10}\text{H}_{17}\text{O}_5\text{N}_3$ requires $\text{N} = 16.2$ per cent.

Ethyl γ-Acetylpimelate, $\text{CHAc}(\text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{Et})_2$.—This ester is obtained when the solution of the crude acid (150 grams) in 3 per cent. alcoholic hydrogen chloride (300 c.c.) is allowed to stand for thirty-six hours. On pouring into water, a heavy oil separates, which is extracted with ether, the ethereal solution is washed with dilute sodium carbonate, dried over calcium chloride, evaporated, and the ester purified by fractionation under reduced pressure :

0.1649 gave 0.3619 CO_2 and 0.1257 H_2O . $\text{C} = 59.8$; $\text{H} = 8.5$.

$\text{C}_{13}\text{H}_{22}\text{O}_5$ requires $\text{C} = 60.5$; $\text{H} = 8.5$ per cent.

Ethyl γ-acetylpimelate distils at $186\text{--}192^\circ$ (14 mm.) and has a pleasant ethereal odour.

In preparing the lactone, ethyl γ -acetylpmelate (50 grams), dissolved in ether (300 c.c.), was slowly added to a well cooled ethereal solution of magnesium methyl iodide (prepared from 9.4 grams of magnesium), when an extremely vigorous action took place and a large quantity of a white magnesium compound separated.

After remaining overnight, the magnesium compound was decomposed by dilute hydrochloric acid in the usual manner, when nearly the whole of the lactone remained in the ethereal solution. This was well washed with sodium sulphite to remove iodine, dried over calcium chloride, evaporated, and the resulting oil fractionated under reduced pressure (22 mm.), when the main portion distilled at about 200° :

0.1987 gave 0.4603 CO_2 and 0.1522 H_2O . $\text{C} = 63.2$; $\text{H} = 8.5$.

$\text{C}_{12}\text{H}_{20}\text{O}_4$ requires $\text{C} = 63.2$; $\text{H} = 8.8$ per cent.

The lactone of ethyl hydrogen γ -isopropenolpimelate is a colourless oil possessing a pleasant odour of camphor.

Ethyl hydrogen γ -(bromoisopropyl)pimelate is obtained when the lactone is dissolved in five times its weight of a solution of hydrogen bromide in glacial acetic acid (saturated at 0°) and allowed to stand for twenty-four hours. On pouring into water, a heavy oil separates, which is extracted with ether, and the ethereal solution, after thoroughly washing with water to remove acetic and hydrobromic acids, is dried over calcium chloride and the ether evaporated.

A small quantity of the oil, after remaining over sulphuric acid in an evacuated desiccator for some days, gave the following approximate results on analysis:

0.2257 gave 0.1308 AgBr. $\text{Br} = 24.7$

$\text{C}_{12}\text{H}_{21}\text{O}_4\text{Br}$ requires Br 25.9 per cent.

Ethyl γ -(Bromoisopropyl)pimelate, $\text{CMe}_2\text{Br} \cdot \text{CH}(\text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{Et})_2$.—In preparing this ester, ethyl hydrogen γ -(bromoisopropyl)pimelate (50 grams) was dissolved in 15 per cent. alcoholic hydrogen chloride (100 c.c.) and allowed to stand for twenty-four hours. The oil, which separated on dilution with water, was extracted with ether, the ethereal solution washed with sodium carbonate, dried over calcium chloride, and evaporated, when the residual, viscid, brown oil, after remaining for some days over sulphuric acid in an evacuated desiccator, had decomposed somewhat with evolution of hydrogen bromide, and therefore gave only approximate results on analysis.

γ -isoPropyldenepimelic Acid, $\text{CMe}_2\cdot\text{C}(\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H})_2$, and its Ethyl Ester.

Ethyl γ -isopropylidenepimelate is obtained when ethyl γ -(bromoiso-propyl)pimelate is digested for four hours on the water-bath with five times its volume of anhydrous pyridine, during which operation quantities of pyridine hydrobromide separate. The product is cooled, acidified with dilute hydrochloric acid and extracted with ether, the ethereal solution is well washed, dried over calcium chloride, evaporated, and the ester purified by distillation under reduced pressure :

0.1624 gave 0.3917 CO_2 and 0.1398 H_2O . $\text{C} = 65.8$; $\text{H} = 9.6$.

$\text{C}_{14}\text{H}_{24}\text{O}_4$ requires $\text{C} = 65.6$; $\text{H} = 9.4$ per cent.

Ethyl γ -isopropylidenepimelate distils at 168° (13 mm.) and has a faint odour of peppermint. The free acid is obtained when the ester is digested with an excess of methyl-alcoholic potash on the water-bath for half an hour. After diluting with water, the solution is evaporated until quite free from methyl alcohol, cooled, acidified with dilute hydrochloric acid, and the acid extracted with pure ether. The ethereal solution is dried over calcium chloride and evaporated, when a colourless syrup is obtained which soon almost completely crystallises, and, after remaining in contact with porous porcelain until quite free from oily impurity, the acid was finally purified by crystallisation from pure dry ether :

0.1326 gave 0.2919 CO_2 and 0.0981 H_2O . $\text{C} = 60.0$; $\text{H} = 8.2$.

$\text{C}_{10}\text{H}_{16}\text{O}_4$ requires $\text{C} = 60.0$; $\text{H} = 8.0$ per cent.

γ -isoPropyldenepimelic acid melts at about 97° and is readily soluble in ether, chloroform, or ethyl acetate, but sparingly so in water or light petroleum. Its solution in sodium carbonate instantly reduces permanganate, but when dissolved in chloroform the acid does not decolorise bromine. The basicity of the acid was determined by titration with decinormal sodium hydroxide, when 0.0557 neutralised 0.0022 NaOH , whereas this amount of a dibasic acid, $\text{C}_{10}\text{H}_{16}\text{O}_4$, should neutralise 0.0022 NaOH .

Oxidation of γ -isoPropyldenepimelic Acid to Acetone and Succinic Acid.—In carrying out this oxidation, the acid (3 grams) was dissolved in dilute sodium carbonate and oxidised at 0° , in an apparatus fitted with a turbine, with dilute permanganate until the colour just remained. The slight excess of permanganate was removed by the addition of sodium sulphite, and the filtrate and washings of the manganese precipitate evaporated to a small bulk, transferred to an ordinary distilling flask, and, after heating to boiling, a strong solution of potassium dichromate and sulphuric acid added until no

1744 PERKIN AND SIMONSEN: EXPERIMENTS ON THE

further action took place. On the addition of *p*-bromophenylhydrazine acetate to the distillate, a copious precipitate separated which, after collecting and drying on porous porcelain, melted at 95—97° and consisted of acetone-*p*-bromophenylhydrazone.

The residue in the distillation flask was saturated with ammonium sulphate and extracted with ether, when the ethereal solution, after drying over calcium chloride and evaporating, deposited a solid acid which was recrystallised from water. It separated in colourless plates, melted at 185°, and consisted of succinic acid:

0.1343 gave 0.1995 CO₂ and 0.0650 H₂O. C = 40.5; H = 5.3.

C₄H₆O₄ requires C = 40.7; H = 5.1 per cent.

Action of Sodium on Ethyl γ-isopropylidenepimelate. Formation of Ethyl 4-isopropylidenecyclohexanone-2-carboxylate,

In carrying out this condensation, sodium (5 grams) is melted under boiling toluene, shaken vigorously in order to bring it into as fine a state as possible, and, after cooling, ethyl γ-isopropylidenepimelate (28 grams) is added, and the whole heated in an oil-bath at 110—120° until decomposition commences. A vigorous action ensues, and is controlled by removing the flask from the oil-bath from time to time, and, finally, the process is completed by heating for two to three hours at 110—120°, when practically the whole of the sodium will have disappeared. After cooling, the sodium derivative is cautiously decomposed by adding ice-water and dilute hydrochloric acid and the product extracted with ether. The ethereal solution is well washed with dilute sodium carbonate, dried over calcium chloride, and the ether distilled off; the toluene is then removed as far as possible by distillation under reduced pressure. The residual oil, which decomposes considerably even when distilled under 15 mm. pressure, could not be obtained quite free from toluene, and gave therefore only approximate results on analysis:

0.1312 gave 0.3416 CO₂ and 0.1012 H₂O. C = 71.0; H = 8.6.

C₁₂H₁₈O₃ requires C = 68.6; H = 8.6 per cent.

Ethyl 4-isopropylidenecyclohexanone-2-carboxylate has a pleasant odour somewhat resembling that of ethyl acetoacetate, and gives, in alcoholic solution, a deep violet coloration on the addition of ferric chloride.

Ethyl 4-β-Bromoisopropylcyclohexanone-2-carboxylate,

Ethyl 4-*isopropylidenecyclohexanone*-2-carboxylate dissolves readily in a solution of hydrogen bromide in glacial acetic acid (saturated at 0°) with little evolution of heat, and if, after standing for an hour and a half, water is added, the addition product is precipitated as a heavy oil. This was extracted with ether, the ethereal solution washed with water and sodium carbonate, and evaporated, when a thick, brown oil was obtained which, after remaining over sulphuric acid in an evacuated desiccator for twenty-four hours, gave the following results on analysis :

0.2607 gave 0.1722 AgBr. Br = 28.1.

C₁₂H₁₉O₃Br requires Br = 27.5 per cent.

The preparation of this ketone from ethyl 4-*isopropylidenecyclohexanone*-2-carboxylate by hydrolysis is a matter of considerable difficulty, and the yield is always poor. After many comparative experiments, the following process was thought to give the best results.

The keto-ester (12 grams) is mixed with a cold solution of potassium hydroxide (7 grams) in methyl alcohol (100 c.c.) and, after remaining for twenty-four hours, heated on the water-bath in a reflux apparatus for two hours, during which operation a quantity of potassium carbonate separates. The product is diluted with water and distilled in steam, when the readily volatile ketone rapidly passes over.*

After saturating with ammonium sulphate, the distillate is extracted with ether, the ethereal solution dried over calcium chloride, evaporated, and the residual oil fractionated under reduced pressure :

0.1350 gave 0.3865 CO₂ and 0.1304 H₂O. C = 78.1 ; H = 10.7.

C₉H₁₄O requires C = 78.2 ; H = 10.1 per cent.

4-*isoPropylidenecyclohexanone* distils at about 160° under 100 mm., and at 219—221° under 749 mm., pressure ; it is a colourless, mobile oil and possesses the pleasant odour characteristic of cyclic ketones.

* The residue in the distillation flask contains unchanged keto-ester, and, after extraction with ether and treatment with alcoholic potash, yields a further small quantity of ketone.

1746 PERKIN AND SIMONSEN : EXPERIMENTS ON THE

The *semicarbazone* separates rapidly when the ketone is shaken with an excess of a concentrated solution of semicarbazide hydrochloride and sodium acetate. It crystallises from methyl alcohol in prismatic needles and melts at 201° with decomposition :

0.2089 gave 38.5 c.c. of nitrogen at 12° and 757 mm. $N = 21.7$.

$C_{10}H_{17}ON_3$ requires $N = 21.5$ per cent.

4- β -Bromoisopropylcyclohexanone, $CM_eBr \cdot CH \begin{smallmatrix} \diagup CH_2 \cdot CH_2 \\ \diagdown CH_2 \cdot CH_2 \end{smallmatrix} > CO$.

This substance is readily obtained when the pure ketone is dissolved in five times its volume of a solution of hydrogen bromide in glacial acetic acid (saturated at 0°). After remaining for half an hour, the addition product is precipitated by water, the heavy oil extracted with ether, the ethereal solution washed with dilute sodium carbonate, dried over calcium chloride, and evaporated, when a viscid oil is obtained which has a strong odour of peppermint and becomes brown on exposure to the air :

0.1486 gave 0.1289 AgBr. $Br = 36.9$.

$C_9H_{15}OBr$ requires $Br = 36.5$ per cent.

4-*iso*Propylidenecyclohexanone is isomeric with, and closely allied to, 4-*isopropenyl*cyclohexanone (*isopropenyl-p-ketohexamethylene*),

which had previously been obtained in small quantities by one of us (*Trans.*, 1904, **85**, 670)* during the course of experiments on the action of magnesium methyl iodide on ethyl *cyclohexane-4-carboxylate*.

A ketone, which is probably identical with 4-*isopropenyl*cyclohexanone, has also been described by Semmler (*Ber.*, 1904, **37**, 239) under the name *pinophorone*. It was prepared by the distillation of the calcium salt of crude pinonic acid, a decomposition which Semmler formulates thus :

The intermediate product (nopinone) is assumed to be unstable at the high temperature necessary for the decomposition of the calcium salt and to undergo isomeric change with formation of pinophorone.

* By an unfortunate mistake, the boiling point of 4-*isopropenyl*cyclohexanone was given as $184-186^{\circ}$ under the ordinary pressure, whereas the distillation was actually carried out under a pressure of 300 mm.

Quite recently, Wallach (*Nachr. k. Ges. Wiss. Göttingen*, 1907, p. 10; *Annalen*, 1907, **356**, 235) has shown that the bridge in nopinone very readily undergoes fission when this ketone is boiled with dilute sulphuric acid, and the 4-isopropyl- Δ^2 -cyclohexenone,

thus obtained, and which distils at 220—224°, is again isomeric with the 4-isopropylidenecyclohexanone described in the present communication.

Attempts to Synthesise Nopinone.

It is explained in the introduction that the object of the present research was the synthesis of nopinone, and the following are some of the experiments which were made in the hope of accomplishing this important synthesis.

I. The Decomposition of the Sodium Derivative of Ethyl 4- β -Bromoisopropylcyclohexanone-2-carboxylate,

In this experiment, an alcoholic solution of the bromo-ester (4.1 grams) was added to a cold solution of sodium (0.32 gram) in alcohol and, since no decomposition appeared to take place after remaining at the ordinary temperature for three hours, the solution was heated on the water-bath in a reflux apparatus, when sodium bromide rapidly separated. The product was diluted with water, the ester extracted with ether, hydrolysed with alcoholic potash (compare p. 1745), and then distilled in steam, when a small quantity of a ketone was obtained which yielded a semicarbazone of melting point 191° with decomposition. That this was not the semicarbazone of nopinone (m. p. 188°) was proved by mixing equal quantities of the two specimens, when the mixture melted at about 157°. On the other hand, when mixed with the semicarbazone of 4-isopropylidenecyclohexanone (m. p. 201°), the mixture melted at about 195°, indicating that this ketone had been produced in the above experiment.

II. The Action of Alcoholic Potash on Ethyl 4- β -Bromoisopropylcyclohexanone-2-carboxylate.

This experiment was carried out under the conditions employed by Baeyer (*Ber.*, 1894, **27**, 1919) in his experiments on the conversion of dihydrocarvone hydrobromide into carone. The bromo-ester (36 grams) was dissolved in alcohol, cooled to -10° in ice and salt, and

1748 EXPERIMENTS ON THE SYNTHESIS OF THE TERPENES.

then alcoholic potash (8 grams KOH) added drop by drop, any rise of temperature being carefully avoided. After remaining overnight in the ice-chest, it was found that much potassium bromide had separated.

The product was cooled to -5° , mixed again with the same quantity of alcoholic potash, and, after twenty-four hours, the solution was boiled for two hours in a reflux apparatus with the gradual addition of alcoholic potash (KOH = 5 grams). After dilution with water and distillation in steam, an oil was obtained which contained 4-isopropylidenecyclohexanone and the careful investigation of which failed to indicate the presence even of traces of nopinone.

III. *The Action of Alcoholic Potash on 4- β -Bromoisopropylcyclohexanone*, $\text{CMe}_2\text{Br}\cdot\text{CH}\left\langle\begin{smallmatrix}\text{CH}_2\cdot\text{CH}_2\\ \text{CH}_2\cdot\text{CH}_2\end{smallmatrix}\right\rangle\text{CO}$.

This experiment need not be described in detail, since the conditions were very similar to those employed in experiment II.

The product consisted mainly of 4-isopropylidenecyclohexanone and did not appear to contain nopinone.

One of the principal difficulties which we had to deal with in the above experiments was the impossibility of obtaining ethyl 4-isopropylidenecyclohexanone-2-carboxylate, and especially 4-isopropylidenecyclohexanone, in sufficient quantity for detailed investigation. Owing to the very large quantities of ethyl β -iodopropionate required, the preparation of these substances is very costly, and, in spite of a large number of comparative experiments, the yield was always very small. Possibly, when better methods of preparation are available, it may still be found possible to carry out a synthesis of nopinone on the lines indicated above.

We are greatly indebted to the Royal Society and to the Chemical Society for grants which have covered much of the heavy expense of this investigation.

THE SCHUNCK LABORATORY,
THE UNIVERSITY,
MANCHESTER.