[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORY, COLLEGE OF ENGINEERING AND TECHNOLOGY, BENGAL]

# INVESTIGATIONS ON THE CONSTITUTION OF ISOCARVESTRENE

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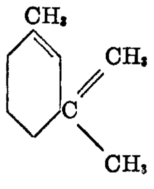
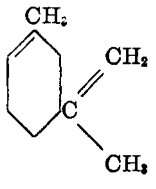
Sylvestrene (I), the only monocyclic terpene of the *m*-cymene series was isolated by Atterberg in 1877 (1). Later, in 1894 Baeyer prepared a hydrocarbon, carvestrene, having the formula $C_{10}H_{16}$ from carone (2) and concluded that sylvestrene was an optical antipode of carvestrene (3).[2] Perkin and Tattersall (4) synthesized a terpene having the structure (I) and a direct comparison of the dihydrochloride of the synthetic terpene with that prepared from Baeyer's carvestrene proved them to be identical.



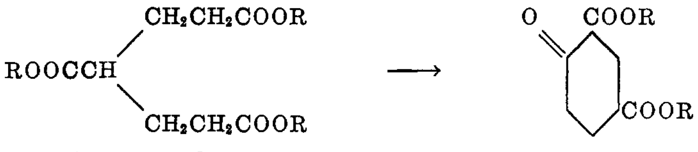
I



II

In 1913 Haworth, Perkin, and Wallach (5) suggested that sylvestrene was in all probability an inseparable mixture of two substances represented by the structures (I) and (II). Prior to this Fisher and Perkin (6) attempted to synthesize a hydrocarbon having the structure (II) and the synthesis is discussed below.

By the action of sodium ethoxide on ethyl pentane-1,3,5-tricarboxylate (IIIa) there was prepared the $\beta$-ketoester (IVa), the sodium derivative of which in methanolic solution by treatment with methyl iodide furnished the methylated $\beta$-ketoester (Va). This ester (Va) was hydrolyzed and decarboxylated with dilute sulfuric acid to yield 3-methyl-4-ketocyclohexanecarboxylic acid (VI) which was converted to the hydroxy acid (VII) by reduction with 3% sodium amalgam.



III a, R = $C_2H_5$
b, R = $CH_3$
c, R = H

IV a, R = $C_2H_5$
b, R = $CH_3$

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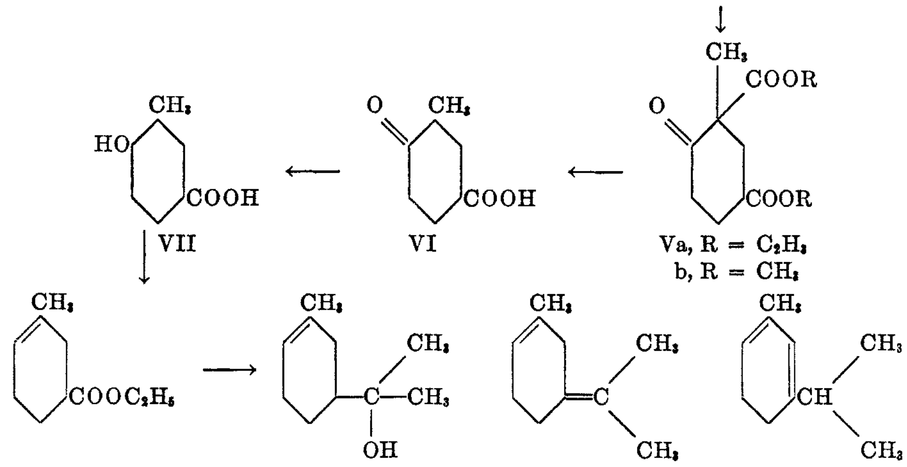
[2] For a detailed discussion see J. L. Simonsen, *The Terpenes*, The University Press, Cambridge, 1947, Vol. 1, pp. 214–229.

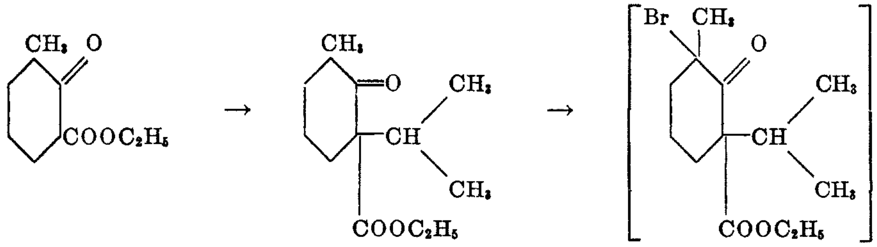


VII VI Va, R = $C_2H_5$
b, R = $CH_3$

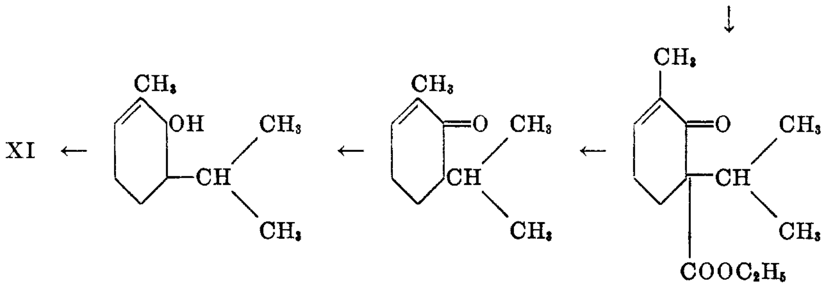
VIII IX X XI

The acid (VII) was refluxed with hydrobromic acid and the resulting crude product, after esterification, was dehydrobrominated by treatment with diethylaniline to yield the unsaturated ester (VII), which on treatment with an excess of methylmagnesium iodide yielded the carbinol (IX). The latter was then dehydrated to a diene, which was expected to be II; but its properties did not conform to this structure and this hydrocarbon was named isocarvestrene by the authors. The product showed a marked exaltation in molecular refraction and on treatment with hydrogen chloride, it did not yield any crystalline dihydrochloride. Later Auwers and Eisenlohr (7) suggested that isocarvestrene was probably represented by either of the two structures (X) and (XI). It has been shown in the present work, by an unequivocal synthesis of XI and a confirmation of its diene character that XI is not one of the possible components of isocarvestrene of Fisher and Perkin.

The synthesis of XI was carried out by the following method: Isopropyl iodide was condensed with the potassio-derivative of ethyl 2-keto-3-methylcyclohexanecarboxylate (XII) in toluene solution to furnish ethyl 1-isopropyl-2-keto-3-methylcyclohexanecarboxylate (XIII) in 75% yield. The ketoester (XIII) was brominated in dry carbon tetrachloride solution and the crude bromo compound (XIV) was dehydrobrominated by heating at 150–155° with dimethylaniline to yield the unsaturated ketoester (XV), which was hydrolyzed and

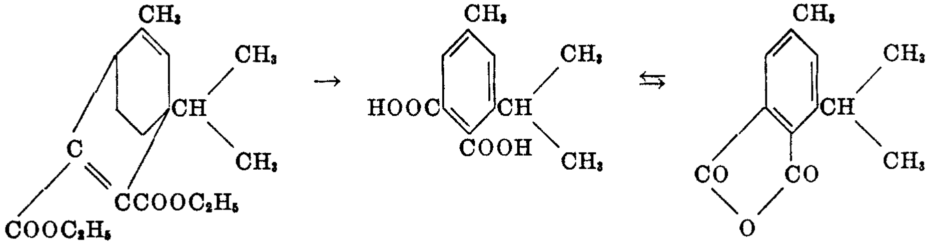


XII XIII XIV



XVII XVI XV

decarboxylated by refluxing with a 20% solution of methanolic potassium hydroxide according to the procedure of Walker (8). 2-Methyl-3-keto-4-isopropylcyclohexene (XVI), thus obtained in 82% yield, was treated with aluminum isopropoxide in isopropyl alcohol to yield the carbinol (XVII), which was dehydrated by distillation over a few crystals of *p*-toluenesulfonic acid to give the hydrocarbon (XI), as a mobile oil with a pungent odor of lemon. The diene (XI) condensed smoothly with ethyl acetylenedicarboxylate, following the method of Alder and Rickart (9), to give an adduct [presumably (XVIII)] which, on heating at 200° for one hour followed by hydrolysis, gave, as expected, a methylisopropylphthalic acid (XIX), m.p. 164°. On evaporative distillation the phthalic acid yielded the corresponding anhydride (XX), m.p. 96–98°.



XVIII XIX XX

With a view to comparing our product with that obtained by Fisher and Perkin (6) we repeated their synthesis described before with some modifications in the preparation of starting materials. It was found that condensation of ethylacetylene dicarboxylate with the isocarvestrene of Fisher and Perkin followed by hydrolysis, in the manner described for our diene (XI), did not yield any phthalic acid. This experiment strongly suggests that isocarvestrene does not possess any conjugated diene system in the cyclohexane ring. This point is further supported by the fact that the ultraviolet absorption spectra of Fisher and Perkin's hydrocarbon did not exhibit any absorption maxima in the region 255–290 m$\mu$, characteristic of the structure XI (10). Nevertheless, it shows two small inflexions at $\lambda_{max}$ 234 m$\mu$ (log $\epsilon$ 2.95) and $\lambda_{max}$ 243 m$\mu$ (log $\epsilon$, 2.90) which may be due to some other conjugated system in small quantities. The results of our experiment definitely prove that the structure XI does not represent isocarvestrene.

As mentioned before, some modifications were made in the preparation of starting materials of Fisher and Perkin's synthesis. $\gamma,\gamma$-Dicarbethoxypimelonitrile, prepared by the method of Bruson and Reiner (11) was hydrolyzed and decarboxylated to pentane-1,3,5-tricarboxylic acid (IIIc), which was esterified with methyl alcohol and ethyl alcohol to furnish the respective triesters in 58% and 68% yields.

The Dieckmann condensation of the trimethylester (IIIb) was carried out according to the procedure of Oppenshaw and Robinson (12) in an atmosphere of nitrogen and the corresponding $\beta$-ketoester (IVb) was methylated with potassium-*tert*-butoxide and methyl iodide to give the methylated product (Vb) in 89% yield. An attempt to effect the methylation *in situ* by treatment of the sodio derivative of the Dieckmann condensation with a huge excess of methyl iodide resulted in incomplete methylation. But the methylated produce could be easily separated by filtration from the unreacted highly-insoluble sodio derivative. The methylated ketoester (Vb) was hydrolyzed and decarboxylated to the keto acid (VI).

In another experiment the triethylester (IIIa) was cyclized in an atmosphere of nitrogen with sodium dust in benzene solution and the clear solution of the sodio derivative was refluxed with an excess of methyl iodide to yield a ferric chloride coloration-free methylated product (Va) in 91% yield.

The remaining steps starting from the keto acid (VI) were carried out exactly in the manner described by Fisher and Perkin (6).

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## EXPERIMENTAL

*Ethyl 1-isopropyl-2-keto-3-methylcyclohexanecarboxylate* (XIII). The condensation of isopropyl iodide with ethyl 2-keto-3-methylcyclohexanecarboxylate (XII) was carried out previously by Kotz and Michels (13, 14), but the experimental details were lacking. The condensation was conveniently effected by the following modified procedure.

A solution of the $\beta$-ketoester (XII, 17.5 g.) in 20 cc. of toluene was added dropwise to a cooled suspension of potassium dust (3.5 g.) in 100 cc. of toluene, when the solid potassioderivative was slowly formed. The mixture was allowed to stand overnight and, after the addition of isopropyl iodide (35 cc.), was first heated for three hours on a steam-bath and finally refluxed for 24 hours at 130–150° in an oil-bath. The product was cooled and filtered from potassium iodide and, after washing with water, the toluene solution was dried over calcium chloride. The toluene was then removed under reduced pressure and the ketoester (XIII) was distilled, b.p. 95–98°/1.5 mm., yield 15.8 g. (75%); $n_D^{21}$ 1.4596. The product did not produce any color with an alcoholic solution of ferric chloride.

*Ethyl 2-methyl-3-keto-4-isopropylcyclohexene-4-carboxylate* (XV). A solution of bromine (4 cc.) in 4 cc. of dry carbon tetrachloride was added dropwise with constant shaking to a cooled solution of the alkylated $\beta$-ketoester (XII, 14.5 g.) in dry carbon tetrachloride (15 cc.). After the addition of bromine, the solvent was removed at 60° under reduced pressure from the straw yellow-colored solution. Freshly distilled dimethylaniline (20 cc.) was then added and the mixture was heated at 150–160° in an oil-bath for 30 minutes. The reaction product was rapidly cooled and poured into an excess of hydrochloric acid and ice and the precipitated oil was extracted with ether. The ethereal layer was washed with ice-cold dilute hydrochloric acid, dilute sodium carbonate solution, and finally with water and dried over sodium sulfate. After the removal of solvent, the unsaturated ketoester (XV) was distilled, b.p. 100–102°/2 mm.; yield, 11.7 g. (81%); $n_D^{20}$ 1.4790.

*Anal.* Calc'd for $C_{13}H_{20}O_3$: C, 69.64; H, 8.92.

Found: C, 69.41; H, 8.59.

*2-Methyl-3-keto-4-isopropylcyclohexene* (XVI). The hydrolysis and decarboxylation of XV was carried out by the method of Walker (8). The ketoester (XV, 5 g.) was refluxed for 12 hours with a solution of potassium hydroxide (3.8 g.) in 15.2 cc. of methanol in an oil-bath at 150°. The product was diluted with cold water and the precipitated oil was extracted with ether, washed with water, and dried over sodium sulfate. After removing the solvent, the unsaturated ketone (XVI) was distilled, b.p. 118–120°/28–30 mm.; yield, 2.8 g. (82.5%); $n_D^{24}$ 1.4764; a colorless mobile oil with peppermint-like odor.

*Anal.* Calc'd for $C_{10}H_{16}O$: C, 78.94; H, 10.52.

Found: C, 78.65; H, 10.76.

*2,4-Dinitrophenylhydrazone of XVI.* A solution of the above ketone (0.45 g.) in 95% ethanol (20 cc.) was added to a solution of 2,4-dinitrophenylhydrazine (0.4 g.), concentrated sulfuric acid (2 cc.), water (3 cc.), and 95% ethanol (10 cc.). After three days 0.55 g. (76%) of shining red crystals, characteristic of the phenylhydrazones of $\alpha,\beta$-unsaturated ketones, was obtained, m.p. 128–130°. On recrystallization from dilute ethanol, the dinitrophenylhydrazone of XVI melted at 130–131°.

*Anal.* Calc'd for $C_{16}H_{20}N_4O_4$: C, 57.83; H, 6.03.

Found: C, 58.09; H, 6.47.

*2-Methyl-3-hydroxy-4-isopropylcyclohexene* (XVII). The above unsaturated ketone (XVI, 9 g.), aluminium isopropoxide (12 g.), and isopropyl alcohol (75 cc.) were placed in a flask fitted with a Hahn condenser and the mixture was heated at such a rate that four to six drops of the distillate were collected per minute. After 48 hours the distillate did not respond to the test for acetone with 2,4-dinitrophenylhydrazine solution. The operation was continued for another six hours after the addition of a further 25 cc. of isopropyl alcohol. Most of the isopropyl alcohol was removed by distillation and the product was treated with an ice-cold solution of 10% sulfuric acid. The oil was extracted with ether, washed with water, and dried over sodium sulfate. The ether was removed and the unsaturated carbinol (XVII) distilled as a mobile oil, b.p. 115–120°/18–20 mm.; yield 7.7 g. (85%); $n_D^{26}$ 1.4740.

*Anal.* Calc'd for $C_{10}H_{18}O$: C, 77.92; H, 11.68.

Found: C, 78.22; H, 11.51.

*2-Methyl-4-isopropylcyclohexa-1,3-diene* (XI). A solution of the carbinol (XVII, 6 g.) in 6 cc. of ether was allowed to stand for two hours at room temperature (26°) with a few crystals of *p*-toluenesulfonic acid. The ether was slowly distilled off and then the diene (XI) along with the water formed was distilled. The diene was taken up in ether, decanted from water, and dried over sodium sulfate. After the removal of ether, the diene (XI) was purified by distillation over a few crystals of hydroquinone, b.p. 95°/20 mm., yield 2 g.; $n_D^{26}$ 1.4804 (Reported for isocarvestrene by Fisher and Perkin, $n_D$ 1.4779).

*Anal.* Calc'd for $C_{10}H_{16}$: C, 88.24; H, 11.76.

Found: C, 88.46; H, 11.51.

The diene was a mobile oil having a pungent odor of lemon which polymerized on keeping.

*Condensation of ethyl acetylenedicarboxylate with the diene* (XI). This condensation and the pyrolysis of the adduct were carried out by the method of Alder and Rickert (9).

A mixture of the diene (XI, 1.3 g.) and ethyl acetylenedicarboxylate (1.5 g.) was taken in a test tube fitted with a reflux condenser. The mixture was allowed to stand at room temperature (28°) for 20 minutes and then was heated at 180–200° in an oil-bath for one hour. The product was fractionated under reduced pressure. A small amount of unchanged material came over as a forerun and the second fraction, 1.83 g. (66%) distilled at 140–150°/2.5 mm. leaving a small quantity of high-boiling residue which was not investigated.

The second fraction (1.83 g.) was saponified by refluxing for four hours with a solution of potassium hydroxide (2.5 g.) in methanol (50 cc.). After the removal of solvent under reduced pressure, the potassio salt was dissolved in water and the aqueous solution, after extraction with ether to remove neutral material, was acidified with cold dilute hydrochloric acid. The precipitated gum, purified by extraction with an aqueous solution of sodium bicarbonate and reacidification, furnished a crystalline solid, crude m.p. 156–162°; yield 0.8 g. On recrystallization from dilute hydrochloric acid the phthalic acid (XIX) melted at 164°.

*Anal.* Calc'd for $C_{12}H_{14}O_4$: C, 64.86; H, 6.30; Neut. equiv., 111.
Found: C, 64.75; H, 6.00; Neut. equiv., 110.2.

*Anhydride of 3-isopropyl-5-methylphthalic acid* (XX). The above acid (XIX), m.p. 164°, was distilled evaporatively at 150° (bath temperature) and 0.25 mm., when the anhydride (XX) was obtained as needle-shaped crystals, m.p. 96–98°. The melting point was not improved by redistillation.

*Anal.* Calc'd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.88.
Found: C, 70.81; H, 6.02.

On boiling with water the anhydride (XX) gave back the acid (XIX), m.p. 164°.

### PREPARATION OF STARTING MATERIALS IN FISHER AND PERKIN'S SYNTHESIS

*γ,γ-Dicarbethoxypimelonitrile.* This was prepared essentially by the method of Bruson and Reiner (11), but by using peroxide-free dioxane the yield was raised to 89.5% (reported yield, 82.5%).

*Methyl pentane-1,3,5-tricarboxylate* (IIIb). The above nitrile (59.5 g.) was refluxed for 40 hours with concentrated hydrochloric acid (275 cc.). The reaction product was evaporated to dryness on a steam-bath. The dried solid mixture was added to a solution of absolute methanol (175 cc.) and concentrated sulfuric acid (*d.* 1.84; 24.5 cc.) and refluxed for 40 hours. The solution was cooled and poured into a large volume of iced water and the precipitated oil was extracted with ether. The ether solution was washed with ice-cold 2% sodium hydroxide solution followed by water and dried over sodium sulfate. The ether was removed and the trimethylester (IIIb) was distilled, b.p. 140–144°/3 mm. [Oppenshaw and Robinson (12) report b.p. 162°/12 mm.], yield 64 g. (58%).

*Ethyl pentane-1,3,5-tricarboxylate* (IIIa). In another experiment the solid mixture obtained by the hydrolysis of 58 g. of the aforementioned nitrile was esterified by refluxing for 40 hours with a solution of absolute ethanol (200 cc.) and concentrated sulfuric acid (*d.* 1.84; 28 cc.). On working up as usual, the triethylester (IIIa) was distilled, b.p. 150–154°/1 mm.; yield 49 g. (68%).

*Methyl 1-keto-2-methylcyclohexane-2,4-dicarboxylate* (Vb). The trimethylester (IIIb, 38 g.) was added to a suspension of sodium dust (4.5 g.) in benzene (200 cc.) followed by two drops of absolute methanol and the mixture was refluxed for eight hours in an atmosphere of nitrogen. On working up as usual (12) the β-ketoester (IVb) was distilled, b.p. 130–132°/2.5 mm.; yield 28 g. (83%).

The above β-ketoester (IVb, 10 g.) was added with stirring to a solution of potassium *tert*-butoxide from potassium (1.9 g.) and *tert*-butyl alcohol (48 cc.). The mixture was cooled slightly and methyl iodide (8 cc.) was added all at once. The stirring was continued for one hour at room temperature and then refluxed for three hours, when the product was neutral to litmus. The *tert*-butyl alcohol was removed by distillation and the residue was taken up in ether, washed thoroughly with water, and dried over sodium sulfate. The ether was removed and the methylated product (Vb) was distilled, b.p. 130–135°/3.5 mm.; yield 9.5 g. (89%); $n_D^{32}$ 1.4601. The product did not produce any color with an alcoholic solution of ferric chloride.

*Anal.* Calc'd for $C_{11}H_{16}O_5$: C, 57.89; H, 7.00.
Found: C, 57.40; H, 7.10.

In another experiment the crude sodio-derivative, formed by the Dieckmann condensation from the trimethylester (IIIb, 20 g.), sodium dust (2.8 g.), and benzene (150 cc.), was refluxed for 48 hours with methyl iodide (50 cc.). The mixture produced coloration with an alcoholic solution of ferric chloride and was alkaline to moist litmus. The benzene solution was filtered from the solid residue and the benzene was removed. The residue, which gave no color with an alcoholic ferric chloride solution, was distilled and 12 g. (67%) of the methylated ester (Vb), b.p. 132–135°/3.5 mm. was obtained.

*Ethyl-1-keto-2-methylcyclohexane-2,4-dicarboxylate* (Va). The triethylester (IIIa, 3.5 g.) was added to a suspension of sodium dust (3.4 g.) in benzene (150 cc.) and, after the addition of one drop of absolute ethanol, the mixture was refluxed in an atmosphere of nitrogen. After two hours the reaction was complete and to the clear solution cooled in a freezing mixture was added methyl iodide (15 cc.). After standing overnight, the mixture was refluxed for 16 hours with a further addition of methyl iodide (15 cc.). The product, which was neutral to litmus and did not produce any color with an alcoholic ferric chloride solution, was worked up in the usual way and the ester (Va) was distilled, b.p. 138–140°/1 mm.; yield 29 g. (91%).

*3-Methyl-4-ketocyclohexanecarboxylic acid* (VI). The methylated keto ester (Vb, 10 g.) was refluxed for ten hours with 146 cc. of 10% sulfuric acid solution. The clear solution was cooled, saturated with ammonium sulfate, and extracted ten times with ether. The ether was removed and the residue solidified on scratching with a glass rod, m.p. 92–95° (reported melting point for VI, 94–96°), yield 5.1 g. (75%).

### ISOCARVESTRENE

Starting from the keto acid (VI), isocarvestrene was prepared exactly by the method described by Fisher and Perkin (6).

The ultraviolet absorption spectra of the diene in 95% ethanolic solution exhibited only two small inflexions at $\lambda_{max}$ 234 m$\mu$ (log $\epsilon$ 2.95) and $\lambda_{max}$ 243 m$\mu$ (log $\epsilon$ 2.90).

*Attempt to effect a condensation between isocarvestrene and ethyl acetylenedicarboxylate.* Isocarvestrene (0.87 g.) was treated with ethyl acetylenedicarboxylate (1 g.) and following the same method as described above for our diene (XI), we failed to obtain any phthalic acid derivative in this case.

### SUMMARY

2-Methyl-4-isopropylcyclohexa-1,3-diene, one of the two suggested structures of isocarvestrene, has been synthesized. This hydrocarbon on condensation with ethyl acetylenedicarboxylate followed by pyrolysis and hydrolysis yielded, as expected, a phthalic acid derivative.

Isocarvestrene was prepared by the method of Fisher and Perkin and it failed to react with ethyl acetylenedicarboxylate. This experiment, coupled with an ultraviolet absorption study of isocarvestrene, definitely suggests that 2-methyl-4-isopropylcyclohexa-1,3-diene cannot represent isocarvestrene.

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