SYNTHESIS OF MONO- AND SESQUITERPENOIDS—I
RACEMIC NORCARAN-2-ONE, trans-CARAN-2-ONE AND
trans-DIHYDROSESQUICARAN-2-ONE

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(Received in Japan 22 May 1969; Received in the UK for publication 1 July 1969)

Abstract—The title compounds were synthesized by the application of the intramolecular α-ketocarbene-olefin addition reaction.

BICYCLO[4.1.0]HEPTANE ring system is found in some terpenes such as carenes,1 susquicarene2 and sirenin.3 We focused our attention on the synthesis of these compounds because of the interesting biological activity of the last mentioned plant sex hormone, sirenin.

In 1961 Stork and Ficini devised a simple method for the construction of this ring system.4 They converted the unsaturated α-diazoketone (A) into bicyclo[4.1.0]heptan-2-one (B) by intramolecular α-ketocarbene-olefin addition. Application of this reaction to some α-diazoketones with a tri-substituted double bond is the theme of this paper.

Racemic norcaren-2-one. 4-Methylnpent-3-enyl bromide (Ia)5 was condensed with diethyl malonate to give a mono-substituted malonic ester (IIa). This gave an acid (IIIa) after hydrolysis and decarboxylation. Its sodium salt was treated with oxalyl chloride to give an acyl chloride (IVa) which was converted into a diazoketone (Va), a solution of which was heated in the presence of powdered copper and cupric sulfate to give crude (+)-norcaren-2-one (VIa)6 in 44% yield from IIIa. This was shown to be 90% pure by the GLC analysis. IR and NMR spectra of both the crude ketone (VIa) and its pure crystalline 2,4-dinitrophenylhydrazone supported the assigned structure.

Racemic trans-caran-2-one. The bromide (Ia) was condensed with diethyl methylmalonate to give a di-substituted malonic ester (IIb). Subsequent steps (IIb → II′b → IVb → Vb →) were carried out as described in the preceding section to yield a crude ketone (VIb) in 28% yield from Vb. The ketone was estimated to be 90% pure by GLC on a capillary column. This was purified by chromatography on silicic acid impregnated with silver nitrate.7 The IR and NMR spectra of the pure ketone are in good accord with the published values of (−)-trans-caran-2-one (VIb)8 which is known to be more stable than cis-caran-2-one.9 A pure crystalline 2,4-dinitrophenylhydrazone was obtained from the crude ketone.

* Although the formulas depicted represent only one enantiomer, they are taken to mean a racemate in the case of synthetic products.
A mixture of racemic trans-dihydrosesquicaran-2-one and its C-7 epimer. The starting C₁₁,-bromide (Ic) was synthesized as follows. Methyl cyclopropyl ketone was added to a Grignard reagent prepared from the bromide (Ia) to give an alcohol (VII). This was hydrogenated over Pd-C to afford a saturated alcohol (VIII) in 61% yield. The rest of the material was a low-boiling mixture of hydrogenolysis products. The alcohol (VIII) was treated with 48% hydrobromic acid to give the desired bromide (Ic) in fair yield. This was condensed with diethyl methylmalonate to give a di-substituted malonic ester (IIc). Subsequent manipulations as described before (IIc → IIIc → IVc → Vc →) yielded a crude ketonic product in 55% yield from the diazoketone (Vc). This was purified by chromatography on silicic acid impregnated with silver nitrate to give an analytically pure product which was shown to be a mixture of racemic trans-dihydrosesquicaran-2-one (Vlc) and its C-7 epimer (1:1) by the GLC analysis.* The 7β-methyl isomer (Vlc) was assumed to exhibit a longer retention time owing to its extending C₆ side chain. The assignment of the α-configuration to the C-3 Me group is in analogy to the formation of trans-caran-2-one (Vlb) by this carbene-olefin addition.

* Although it is difficult to entirely exclude the possibility that the mixture consists of two epimers at C-3 instead of C-7 as a referee questioned, the following facts support our assignment. (i) The acid IIIc is a mixture of Δ₅-cis and trans isomers (1:2.8) as evidenced by the GLC analysis of the corresponding methyl ester (Experimental). Since no reaction is involved in the synthetic sequence which will affect the geometry of the double bond, all the other intermediates, Ic, IIc, IVc and Vc, are also mixtures of each two geometrical isomers. The intramolecular carbene addition of the diazoketone Vc should, therefore, give a mixture of C-7 epimers regardless of the configuration at C-3. Our unpublished observation on the cyclization of a mixture of Δ₅-cis- and trans-1-diazo-7,11-dimethylodocadeca-6,10-dien-2-one, which gives a mixture of 3-demethylesquicaran-2-one and its C-7 epimer, supports this argument. The discrepancy between the ratio of the Δ₅-cis and trans isomers of IIIc (1:2.8) and the ratio of the two isomeric ketones (Vlc and Vlc, 1:1) may be due to the difference in the yields of the two ketones from the corresponding starting diazoketones (Vc). A synthesis of a stereochemically pure diazoketone (Vc) and its cyclization are an interesting problem. (ii) Some information is obtained by the comparison of the NMR data of cis- and trans-caran-2-ones with that of the mixture of two dihydrosesquicaran-2-ones as shown in the Table. (It is doubtful whether the conformations of cis- and trans-dihydrosesquicaran-2-ones are similar to those of cis- and trans-caran-2-ones which have been discussed by Acharya and Brown, and hence the NMR spectral comparison is not on a sound basis.) Firstly, the C-7 Me protons of the dihydrosesquicarane mixture absorb at δ = 1.14 ppm as a broad 3-proton singlet with a half-band width of 4 Hz. This is in accord with our assumption that the mixture consists of two C-7 epimers of trans-dihydrosesquicaran-2-ones (Vlc). The NMR spectrum of a mixture of any other isomeric ketones should exhibit two separate absorptions due to the C-7 Me protons, for two signals with a difference of 0.05 ppm or more in their chemical shifts are easily distinguishable in the 100 MHz spectrum. Secondly, the C-3 Me protons of the epimeric mixture (Vlc and Vlc') absorb at δ = 0.98 ppm as 3-proton doublet (J = 6 Hz). These values including the half-band width (2 Hz) of each lines are exactly the same as those of trans-caran-2-one (Vlb) and exclude the possibility that one of the two cis-dihydrosesquicaran-2-one is the component of the mixture. The stereo-selective formation of trans-caran-2-one (Vlb) from the diazoketone Vb also supports the view described in the text.

TABLE 1. CHEMICAL SHIFT (δ FROM TMS, ppm) OF THE METHYL PROTONS IN CARANONES

<table>
<thead>
<tr>
<th>Name</th>
<th>Methyl at C-3</th>
<th>β-Methyl at C-7</th>
<th>α-Methyl at C-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>cis-Caran-2-one*</td>
<td>0.96 (d, J = 6 Hz)</td>
<td>1.07</td>
<td>1.12</td>
</tr>
<tr>
<td>trans-Caran-2-one*</td>
<td>0.98 (d, J = 6 Hz)</td>
<td>1.17</td>
<td>1.19</td>
</tr>
<tr>
<td>The mixture of dihydrosesquicaran-2-ones</td>
<td>0.98 (d, J = 6 Hz)</td>
<td>1.14</td>
<td></td>
</tr>
</tbody>
</table>
GCMS measurements revealed that the mass spectra of both the racemic ketone (Vlc) and its C-7 epimer were identical with that of the optically active ketone (VIc). This established the identity of the plane structure of the three compounds. The position of the major absorptions in the IR and NMR spectra of the synthetic mixture are almost identical with those of the optically active dihydrosesquicaran-2-one, although small differences are observed in the relative intensities of the major absorptions and in the position and intensity of small peaks. This may be due to the presence of the C-7 epimer in the synthetic product.

The direct GLC comparison of the synthetic product with the optically active ketone was impossible, since an authentic sample was not available.

In conclusion this study added further examples to the application of the α-ketocarbene-olefin addition\(^1\) in terpene synthesis\(^2\) and opened the way to the synthesis of sesquicarene\(^3\) and sirenin.

**EXPERIMENTAL**

All m.ps and b.ps were uncorrected. IR spectra refer to Nujol mulls for solid samples and films for liquids. NMR spectra were recorded at 100 MHz in CDCl\(_3\) with TMS as an internal standard unless otherwise stated.

**Diethyl 4-methylpent-3-enylmalonate (IIa).** A soln of diethyl malonate (80 g) in EtOH (50 ml) was added to a soln of NaOEt (from 11.5 g of Na) in EtOH (200 ml). To this mixture Ia (80 g) in EtOH (50 ml) was
added with stirring at 0–5°. After stirring for 1 hr at 0–5°, the mixture was heated under reflux for 2 hr with stirring, concentrated in vacuo, poured into water and extracted with ether. The ethereal soln was washed with sat NaCl aq, dried (MgSO₄) and concentrated. The residue was distilled to give 90 g (75%) of IIa, b.p. 103–123°/5 mm. An analytical sample boiled at 104–105°/2 mm, n₀⁻¹ 1.4433; νₚmax 1730 (broad), 1290, 1240, 1220, 1130, 1080, 1040, 1020, 855 cm⁻¹; δ 1.23 (6H, t, J = 6 Hz), 1.55 (3H, s), 1.65 (3H, s), 4.05 (4H, q, J = 6 Hz) 5.00 (1H, broad t) ppm. (Found: C, 64.64; H, 9.02. C₁₉H₂₂O₂ requires: C, 64.44; H, 9.15%).

6-Methylhept-5-en-1-oic acid (IIa). A soln of IIa (87 g) in 95% EtOH (150 ml) was mixed with KOH aq (87 g in 200 ml). The mixture was heated under reflux for 2 hr with stirring and concentrated in vacuo to remove EtOH. After acidification with AcOH (200 ml) the mixture was heated under reflux for 2 days, cooled, diluted with water and extracted with ether. The ethereal soln was washed with water and sat NaCl aq, dried (MgSO₄) and concentrated in vacuo. The residue was distilled to give 46 g (92%) of IIa, b.p. 125–126°/13 mm. An analytical sample boiled at 110–111°/4 mm, n₀⁻¹ 1.4492; νₚmax ~3400–~2600, 1705, 960 cm⁻¹; δ 1.58 (3H, s), 1.67 (3H, s), 5.00 (1H, t), 12.08 (lH, s) ppm. (Found: C, 67.46; H, 9.93); C₁₉H₂₂O₂ requires: C, 67.13; H, 9.92%.

6-Methylhept-5-en-1-yl chloride (IVa). A soln of IIIa (23 g) in 95% EtOH (100 ml) was neutralized with NaOH aq employing phenolphthalein as an indicator. The soln was concentrated in vacuo. The wet Na salt of IIIa was suspended in benzene and the benzene was removed in vacuo. This was repeated several times to remove water and the dry Na salt was suspended in dry benzene (150 ml). Oxalyl chloride (35 g) was added with stirring at 0–5°. The mixture was stirred for 1 hr at 0–5°, filtered through celite and concentrated in vacuo to give an oily IVa. This was employed for the next step without further purification.

1-Diazo-7-methyloct-6-en-2-one (Va). A soln of the above IVa in dry benzene (50 ml) was added to a soln of CH₂N₂ (from 50 g of N-nitroso-N-methylurea) in ether (ca. 600 ml) under ice-cooling. The mixture was left to stand at 0–5° for 2 hr and then at room temp for 16 hr, filtered and concentrated in vacuo to give crude Va, νₚmax 2130, 1730 (w, due to impurities), 1645, 1380, 1150, 1040 cm⁻¹. This was employed for the next step without further purification.

(±)-3-Norcan-2-one (Vla). A soln of the above Va in cyclohexane (300 ml) was added dropwise to a stirred and refluxing suspension of powdered Cu (1.5 g) and CuSO₄ (0.4 g) in cyclohexane (700 ml) during 1.5 hr. After the addition the mixture was stirred and heated under reflux for 8 hr, then cooled, filtered, and concentrated in vacuo. The residue was distilled to give 100 g (44%) from IIIa of crude Vla, b.p. 88–105°/12 mm. An analytical sample boiled at 91–92°/15 mm, n₀⁻¹ 1.4783; νₚmax 1730 (w, due to impurities), 1675 (s), 1450, 1420, 1370, 1340, 1325, 1240, 1210, 1180, 1115, 1070, 1040, 890, 755 cm⁻¹; δ 1.18 (3H, s), 1.20 (3H, s) ppm. (Found: C, 76.97; H, 10.22. C₁₈H₂₄O₂ requires: C, 76.78; H, 10.21%). This figure indicates the presence of impurities. GLC analysis: Column, SE30 2a m x 3 mm; Column temp, 105°; Carrier gas, He 1.0 mm. An analytical sample boiled at 91–92°/15 mm, n₀⁻¹ 1.4470; νₚmax 1730, 1280, 1250, 1190, 1130, 1050, 860 cm⁻¹. This was employed for the next step without further purification.

Ethyl 2-carbethoxy-2,6-dimethylhept-5-en-1-yl chloride (Ivb). The bromide Ia (25 g) and diethyl methylmalonate (25 g) were condensed as described for IIa to give 23.3 g (57%) of Ib, b.p. 115–120°/4 mm. An analytical sample boiled at 110–111°/4 mm, n₀⁻¹ 1.4470; νₚmax 1730, 1280, 1250, 1190, 1130, 1050, 860 cm⁻¹; δ 1.26 (6H, t, J = 6 Hz), 1.36 (3H, s), 1.58 (3H, s), 1.66 (3H, s), 4.10 (4H, q, J = 6 Hz), 5.05 (1H, broad t) ppm. (Found: C, 56.55; H, 5.73; N, 17.75. C₁₉H₂₄O₂N₄ requires: C, 56.59; H, 5.70; N, 17.60%).

2,6-Dimethylhept-5-en-1-oyl chloride (IVb). The acid IIb (11 g) was converted into its Na salt by neutralizing with NaOMe (3.8 g) in EtOH. The Na salt was treated with oxalyl chloride (25 g) as described in the preparation of IVa to give an oily IVb.
prepared from SiO₂ (50 g) and AgNO₃ aq (4 g in 20 ml). The crude V (1.3 g) was concentrated in vacuo. The residue was fractionated by column chromatography (SiO₂-AgNO₃). A column (55 cm x 4 cm) in pet. ether was used to purify the analytically pure V. (Found: C, 81.32; H, 10.7%; requires: C, 81.47; H, 10.4%).

The product was then treated with oxalyl chloride (25 g) as described in the preparation of IVa to give an oily IVc.

2-Cyclopropyl-6-methylheptan-2-ol (VIII). An alcohol VII (59 g) in 95% EtOH (200 ml) was hydrogenated over 10% Pd-C (3 g) at room temp under atm press for 4 hr. The catalyst was filtered off and the filtrate was concentrated in vacuo. The residue was fractionally distilled to give 36 g (78%) of crude VIII, b.p. 82-85°/12 mm. The following spectral and analytical data indicate that this is contaminated with some impurities; v, 1724 (w. due to impurities), 1700 (s), 1680 (s), 1640 (s) cm⁻¹; δ 0.98 (6H, d, J = 6 Hz), 1.25 (6H, t, J = 6 Hz), 1.35 (3H, s), 1.56 and 1.65 (3H), 4.10 (4H, q, J = 6 Hz), 5.05 (1H, broad) ppm. (Found: C, 69.95; H, 10.51. C₁₅H₂₀O₄ requires: C, 69.90; H, 10.50%).

2,6,10-Trimethylundec-5-en-1-oyl chloride (IVc). The acid IIC (140 g) was converted into its Na salt by neutralizing with NaOCH₃ (3-3 g) in EtOH. The Na salt was treated with oxalyl chloride (25 g) as described in the preparation of IVa to give an oily IVc.

1-Diazo-3,7,11-trimethyl-6-endo-2-one (Vc). The above IVc was treated with ethereal CH₃N₂ to give 6.3 g of Vc. (Found: C, 74.32; H, 11.56. C₁₄H₂₆O₂ requires: C, 74.28; H, 11.58%).

Summary: The syntheses of various mono- and sesquiterpenoids were described, focusing on the isolation and purification of key compounds using chromatography and spectral analysis. The purity of the final products was confirmed through various spectroscopic methods and analytical data.
with AgNO₃ aq in a separatory funnel prior to use. All fractions were 250 ml. Eluants were as follows: fractions No. 1–3, pet. ether; No. 4–17, pet. ether: benzene = 5:1; No. 18–20, pet. ether: benzene = 1:1. Fractions No. 1–5 gave 326 mg of oily impurity. Fractions No. 6–12 gave 2982 g of almost pure Vlc + Vlc', b.p. 130–133°/7 mm, n₀^1 1.4692; ν₅ max 1680 (s), 1724 (w, due to impurities). Fractions No. 13–19 gave 528 mg of pure Vlc + Vlc', b.p. 123–124°/5 mm, n₀^1 1.4720; ν₅ max 1680, 1460, 1380, 1370, 1360, 1350, 1325, 1230, 1215, 1190, 1170, 1120, 1095, 1045, 1010, 885 cm⁻¹; δ 0.88 (6H, d, J = 6 Hz), 0.98 (3H, d, J = 6 Hz), 1.14 (3H, s) ppm. The positions of major absorptions in these two spectra are in good accord with those of the optically active dihydrosesquicar-2-one derived from the natural product. The details, however, were somewhat different. (Found: C, 81.09; H, 11.82. C₁₅H₂₂O requires: C, 81.02; H, 11.79%). GLC analysis: Column, Castor wax 45 m x φ5 mm; Column temp 190°; Carrier gas, N₂, 0.5 kg/cm²; Retention time: 14.9 min (Vlc'), 19.2 min (Vlc) (area ratio 1:1). MS of Vlc: m/e 222, 151, 138, 125, 109, 96, 81, 69, 55, 41 (base peak). Vlc' exhibited an entirely identical mass spectrum with that of Vlc. The mass spectra of both Vlc and Vlc' were identical with that of the optically active dihydrosesquicar-2-one.

Acknowledgements—We are indebted to Prof. W. Cocker, University of Dublin, and to Dr. Y. Ohta, Institute of Food Chemistry, Osaka for kindly sending to us the spectral data of the optically active trans-car-2-one and dihydrosesquicar-2-one, respectively. Our thanks are due to Dr. H. Kurihara of Takasaga Perfume Industry Co, Tokyo, and to Mr. M. Ohki of this laboratory for GLC analyses and GCMS measurements. We appreciate the help of Prof. T. Yamanishi, Ochanomizu Women's University, Tokyo, in some of the GLC analyses. A gift of α-acetyl-γ-butyrolactone, the starting material, by Daicel Co., Tokyo, is gratefully acknowledged.

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