The Transformation of Carvone into Racemic Grandisol

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Grandisol (**1**) is one of the components of the pheromone complex emitted by the male boll weevil. We report the transformation of readily available eucarvone (**3**), via the photoisomer **4**, into grandisol in 20% overall yield. A key step in the synthesis is the Beckmann cleavage of oxime **15**, derived in three steps from **4**, to nitrile **16**. Hydrolysis of **16** followed by hydride reduction gives grandisol (**1**).

Le grandisol (**1**) est l'un des composants du complexe phéromone émis par l'antomone male. Nous rapportons la transformation de l'eucarvone (**3**) d'accès facile en grandisol; la synthèse se fait par l'intermédiaire du photoisomère **4** et le rendement global est de 20%. Dans l'étape clef de la synthèse, l'oxime **15**, obtenu en trois étapes à partir de **4**, subit un réarrangement de Beckmann pour conduire au nitrile **16**. L'hydrolyse de ce dernier suivit d'une réduction par l'hydrure de lithium aluminum conduit au grandisol (**1**).
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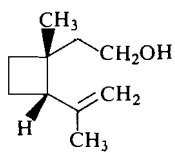
Grandisol (**1**) is one of the components of the sex pheromone of the boll weevil (1). We wish to report a facile stereoselective synthesis of grandisol starting from the monoterpene ketone carvone (**2**). We believe that this synthesis has some advantages over those previously reported (1, 2) in that the starting material is readily available and inexpensive, and the overall yield is reasonably high. Earlier syntheses (1, 2) all



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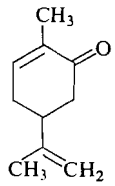
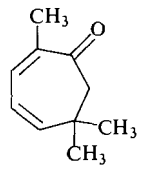


2

involve an *intermolecular* "2 + 2" cycloaddition in the construction of the cyclobutane ring. The synthesis reported herein differs from these in that it employs an efficient *intramolecular* cyclization for the formation of the 4-membered ring.

The initial steps utilize the well-known transformation of carvone into eucarvone (**3**) (3) and the equally well-studied photochemical transformation of eucarvone into the photoisomer **4** (4). The photoisomer **4** possesses not only the proper arrangement of carbon atoms but also has the required *cis*-relationship between the C-1 methyl and the C-5 hydrogen. The plan (Scheme 1) was to modify **4** by hydrogenation



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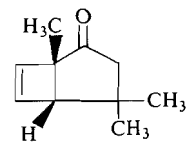

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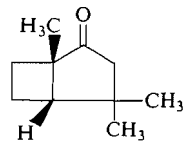
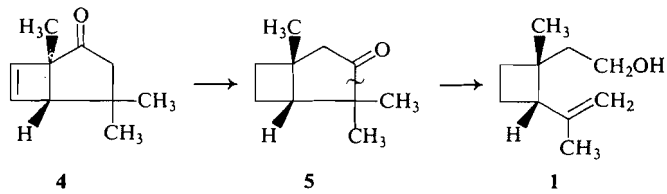


6

and ketone transposition to give **5**. Cleavage of the C_3—C_4 bond in **5** and adjustment of functionality would lead to grandisol (**1**). The method by which this has been accomplished is described below.

The first problem encountered was that of producing substantial amounts of the photoisomer **4** in a reasonably economical manner. In the original Buchi procedure (4*a*) the photoisomer **4** was produced in 36% yield after 22 days photolysis in ethanol. Later work (4*c*–*e*) has shown that the rate of formation of **4** is increased in more polar solvents. We have found that large scale photolysis in trifluoroethanol (4*e*) proceeds to completion (complete disappearance of eucarvone) in 3 days. However the photolysis product is a complex mixture and separation of **4** (in 48% yield) was tedious. This, coupled with

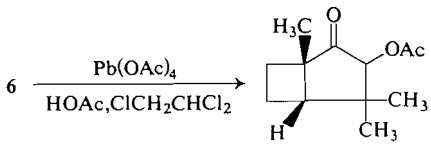


4 5 1

SCHEME 1

the relatively high cost of trifluoroethanol, led us to investigate other solvent systems. After some experimentation we have found that photolysis in ethylene glycol – trifluoroethanol (10:1) is virtually complete in 7 days and that the photoisomer is easily isolated from the photolysis mixture (see Experimental) in 52% yield. Hydrogenation of **4** over palladium-on-charcoal (4*a*) gave **6** in virtually quantitative yield.

Several methods (5) for effecting 1,2-ketone transposition were investigated. In one attempt the ketone **6** was first treated with lead tetraacetate (6) in refluxing acetic acid to give in 89% yield the α-acetoxyketone **7**. Attempted rearrangement of **7** to the isomeric α-acetoxyketone **7***a* under a variety of conditions (tetramethylammonium acetate (7), alumina (8), methanolic sulfuric acid followed by acetylation (9)) was unsuccessful. Compound **7** was recovered in each case which suggests that it is the thermodynamically more stable of the two possible positional isomers.



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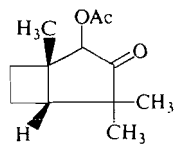
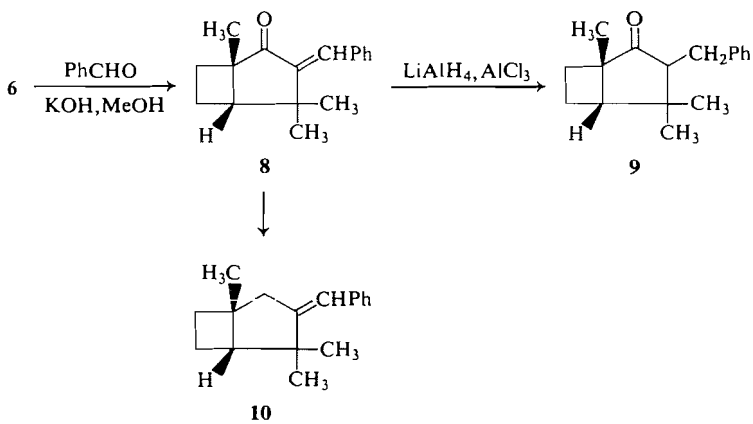


7*a*

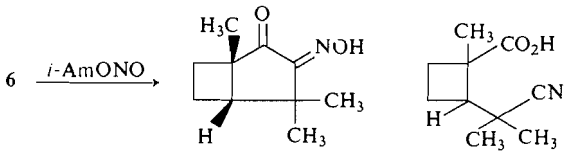
Another potential route (10) to the ketone **5** involves formation of the α-benzylidene ketone **8**. In the cases reported (10), reduction of the α-benzylidene ketone with lithium aluminum hydride – aluminum chloride leads to the corresponding deoxy compound. In this case, however, the major reduction product was the α-benzyl ketone **9**, the product of 1,4-addition of hydride. Reduction of **8** by the Nagata modification (11) of the Wolff–Kishner reaction gave in 58% yield the desired benzylidene compound **10**. However, all attempts at oxidative cleavage (ozone, $KMnO_4$–$NaIO_4$ (12), $RuCl_3$–NaOCl (13)) were unsuccessful, unreacted **10** being recovered in each case. The highly hindered nature of the double bond in the benzylidene compound **10** is reflected in its u.v. spectrum (λ_{max} 249 nm, ε 2150). Normally (5*a*), this type



8 9 10

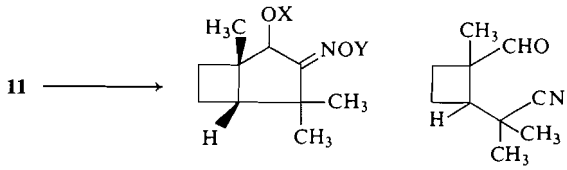
of compound absorbs at somewhat longer wavelength and with an extinction coefficient ten times as great. Presumably in this case steric crowding forces the chromophoric group to deviate from coplanarity.

The ketone transformation method which proved successful involved an intermediate oximinoketone. Initially formation of the oximinoketone presented problems. Treatment of ketone **6** with *n*-butyl nitrite under acid catalysis (14) for 12 h gave only starting ketone, whereas use of isoamyl nitrite with potassium *t*-butoxide in anhydrous *t*-butyl alcohol (15) led to formation of the oximinoketone **11**. When the reaction was carried out on a larger scale, however, very low yields of oximinoketone were obtained. The major compound isolated was the acid nitrile **12**, the product of Beckmann cleavage. When the reaction was carried out in dry benzene as solvent utilizing potassium *t*-amylate (16) as the base the oximinoketone **11** (as a mixture of *E* and *Z* isomers) was obtained consistently in yields of greater than 80%.



11 **12**

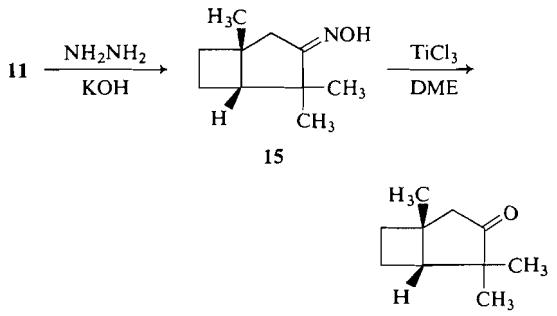
In an attempt to utilize Corey and Richman's ketone transposition method (17), the oximinoketone was reduced quantitatively with sodium borohydride to the oximinoalcohol **13***a*. Mild acetylation gave an acetoximino alcohol **13***b*. More vigorous acetylation gave a mixture of acetoximino acetate **13***c* and another compound which was tentatively identified as the cyanoaldehyde **14**. Attempted mesylation of the acetoximino alcohol gave a mixture of the acetoximino mesylate **13***d* and the cyanoaldehyde. Although this compound was not isolated in pure form, fragmentation to a cyanoaldehyde is well documented for α-hydroxyoximes (18). Since neither the acetoximino acetate nor the acetoximino mesylate could be prepared in good yield, reductive deoximation was attempted on the acetoximino alcohol. The product obtained after treatment with chromous acetate was shown by gas–liquid chromatography to be a mixture of at least eight components, the major of which was the cyanoaldehyde **14**.



13 **14**

a X = Y = H
b X = H; Y = Ac
c X = Y = Ac
d X = Ms; Y = Ac

Utilization of the Wolff–Kishner reaction enabled us to remove the carbonyl group in the oximinoketone. Heating the oximinoketone with excess hydrazine (19) led to isolation of only a small quantity of oxime **15**; however, use of just 1½ equiv. of hydrazine hydrate and excess base (20) gave the crystalline oxime in 82% yield. Deoximation with titanium trichloride (21) gave the transposed ketone **5** in high yield.



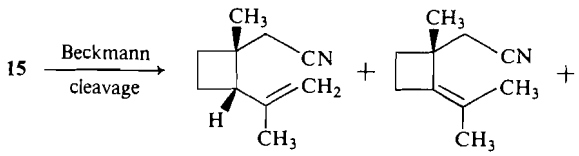
15 **5**

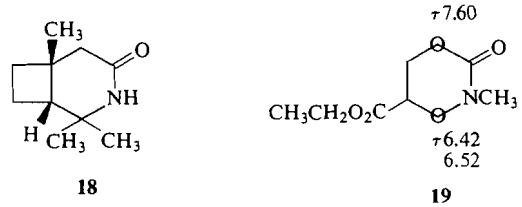
Although it is possible to envision methods for cleaving the C_3—C_4 bond in the ketone **5** itself, Beckmann cleavage of the oxime **15** should proceed in the desired direction (22) and this route was explored first.

When oxime **15** was treated with thionyl chloride in dimethylformamide at 0° for 2 h, the product was a mixture of two compounds. The components of the reaction product were separated by preparative gas–liquid chromatography and were identified as the isomeric nitriles **16** and **17** on the basis of the following spectral data. Compound **16**, which was the minor component, shows nitrile absorption at 2250 and exocyclic methylene at 1650 and 890 cm^{-1} in its i.r. The n.m.r. spectrum shows two vinyl protons as multiplets at τ 5.10 and 5.23, a vinyl methyl group at τ 8.33, and a methyl group at τ 8.64. Compound **17**, which was the major

component of the reaction mixture, shows nitrile absorption at 2220 cm^{-1} in the i.r. The n.m.r. spectrum displays a two proton singlet at τ 7.52 for the methylene adjacent to a cyano group, two three-proton multiplets for vinyl methyl groups at τ 8.50 and 8.55, and a methyl singlet at τ 8.62. When oxime **15** was treated with phosphorus pentachloride in dimethylformamide, with *p*-toluenesulfonyl chloride in refluxing pyridine, or with Beckmann's mixture the same mixture was obtained although the product distribution varied.

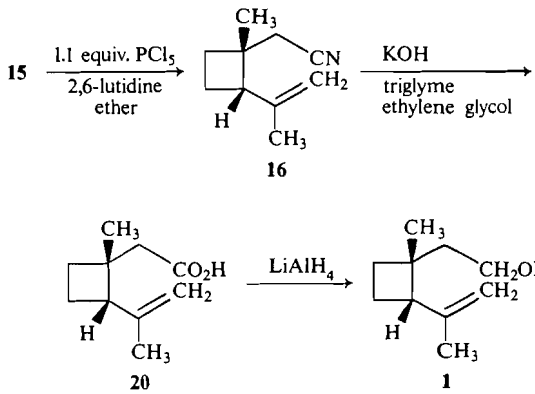
Use of phosphorus pentachloride in ether, ether–benzene, or alone gave, in addition to the two isomeric nitriles **16** and **17**, a third compound isolated in crystalline form. The crystalline compound was purified by chromatography and identified as lactam **18**. The i.r. spectrum of lactam **18** shows N—H absorption at 3510 and 3300 cm^{-1} as well as lactam carbonyl at 1660 cm^{-1}. The n.m.r. spectrum of compound **18** shows three methyl singlets (τ 8.72, 8.78, 8.90) and a two-proton singlet at τ 7.55 assigned to the C-1 methylene protons. Comparison of the chemical shift value of the C-1 methylene of lactam **18** with the C-5 methylene (τ 7.60) of ethyl 1-methyl-6-oxonepacotoate (**19**)[1] confirms that the methylene is α to the carbonyl rather than α to the nitrogen (C-2 methylene in **19** appears as two doublets at τ 6.42, 6.52). When the Beckmann cleavage was attempted using polyphosphoric acid or polyphosphoric ester as a catalyst, the same three compounds were obtained but again the product distribution varied.





[1]R. Dawe, these laboratories, private communication

At this stage it seemed desirable to ascertain the stereochemistry (*E* or *Z*) of the oxime. Spectroscopic methods (23) do not give an unambiguous answer, especially if only one isomer is available. Attempted transoximation caused no change in oxime **15**. Direct oxime formation from ketone **5** furnished oxime **15**. These experiments suggest that the less hindered and presumably more stable (*E*)-oxime is in hand. In addition the cleavage reactions described above give products expected to arise from the (*E*)-oxime. We thus turned our attention to defining reaction conditions which would favor the formation of nitrile **16**. Reasoning that nitrile **17** may arise from proton-catalyzed rearrangement of **16** and that lactam **18** is formed when water is present, the Beckmann reaction was catalyzed by phosphorus pentachloride (1.1 equiv.) in anhydrous ether in the presence of 2,6-lutidine (2 equiv.). Work-up within 5 min (longer reaction times led to lower yields) gave nitrile **16** in *ca.* 85% yield. Since nitrile **16** is quite volatile, the reaction product was not purified at this stage but was directly hydrolyzed with potassium hydroxide in triglyme – ethylene glycol in a sealed tube. The carboxylic acid **20** was isolated as its cyclohexylamine salt in 62% overall yield from oxime **15**. The spectral data obtained for acid **20**, an intermediate in one of the previous syntheses, is in good agreement with that reported (*2a*).



Finally, reduction of the cyclohexylamine salt of acid **20** with lithium aluminum hydride gave compound **1** in 92% yield. The i.r. and n.m.r. spectra of synthetic grandisol were identical with those published (1, 2) for grandisol and the mass spectra were very similar. The overall yield of grandisol (**1**) from eucarvone (**3**) was 20%.

Experimental

Solutions were dried over anhydrous magnesium sulfate unless otherwise specified. Melting points were determined on a Fisher-Johns or Leitz-Wetzlar hot-stage melting point apparatus and are uncorrected. Microanalyses were performed by the Microanalytical Laboratory of this department.

Infrared spectra were recorded on a Perkin-Elmer Model 337 grating i.r. spectrophotometer, a Unicam SP1000 grating i.r. spectrophotometer, or a Perkin-Elmer Model 421 dual grating i.r. spectrophotometer.

Nuclear magnetic resonance spectra were measured using a Varian Associates Model A-60 spectrometer or a Varian Model HR-100 spectrometer with tetramethylsilane as internal standard. Deuterium exchangeable protons are noted in text as D_2O.

Mass spectra were recorded on an A.E.I. Model MS-9 mass spectrometer or an A.E.I. Model GC/MS mass spectrometer with a WB separator and are reported as *m/e* (relative intensity).

The purity of all liquid products was monitored by gas chromatography utilizing a Varian Aerograph Gas Chromatograph Model A-90-P3 with helium as carrier gas on the following Chromsorb W (60–80 mesh) supported columns: 10 ft by $\frac{1}{4}$ in. polyester (10% PDEAS), 5 ft by $\frac{1}{8}$ in. polyethylene glycol (10% Carbowax 20M), 5 ft by $\frac{1}{8}$ in. silicone oil (10% SE-30), 5 ft by $\frac{1}{8}$ in. Zonyl E-7.

Preparation of Eucarvone (3) (3)

Carvone (100 g) was added dropwise to a stirred, cooled solution of hydrobromic acid in glacial acetic acid (500 g, 30% HBr in glacial HOAc). The rate of addition was adjusted such that the temperature of the solution was maintained between 8 and 12°. When addition was complete (approximately 0.5 h), the cooling bath was removed and stirring was continued a further 15 min. The solution was poured into water (800 ml). The lower organic layer was separated and the aqueous layer was extracted with ether. The organic fractions were combined, washed twice with water, neutralized ($NaHCO_3$), washed with water, dried (Na_2SO_4), then added dropwise to a stirred, cooled solution of potassium hydroxide (75 g) in methanol (300 ml). After addition was complete, the solution was concentrated on a steam bath, then poured onto a sulfuric acid (50 ml) – crushed ice (1:1) mixture. Water was added to dissolve the inorganic salts. The upper oily layer was separated and the aqueous layer extracted with ether. The organic fractions were combined, washed with saturated sodium bicarbonate solution, water, and dried (Na_2SO_4). The solution was concentrated and the residual oil fractionated using a spinning band apparatus to give 65 g (65%) eucarvone, **3**; b.p. 82° (7 mm); η_D^{24} 1.5050 (lit. (3) b.p. 82.5–84° (8 mm); η_D^{20} 1.5080).

1,4,4-Trimethylbicyclo[3.2.0]hept-6-en-2-one (4) (4)

A stirred solution of eucarvone (13.0 g) in ethylene glycol (500 ml) and trifluoroethanol (50 ml) was irradiated in a Pyrex vessel with an immersible mercury vapor lamp (250 W, Hanovia medium pressure) for 7 days. The photolysis mixture was diluted with water (500 ml), then continuously extracted with pentane for 48 h. The pentane solution was dried, concentrated *in vacuo* at room temperature, and the residual oil was fractionated through a 40 cm spinning band column to give 6.8 g (52%) unsaturated ketone, **4**; b.p. 90–91° (35 mm); η_D^{23} 1.4561 (lit. (4*a*) b.p. 110–111° (45 mm); η_D^{25} 1.4556); i.r. (neat): 1740 cm^{-1} (C=O); n.m.r. (CCl_4): τ 3.67 (d, 1, J = 2.5 Hz, *cis* C=C*H*), 3.90 (d, 1, J = 2.5 Hz, *cis* C=C*H*), 7.20 (d, 1, J = 17 Hz, *gem* CH_2), 7.44 (s, 1, C*H*), 8.26 (d, 1, J = 17 Hz, *gem* CH_2), 8.78 (s, 3, CH_3), 8.92 (s, 3, CH_3), 9.05 (s, 3, CH_3); 2,4-dinitrophenylhydrazone derivative, m.p. 162–163° (lit. (4*a*) m.p. 161.5–162.5°).

1,4,4-Trimethylbicyclo[3.2.0]heptan-2-one (6)

Unsaturated ketone **4** (5.8 g) was hydrogenated over 30% palladized charcoal (0.1 g) in methanol (100 ml) at room temperature and atmospheric pressure. After 1 equiv. of hydrogen had been consumed, the mixture was filtered and concentrated. The residual clear liquid (one compound by g.l.c. analysis (10% PDEAS, 10 ft × $\frac{1}{4}$ in., column temperature 150°, flow rate 60 ml/min)) was used in subsequent steps without further purification. Yield of saturated ketone **6** was 5.6 g (95%); η_D^{24} 1.4585 (lit. (4*a*) η_D^{25} 1.4556).

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.73; H, 10.35.

The i.r. (neat): 1735 cm^{-1} (C=O); n.m.r. (CCl_4): τ 8.78 (s, 3, CH_3), 8.97 (s, 3, CH_3), 9.10 (s, 3, CH_3); mass spectrum: *m/e* 152.1194 (67) (calcd. for $C_{10}H_{16}O$: 152.1201), 124(29), 109(89), 95(97), 82(100), 81(42), 69(57), 55(28), 41(97), 39(37); 2,4-dinitrophenylhydrazone derivative m.p. 148.5–150.5° (lit. (4*a*) m.p. 147.5–148°).

3-Acetoxy-1,4,4-trimethylbicyclo[3.2.0]heptan-2-one (7) (6)

A mixture of ketone **6** (3.95 g), lead tetraacetate (14.0 g), acetic acid (40 ml), and 1,2,2-trichloroethane (80 ml) was allowed to reflux for 4 days. The mixture was cooled and ethylene glycol (2 ml) was added to destroy excess lead tetraacetate. The mixture was then washed successively with water and sodium hydroxide solution (5%). The aqueous fraction was backwashed with ether. The organic fractions were combined, dried, concentrated, and distilled to give 4.85 g (89%) acetoxy ketone **7**; b.p. 65–71° (0.05 mm); η_D^{24} 1.4607.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 67.89; H, 9.50. Found: C, 68.16; H, 9.53.

The i.r. (neat): 1760 (C=O), 1750 (C=O), 1235 ($OCOCH_3$) cm^{-1}; n.m.r. (CCl_4): τ 4.36 (s, 1, C*H*OAc), 7.83 (s, 3, $OCOCH_3$), 8.77 (s, 3, CH_3), 8.84 (s, 3, CH_3), 9.20 (s, 3, CH_3); mass spectrum: *m/e* 210.1250 (5) (calcd. for $C_{12}H_{18}O_3$: 210.1256), 167(16), 139(10), 100(10), 72(50), 71(14), 43(100), 41(31).

3-Benzylidene-1,4,4-trimethylbicyclo[3.2.0]heptan-2-one (8)

A stirred solution of ketone **6** (1.4 g), benzaldehyde (3 ml), sodium hydroxide (0.9 g), methanol (45 ml), and water (25 ml) was heated on a steam bath for 48 h. The reaction mixture was cooled, diluted with water and extracted with methylene chloride. The organic fraction was dried and concentrated to an oil (0.6 g), which was purified by chromatography over alumina (BDH). Elution with petroleum ether (b.p. 65°) gave an oil which was a mixture of (*Z*)- and (*E*)- benzylidene ketones. Further elution with petroleum ether gave (*E*)-benzylidene

ketone as a crystalline compound (m.p. 57–59°); total yield 1.65 g (75%).

Anal. Calcd. for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 84.68; H, 8.18.

The u.v. (95% EtOH): 290 nm (ε 21 900), 226 nm (ε 11 650); i.r. ($CHCl_3$): 1710 (C=O), 1610 (C=C) cm^{-1}; n.m.r. ($CDCl_3$) *Z* isomer: τ 2.36 (s, 1, *cis* COC=C*H*), 2.70 (s, 5, Ar*H*), 8.12 (m, 5), 8.70 (s, 3, C*H*$_3$), 8.75 (s, 3, C*H*$_3$), 9.07 (s, 3, C*H*$_3$); *E* isomer: τ 3.43 (s, *trans* COC=C*H*), 8.72 (s, C*H*$_3$), 8.82 (s, C*H*$_3$), 8.95 (s, C*H*$_3$); mass spectrum: *m/e* 240.1516 (100) (calcd. for $C_{17}H_{20}O$: 240.1514), 225(35), 212(51), 197(46), 184(25), 170(29), 169(30), 155(32), 143(37), 129(80), 128(56), 115(33), 97(51), 95(83), 91(73), 77(40), 69(48), 41(88), 39(40).

*3-Benzyl-1,4,4-trimethylbicyclo[3.2.0]heptan-2-one (**9**)*

Benzylidene ketone **8** (0.5 g) in ether (20 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (0.2 g) and aluminum chloride (0.98 g) in ether (70 ml). After addition was complete, the mixture was refluxed for 24 h, then cooled. Excess hydride was destroyed by cautious addition of 3 *N* sodium hydroxide, then water. The ether fraction was separated, dried, and concentrated. The crude product was chromatographed over alumina (BDH). Elution with petroleum ether (b.p. 65°) gave benzyl ketone **9**, as an oil (0.29 g, 56.5%); η_D^{24} 1.5230.

Anal. Calcd. for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.10; H, 9.07.

The i.r. (film): 1730 (C=O), 1600, 1500 cm^{-1}; n.m.r. ($CDCl_3$): τ 2.75 (s, 5, Ar*H*), 8.78 (s, 3, C*H*$_3$), 9.13 (s, 3, C*H*$_3$), 9.22 (s, 3, C*H*$_3$): mass spectrum: *m/e* 242.1678 (21) (calcd. for $C_{17}H_{22}O$: 242.1617), 173(100), 97(84), 91(43), 41(28).

*3-Benzylidene-1,4,4-trimethylbicyclo[3.2.0]heptane (**10**)*

Benzylidene ketone **8** (0.21 g), 85% hydrazine hydrate (29 ml), hydrazine dihydrochloride (0.73 g), and triethylene glycol (174 ml) were heated at 120° for 2 h. Potassium hydroxide pellets (1.1 g) were added and the temperature was slowly raised to 230°, allowing the low boiling material to distil. The reaction mixture was held at that temperature for 1.5 h then cooled, diluted with water, and extracted with petroleum ether. The petroleum ether fraction was washed with water, dried, concentrated, and the residual oil molecularly distilled (100°/0.5 mm). Yield 0.11 g (58%).

Anal. Calcd. for $C_{17}H_{22}$: C, 90.20; H, 9.80. Found: C, 89.87; H, 9.77.

The u.v. (methanol): 249 nm (ε 2150); i.r. (film): 1610 (conj. C=C), 1500 cm^{-1}; n.m.r. ($CDCl_3$): τ 2.83 (m, 6, Ar*H* and ArC*H*=C), 8.52 (s, 2), 8.73 (s, 6, C*H*$_3$), 8.95 (s, 3, C*H*$_3$); mass spectrum: *m/e* 226.1715 (6) (calcd. for $C_{17}H_{22}$: 226.1721), 198(9), 145(100), 129(11), 91(39).

*3-Oximino-1,4,4-trimethylbicyclo[3.2.0]heptan-2-one (**11**)*

In t-Butyl Alcohol

Isoamyl nitrite (1.2 g) was added dropwise to a stirred solution of ketone **6** (0.8 g) and potassium *t*-butoxide (1.2 g) in anhydrous *t*-butyl alcohol (15 ml) in a nitrogen atmosphere. The red solution was allowed to stir for 20 h, then was diluted with water, washed with ether, acidified (HCl), and extracted with ether. The ether fraction was dried and concentrated to an oil (0.63 g). Crystallization from ether gave oximinoketone **11**, (0.25 g, 26%). The mother liquor was concentrated and a portion (0.16 g) chromatographed over silica gel (6 g). Elution with chloroform gave a crystalline compound (0.085 g), 1-methyl-2(1-methyl-1-cyanoethyl)cyclobutyl carboxylic acid, **12**; m.p. 189–192°; i.r. ($CHCl_3$): 3400–2500 (CO-OH), 2220 (C≡N), 1710 (C=O) cm^{-1}; n.m.r. ($CDCl_3$): τ 8.86 (s, 3, C*H*$_3$), 8.72 (s, 3, C*H*$_3$), 8.57 (s, 3, C*H*$_3$), 7.83 (s, 4, C*H*$_2$), −1.95 (s, 1, COO*H*, D_2O); mass spectrum: *m/e* 181.1102 (5) (calcd. for $C_{10}H_{15}NO_2$: 181.1103), 155(9), 135(11), 126(14), 109(29), 95(30), 87(21), 69(100), 55(24), 41(86).

In Benzene

Ketone **6** (5.1 g) in anhydrous benzene (10 ml) was added dropwise to a stirred, cooled solution of potassium *t*-amylate (7.5 g, 75 ml of 0.85 *N* potassium *t*-amylate in benzene) (16) in anhydrous benzene, followed by dropwise addition of isoamyl nitrite (3.75 g, distilled and stored over molecular sieve 5A) in anhydrous benzene (10 ml). The purple solution was stirred at room temperature for 24 h. The solution was cooled and diluted with 5% aqueous HCl. The upper organic layer was separated and washed with saturated sodium bicarbonate solution. The aqueous fraction was neutralized ($NaHCO_3$) and extracted with methylene chloride. The organic fractions were combined, washed with brine, dried, and concentrated to an oil. The oil was chromatographed over silicic acid (200 g) using a quartz column and a u.v. light to monitor the separation. Elution with chloroform (400 ml) gave a crystalline mixture of (*E*)- and (*Z*)-oximinoketones (1.2 g). Further elution with chloroform gave crystalline (*E*)-oximinoketone (4.0 g); m.p. 128–131.5°. Total yield of oximinoketone was 5.2 g (88%).

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 65.92; H, 8.14; N, 7.55.

The i.r. ($CHCl_3$) *E* isomer: 3560, 3360 (NOH), 1740 (C=O), 1630 (C=N) cm^{-1}; *Z* isomer: 3200 (NOH), 1690 (C=O), 1580 (C=N) cm^{-1}; n.m.r. ($CDCl_3$) *E* isomer: τ 0.15 (br s, 1, NO*H*, D_2O), 8.59 (s, 3, C*H*$_3$), 8.75 (s, 6, C*H*$_3$); *Z* isomer: τ 8.65 (s, 3, C*H*$_3$), 8.79 (s, 3, C*H*$_3$), 8.82 (s, 3, C*H*$_3$): mass spectrum *E* isomer: *m/e* 181.1100 (21) (calcd. for $C_{10}H_{15}NO_2$: 181.1103), 164(22), 136(33), 109(45), 97(74), 95(25), 69(23), 55(100), 41(83), 39(36); *Z* isomer: *m/e* 181.1104 (19) (calcd. for $C_{10}H_{15}NO_2$: 181.1103) 164(9), 136(31), 109(26), 98(25), 97(100), 95(14), 69(28), 67(3), 55(63), 41(63), 39(30).

*3-Oximino-1,4,4-trimethylbicyclo[3.2.0]heptan-2-ol (**13a**)*

Sodium borohydride (0.050 g) in water (2 ml) was added dropwise to a stirred solution of oximinoketone **11** (0.226 g) in dimethoxyethane (8 ml). After addition was complete, stirring was continued for 30 min. The solution was diluted with water, carefully acidified (HCl), neutralized ($NaHCO_3$), and extracted with methylene chloride. The organic fraction was dried and concentrated to give 0.545 g (100%) of a crystalline oximino alcohol, **13***a*; m.p. 69–72.5°.

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.11; H, 9.25; N, 7.97.

The i.r. ($CHCl_3$): 3580, 3300, 1070 (NOH, OH), 1680 (w, C=N) cm^{-1}; n.m.r. ($CDCl_3$): τ 5.65 (s, 1, C*H*OH), 8.60 (s, 3, C*H*$_3$), 8.65 (s, 3, C*H*$_3$), 8.84 (s, 3, C*H*$_3$); a small quantity of another epimer was present as shown by a signal at τ 5.50 (C*H*OH); mass spectrum: *m/e* ($M^+ - OH$) 166.1235 (16) (calcd. for $C_{10}H_{16}NO$:

166.1231), 122(13), 114(12), 109(13), 97(45), 95(22), 87(43), 81(27), 69(100), 55(37), 53(21), 43(23).

*3-Acetoximino-1,4,4-trimethylbicyclo[3.2.0]heptan-2-ol (**13b**)*

Oximino alcohol **13***a* (0.1 g), benzene (1 ml), pyridine (1 drop), and acetic anhydride (0.14 g) were heated in an oil bath at 65° for 1 h. The mixture was concentrated by azeotropic distillation with benzene, dried *in vacuo* to give acetoximino alcohol **13***b*; m.p. 89.5–90.5°.

Anal. Calcd. for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.91; H, 8.52; N, 6.11.

The i.r. ($CHCl_3$): 3550, 3450, 1070 (OH), 1755 (C=O), 1660 (C=N) cm^{-1}; n.m.r. ($CDCl_3$): τ 5.45 (s, 1, C*H*OH), 6.20 (s, 1, O*H*, D_2O), 7.82 (s, 3, OCOCH_3), 8.63 (s, 6, CH_3), 8.80 (s, 3, CH_3); mass spectrum: *m/e* (M^+ − OAc) 182.1179 (2) (calcd. for $C_{10}H_{16}NO_2$: 182.1181), 136(24), 122(41), 109(39), 107(28), 97(60), 95(34), 82(30), 81(86), 69(100), 68(50), 67(27), 60(36), 55(46), 53(23), 45(32), 43(54), 41(59).

*Attempted Formation of Acetoximino Acetate (**13c**)*

Oximino alcohol **13***a* (0.125 g), acetic anhydride (0.2 g), pyridine (0.16 g), and benzene (2 ml) were heated in an oil bath (65°) for 0.5 h. Excess solvents were removed by azeotropic distillation with benzene and the residual oil (0.153 g) was dried *in vacuo*. This oil was a mixture of two compounds (t.l.c.: silica gel, chloroform–methanol). The i.r. and n.m.r. spectra were consistent with a mixture of acetoximino acetate **13***c* and cyanoaldehyde **14**.

The i.r. ($CHCl_3$): 2730 (CHO), 2230 (CN), 1720 (C=O); 1770, 1745 (C=O) cm^{-1}; n.m.r. ($CDCl_3$): τ −0.33 (s, C*H*O), 8.68 (s, CH_3), 8.70 (s, CH_3); 4.06 (s, C*H*OAc), 7.82 (s, OCOCH_3), 7.85 (s, OCOCH_3), 8.62 (s, CH_3), 8.77 (s, CH_3).

*Attempted Formation of Acetoximino Mesylate (**13d**)*

Acetoximino alcohol **13***b* (0.122 g), pyridine (2 drops), methanesulfonyl chloride (0.098 g), and benzene (1 ml) were allowed to stand at 0° overnight. Excess solvent was removed by azeotropic distillation with benzene and the residue (0.150 g) was dried *in vacuo*. The i.r. and n.m.r. spectra of the residue are consistent with a mixture of acetoximino mesylate **13***d*, cyanoaldehyde **14**, and acetoximino alcohol **13***b*.

*Attempted Reduction of Acetoximino Alcohol (**13b**) with Chromous Acetate (**17**)*

Acetoximino alcohol (0.4 g), tetrahydrofuran (6.4 ml), chromous acetate (1.6 g), and water (2 ml) were heated at 65° in a nitrogen atmosphere for 36 h. The mixture was allowed to cool, diluted with water, filtered, and extracted with methylene chloride. The methylene chloride fraction was washed with 10% hydrochloric acid, saturated sodium bicarbonate, water, then dried, and concentrated. Analysis of the residual oil by g.l.c. – mass spectrometry showed a mixture of eight compounds; three minor compounds had a molecular ion of 152. The i.r. and n.m.r. spectra are consistent with impure cyanoaldehyde, **14**; i.r. ($CHCl_3$): 2730, 2230, 1720 cm^{-1}; n.m.r. (CCl_4): τ −0.33 (s, C*H*O), 8.68 (s, CH_3), 8.70 (s, CH_3).

*3-Oximino-1,4,4-trimethylbicyclo[3.2.0]heptane (**15**)*

A mixture of oximinoketone **11** (0.760 g), hydrazine hydrate (85%, 0.238 ml), potassium hydroxide (0.3 g), and ethylene glycol (15 ml) was heated at 150° for 4 h. The reaction mixture was allowed to cool, diluted with water, acidified (HCl), neutralized ($NaHCO_3$), and extracted with pentane. The pentane fraction was washed with brine, dried, and concentrated to give 0.570 g (81.5%) crystalline oxime **15**; m.p. 118–119.5°.

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 71.53; H, 10.36; N, 8.56.

The i.r. ($CHCl_3$): 3580, 3290 (NOH), 1670 (C=N) cm^{-1}; n.m.r. (CCl_4): τ 0.80 (s, 1, NO*H*, D_2O), 7.07 (d, 1, J = 19 Hz, *gem* CH_2), 7.73 (d, 1, J = 19 Hz, *gem* CH_2), 8.70 (s, 3, CH_3), 8.93 (s, 6, CH_3); mass spectrum: *m/e* 167.1315 (7) (calcd. for $C_{10}H_{17}NO$: 167.1310), 152(38), 150(35), 138(15), 125(38), 124(57), 122(40), 109(24), 81(21), 79(23), 69(74), 68(20), 55(32), 53(24), 41(100).

*1,4,4-Trimethylbicyclo[3.2.0]heptan-3-one (**5**)*

Oxime **15** (0.430 g), dimethoxyethane (8 ml), water (4 ml), and titanium trichloride (1.5 equiv., 3.1 ml) were allowed to reflux 15 min. The cooled solution was diluted with water and extracted with methylene chloride. The methylene chloride fraction was washed with sodium bicarbonate solution, dried, and concentrated by distillation at atmospheric pressure; η_D^{22} 1.4590; i.r. (neat): 1735 (C=O) cm^{-1}; n.m.r. (CCl_4): τ 7.69 (q, 2, J = 19 Hz, CH_2CO), 8.67 (s, 3, CH_3), 9.05 (s, 3, CH_3), 9.10 (s, 3, CH_3); mass spectrum: *m/e* 152.1203 (2) (calcd. for $C_{10}H_{16}O$; 152.1201), 73(73), 67(100), 45(96), 41(20); 2,4-dinitrophenylhydrazone derivative: m.p. 169–171.5°.

Beckmann Cleavage Reaction

(a) Thionyl Chloride – DMF

Thionyl chloride (0.18 ml) was added to a cooled (0°), stirred solution of oxime **15** (0.5 g) in dimethylformamide (4 ml). The mixture was maintained at this temperature for 2 h, then diluted with water, neutralized ($NaHCO_3$), and extracted with pentane. The pentane extract was dried and excess solvent removed by distillation through a 12 ft column packed with glass helices. The mixture was separated by preparative gas–liquid chromatography on a Zonyl E-7 column (10 ft × ⅛ in., column temperature 180°, 60 ml/min).

Compound **16** 0.057 g; retention time: 5.4 min; i.r. (CCl_4): 2250 (CN), 1650, 890 (C=CH_2) cm^{-1}; n.m.r. (CCl_4): τ 5.10 (m, 1, C=CH_2), 5.23 (m, 1, C=CH_2), 8.33 (br s, 3, C=C—CH_3), 8.64 (s, 3, CH_3); mass spectrum: *m/e* 149.1198 (1) (calcd. for $C_{10}H_{15}N$: 149.1204), 148(2), 134(3), 110(4), 94(5), 81(6), 79(12), 68(100), 67(80), 53(29).

Compound **17** 0.120 g; retention time: 6.6 min; i.r. (CCl_4): 2220 (CN), 1455, 1440 (C=C—CH_2) cm^{-1}; n.m.r. (CCl_4): τ 7.52 (s, 2, CH_2CN), 8.50 (m, 3, C=C—CH_3), 8.55 (m, 3, C=C—CH_3), 8.62 (s, 3, CH_3); mass spectrum: *m/e* 149.1200 (48) (calcd. for $C_{10}H_{15}N$: 149.1204), 134(22), 109(100), 107(28), 93(23), 81(42), 79(25), 69(30), 68(20), 67(67), 53(22), 41(32).

(b) Phosphorus Pentachloride – Ether

Oxime **15** (0.25 g) in ether (10 ml) was added dropwise to a stirred suspension of phosphorus pentachloride (0.34 g) in ether (10 ml). The reaction mixture was stirred overnight, then diluted with water, and the layers separated. The aqueous layer was washed with ether, the ether extracts combined, dried, and concentrated.

Chromatography of the residue over alumina (BDH) gave a crystalline lactam **18** (0.047 g); m.p. 110–111°.

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 72.14; H, 9.99; N, 8.23.

The i.r. ($CHCl_3$): 3510, 3300 (NH), 1660 (C=O) cm^{-1}; n.m.r. ($CDCl_3$): τ 7.55 (s, 2, CH_2CO), 8.72 (s, 3, CH_3), 8.78 (s, 3, CH_3), 8.90 (s, 3, CH_3); mass spectrum: *m/e* 167.1318 (3) (calcd. for $C_{10}H_{17}NO$: 167.1310), 152(100), 124(50), 70(76), 58(34), 41(14), 40(12).

*2-Isopropenyl-1-methylcyclobutane Acetic Acid (**20**)*

Oxime **15** (0.500 g) in anhydrous ether (10 ml) was added dropwise to a stirred suspension of phosphorus pentachloride (0.680 g) and 2,6-lutidine (0.690 ml) in ether (50 ml). The reaction mixture was stirred in an atmosphere of nitrogen for 5 min, then quenched with a saturated ammonium chloride solution. The aqueous and ethereal layers were separated and the aqueous layer was washed with ether. The ether extracts were combined, washed (saturated $NaHCO_3$ solution), dried, and concentrated by distillation through a 1 ft column packed with glass helices to give seconitrile **16**.

Crude seconitrile **16** was hydrolyzed with potassium hydroxide (2.5%) in ethylene glycol – triethylene glycol dimethyl ether (1:1) in a sealed tube at 200° for 24 h. The reaction mixture was cooled, diluted with water, and washed with ether. The ether washing was extracted with sodium bicarbonate solution and the aqueous fractions combined. The aqueous fractions were acidified to p*H* 5 with buffer solution and extracted with ether. The ether extract was washed (water) and dried. Cyclohexylamine (0.300 g) was added. The cyclohexylamine salt (0.491 g) of secocarboxylic acid **20** was collected (62% from oxime); m.p. 112.5–114.5°.

Anal. Calcd. for $C_{16}H_{29}NO_2$: C, 71.87; H, 10.93. Found: C, 71.68; H, 11.09.

The i.r. ($CHCl_3$): 3300–2400, 2000 ($\overset{+}{N}H_3$), 1570 (COO^-) cm^{-1}. In another experiment, salt formation was omitted and secocarboxylic acid **20** was isolated as an oil; b.p. 108–110° (0.5 cm); i.r. (CCl_4): 3300–2500 (COOH), 1710 (C=O), 1650, 890 (C=CH_2) cm^{-1}; n.m.r. (CCl_4): τ 0.4 (1, m, COO*H*, D_2O), 5.16 (m, 1, C=CH_2), 5.34 (m, 1, C=CH_2), 8.33 (br s, 3, C=C—CH_3), 8.67 (s, 3, CH_3); mass spectrum: *m/e* 168.1146 (5) (calcd. for $C_{10}H_{16}O_2$: 168.1150), 125(29), 109(16), 108(92), 93(23), 81(28), 69(26), 68(100), 67(62), 43(26), 41(28).

*cis-2-Isopropenyl-1-methylcyclobutane Ethanol (Grandisol) (**1**)*

A solution of lithium aluminum hydride in anhydrous ether (1 *M*, 2.5 ml) was added dropwise to a cooled (ice bath), stirred suspension of secocarboxylic acid **20** cyclohexylamine salt (0.350 g) in anhydrous ether (25 ml). The reaction mixture was stirred for 3 h then excess hydride destroyed by successive dropwise addition of water, 5% NaOH, and water. The precipitate was filtered and washed extensively with ether. The ether fractions were combined, washed successively with 5% HCl, brine, and dried. Excess solvent was removed by distillation through a 12 ft column packed with glass helices to give 0.189 g of an oil. Molecular distillation (1 mm/100°) gave racemic grandisol (0.186 g, 92%). The i.r. and n.m.r. are identical with the published spectra (1*b*); i.r. (CCl_4): 3620, 3500 (OH), 1640, 885 (C=C) cm^{-1}; n.m.r. (CCl_4): τ 5.18 (m, 1, C=CH_2), 5.37 (m, 1, C=CH_2), 6.43 (t, 2, J = 7.5 Hz, CH_2CH_2OH), 6.92 (br s, 1, O*H*, D_2O), 8.33 (br s, 3, C=CCH_3), 8.83 (s, 3, CH_3); mass spectrum: *m/e* 154.1354 (13) (calcd. for $C_{10}H_{18}O$: 154.1358), 139(11), 136(23), 121(25), 110(23), 109(53), 93(22), 81(26), 69(18), 68(100), 67(53), 56(21), 55(28), 53(27), 41(21), 39(26).

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