231. The Chemistry of Thujone. VI[1]). Thujone as a Chiral Synthon for the Synthesis of Optically Active Steroid Analogues

by **James P. Kutney, Peter Grice, Keith O. Pascoe, Krystyna Piotrowska, Steven J. Rettig, Jerzy Szykula** and **James Trotter**[2])

Department of Chemistry, University of British Columbia, Vancouver, B.C., V6T 1Y6, Canada

(12.V.82)

Summary

The thujone derived enone **1** is converted in one step to the pentacyclic compound **4**. The structure of **4** was determined by X-ray diffraction analysis. The acid-catalyzed cyclopropane-ring opening of **4** and of the model compound **9** are described.

We have previously reported the use of thujone as a chiral synthon in the synthesis of optically pure sesquiterpenes (+)-β-cyperone [1] and (+)-carrisone [2]. We now report the synthesis and chemistry of the steroid-like molecule **4**.

As part of our synthetic program we wished to prepare the tetracyclic dienone **3** *(Scheme 1)*. We expected to achieve this by *Robinson* annelation of **1** [1], exploiting the enone functionality to direct attack of ethyl vinyl ketone, or an equivalent reagent, in the desired sense. Indeed, treatment of **1** with a small excess of *Mannich* salt **5** in boiling ethanol containing potassium hydroxide gave a mixture of products from which **3** was isolated in 33% yield. The major product of this reaction was the pentacyclic compound **4**, obtained in 39% yield.

Clearly **4** is the result of addition of two molecules of ethyl vinyl ketone to **1** and subsequent dehydration. The gross structure of **4** was evident from its spectroscopic properties. However, the relative configuration of the C(19) (steroid numbering) angular methyl group remained uncertain. The CD. curve of **4** displayed a positive *Cotton* effect, but unfortunately no reliable examples could be found to allow a positive assignment of the configuration of C(19) to be made.

Compound **4** crystallized from ethanol and provided suitable crystals for X-ray-diffraction analysis. The structure and absolute configuration of **4** is shown in the *Figure*.

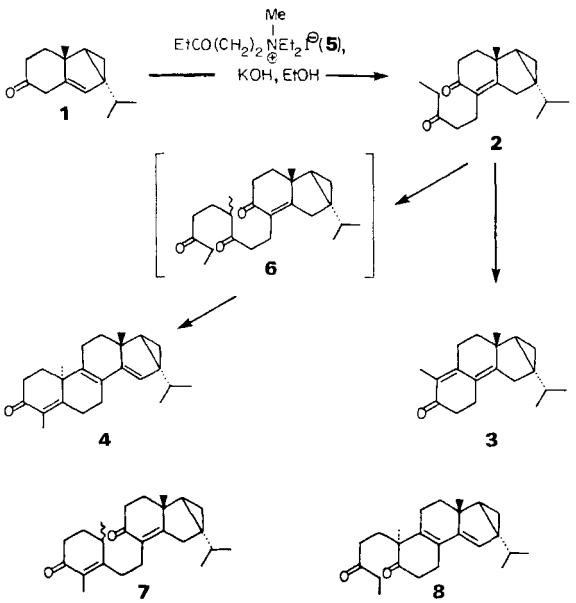
The A and C rings have distorted C(1)β and C(13)β sofa-(1,2-diplanar) [3] conformations and the B ring has a distorted 1,3 diplanar [3] conformation. As a result of the C(14),C(15) double bond and the fused cyclopropane ring, the D

[1]) For Part V, see [2].

[2]) Authors to whom correspondence should be addressed.

0018-019X/82/7/2345-10$01.00/0 © 1982 Schweizerische Chemische Gesellschaft

Scheme 1



ring in **4** is almost planar. Related steroids with a C(14),C(15) double bond are found to have C(17) envelope conformations for the D-ring [4] [5]. The maximum angle of torsion (ϕm) and the phase angle of pseudorotation (Δ) [6] for the D-ring in **4** are 2.5° and 92.9° respectively. The geometry of the C/D-ring junction is similar

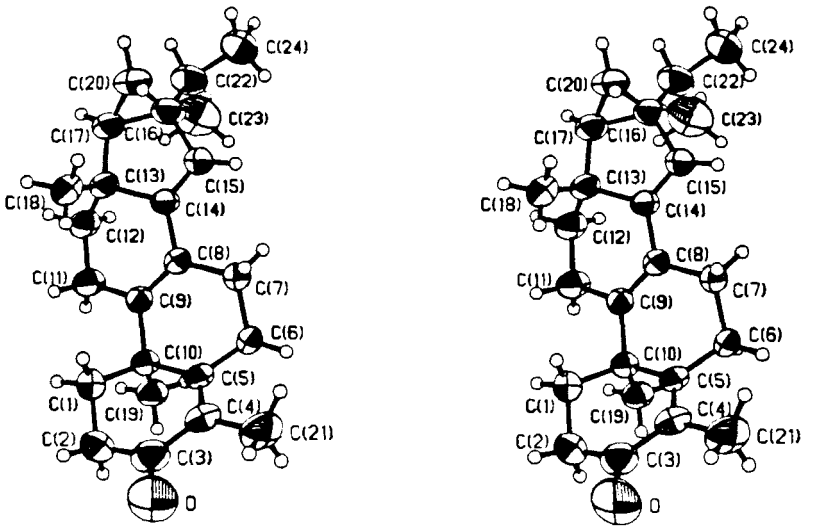


Figure. *Stereoview of* **4** (50% probability thermal ellipsoids are shown for O- and C-atoms. H-atoms have been assigned artificially small thermal parameters for the sake of clarity)

to that observed for other related structures with C(14), C(15) double bonds [4] [5]. The molecule is substantially bowed, being convex towards the α face.

Bond lengths and angles are generally as expected; mean C,C-double bond-, $C(sp^3)$, $C(sp^3)$-(excluding those in the cyclopropane ring), $C(sp^3)$, $C(sp^2)$- and $C(sp^2)$, $C(sp^2)$-distances being 1.340, 1.528, 1.507 and 1.477 Å, respectively. Some bond distances differ significantly from the expected values: C(1), C(2), C(9), C(11) and C(14), C(15) bonds are shortened, while C(5), C(10), C(8), C(9), C(9), C(10) and C(10), C(19) are lengthened. The mean C,C distance in the cyclopropane ring (1.500(7)Å) is in good agreement with the value of 1.510(2)Å in gaseous cyclopropane [7]. The bond to the isopropyl group (C(16), C(22), 1.506(6)Å) is significantly shortened, probably a σ-hybridization effect.

At first sight it seemed that **4** arose *via Robinson* annelation of **3** with ethyl vinyl ketone. However, examination of relevant literature [8], and our own experiments showed that this is not the case. Thus, treatment of **3** with methyl vinyl ketone, ethyl vinyl ketone or *Mannich* salt **5** under a variety of conditions led only to recovery of **3** (see *Table 1*). No pentacyclic products were formed.

Table 1. *Attempted* Robinson *annelation of* **3**[a])[b])

Reagent (mmol)	Base (mmol)	Solvent (ml)	Temp. (°C)	Time (h)	Product
MVK (2)	KOH (0.27)	EtOH (10)	25°	52	**3**
MVK (2)	KOH (0.27)	EtOH (10)	reflux	24	**3**
MVK (4)	KOH (0.27)	EtOH (10)	25°	48	**3**
MVK (4)	KOH (0.27)	EtOH (10)	reflux	6	**3**
MVK (2)	KOH (68)[c])	H_2O(15)CH_2Cl_2 (10)	25°	24	**3**
MVK (5)	KOH (68)[c])	H_2O(15)CH_2Cl_2 (10)	25°	24	**3**
EVK (2)	KOH (0.27)	EtOH (10)	25°	52	**3**
EVK (2)	KOH (0.27)	EtOH (10)	reflux	24	**3**
EVK (4)	KOH (0.27)	EtOH (10)	25°	48	**3**
EVK (4)	KOH (0.27)	EtOH (10)	reflux	6	**3**
5 (2)	KOH (2.2)	EtOH (15)	reflux	16	**3**
EVK (2)	KOH (68)[c])	H_2O (15) CH_2Cl_2 (10)	25°	16	**3**

[a]) MVK = methyl vinyl ketone; EVK = ethyl vinyl ketone.
[b]) All reactions were carried out using **3** (270 mg, 1 mmol).
[c]) In these experiments benzyltriethylammonium chloride (57 mg, 0.25 mmol) was added as a catalyst.

The failure of **3** to undergo reaction with ethyl vinyl ketone, combined with the absolute configuration of C(19) in **4** led us to postulate that **4** is formed *via* the intermediacy of triketone **6** *(Scheme 1)*. This may be formed by the addition of ethyl vinyl ketone to diketone **2**. Examination of molecular models led to the conclusion that **6** should cyclize to give exclusively **4**. In the transition state leading to gross structure **4**, but possessing the β-configuration of C(19), severe steric interactions between the two methyl groups (C(18) and C(19)) are present. On the other hand, the transition state leading to **4** with C(19) in the α-configuration reveals minimal interactions. This argument is equaly valid if the formation of **4** were to proceed *via* the intermediates **7** or **8**.

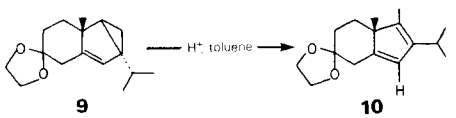
Treatment of **1** with ethyl vinyl ketone in ethanol containing a catalytic amount of potassium hydroxide allowed the isolation of diketone **2**, albeit in low yield (17%). A considerable amount of **1** remained unreacted. Very mild conditions were necessary to prevent premature cyclization to **3**. When **2** was heated in ethanol containing potassium hydroxide, dienone **3** was isolated in 91% yield.

Although we were unable to isolate the proposed intermediate triketone **6** it seems clear that during *Robinson* annelation of **1** with ethyl vinyl ketone the initially formed diketone **2** may either undergo cyclization to give dienone **3** or react with a second molecule of ethyl vinyl ketone to give, ultimately, **4**.

We have initiated a program to convert **1** into other steroid-like molecules having the correct, *i.e.* β-configuration at C(10), and hope to report successful results shortly.

In the meantime we have investigated ways to modify the ring-D portion of **4**. A model reaction *(Scheme 2)* was carried out to investigate the acid-catalyzed opening of the cyclopropane ring. The acetal **9** [1] was treated with a catalytic amount of *p*-toluenesulfonic acid in boiling toluene for 100 h, at which time only a trace of **9** remained. The cyclopentadiene **10** was the major product and was isolated in 25% yield.

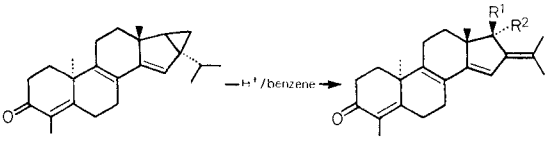
Scheme 2



9 **10**

Treatment of **4** with acetic acid and *p*-toluenesulfonic acid in boiling benzene for 16 h caused this molecule to undergo cyclopropane-ring opening to give **11a** and **11b** (ratio 1:1 by ^{1}H-NMR. and GC.) with a total yield of 65% *(Scheme 3)*.

Scheme 3



4

11a $R^1 = CH_3$, $R^2 = H$

b $R^1 = H$, $R^2 = CH_3$

One isomer was obtained pure by fractional crystallization. On the basis of a nuclear *Overhauser*-effect-difference experiment this isomer was assigned structure **11b**, though since the second isomer could not be obtained pure enough for a similar study this assignment must remain tentative.

It will be noted that ring opening of **4** leads to the formation of an exocyclic double bond. This is in contrast to **9** which leads to the formation of a diene **10** possessing endocyclic double bonds. The reasons for this difference and for the large difference in rates of ring opening are not clear.

In both cases cyclopropane-ring opening leads to the formation of a 5-membered ring *via* protonation of the cyclopropane methylene C-atom. The alternate mode of ring opening *via* protonation of the cyclopropane methine C-atom was not observed.

Hence, thujone may be transformed into the pentacyclic compound **4**, optically pure, in only 3 steps using very readily available reagents with an overall yield of 19%. We have also demonstrated that **4** undergoes cyclopropane ring opening to give **11** whose functionality should allow further modification of ring D to that of biologically active steroids. Further studies are underway.

Financial aid from the *Science Council of British Columbia* and the *Natural Sciences and Engineering Research Council of Canada* is gratefully acknowledged. The authors would also like to thank *MacMillan Bloedel Limited* and Mr. *Alan Moss and Associates* for generous samples of cedar leaf oil. Computing funds for the structure analysis were provided for by the *Xerox Corporation of Canada* and the *University of British Columbia Computing Centre.*

Experimental Part

General remarks. Melting points (m.p.) and boiling points (b.p.) are uncorrected. M.p. were determined on a *Kofler* block. UV. spectra were recorded on a *Cary-15* spectrophotometer. IR. spectra were recorded using a *Perkin Elmer 257* infrared spectrophotometer. ^{1}H-NMR. and ^{13}C-NMR. were recorded at ambient temperature using a *Bruker WH-400* spectrometer. Coupling constants (J) are given in Hertz. Tetramethylsilane was used as internal standard. MS. were recorded on either an *AEI MS-902* or an *Atlas CH-4B* spectrometer. High resolution molecular weight determinations were made using an *AEI MS-902* spectrometer. Optical rotations were measured on a *Perkin Elmer 141* automatic polarimeter. Circular dichroism curves were recorded on a *Jasco J-20* spectropolarimeter. Microanalyses were carried out by Mr. *P. Borda,* Microanalytical Laboratory, University of British Columbia.

Synthesis of 13β-isopropyl-6,10α-dimethyl-tetracyclo[8.4.0.0^{2,7}.0^{11,13}]tetradeca-1,6-dien-5-one (**3**) *and 16β-isopropyl-16,17-methano-4,10β,13α-trimethyl-1,2,6,7,10,11,12,13,16,17-3*H*-decahydrocyclopentano-phenanthren-3-one* (**4**). To a stirred and cooled solution of potassium hydroxide (0.9 g, 13.7 mmol) in EtOH (50 ml) was added a solution of enone **1** (2.04 g, 10 mmol) in EtOH (10 ml) over a period of 10 min. After 30 min 1-diethylamino-3-pentanone methiodide (**5**) (3.9 g, 13 mmol) in EtOH (10 ml) was added during 15 min. After 1 h the solution was heated to reflux for 16 h. The reaction was cooled, acidified with acetic acid, diluted with water (50 ml) and then evaporated. The residue was extracted with CH_2Cl_2 (3×20 ml). The combined extracts were washed with hydrochloric acid (2×15 ml of 2N), $NaHCO_3$-solution (2×15 ml of 5% *w/v*), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silicagel to give a TLC. homogeneous, pale yellow gum, yield 2.8 g. This gum was chromatographed on a reversed-phase HPLC. column (2.5×30 cm, *Waters C-18* packing) using methanol and water (9:1, *v/v*) as eluant. Pure **3** was eluted first as a colourless oil, yield 0.9 g (33%). $[\alpha]_D = -347°$ ($c = 2$, $CHCl_3$). – UV. (EtOH): 309 (4.21). – IR. (film): 1665, 1630. – ^{1}H-NMR. (400 MHz, $CDCl_3$): 0.65 (*t*, $J = 5$, 1 H, H_{endo}–C(12)); 0.73 (*m*, 1 H); 0.86 and 0.89 (2*d*, $J = 7$, 6 H, $(H_3C)_2C$); 0.93 (*s*, 3 H, H_3C–C(10)); 1.08 (*d*×*d*, $J = 5$ and 8.5, 1 H, H–C(14)); 1.29 (*sept.*, $J = 7$, 1 H, *H*–C$(CH_3)_2$); 1.60 (*d*×*t*, $J = 8$ and 12, 1 H); 1.80 (*s*, 3 H, H_3C–C(6)); 1.92 (*d*×*d*×*d*, $J = 2$, 5 and 12, 1 H); 2.25–2.70 (*m*, 8 H). – ^{13}C-NMR. (100.6 MHz, $CDCl_3$): 10.63, 19.75, 19.85, 21.05, 21.51, 25.86, 26.57, 33.42, 35.05, 35.39, 35.94, 36.15, 37.25, 42.08, 122.44, 128.25, 149.09, 157.51 and 198.78. – MS.: 270 (100, M^+), 255, 237. – High resolution molecular weight determination: calc. 270.1984, found 270.1985.

$C_{19}H_{26}O$ (270.20) Calc. C 84.38 H 9.62% Found C 84.67 H 9.79%

Continued elution gave pure **4**, yield 1.3 g (39%). Crystallization from ethanol gave an analytical sample, m.p. 126–128°. $[\alpha]_D = -173°$ ($c = 1.62$, $CHCl_3$). – UV. (EtOH): 252 (4.10). – CD.: 265 ($\Delta\varepsilon + 2.83$); 237 ($\Delta\varepsilon - 7.80$), $c = 3.6 \times 10^{-5}$, EtOH. – IR. ($CHCl_3$): 1665. – ^{1}H-NMR. (400 MHz, $CDCl_3$): 0.45 (*t*, $J = 4$, 1 H, H_{endo} of the methano group); 0.71 (*d*×*d*, $J = 4$ and 8, 1 H, H_{exo} of the methano group); 0.91, 0.93 (2*d*, $J = 7$, 6 H, $(H_3C)_2C$); 0.94 (*s*, 3 H, $H_3C(18)$); 1.24 (*d*×*d*, $J = 4$ and 8, 1 H, H–C(17));

1.35 (*s*, 3 H, $H_3C(19)$); 1.42 (*sept.*, $J=7$, 1 H, H–$C(CH_3)_2$); 1.50–2.80 (*m*, 15 H); 5.52 (*s*, 1 H, H–C(15)). – ^{13}C-NMR. (100.6 MHz, $CDCl_3$): 10.77, 19.94, 20.18, 20.60, 20.97, 22.48, 23.36, 26.03, 27.13, 31.56, 33.89, 33.98, 34.25, 37.02, 40.29, 41.38, 45.45, 124.68, 124.96, 127.66, 136.06, 149.65, 163.02 and 198.22. – MS.: 336 (47, M^+), 321 (100). – High resolution molecular weight determination: calc. 336.2453, found 336.2453.

$C_{24}H_{32}O$ (336.25) Calc. C 85.65 H 9.52% Found C 85.39 H 9.69%

Typical experiments for attempted annelation of **3** *to* **4**. To a solution of **3** (270 mg, 1 mmol) and KOH (18 mg, 0.27 mmol) in EtOH (10 ml) maintained under N_2 was added methyl vinyl ketone (140 mg, 2 mmol) over 30 min. After 52 h the mixture was acidified with acetic acid to pH 6 (pH paper), diluted with water (10 ml) and evaporated. The residue was taken-up in ether (50 ml) and washed with saturated $NaHCO_3$-solution (3×25 ml), water (2×25 ml) and NaCl-solution (2×25 ml), then dried (Na_2SO_4) and evaporated to leave pure **3** (230 mg).

To a rapidly stirred mixture of KOH-solution (15 ml, 30% *w/v*), benzyltriethylammonium chloride (57 mg, 0.25 mmol), and **3** (270 mg, 1 mmol) in CH_2Cl_2 (5 ml), was added methyl vinyl ketone over 30 min. After 24 h the organic layer was washed with water (5×10 ml), dried (Na_2SO_4) and evaporated to leave pure **3** (220 mg).

Synthesis of 8β-isopropyl-7,8-methano-6α-methyl-2-(3'-oxopentyl)-bicyclo[4.3.0]non-1-en-3-one (**2**). To a stirred and cooled (0°) solution of KOH (25 mg, 0.4 mmol) and enone **1** [1] (1.02 g, 5 mmol) in ethanol (15 ml) under N_2 was added a solution of ethyl vinyl ketone (0.42 g, 5 mmol) in ethanol (5 ml) over 30 min. After 3 h the reaction was warmed to RT. and stirred for 16 h. The mixture was acidified with acetic acid to pH 6 (pH paper), diluted with water (25 ml) and evaporated. The residue was taken-up in ether and washed with saturated $NaHCO_3$-solution (3×20 ml), water (2×20 ml) and NaCl-solution (2×20 ml) then dried ($MgSO_4$) and evaporated to leave 0.95 g of yellow gum. Chromatography on silicagel gave pure **2** as a colourless oil, yield 0.24 g (17%). $[\alpha]_D = +57°$ ($c=2$, $CHCl_3$). – UV. (EtOH): 245 (3.99). – IR. (film): 1715, 1670, 1640. – ^{1}H-NMR. (400 MHz, $CDCl_3$): 0.77 (*m*, 2 H); 0.88 and 0.91 (2 *d*, $J=7$, 6 H, $(H_3C)_2C$); 1.03 (*t*, $J=7$, H_3C–C(5')); 1.06 (*s*, 3 H, H_3C–C(6)); 1.25 (*sept.*, $J=7$, 1 H, H–$C(CH_3)_2$); 2.03 (*m*, 2 H); 2.30 (*d*, $J=18$, 1 H, H_α–C(9)); 2.35–2.65 (*m*, 8 H); 2.77 (*d*×*d*, $J=1$ and 18, 1 H, H_β–C(9)). – ^{13}C-NMR. (100.6 MHz, $CDCl_3$): 7.84, 19.74, 19.88, 21.17, 21.79, 33.50, 34.38, 35.26, 35.52, 35.97, 36.21, 41.05, 42.19, 128.15, 176.31, 197.86, 211.10. – MS.: 288 (100, M^+), 273, 245. – High resolution molecular weight determination: calc. 288.2089, found 288.2091.

$C_{19}H_{28}O_2$ (288.21) Calc. C 79.11 H 9.72% Found C 78.98 H 9.79%

Cyclization of **2** *to give* **3**. A solution of **2** (0.41 g, 1.42 mmol) and KOH (25 mg, 0.4 mmol) in ethanol (15 ml) was heated to reflux under N_2 for 4 h. The mixture was acidified with acetic acid, diluted with water (15 ml) and evaporated. The residue was taken-up in ether and washed with sat. $NaHCO_3$-solution (3×25 ml), water (2×25 ml) and NaCl-solution (2×25 ml), then evaporated to leave pure **3** (0.35 g, 91%), identical in all respects (GC., TLC., IR., ^{1}H-NMR., MS.) with an authentic sample of **3**.

Preparation of 8-isopropyl-6α,7-dimethyl-bicyclo[4.3.0]nona-7,9-dien-3-one ethylene acetal (**10**). A solution of acetal **9** [1] (24.8 g, 0.1 mol) and *p*-toluenesulfonic acid (0.75 g, 3.9 mmol) in toluene (1400 ml) was heated to reflux under N_2 for 100 h. Further portions of *p*-toluenesulfonic acid (50 mg, 0.26 mmol) were added after 30, 50 and 80 h. The cooled mixture was washed with sat. aqueous $NaHCO_3$-solution (2×250 ml), water (2×250 ml) and NaCl-solution (2×250 ml) then dried (Na_2SO_4) and evaporated. The crude product was distilled, collecting the fraction b.p. 79–81°/1 Torr. Chromatography of the distillate on silicagel gave **10** as a colourless solid (yield 6.0 g, 25%). Crystallization from petroleum ether gave an analytical sample, m.p. 40–42°. $[\alpha]_D = +175°$ ($c=5$, $CHCl_3$). – UV. (EtOH): 255 (3.76). – ^{1}H-NMR. (400 MHz, $CDCl_3$): 1.00 (*s*, 3 H, H_3C–C(6)); 1.06, 1.10 (2*d*, $J=7$, 6 H, $(H_3C)_2C$); 1.50–2.00 (*m*, 7 H); 2.30–2.90 (*m*, 3 H); 4.00 (*m*, 4 H, ethylene acetal group); 6.02 (*s*, 1 H, H–C(9)). – ^{13}C-NMR. (100.6 MHz, $CDCl_3$): 9.26, 18.31, 22.32, 22.39, 25.96, 30.77, 31.84, 36.80, 52.39, 64.39, 111.81, 122.44, 141.79, 142.52, 150.07. – MS.: 248 (20, M^+), 99 (100). – High resolution molecular weight determination: Calc. 248.1777, Found 248.1778.

$C_{16}H_{24}O_2$ (248.18) Calc. C 77.41 H 9.67% Found C 77.50 H 9.72%

*Preparation of 16-isopropylidene-13,17-dimethyl-1,2,6,7,10,11,12,13,14,15-3*H*-decahydrocyclopentanophenanthren-3-one* (**11**). A solution of **4** (1.0 g, 2.98 mmol) in benzene (75 ml) was deaerated with

Table 2. *Final positional* (fractional $\times 10^4$, H $\times 10^3$) *and isotropic thermal parameters* ($U \times 10^3$ Å^2) *with estimated standard deviations in parentheses*

Atom	x	y	z	U_{iso}
O	5600 (5)	3320	9800 (4)	
C(1)	3242 (4)	969 (5)	8533 (4)	
C(2)	4419 (5)	1492 (6)	9558 (4)	
C(3)	5077 (4)	2578 (6)	9005 (4)	
C(4)	5167 (4)	2678 (5)	7493 (4)	
C(5)	4625 (3)	1835 (5)	6630 (3)	
C(6)	4772 (3)	1858 (5)	5090 (3)	
C(7)	3240 (3)	1909 (5)	4303 (4)	
C(8)	2177 (3)	1072 (5)	4873 (3)	
C(9)	2500 (3)	467 (5)	6061 (3)	
C(10)	3825 (3)	759 (5)	7099 (3)	
C(11)	1534 (5)	−510 (5)	6469 (5)	
C(12)	278 (5)	−868 (5)	5413 (5)	
C(13)	−450 (3)	207 (5)	4715 (4)	
C(14)	800 (3)	789 (5)	4006 (3)	
C(15)	513 (4)	815 (5)	2649 (4)	
C(16)	−956 (4)	276 (6)	2178 (4)	
C(17)	−1584 (4)	−82 (5)	3494 (4)	
C(18)	−1133 (5)	988 (6)	5778 (5)	
C(19)	4947 (4)	−267 (5)	7193 (5)	
C(20)	−2277 (4)	907 (6)	2666 (5)	
C(21)	5925 (7)	3766 (6)	6994 (7)	
C(22)	−1150 (6)	−432 (6)	863 (4)	
C(23)	−1 (10)	−1417 (8)	863 (8)	
C(24)	−1137 (6)	325 (8)	−416 (5)	
H(1a)	242 (4)	148 (3)	838 (3)	50 (9)
H(1b)	285 (4)	20 (4)	894 (4)	54 (9)
H(2a)	528 (7)	96 (6)	978 (6)	115 (18)
H(2b)	393 (4)	173 (4)	1034 (5)	74 (12)
H(6a)	531 (4)	103 (3)	480 (4)	55 (9)
H(6b)	541 (4)	244 (4)	479 (4)	57 (10)
H(7a)	293 (5)	265 (5)	431 (5)	83 (13)
H(7b)	323 (4)	168 (4)	326 (4)	65 (10)
H(11a)	220 (6)	−122 (5)	675 (5)	99 (15)
H(11b)	105 (4)	−24 (4)	737 (5)	75 (12)
H(12a)	68 (6)	−136 (6)	462 (6)	116 (19)
H(12b)	−47 (6)	−130 (5)	584 (5)	86 (13)
H(15)	114 (3)	100 (3)	204 (3)	36 (8)
H(17)	−219 (5)	−82 (4)	356 (4)	78 (12)
H(18a)	−187 (5)	59 (5)	627 (4)	83 (13)
H(18b)	−168 (5)	172 (4)	533 (4)	75 (12)
H(18c)	−54 (5)	130 (4)	646 (5)	68 (12)
H(19a)	537 (5)	−38 (4)	633 (5)	80 (13)
H(19b)	453 (5)	−97 (5)	754 (4)	75 (12)
H(19c)	571 (6)	2 (5)	781 (6)	93 (17)
H(20a)	−321 (5)	77 (5)	212 (5)	92 (13)
H(20b)	−210 (7)	180 (7)	300 (6)	135 (21)
H(21a)	530 (10)	416 (9)	618 (9)	169 (29)
H(21b)	686 (7)	371 (6)	708 (7)	127 (23)
H(21c)	591 (8)	426 (8)	770 (8)	142 (25)
H(22)	−217 (7)	−83 (6)	42 (6)	123 (18)
H(23a)	108 (5)	−113 (4)	79 (5)	77 (12)

Table continued

Atom	x	y	z	U_{iso}
H(23b)	−17 (13)	−192 (11)	10 (13)	221 (42)
H(23c)	7 (9)	−200 (8)	177 (9)	172 (32)
H(24a)	−12 (7)	53 (6)	−34 (6)	119 (18)
H(24b)	−132 (7)	−13 (6)	−140 (7)	124 (20)
H(24c)	−213 (9)	118 (10)	−35 (9)	210 (34)

Ar for 15 min. To this solution was added glacial acetic acid (1.0 g, 16.7 mmol) and *p*-toluenesulfonic acid (95 mg, 0.5 mmol). The mixture was heated to reflux under Ar for 16 h. The cooled mixture was washed with sat. aq. $NaHCO_3$-solution (2×25 ml), dried (Na_2SO_4) and evaporated to leave a yellow solid. Chromatography on silicagel gave 647 mg (65%) of **11**, a 1:1 mixture of isomers (GC., ^{1}H-NMR.), as a colourless solid, m.p. 75–90°. Crystallization from ethanol gave an analytical sample of the longer retention time isomer, m.p. 177–178°. $[\alpha]_D = -163°$ ($c = 1.35$, $CHCl_3$). – UV. (EtOH): 298 (4.47), 254 (4.27). – IR. (mull): 1655, 1620. – ^{1}H-NMR. (400 MHz, $CDCl_3$): 0.86 (*d*, $J = 7$, 3 H, $H_3C(20)$); 0.88 (*s*, 3 H, $H_3C(18)$); 1.39 (*s*, 3 H, $H_3C(19)$); 1.45–1.70 (*m*, 4 H); 1.76, 1.77, 1.83 (3*s*, 9 H, $H_3C(21)$, $H_3C(23)$ and $H_3C(24)$); 2.05–2.90 (*m*, 9 H); 6.02 (*s*, 1 H, H–C(15)). – MS. 336 (29, M^+), 321 (100). – High resolution molecular weight determination: calc. 336.2453, found 336.2453.

$C_{24}H_{32}O$ (336.25) Calc. C 85.65 H 9.52% Found C 85.86 H 9.42%

X-ray crystallographic analysis. A crystal *ca.* 0.15×0.22×0.38 mm was used. Unit-cell parameters were calculated from θ-values for 25 reflections measured on a diffractometer with Mo$K\alpha$ Radiation

Table 3. *Final anisotropic thermal parameters* ($U_{ij} \times 10^3$ Å^2)[a]) *and their estimated standard deviations*

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O	161 (4)	122 (3)	91 (2)	−59 (3)	11 (2)	−59 (2)
C(1)	52 (2)	67 (2)	50 (2)	−5 (2)	7 (2)	2 (2)
C(2)	68 (2)	95 (3)	48 (2)	−6 (2)	2 (2)	−11 (2)
C(3)	61 (2)	81 (3)	68 (3)	−6 (2)	0 (2)	−23 (2)
C(4)	41 (2)	51 (2)	68 (2)	−4 (1)	−6 (1)	−8 (2)
C(5)	31 (1)	44 (2)	54 (2)	2 (1)	−4 (1)	2 (2)
C(6)	39 (2)	54 (2)	52 (2)	−9 (2)	4 (1)	7 (2)
C(7)	44 (2)	53 (2)	48 (2)	−2 (2)	3 (1)	7 (2)
C(8)	41 (1)	49 (2)	46 (2)	−7 (1)	0 (1)	2 (1)
C(9)	41 (1)	40 (2)	46 (2)	1 (1)	3 (1)	2 (1)
C(10)	41 (1)	46 (2)	45 (2)	0 (1)	−1 (1)	1 (1)
C(11)	56 (2)	53 (2)	76 (3)	−12 (2)	−14 (2)	19 (2)
C(12)	58 (2)	55 (2)	77 (3)	−23 (2)	−10 (2)	15 (2)
C(13)	42 (2)	58 (2)	60 (2)	−15 (2)	−6 (1)	6 (2)
C(14)	42 (1)	47 (2)	48 (2)	−2 (1)	−5 (1)	3 (1)
C(15)	51 (2)	62 (2)	53 (2)	−6 (2)	−3 (2)	7 (2)
C(16)	61 (2)	69 (2)	59 (2)	−9 (2)	−15 (2)	1 (2)
C(17)	52 (2)	74 (3)	67 (3)	−17 (2)	−11 (2)	8 (2)
C(18)	46 (2)	89 (3)	69 (3)	−5 (2)	7 (2)	−1 (2)
C(19)	50 (2)	54 (2)	63 (3)	4 (2)	−6 (2)	7 (2)
C(20)	53 (2)	97 (3)	78 (3)	0 (2)	−18 (2)	9 (3)
C(21)	85 (4)	66 (3)	104 (4)	−29 (3)	−11 (3)	−6 (3)
C(22)	84 (3)	105 (4)	58 (3)	−22 (3)	−18 (2)	−6 (2)
C(23)	143 (6)	99 (5)	99 (5)	−10 (4)	−10 (4)	−36 (4)
C(24)	91 (3)	172 (6)	56 (3)	−23 (4)	−7 (2)	4 (3)

[a]) The anisotropic thermal parameters employed in the refinement are U_{ij} in the expression: $f = f^0 \exp(-2\pi^2 \Sigma\Sigma U_{ij} h_i h_j a_i^* a_j^*)$

($\lambda = 0.71073$ Å). Crystal data at 22° are: $C_{24}H_{32}O$ f.w. = 336.25. Monoclinic: $a = 9.022$ (1), $b = 11.477$ (2), $c = 9.636$ (1) Å, $\beta = 94.540$ (5)°, $V = 994.6$ (2) Å^3, $Z = 2$, $\rho_c = 1.124$ gcm^{-3}, $F(000) = 368$, μ(Mo$K\alpha$) = 0.34 cm^{-1}. Absent reflections: $0k0$, $k \neq 2n$, space group $P2_1$ (C_2^2, No. 4).

Intensities were measured with graphite-monochromatized Mo$K\alpha$ radiation on an *Enraf-Nonius CAD4-F* diffractometer. An ω-2θ scan at 1.55–10.06° min^{-1} over a range of (0.70 + 0.35 tanθ) degrees in ω (extended by 25% on both sides for background measurement) was employed. Data were measured to $2\theta = 50°$. The intensities of 3 check reflections, measured every 3600 s throughout the data collection, remained constant to within ±2.5%. After data reduction, no absorption correction was made in view of the low value of μ. Of the 1836 independent reflections measured, 1301 (70.9%) had intensities greater than $3\sigma(I)$ above background where $\sigma^2(I) = S + 2B + (0.04(S - B))^2$ with S = scan count and B = background count.

The structure was solved by direct methods, all 25 non-hydrogen atoms being positioned from an E-map. After full-matrix least-squares refinement of the non-hydrogen atoms with anisotropic thermal parameters to $R = 0.078$, a difference map gave the positions of all 32 H-atoms which were refined with isotropic thermal parameters in subsequent least-squares cycles. The scattering factors of ref. [9] were used for non-hydrogen atoms and those of ref. [10] for H-atoms. The weighting scheme, $w = 1/\sigma^2(F)$ where $\sigma^2(F)$ is derived from the previously defined $\sigma^2(I)$ gave uniform average values of $w(|Fo| - |Fc|)^2$ over ranges of $|Fo|$ and was employed in the final stages of refinement. Convergence was reached at $R = 0.037$ and $Rw = 0.043$ for 1301 reflections with $I \geq 3\sigma(I)$. For all 1836 reflections $R = 0.059$ and $Rw = 0.043$. The function minimized was $\Sigma w(|Fo| - |Fc|)^2$, $R = \Sigma||Fo| - |Fc||/\Sigma|Fo|$ and $Rw = (\Sigma w(|Fo| - |Fc|)^2/\Sigma w|Fo|^2)^{1/2}$.

On the final cycle of refinement the mean and maximum parameter shifts corresponded to 0.08 and 0.90σ, respectively. The mean error in an observation of unit weight was 1.899. A final difference map showed maximum fluctuations of ±0.15 eÅ^{-3}. The final positional and thermal parameters appear in *Tables 2* and *3*, respectively.

Table 4. *Bond lengths* (Å) *with estimated standard deviations in parentheses*

Bond	Uncorr.	Corr.	Bond	Uncorr.	Corr.
O–C(3)	1.216 (5)	-	C(10)–C(19)	1.550 (5)	1.554
C(1)–C(2)	1.515 (5)	1.517	C(11)–C(12)	1.519 (5)	1.522
C(1)–C(10)	1.537 (5)	1.542	C(12)–C(13)	1.528 (5)	1.533
C(2)–C(3)	1.496 (7)	1.502	C(13)–C(14)	1.519 (5)	1.524
C(3)–C(4)	1.470 (6)	1.474	C(13)–C(17)	1.533 (5)	1.534
C(4)–C(5)	1.343 (5)	1.346	C(13)–C(18)	1.527 (6)	1.531
C(4)–C(21)	1.520 (6)	1.520	C(14)–C(15)	1.314 (5)	1.317
C(5)–C(6)	1.500 (5)	1.505	C(15)–C(16)	1.500 (5)	1.502
C(5)–C(10)	1.517 (4)	1.523	C(16)–C(17)	1.487 (6)	1.493
C(6)–C(7)	1.524 (4)	1.527	C(16)–C(20)	1.501 (6)	1.506
C(7)–C(8)	1.492 (5)	1.497	C(16)–C(22)	1.504 (6)	1.506
C(8)–C(9)	1.351 (4)	1.356	C(17)–C(20)	1.496 (6)	1.500
C(8)–C(14)	1.477 (4)	1.480	C(22)–C(23)	1.534 (9)	1.535
C(9)–C(10)	1.534 (4)	1.537	C(22)–C(24)	1.509 (8)	1.511
C(9)–C(11)	1.491 (5)	1.496			

The ellipsoids of thermal motion for the non-hydrogen atoms are shown in the *Figure*. The thermal motion has been analyzed in terms of the rigid-body modes of translation, libration, and screw motion [11]. The rms-standard error in the temperature factors σU_{ij} (derived from the least-squares analysis) is 0.0024 Å^2. Analysis of all non-hydrogen atoms except. O gave rms $\Delta U_{ij} = 0.0054$ Å^2 and physically reasonable thermal parameters. The relatively large vibrational amplitude observed for the O-atom is not uncommon for carbonyl O-atoms. The approrpriate bond distances have been corrected for libration, using shape parameters q^2 of 0.08 for all atoms involved [11] [12]. Corrected bond lengths appear in *Table 4* along with the uncorrected values; corrected bond angles do not differ by more than 1σ from the uncorrected values. Bond lengths involving H-atoms, bond angles, a complete listing of torsion angles, and measured and calculated structure factor amplitudes are available on request from Dr *J. Trotter*.

REFERENCES

[1] *J. P. Kutney, J. Balsevich & P. Grice,* Can. J. Chem. *58,* 2641 (1980).
[2] *J. P. Kutney & A. K. Singh,* Can. J. Chem. *60,* in press (1982).
[3] *R. Burcourt & D. Hainaut,* Bull. Soc. Chim. Fr. *1965,* 1366.
[4] *W. L. Duax, D. C. Rohrer, R. H. Blessing, P. D. Strong & A. Segaloff,* Acta Crystallogr. Sect. B, *35,* 2656 (1979).
[5] *W. L. Duax, P. D. Strong, D. C. Rohrer & A. Segaloff,* Acta Crystallogr. Sect. B *36,* 824 (1980).
[6] *C. Altona, H. J. Geise & C. Romers,* Tetrahedron *24,* 13 (1968); *W. L. Duax & D. A. Norton,* 'Atlas of Steroid Structures', p. 17, Plenum, New York 1975.
[7] *O. Bastianen, F. N. Fritsch & K. Hedberg,* Acta Crystallogr. *14,* 538 (1964).
[8] *A. Eschenmoser, J. Schreiber & S. A. Julia,* Helv. Chim. Acta *36,* 482 (1953); *C. Sannié, C. Neuville & J. J. Panouse,* Bull. Soc. Chim. Fr. *1958,* 635.
[9] *D. T. Cromer & J. B. Mann,* Acta Crystallogr. Sect. A, *24,* 321 (1968).
[10] *R. F. Stewart, E. R. Davidson & W. T. Simpson,* J. Chem. Phys. *42,* 3175 (1965).
[11] *V. Schomaker & K. N. Trueblood,* Acta Crystallogr. Sect. B, *24,* 63 (1968).
[12] *D. W. J. Cruickshank,* Acta Crystallogr. *9,* 747 (1956); *9,* 754 (1956); *14,* 896 (1961).