Structure of 3α-Hydroxy-15-rippertene. Evidence for 1,2-Methyl Migration during Biogenesis of a Tetracyclic Diterpene in Termites

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Abstract: The structure of the title compound, isolated from the gluelike soldier defense secretions of the higher termites *Nasutitermes rippertii* and *N. ephratae*, was established by spectroscopic methods and by single-crystal X-ray diffraction experiments on the 3α-acetate 15,16-epoxide derivative. It is an unusual tetracyclic diterpene containing a single tetrasubstituted double bond, endocyclic to a seven-six ring fusion and exocyclic to five- and six-membered rings. The six-membered rings both occupy boatlike conformations. One angular methyl group has apparently suffered a 1,2 shift via intramolecular cyclization of a cembrene-derived, tricyclic trinervitane-type intermediate.

Introduction

Chemical defense by the highly evolved nasute termite soldiers is effected by squirting potential predators with an irritating gluelike secretion consisting of a diverse array of cembrene-derived diterpenes dissolved in monoterpene hydrocarbons.[1] We have recently described the structures of the tricyclic trinervitanes[2] (e.g. **1**) and the tetracyclic kempanes[3,4] (e.g., **2**, **3**), isolated from the soldiers of several Old and New World nasute termite genera. An unusual tetracyclic compound with a tetrasubstituted olefin was first isolated from *Nasutitermes rippertii*[5] and subsequently from *N. ephratae*[6] and *Grallatotermes africanus*.[7] On the basis of spectral data and biogenetic considerations, structure **4** was suggested[6,7] for this compound. We now reveal that structure **5** is correct on the basis of X-ray diffraction experiments using epoxy acetate derivative **7**, and we present complete spectral data for this new class of compounds, the rippertanes.[8,9] This unusual "buried-olefin" diterpene represents the first evidence for a 1,2-methyl migration occurring during insect diterpene biosynthesis.

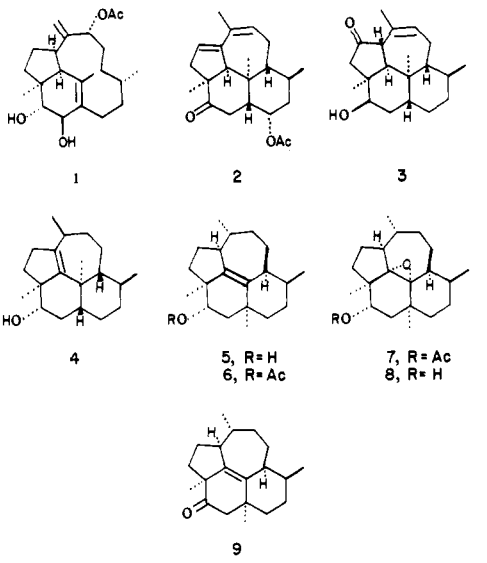
Results and Discussion

3α-Hydroxy-15-rippertene (**5**) was isolated as an oily solid from *N. rippertii* and from *N. ephratae* by chromatography of the hexane extracts of crushed heads over Florisil followed by high-performance liquid chromatography.

Acetylation of **5** gave noncrystalline acetate **6** in 95% yield after chromatography on Florisil. Epoxidation of **6** afforded a single epoxide, **7** (*m/z* 346), in 90% yield after chromatography. Recrystallization from ethanol–hexane at −20 °C gave colorless prisms, mp 95.5–97 °C. Crystalline derivatives of **5** were also prepared by reaction with *p*-bromophenyl isocyanate and *p*-bromobenzoyl chloride; however, single crystals suitable for X-ray experiments could not be obtained from these products or their epoxides. Epoxide **7** was highly unreactive. Attempted ring opening with aqueous perchloric acid in tetrahydrofuran afforded epoxy alcohol **8** (*m/z* 304) as the exclusive product, with no detectable diol formation. Oxidation of **5** with Jones' reagent gave quantitative conversion to ketone **9** which exhibited a strong positive Cotton effect with considerable fine structure ($\Delta\epsilon_{310}^{hexane}$ + 2.87, $\Delta\epsilon_{301}$ + 3.51, $\Delta\epsilon_{293}$ + 3.37). The sense of dissymmetry of the β, γ-unsaturated ketone chromophore[10] supports the absolute configuration postulated on biogenetic grounds.

The structure of **7** was solved by single-crystal X-ray diffraction experiments. The molecule possesses a dome-shaped array of five-, six-, and seven-membered rings, in which both six-membered rings occupy boat conformations, the seven-membered ring occcupies a lounge-chair conformation, and the five-membered ring is near planar. In contrast to the kempanoid diterpenes such as **2** and **3**, the C(10)–C(11) bond of the rippertane system is axial to the six-membered ring. The absolute stereochemistry shown in **7** and in the computer-generated perspective drawing (ORTEP, Figure 1) agrees with biogenetic considerations and with the large positive Cotton effects in the n → π* transition region of the circular

Chart I



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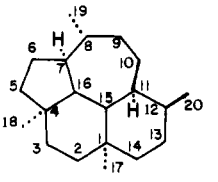
(8) The trivial name rippertane is assigned to this new skeleton, with the indicated numbering system. Semisystematic IUPAC naming of derivatives has been followed.[9]



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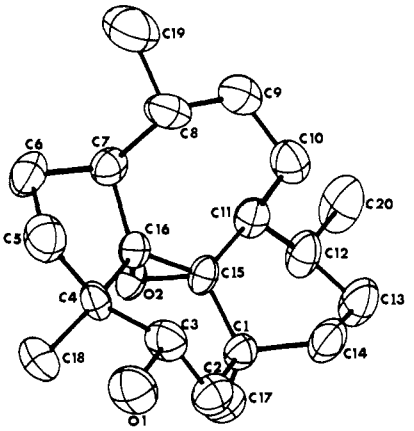

Figure 1. A computer-generated perspective drawing of 3α-acetoxy-15-epoxyrippertane **7**. The acetate moiety and hydrogens have been omitted for clarity.

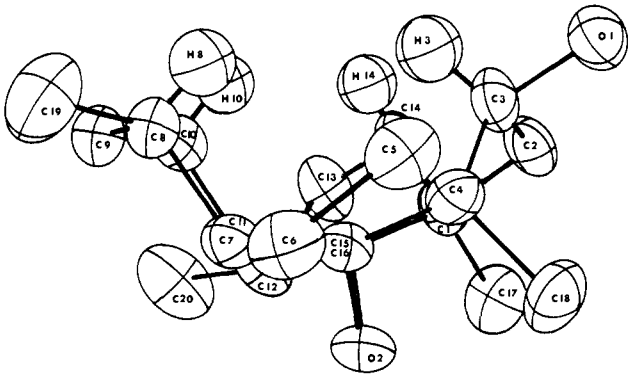

Figure 2. ORTEP view of **7** along the C(16) to C(15) (epoxide C–C) bond axis. Epoxidation ("O(2)") proceeds at the convex α face, despite the 1,3 interactions provided by methyls C(17) and C(18), since the concave β face is blocked by hydrogens (unrefined) on C(3), C(8), C(10), and C(14) directed into the cavity. The five-membered ring is in the foreground and the chair-shaped seven-membered ring to the left.

dichroism spectrum of β,γ-unsaturated ketone **9**.

Epoxidation of the "buried olefin" in rippertenol **5** is unexpectedly facile and occurs exclusively on the convex α face. The β face is blocked by four axial hydrogens directed into a concave region of the molecule, and the α face is partially blocked from one side by two pseudo-axial 1,3-methyl groups (Figure 2). The possibility that **7** is an artifact of the derivatization reactions is ruled out by the absence of a reasonable tetrasubstituted olefinic precursor to a migration-susceptible species like **11** during epoxidation.

Preliminary biosynthetic studies (Vrkoč, unpublished results) have been carried out in Prague by feeding a small piece of wood impregnated with 10 μCi of [2-^{14}C]mevalonate to freshly imported, starved, small colonies of *N. rippertii*. Wood was consumed within 1 h, the colonies were sacrificed at 48 h, and the diterpenes were isolated from soldiers and workers separately by PTLC. Repeated chromatography of three main soldier diterpene fractions afforded approximately 0.1% incorporation into the trinervitane[11] and rippertane diterpene fractions. No trinervitanes or rippertanes were detectable in the workers.

The new rippertane skeleton may arise via 1,2-methyl migration from a tetracyclic intermediate such as **11**, derived in turn from proton-induced intramolecular cyclization of a trinervitadiene such as **10**. Dreiding models show that unfavorable steric interactions resulting from the two boatlike-fused six-membered rings and the axial C(10)–C(11) bond are alleviated by this migration and by subsequent flattening of the convex dome cap by proton loss to the tetrasubstituted olefin. We are currently investigating the

Scheme I

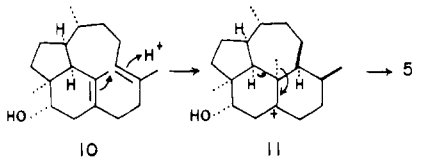

Table I. ^{13}C Chemical Shifts (δ) of Rippertanes ($CDCl_3$)

	5	6	7
C(1)	38.43 s	38.38 s	35.01 s
C(2)	45.76 t	41.83 t	*a*
C(3)	75.84 d	78.02 d	76.41 d
C(4)	48.68 s	47.26 s	43.79 s
C(5)	37.45 t	37.38 t	*a*
C(6)	37.07 t (a)[b]	36.93 t (a)	*a*
C(7)	45.46 d	45.71 d	51.79 d
C(8)	35.75 d (b)	35.65 d (b)	*a*
C(9)	28.30 t (c)	28.20 t (c)	*a*
C(10)	27.35 t (c)	27.18 t (c)	*a*
C(11)	41.65 d	41.71 d	48.08 d
C(12)	33.15 d (b)	33.10 d (b)	*a*
C(13)	30.02 t	29.88	*a*
C(14)	36.39 t (a)	36.46 t (a)	*a*
C(15)	145.10 s	144.61 s	79.01 s
C(16)	136.21 s	136.62 s	68.86 s
C(17)	29.58 q	29.58 q	*a*
C(18)	18.27 q	19.62 q	18.89 q
C(19)	21.79 q (d)	21.75 q (d)	21.03 q (a)
C(20)	17.29 q (d)	17.38 q (d)	15.96 q
C(acetate CH_3)		21.30 q	21.15 q (a)
C(acetate CO)		170.69 s	170.64 s

[a] The remaining aliphatic carbon signals for the epoxide could not be assigned: 40.85, 39.68, 36.62, 34.76, 35.59, 29.58, 28.44, 27.09, 26.46, 25.73. [b] Resonances in the same column bearing the same letter may be interchanged.

division of biosynthetic labor which may exist among termite workers and soldiers in an effort to establish which caste can effect the hypothesized conversion of mevalonate to geranylgeranyl pyrophosphate to (*R*)-cembrene-*A*, and thence via intramolecular cyclizations to the nasute diterpenes.

Experimental Section

Melting points were determined in capillary tubes by using a Thomas-Hoover melting apparatus and are uncorrected. IR spectra were recorded as neat films or as CCl_4 solutions (0.2 mm) on a Perkin-Elmer Model 721 spectrometer. Circular dichroism spectra were determined on a JASCO Model J-20 scanning spectropolarimeter. Mass spectrometry was performed by using an HP 5980A mass spectrometer interfaced to an HP 5710A gas chromatograph equipped with a 2 m × 2 mm i.d. glass column packed with 3% OV-17 on 100/120 Gas Chrom Q and operating at 200–280 °C at 4 °C/min.

NMR spectra were recorded on Varian CFT-20 pulsed-FT instruments operating at 80 MHz for ^{1}H and 20 MHz for ^{13}C. Use of a 1.7-mm microprobe for ^{13}C enabled selective decoupling experiments on 2–10 mg of samples. ^{13}C assignments are based on these measurements and on comparison of ^{13}C spectra of derivatives **6** and **7** as summarized in Table I. All shifts were measured relative to the $CHCl_3$ resonance (δ 7.25) for ^{1}H and the $^{13}C_6D_6$ resonance (δ 128.0) for ^{13}C microprobe or the $^{13}CDCl_3$ resonance for 8-mm samples and are reported in parts per million relative to Me_4Si at δ 0.00. ^{1}H shift reagent experiments were performed at 360 MHz by using a Brucker 360 instrument located at Brookhaven National Laboratories, Upton, N.Y.

Carbon resonances were assigned by using the fractional atomic coordinates for **5**, the Eu(fod)$_3$-shifted ^{1}H NMR spectrum of **5**, and the Eu(fod)$_3$-shifted ^{13}C spectrum of **5**. Atomic coordinates for **5** were assumed to be identical with those obtained from X-ray experiments using derivative **7**, except that the C(16)–C(15)–O(2) fragment was replaced by two "olefinic" C(15′) and C(16′) carbons appropriately positioned in the C(4)–C(7)–C(1)–C(11) plane. The lanthanide position was calculated by computer fitting (PDIGM[12]) of the Eu(fod)$_3$-shifted 360-MHz ^{1}H resonances to the atomic positions obtained from these

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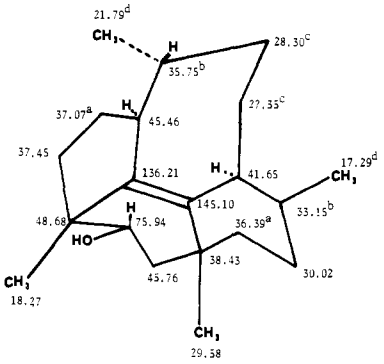

Figure 3. Stereostructure and ^{13}C shifts for 3α-hydroxy-15-rippertene (**5**). Resonances bearing the same superscript may be interchanged.

fractional coordinates and the unit cell parameters for **7**. Concentric shells at distances of 2.0–4.0 Å from O(1) were scanned through latitude angles of ρ = 0–180° and azimuth angles of ϕ = 0–360°. The final Eu position at 2.50 Å, ρ = 30°, and ϕ = 80° gave a minimum residual of 4.87%. Holding the Eu in this position, observed $\Delta(^{13}C)$ shifts were entered as input and resonance assignments were allowed to vary with the following groups: C(8), C(12); C(15), C(16); C(7), C(11); C(6), C(14), C(9), C(10), C(13); C(19), C(20). The following atoms were assigned by consideration of steric and electronic α, β, and γ effects on the basis of comparisons with derivatives **6** and **7**: C(1), C(2), C(3), C(4), C(5), C(17), C(18). A least-squares line using 17 $\Delta(^{13}C)$ shifts (C(2), C(3), and C(4) were omitted due to large Fermi contact shifts) gave a residual of 17.8%.

Solvents for chromatography were Fisher LC-grade hexanes, ethyl acetate, methylene chloride, and methanol and were used without further purification. Liquid chromatography was performed by using a Waters LC system using conditions described below; effluents were monitored at 254 nm, by differential refractive index and by gas chromatography. Thin-layer chromatography was performed on Machery-Nagel Polygram Sil-G-UV-254 4 × 8-cm plates by elution with 15% ethyl acetate in hexane. Visualization with a vanillin reagent gives multiple colors for the termite diterpenes.[7] Relative chromatographic behavior for the compounds in this paper is as follows: TLC R_f values (15% ethyl acetate–hexane) were as follows: **5**, 0.22; **6**, 0.56; **7**, 0.48; **8**, 0.13; **9**, 0.48. GLC (3% OV-17, T_i = 200 (2 min); T_f = 250° (6 min), T_p = 6°/min) relative retention times: **5**, 1.0; **6**, 1.08; **7**, 1.28; **8**, 1.28; **9**, 0.97.

Isolation of 3α-Hydroxy-15-rippertene (5). *Nasutitermes ephratae* (Isoptera: Termitidae: Nasutitermitinae) colonies were collected in Frijoles, Panama, and *N. rippertii* was obtained near Havana, Cuba. Soldiers were removed from arboreal carbon nests, cooled to 0 °C, and decapitated and the combined heads were crushed in hexane. Crude secretions (80 mg from 1000 soldiers) were chromatographed on Florisil (100–200 mesh) by elution with increasing percentages of ethyl acetate in hexane. Final separation from monohydroxytrinervitadienes was achieved by LC on a 1 × 50-cm column of 10 μm Lichrosorb SI-60 with 10% ethyl acetate in hexane at 1.0 mL/min. The monohydroxyrippertenes isolated from these two species were identical (GLC, TLC, MS).

The physical constants for **5** are as follows: mass spectrum, m/z 288 (M^+), 273 ($M^+ - CH_3$), 270 ($M^+ - H_2O$), 255 (base peak, $M^+ - H_2O - CH_3$); IR (CCl_4) 3630 cm^{-1} (free OH), 360-MHz ^1H NMR (negative numbers indicate magnitude of Eu(fod)$_3$-induced shift in ppm at L/S = 0.3), δ 3.49 (1 H, dd, J = 11.7, 5.3 Hz, H(3), -3.6), 2.61 (1 H, br m, H(7), -0.6) 2.54 (1 H, br t, J = 9 Hz, H(11), -0.5), 1.57 (1 H, s, OH, -8.1), 1.18 (3 H, s, H(17) -0.6), 0.96 (3 H, s, H(18), -1.7), 0.92 (3 H, d, J = 6.5 Hz, H(19), (20), -0.2), 0.84 (3 H, d, J = 6.5 Hz, H(20), (19), -0.2). Multiplets for H(1), H(2), and H(5) can be located in the methylene–methine envelope of the unshifted spectrum by extrapolation of the plot of lanthanide-induced shift vs. lanthanide/substrate ratio. These signals move downfield by -1.6 to -2.0 ppm, depending on their spatial position with respect to the lanthanide atom. ^{13}C NMR assignments, based on off-resonance decoupling experiments, comparison of ^{13}C resonance positions in derivatives of **5**, and Eu(fod)$_3$-shifted spectra of **5** and **9**, are shown in Figure 3.

3α-Acetoxy-15-rippertene (6). To a solution of 12.3 mg of alcohol 5 in 2 mL of dry hexane (distilled under N_2 from molecular sieves) was added 0.5 mL of acetic anhydride (freshly distilled) and 1.0 mL of pyridine (distilled from BaO, stored over molecular sieves). The reaction mixture was stirred 48 h at 20 °C, diluted with 10 mL of ether, washed with dilute HCl, saturated $NaHCO_3$ and NaCl, and dried over $MgSO_4$. Filtration through a short column of Florisil gave 12.0 mg of the acetate as a TLC and GLC homogeneous clear oil: ^1H NMR ($CDCl_3$) δ 0.84 (d, J = 7 Hz, CH_3(19), (20)), 0.94 (d, J = 7 Hz, CH_3(20), (19)), 1.03 (s, CH_3(18)), 1.20 (s, CH_3(20)), 2.02 (s, CH_3CO–), 4.70 (dd, J = 9.8, 8.1 Hz, H(3)).

Table II. Fractional Atomic Coordinates for 3α-Acetoxy-15-epoxyrippertane (**7**)

	x	y	z
C(1)	0.366 475	0.418 223	0.985 319
C(2)	0.494 089	0.433 623	1.050 962
C(3)	0.562 121	0.397 125	1.180 191
C(4)	0.574 297	0.351 645	1.061 934
C(5)	0.637 641	0.312 606	1.188 353
C(6)	0.568 690	0.268 459	1.128 540
C(7)	0.438 565	0.284 519	1.144 753
C(8)	0.392 091	0.285 493	1.375 792
C(9)	0.259 225	0.295 288	1.394 909
C(10)	0.214 049	0.342 034	1.318 715
C(11)	0.220 499	0.349 686	1.078 589
C(12)	0.126 421	0.383 134	0.991 200
C(13)	0.144 270	0.432 318	1.083 902
C(14)	0.275 999	0.444 439	1.127 371
C(15)	0.344 448	0.365 007	1.008 238
C(16)	0.445 224	0.332 815	1.040 039
C(17)	0.349 321	0.434 404	0.754 355
C(18)	0.635 657	0.356 855	0.845 474
C(19)	0.418 934	0.240 220	1.494 101
C(20)	-0.002 572	0.366 867	1.020 026
C(21)	0.695 215	0.444 377	1.384 322
C(22)	0.823 267	0.456 122	1.416 150
O(3)	0.614 798	0.458 693	1.490 764
O(2)	0.391 659	0.337 413	0.831 988
O(1)	0.682 628	0.414 096	1.223 523
H(2A)	0.493 599	0.462 029	1.124 858
H(2B)	0.541 377	0.438 340	0.920 187
H(3)	0.516 691	0.392 586	1.307 539
H(5A)	0.633 395	0.318 125	1.332 555
H(5B)	0.718 207	0.310 674	1.140 807
H(6A)	0.585 429	0.243 777	1.222 462
H(6B)	0.589 105	0.258 285	0.985 218
H(7)	0.377 140	0.265 069	1.071 320
H(8)	0.431 466	0.311 222	1.439 751
H(9A)	0.242 331	0.288 336	1.541 815
H(9A)	0.224 715	0.270 331	1.311 584
H(10A)	0.265 001	0.367 459	1.390 212
H(10B)	0.136 176	0.347 930	1.372 317
H(11)	0.206 604	0.318 774	1.023 700
H(12)	0.133 992	0.387 035	0.836 294
H(13A)	0.100 679	0.434 333	1.217 151
H(13B)	0.113 012	0.456 047	0.992 484
H(14A)	0.296 799	0.433 809	1.272 155
H(14B)	0.291 818	0.476 050	1.117 696
H(17A)	0.404 000	0.418 638	0.664 955
H(17B)	0.269 752	0.428 126	0.707 431
H(17C)	0.362 891	0.467 516	0.743 355
H(18A)	0.635 390	0.326 647	0.776 783
H(18B)	0.586 239	0.377 206	0.756 520
H(18C)	0.709 935	0.368 555	0.860 085
H(19A)	0.494 714	0.230 881	1.488 202
H(19B)	0.387 661	0.240 462	1.638 280
H(19C)	0.367 785	0.214 031	1.426 072
H(20A)	-0.010 766	0.332 349	0.967 993
H(20B)	-0.015 338	0.359 414	1.181 342
H(20C)	-0.063 412	0.382 535	0.975 555
H(22A)	0.835 486	0.478 624	1.527 942
H(22B)	0.875 679	0.430 383	1.440 457

3α-Acetoxy-15-epoxyrippertane (7). To a stirred solution of 50 mg of *m*-chloroperbenzoic acid (purified by washing with pH 7.5 phosphate buffer and then drying in vacuo) in 4 mL of dry CH_2Cl_2 at 0 °C was added 12 mg of acetate **6**. The solution was stirred 1 h as it warmed to 20 °C, at which time TLC confirmed the disappearance of starting olefin and the presence of a single more polar product. The reaction mixture was diluted with 20 mL of hexane, filtered through glass wool, and concentrated in vacuo. The crude epoxide was purified by chromatography on Florisil (100–200 mesh) by elution with 10% ethyl acetate in hexane to give 7.0 mg of a clear oil which crystallized when traces of solvent were removed: mass spectrum (70 eV), m/z (relative intensity) 346 (M^+, 1%), 331 ($M^+ - CH_3$, 4), 304 ($M - H_2C{=}C{=}O$, 3), 286 ($M^+ - CH_3CO_2H$, 30), 271 (71), 253 (49), 228 (49), 162 (82), 107 (100); ^1H NMR ($CDCl_3$) δ 0.84 (overlapping doublets, CH_3(19), (20)), 0.96 (s,

CH_3(18)), 1.16 (s, CH_3(17)), 2.01 (s, CH_3CO-), 4.74 (dd, J = 10.4, 6.9 Hz, H(3)). Recrystallization from ethanol-hexane at -20 °C gave colorless prisms, mp 95.5-97 °C.

Attempted Acid Hydrolysis of 7. To 2 mg of epoxy acetate **7** was added 0.5 mL of tetrahydrofuran (distilled under N_2 from Na) and 0.2 mL of 7% perchloric acid. The mixture was heated in a Microflex vial for 4 days at 55 °C, at which time TLC indicated the absence of starting **7** and appearance of a more polar product. Product isolation with ether (aqueous NaCl wash, $MgSO_4$) and chromatography on Florisil with 10% ethyl acetate in hexane afforded 1.5 mg of a solid which showed no ester absorption in the IR: mass spectrum (70 eV) m/z (relative intensity) 304 (M^+, 12), 271 (22), 260 (24), 205 (32), 189 (70), 81 (100); ^1H NMR δ 3.56 (dd, J = 10.2, 7.0 Hz, H(3)). These data suggest the retention of the epoxide and the acid-catalyzed hydrolysis of the acetate to the epoxy alcohol **8**.

3-Keto-15-rippertene (9). To a stirred, 5-10 °C solution of 9.5 mg of alcohol **5** in 0.4 mL of spectrograde acetone was added dropwise Jones' reagent until TLC indicated absence of starting material. Excess Jones' reagent was quenched with 1 drop of 2-propanol, the solvent was removed, and the crude oil was chromatographed on Florisil with 5% ethyl acetate-hexane to give 9 mg of ketone **9** which was homogeneous by TLC and GLC. ^1H NMR showed the absence of the H(3) carbinyl proton and methyl resonances at δ 0.94 (d, J = 7 Hz), 0.99 (d, J = 7 Hz), and 1.27 (s, s, CH_3 (17), (18)). Mass spectrum (70 eV): m/z (relative intensity) 286 (M^+, 61), 271 ($M^+ - CH_3$, 100). Measurement of the CD spectrum of a 1:10 dilution of the 9 mg of ketone in 5 mL of purified hexane gave $\Delta\epsilon_{310}$ = +2.87, $\Delta\epsilon_{301}$ = +3.51, and $\Delta\epsilon_{293}$ = +3.37. Multiple Cotton effects for β,γ-unsaturated ketones have also been observed for testosterone derivatives.[10]

X-ray Structure Determination of 7. The data crystal of 3α-acetoxy-15-epoxyrippertane, a colorless prism obtained from hexane-ethanol at -20 °C, was mounted on an Enraf-Nonius CAD 4A diffractometer under the control of a PDP 11/45 computer system and subjected to Cu X radiation (λ = 1.5418 Å). The space group was $P2_12_12_1$ with a = 11.202 (1) Å, b = 28.575 (7) Å, c = 6.299 (2) Å, and Z = 4 and ρ_{calcd} = 1.14 g/cm^3. The data were reduced (p = 0.04), and the structure was solved by using the MULTAN direct-method series, using the programs of the Enraf-Nonius structure determination package developed chiefly by Okaya and Frenz. Of the 1899 reflections measured ($0° < 2\theta < 72°$), 1167 with $F_o^2 > 3\sigma(F_o^2)$ were used in the subsequent refinement, which converged to values of 0.047 and 0.051 for R and R_w respectively. Fractional atomic coordinates are presented in Table II. The thermal parameters, bond angles and distances, and observed and calculated structure factors can be obtained as supplementary material.

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Supplementary Material Available: Atomic parameters (Table SI), important bond distances and bond angles (Table SII), and observed and calculated structure factors (Table SIII) (10 pages). Ordering information is given on any current masthead page.

Structure-Reactivity Studies on the Equilibrium Reaction between Phenolate Ions and 2-Aryloxazolin-5-ones: Data Consistent with a Concerted Acyl-Group-Transfer Mechanism

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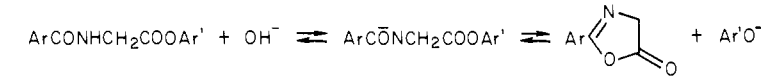
Abstract: The rate and equilibrium constants for the reaction between phenolate anions and 2-aryloxazolin-5-ones have been measured as a function of the structures Ar and Ar'. The change in "effective" charge on both phenol-leaving oxygen and



endocyclic oxygen from ground to transition state, as determined from the relevant Brønsted parameters, is substantial and essentially additive consistent with a concerted displacement mechanism. The stepwise mechanism requires a small change in effective charge on the phenol oxygen because departure of phenolate ion from the tetrahedral intermediate cannot be rate limiting. Hydroxide ion attack on the C-5 atom of the oxazolinone to yield a benzoylglycine has a Hammett σ^- dependence which can only arise from a concerted displacement; the rate-limiting step for the stepwise mechanism is the addition of hydroxide and the transition state of the rate-limiting step will therefore not involve much endocyclic C-O bond fission. An inverse deuterium oxide solvent isotope effect indicates that the observed general-acid catalysis has a specific-acid/nucleophilic mechanism; both hydroxide and oxonium ion catalysis are demonstrated by using ^{18}O-labeling experiments to involve nucleophilic attack at the carbonyl (C-5) center. The equilibrium constant for reaction of azide ion with 2-phenyloxazolin-5-one has been measured; it is suggested that the absence of racemization during azide coupling in peptide synthesis is related to the very unfavorable equilibrium constant for oxazolinone formation compared with that of activated oxygen esters.

Introduction

The ring closure of acyl-α-amino acids to yield unsaturated oxazolin-5-ones was first investigated by Plöchl[1a] and Erlenmeyer[1b] and later by Mohr and Geis[1c] for the saturated species. Work in the past decade[1d,2,3] has indicated that activated esters of acyl-α-amino acids hydrolyze in alkali through the oxazolinone. Williams and Young[4] have shown that aryl acyl-α-amino acid esters undergo a readily reversible reaction to yield oxazolinone and phenol in basic solutions in chloroform. In recent years the

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