Some Stereochemical Aspects of the Claisen Rearrangement of Allyl Vinyl Ethers[1]

Herbert O. House,* Jacek Lubinkowski, and James J. Good

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

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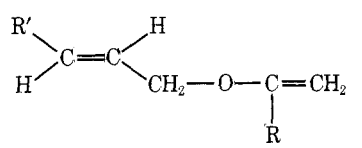
The Claisen rearrangement of the allyl vinyl ethers **9** and **19a** has been used to explore the possibility that reactions proceeding by six-membered cyclic transition states may exhibit a selectivity for either axial or equatorial attack at a double bond exocyclic to a cyclohexane ring. In the two cases studied there was a slight preference for attack to form a new equatorial bond, the product ratios being 52% equatorial and 48% axial for enol ether **9** and 75–77% equatorial and 23–25% axial for the enol ether **19a**.

Previous studies of the Claisen rearrangement of allyl vinyl ethers **1** have shown this reaction to be a concerted intramolecular process involving a cyclic six-centered transition state.[2] The stereochemical results[2b-d,3] obtained in studies of this rearrangement have established that a chair conformation **2** is preferred for the cyclic six-centered transition state and that the stereochemically favored path for rearrangement is remarkably sensitive to steric factors in spite of the relatively high reaction temperatures (110–200°) employed. Because of these properties, this rearrangement offered a useful tool with which to explore the question of whether the intervention of a cyclic six-centered transition state **4** in additions to a double bond exocyclic to a cyclohexane ring (*e.g.*, **3**) offered any inherent stereoselectivity for either axial (*e.g.* **5a**) or equatorial (*e.g.*, **5b**) attack. Such cyclic transition states have frequently been invoked in additions of organometallic reagents or metal hydrides to cyclohexanone derivatives (**3**, X = O), and yet it is presently unclear whether or not there is a clear energetic preference for one of the transition states **4a** or **4b**.



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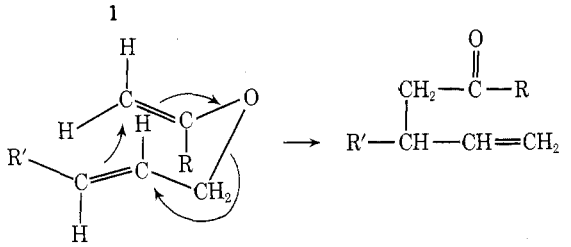

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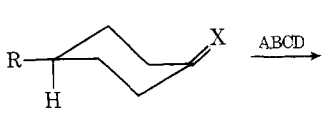

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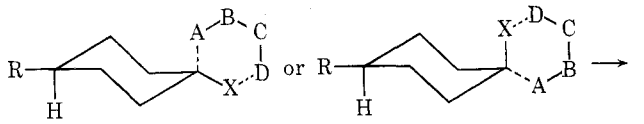
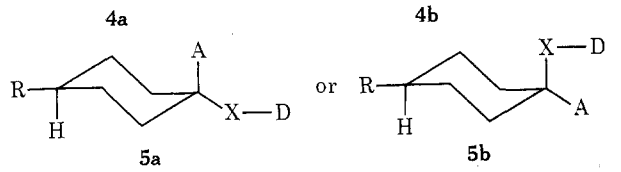
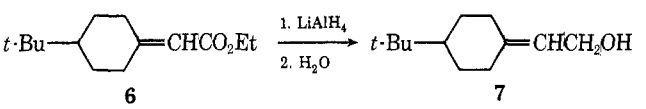


4a **4b**

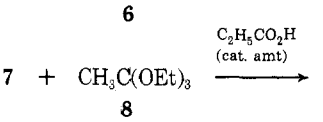


5a **5b**

Scheme I



6 **7**



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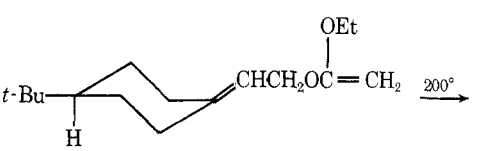

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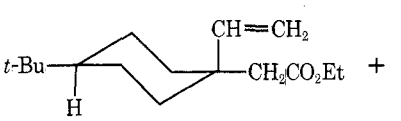

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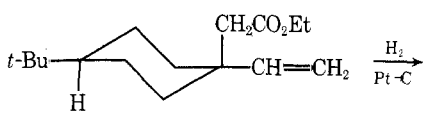

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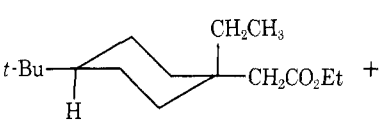

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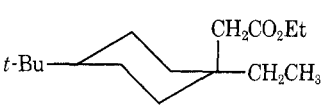
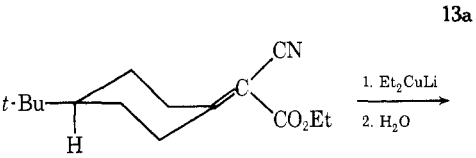


13a



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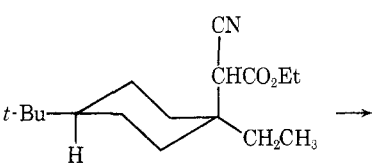

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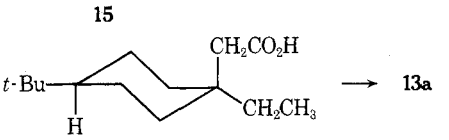


13b

We have selected two systems with which to study this question. In the first study, the known[4] ester **6** (Scheme I) was reduced to the allylic alcohol **7** and then treated with ethyl orthoacetate (**8**) in the presence of an acid catalyst to form the enol ether **9.** Thermal rearrangement produced a mixture of the stereoisomeric esters **10** and **11** that we were unable to resolve by a variety of chromatographic techniques. However, nmr analysis indicated the composition of the mixture to be 52% **10** and 48% **11.** Hydrogenation of the mixture of esters **10** and **11** afforded the saturated esters **12** (52% of the mixture) and **13a** (48% of the mixture) that were separable by gas chromatography. To establish the configuration of these esters **12** and **13a,** we used the known[4,5] stereospecificity of the addition of lithium dialkylcuprates to the alkylidene derivative **14** to form the cyano ester **15** with an equatorial ethyl group. Hydrolysis, decarboxylation, and reesterification converted the cyano ester **15** to the ester **13a.**

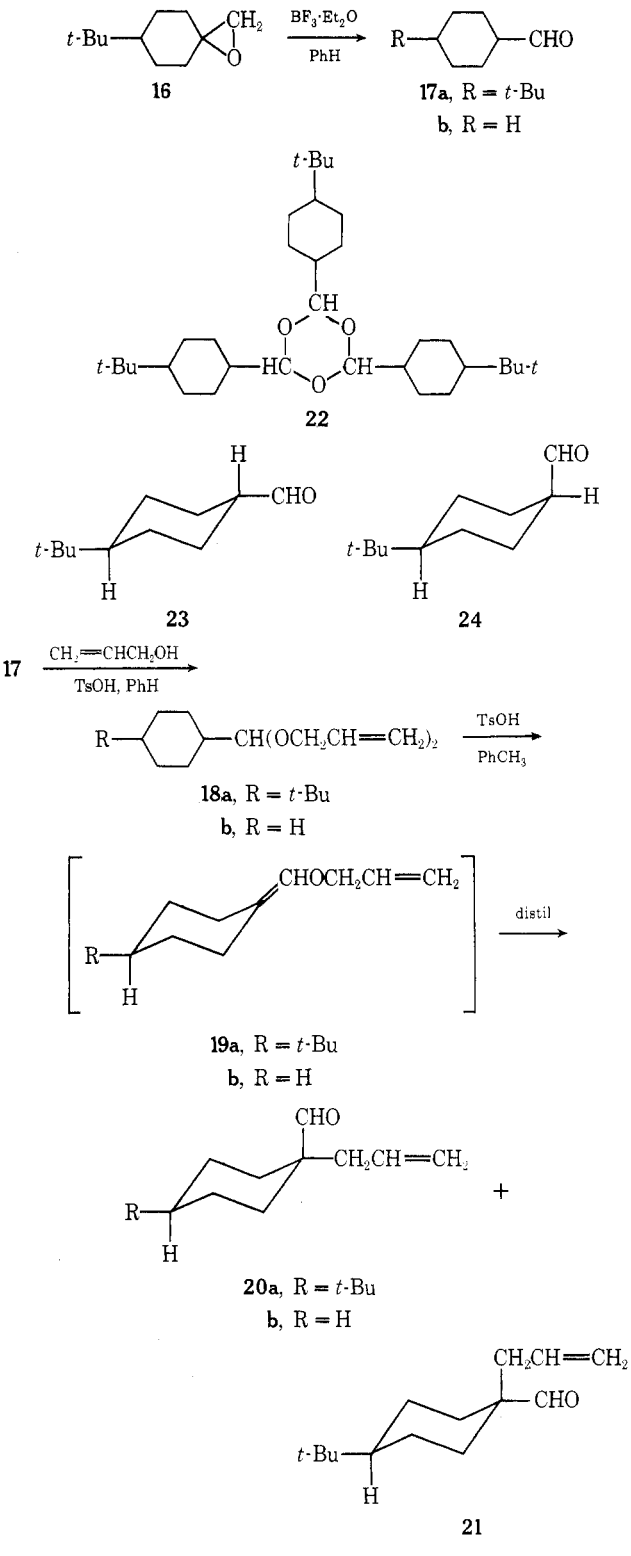
Further evidence supporting these stereochemical assignments was obtained from the proton and ^{13}C nmr spectra of the saturated esters **12** and **13a.** The proton nmr signal (δ 2.23) for the axial CH_2CO_2R group of the more rapidly eluted (glpc) ester **13a** was found at lower field than the signal (δ 2.05) for the equatorial CH_2CO_2R group of the more slowly eluted ester **12** corresponding to the usual generalization for axial and equatorial methyl groups.[6a] The ^{13}C nmr spectrum of ester **13a** has a signal (relative to TMS) at 36.1 ppm for the CH_2 of the axial CH_2CO_2Et group and at 34.5 ppm for the CH_2 of the equatorial ethyl group. In ester **12,** the corresponding values are 45.6 ppm for the CH_2 of the equatorial CH_2CO_2Et group and 25.0 ppm for the CH_2 of the axial ethyl group. Thus, in each case a change from an axial to an equatorial sp^3 carbon results in a downfield shift of about 9 ppm in agreement with previous generalizations.[6b,c]

For the second study, the known[7] epoxide **16** (Scheme II) was isomerized with $BF_3 \cdot Et_2O$ in PhH solution to produce a PhH solution of the aldehyde **17a.** Although we were able to collect small amounts of the aldehyde **17a** from a glpc column as a mixture of diastereoisomers **23** (*ca.* 83%) and **24** (*ca.* 17%),[8] the isolation of substantial quantities of the pure aldehyde **17a** was thwarted by the tendency of this aldehyde **17a** to undergo a variety of condensation reactions including formation of various isomers of the cyclic trimer **22.**

As a model for further study, the aldehyde **17b** was converted to its acetal **18b** which was isolated in pure form. Subsequent reaction of the acetal **18b** with TsOH followed by distillation to effect thermal rearrangement of the intermediate enol ether **19b**[9] afforded the aldehyde **20b** in 50% yield. This same product **20b** was also obtained (Scheme III) by successive conversion of the aldehyde **17b** to the imine **25** and its Li^+ salt **26** followed by alkylation to form the imine **27** and hydrolysis to form the aldehyde **20b.**[10]

Reaction of the benzene solution of aldehyde **17a** with allyl alcohol and TsOH followed by acid-catalyzed cleavage of the crude acetal **18a** and thermal rearrangement of the enol ether **19a** afforded a mixture of aldehydes **20a** and **21** in an overall yield of 31% (based on the epoxide **16**). The aldehyde mixture contained 75–77% of the axial aldehyde **20a** and 23–25% of the equatorial aldehyde **21.** To provide chemical evidence for these stereochemical assignments, the major product **20a** was also synthesized by an alternative route involving alkylation of the lithium salt **29** of the nitrile **28** to form nitriles **30** (88% of the mixture) and **31** (12% of the mixture). Alkylation of this lithium salt **29** had previously been shown[11] to form predominantly the product with an equatorial alkyl group. Subsequent reduction

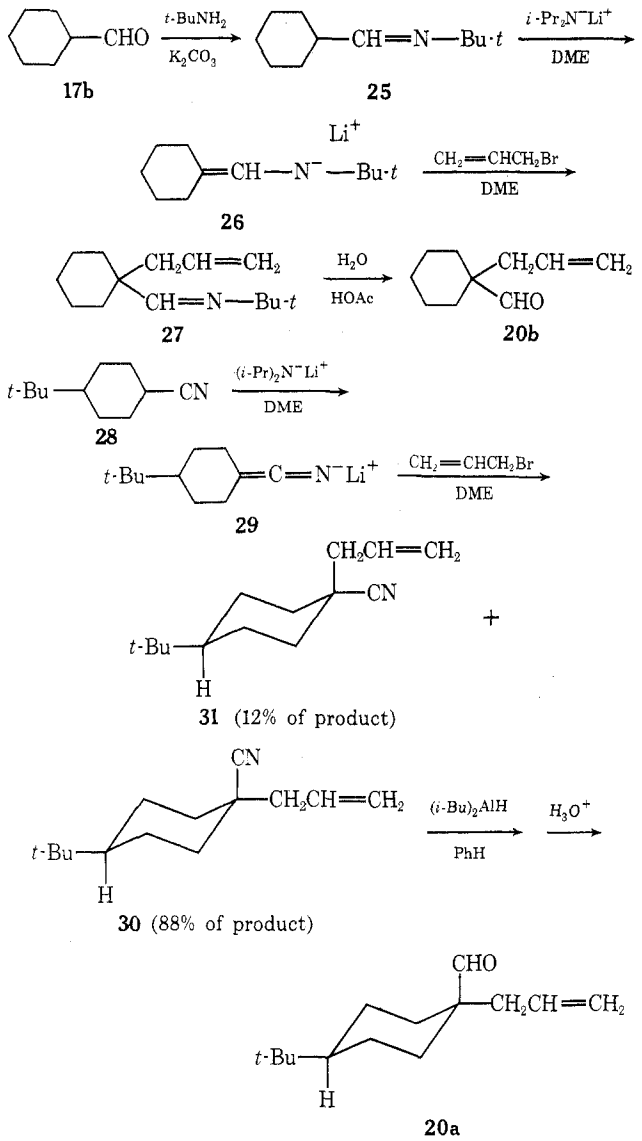
Scheme II



of the nitrile **30** with $(i\text{-Bu})_2AlH$ and hydrolysis yielded the aldehyde **20a.** Our efforts to form this aldehyde **20a** by alkylation of an imine lithium salt analogous to **26** were not successful apparently because of the very limited solubility of the lithium salt in DME.

Further evidence for the stereochemical assignments given products **20a** and **21** were obtained from their proton and ^{13}C nmr spectra. Thus, the proton nmr signal for the axial allylic CH_2 group in **21** occurred at lower field (δ 2.36) than the corresponding signal (δ 2.08) for the equatorial allylic CH_2 group in **20a.** The ^{13}C nmr signal for this axial al-

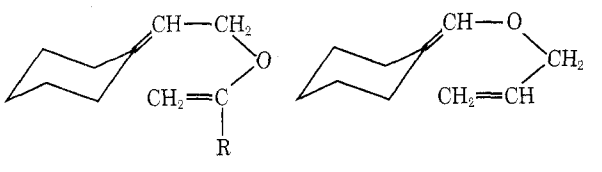
Scheme III



17b 25 26 27 20b 28 29 31 (12% of product) 30 (88% of product) 20a

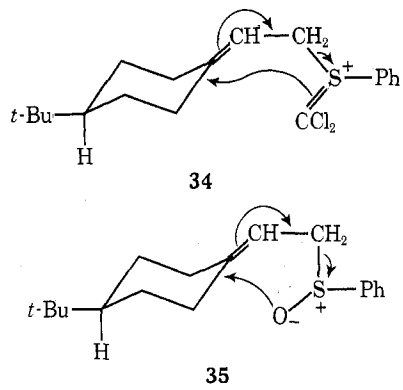
lylic CH_2 group in **21** occurred at about 8 ppm higher field (34.6 ppm) than the corresponding signal (42.7 ppm) for the equatorial allylic CH_2 group in **20a.** Both of these chemical shift differences correspond to the previously mentioned generalizations.[6]

Thus, for the two general systems **32** and **33** we have studied, we have observed only a slight energy preference (0.1–0.9 kcal/mol) favoring attack from an equatorial rath-



32 33

er than an axial direction in reactions that almost certainly involve a six-centered cyclic transition state. The closest related examples of which we are aware are the rearrangements (presumably involving five-center cyclic transition states) of compounds **34**[12a] and **35.**[12b] In both cases the indicated rearrangement to form a new equatorial bond is kinetically favored, the ratio being estimated as 82:18 for compounds **35.**[12b] Although slight preference for equatorial attack that we have observed would appear to be adequately explained by the usual assumption that attack from the



34 35

"equatorial direction" is subject to less steric hindrance, the possibility that some more profound phenomenon might be involved[13] certainly cannot be excluded. In any case, our data indicate that there is no inherent reason for an addition to a double bond exocyclic to a cyclohexane ring (*e.g.*, **3**) to favor axial attack (*e.g.*, **5a**) simply because a cyclic six-membered transition state (**4a**) is involved.

Experimental Section[14]

Preparation of the Allylic Alcohol 7. Following a previously described procedure,[4] the ester **6** was obtained in 75% yield as a colorless liquid, bp 114–121° (2.1 mm), n^{25}D 1.4783–1.4784 [lit.[4] bp 77–84° (0.1 mm), n^{21}D 1.4773]. This product **6** had ir and nmr absorption corresponding to the spectra previously determined and it lacked nmr absorption at δ 2.93 characteristic[4] of material contaminated with the isomeric β,γ-unsaturated ester. To a solution of 1.44 g (38 mmol) of $LiAlH_4$ in 175 ml of Et_2O was added, dropwise and with stirring during 1 hr, a solution of 10.0 g (46 mmol) of the ester **6** in 60 ml of Et_2O. After the resulting solution had been stirred for 2 hr at 25°, it was treated successively with 0.64 g of EtOH and with 20 ml of Et_2O saturated with H_2O. The precipitated Al salts were filtered and washed with Et_2O and the combined Et_2O solutions were washed with aqueous $NaHCO_3$, dried, and concentrated. The residual yellow liquid (8.17 g, free of C=O groups by ir analysis) was distilled to separate 6.23 g (78%) of the alcohol **7** as a colorless liquid, bp 108–110.5° (1.7 mm), n^{25}D 1.4892: ir (CCl_4) 3620, 3320 (free and associated OH), and 1665 cm^{-1} (C=C); uv (95% EtOH), end absorption with ϵ 1970 at 210 mμ; nmr (CCl_4) δ 5.29 (1 H, t, J = 6.5 Hz, vinyl CH), 4.02 (2 H, d, J = 6.5 Hz, CH_2O), 3.72 (1 H, broad, shifted with pyridine, OH), 0.9–2.9 (9 H, m, aliphatic CH), and 0.84 (9 H, s, *t*-Bu); mass spectrum *m/e* (relative intensity) 182 (M^+, 3), 164 (46), 149 (23), 121 (30), 109 (29), 108 (59), 107 (38), 95 (26), 93 (63), 83 (30), 82 (27), 81 (50), 80 (40), 79 (48), 69 (22), 67 (41), 57 (100), 56 (23), 55 (41), 43 (23), 41 (40), and 39 (23).

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.86; H, 12.22.

Preparation and Rearrangement of the Allyl Vinyl Ether 9. A mixture of 16.01 g (88 mmol) of the allylic alcohol **7,** 308 mg (0.4 mmol) of propionic acid, and 81.0 g (520 mmol) of freshly distilled ortho ester **8** (bp 138–143°) was heated under partial reflux with continuous removal of EtOH until no more EtOH distilled (*ca* 1 hr). The solution was cooled and fractionally distilled under reduced pressure to remove the propionic acid and excess ortho ester **8** [bp 42–45° (35 mm)]. The residual yellow liquid was fractionally distilled at 20 mm to effect rearrangement of the enol ether **9.** The first distillation separated 1.089 g of forerun, bp 46–155° (20 mm), n^{25}D 1.4403, and 16.73 g of fractions, bp 155–162° (20 mm), n^{25}D 1.4642–1.4643, that contained (glpc analysis, Apiezon L on Chromosorb P) a small amount of the unchanged alcohol (retention time 6.3 min) and an unresolved mixture of the esters **10** and **11** (17.9 min). Nmr analysis (CCl_4 solution) of the distillate indicated that the distilled product contained both the subsequently described rearranged esters **10** and **11** and a small amount of the unrearranged enol ether **9** with a quartet (J = 7.4 Hz) of resolved nmr peaks at δ 3.49 attributable to the ethoxyl CH_2 group of the unrearranged enol ether **9.** The amount of this unrearranged enol ether **9** was substantially greater in another preparation in which the final distillation was effected at a lower temperature [bp 122–130° (2 mm), n^{25}D 1.4622–1.4633]. When samples of distilled material containing the unrearranged enol ether **9** either were heated

under N_2 to 200° for 10 min or were passed through a glpc column at 250° and recollected, nmr analysis indicated that rearrangement of the enol ether **9** to the esters **10** and **11** was complete. Redistillation of the above fractions containing esters **10** and **11** with a minor amount of the enol ether **9** afforded 13.29 g of fractions, bp 150–159° (20 mm), n^{25}D 1.4645–1.4646, that were free (nmr analysis) of unrearranged ether **9** and contained (glpc analysis) the esters **10** and **11** accompanied by small amounts of the alcohol **7**. We were unsuccessful in attempts to resolve the two stereoisomeric esters **10** and **11** either with a variety of glpc columns or by tlc analysis with either SiO_2 and Al_2O_3 coatings and a variety of eluents. Consequently, a sample of the mixture of esters **10** and **11** was collected (glpc) for characterization as a colorless liquid, n^{25}D 1.4643: ir (CCl_4) 1730 (ester C=O), 1635 (C=C), and 920 cm^{-1} ($CH=CH_2$); nmr (CCl_4) δ 4.7–6.1 (3 H, m, $CH=CH_2$), 4.01 (2 H, q, J = 7.3 Hz, ethoxyl CH_2), 0.9–2.1 [12 H, m, aliphatic CH including an ethoxy CH_3 triplet (J = 7.3 Hz) at 1.18], with two singlets at 2.12 (52% of 2 H) and 2.32 (48% of 2 H, CH_2CO_2R signals of each epimer) and two singlets at 0.78 and 0.83 (total 9 H, t-Bu signals of each epimer); mass spectrum m/e (relative intensity) 252 (M^+, 30), 195 (54), 194 (63), 165 (58), 164 (70), 153 (45), 151 (48), 150 (58), 149 (74), 135 (50), 123 (58), 122 (64), 121 (66), 110 (40), 109 (70), 108 (77), 107 (74), 106 (40), 97 (44), 96 (53), 95 (61), 94 (42), 93 (44), 83 (56), 81 (44), 79 (41), 71 (43), 69 (45), 58 (74), 57 (75), 43 (100), 42 (40), and 41 (42).

Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.13; H, 11.20.

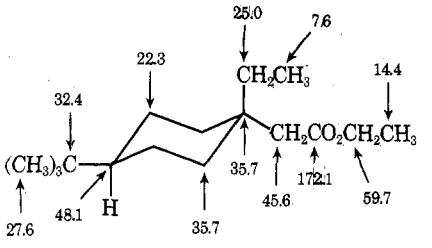
Preparation of the Esters 12 and 13a. A. *Via* Catalytic Hydrogenation. A solution of 2.52 g (10 mmol) of the unsaturated esters **10** and **11** in 60 ml of EtOH was hydrogenated over 50 mg of a 5% Pt-on-carbon catalyst at 25° and 35 psi hydrogen pressure. After a rapid uptake of *ca.* 0.01 mol of H_2, no further hydrogen uptake was observed for 24 hr. The reaction mixture was filtered and concentrated to leave 2.35 g of residual liquid containing (glpc, Apiezon L on Chromosorb P, apparatus calibrated with a known mixture) 48% of the saturated ester **13a** (retention time 18.0 min) and 52% of the ester **12** (19.8 min). A collected (glpc) sample of ester **13a** was obtained as a colorless liquid, n^{25}D 1.4580: ir (CCl_4) 1735 cm^{-1} (ester C=O); nmr (CCl_4) δ 4.07 (2 H, q, J = 7.2 Hz, ethoxyl CH_2), 2.23 (2 H, s, CH_2CO), and 0.8–2.0 (26 H, m, aliphatic CH including at t-Bu singlet at 0.87); mass spectrum m/e (relative intensity), 254 (M^+, 3), 209 (30), 195 (52), 169 (57), 167 (95), 166 (83), 111 (98), 110 (69), 109 (98), 108 (85), 97 (84), 95 (72), 89 (84), 88 (95), 81 (80), 70 (50), 69 (77), 67 (85), 61 (64), 57 (100), 55 (79), and 41 (85).

Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89. Found: C, 75.48; H, 11.88.

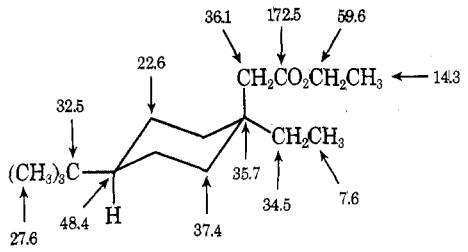
A collected (glpc) sample of ester **12** was obtained as a colorless liquid, n^{25}D 1.4598: ir (CCl_4) 1735 cm^{-1} (ester C=O); nmr (CCl_4) δ 4.05 (2 H, q, J = 7.2 Hz, ethoxyl CH_2), 2.05 (2 H, s, CH_2CO), and 0.7–1.9 (26 H, m, aliphatic CH including a t-Bu singlet at 0.83); mass spectrum m/e (relative intensity), 254 (M^+, 4) 225 (40), 209 (81), 196 (52), 195 (97), 169 (50), 167 (97), 166 (88), 151 (85), 137 (65), 123 (86), 111 (96), 110 (77), 109 (100), 108 (84), 97 (75), 95 (73), 89 (84), 88 (90), 83 (58), 81 (70), 79 (51), 71 (57), 70 (57), 69 (74), 67 (74), 61 (69), 58 (71), 57 (98), 56 (50), 55 (72), 43 (91), and 41 (75).

Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89. Found: 75.47; H, 11.93.

The natural-abundance ^{13}C nmr spectrum of each of the esters **12** and **13a** was measured in $CDCl_3$ solution with added TMS as an internal standard. In each case the spectrum was measured both with broad-band proton decoupling and with off-resonance decoupling. The assignments, indicated in ppm in the accompanying structures, are compatible both with the off-resonance decoupling experiments and with chemical shift values previously assigned to related compounds.[6c]



^{13}C nmr δ values for ester **12**



^{13}C nmr δ values for ester **13a**

B. From the Alkylidenecyanoacetate 14. Reaction of 25.5 g (165 mmol) of 4-*tert*-butylcyclohexanone with 17.4 g (150 mmol) of ethyl cyanoacetate in 100 ml of PhH containing 1.8 g of HOAc and 1.35 g of NH_4OAc as previously described[15] followed by crystallization from EtOH afforded 29.8 g (80%) of the crude cyanoacetate **14** as a white solid, mp 34–36°. Recrystallization from pentane at Dry Ice temperatures afforded 22.05 g of the pure cyano ester **14** as white plates, mp 42–43.5° (lit. mp 41–42°,[16] 45–46° [15]): ir (CCl_4) 2230 (conjugated C≡N), 1730 (ester C=O), and 1605 cm^{-1} (C=C); uv maximum (95% EtOH) 230 mμ (ϵ 27,000); nmr (CCl_4) δ 4.25 (2 H, q, J = 7.0 Hz, ethoxyl CH_2), 1.7–3.4 (9 H, m, aliphatic CH), 1.35 (3 H, t, J = 7.0 Hz, ethoxyl CH_3), and 0.88 (9 H, s, t-Bu); mass spectrum m/e (relative intensity) 249 (M^+, 5), 247 (95), 234 (65), 220 (82), 207 (60), 195 (50), 179 (78), 167 (81), 149 (83), 139 (72), 123 (79), 122 (52), 121 (50), 81 (53), 71 (58), 59 (100), 77 (60), 45 (62), 43 (86), and 41 (58).

A solution of Et_2CuLi was prepared by treating a cold (−50°) slurry of 5.50 g (28.3 mmol) of CuI in 60 ml of Et_2O, dropwise and with stirring, with 43 ml of a PhH solution containing 52.9 mmol of EtLi while the temperature of the mixture was maintained at −40 to −50°. The resulting cold (−30 to −50°), black solution was stirred for 15 min and then a solution of 3.18 g (12.7 mmol) of the cyano ester **14** in 30 ml of Et_2O was added dropwise and with stirring. The reaction mixture was stirred at −20 to −30° for 1 hr and then allowed to warm to room temperature. The reaction mixture was added to excess aqueous NH_4Cl, filtered to remove the precipitated copper, and then extracted with Et_2O. The ethereal extract was washed with aqueous $Na_2S_2O_3$, dried, and concentrated to leave 3.10 g (88%) of the crude cyano ester **15** as a viscous yellow liquid. Crystallization of a 550-mg aliquot of the crude product from pentane at Dry Ice temperature separated 350 mg (corresponding to a 56% yield) of the cyano ester **15**, mp 30.5–31.5°. Recrystallization afforded the pure cyano ester **15** as fine white needles, mp 32.5–32.7°: ir (CCl_4) 2255 (C≡N) and 1735 cm^{-1} (ester C=O); nmr (CCl_4) δ 4.25 (2 H, q, J = 7 Hz, ethoxyl CH_2), 3.79 [1 H, s, $CH(CN)CO_2R$], and 0.8–2.2 [26 H, m, aliphatic CH including a triplet (J = 7 Hz) at 1.34 (ethoxyl CH_3) and a singlet at 0.89 (t-Bu)]; mass spectrum m/e (relative intensity), 264 (6), 194 (19), 148 (29), 114 (88), 57 (100), and 41 (26).

Anal. Calcd for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.46; N, 5.01. Found: C, 73.25; H, 10.61; N, 4.92.

A solution of 1.00 g (3.6 mmol) of cyano ester **15**, 3.0 g (46 mmol) of 85% KOH, and 1 ml of H_2O in 15 ml of $HOCH_2CH_2OH$ was refluxed for 65 hr and then cooled and partitioned between H_2O and Et_2O. The aqueous phase was acidified (HCl) and then extracted with Et_2O. This ethereal extract was washed with aqueous NaCl, dried, and concentrated to leave 616 mg (76%) of the acid **13b**, mp 92.6–93.9°. Sublimation (78–80° at 0.04 mm) afforded the pure acid **13b** as fine white needles, mp 94.4–94.9°: ir (CCl_4) 2600–3400 (carboxyl OH) and 1700 cm^{-1} (carboxyl C=O); nmr (CCl_4) δ 11.8 (1 H, broad, OH), 2.32 (2 H, s, CH_2CO_2R), and 0.8–2.0 [23 H, m, aliphatic CH including a singlet at 0.84 (t-Bu)]; mass spectrum m/e (relative intensity), 171 (35), 141 (30), 111 (24), 109 (46), 108 (24), 57 (100), 56 (27), and 41 (30).

Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.35; H, 11.59.

A solution of 150 mg (0.66 mmol) of the acid **13b** and 1.0 ml (8.8 mmol) of freshly distilled $BF_3 \cdot OEt_2$ in 30 ml of EtOH was refluxed for 65 hr and then cooled and partitioned between H_2O and Et_2O. The ethereal solution was washed successively with aqueous 10% NaOH and with aqueous NaCl and then dried and concentrated. The residual crude ester **13a** (85 mg) was distilled in a short-path still to separate 70 mg (42%) of the pure ester **13b** as a colorless liquid, n^{25}D 1.4580, that was identified with the previously described sample by comparison of ir, nmr, and mass spectra.

Preparation of the Acetal 18b. A solution of 20.0 g (179 mmol) of cyclohexanecarboxaldehyde (**17b**), 62.6 g (1.07 mol) of allyl alco-

hol, and 100 mg of *p*-TsOH in 1 l. of PhH was refluxed with continuous separation of H_2O for 48 hr and then cooled, washed with aqueous $NaHCO_3$, dried, and concentrated. Distillation of the residue afforded 30.39 g (81%) of the crude acetal **18b** as a colorless liquid, bp 79–84° (1 mm), $n^{25}D$ 1.4619–1.4620, that contained (ir analysis) a small amount of the unchanged aldehyde **17b.** Fractional distillation through a 30-cm Holtzmann column afforded the pure acetal **18b,** bp 83–84° (1 mm), $n^{25}D$ 1.4620: ir (CCl_4) 1640 (weak, C=C) and 925 cm^{-1} (CH=CH_2); uv (95% EtOH) end absorption with ϵ 725 at 210 mμ; nmr (CCl_4) δ 4.9–6.2 (6 H, m, vinyl CH), 4.17 [1 H, d, J = 6 Hz, CH(OR)$_2$], 3.8–4.1 (4 H, m, allylic CH_2), and 0.9–2.1 (11 H, m, aliphatic CH); mass spectrum *m/e* (relative intensity) 127 (55), 83 (26), 81 (71), 55 (28), and 41 (100).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.38; H, 10.57.

Formation and Rearrangement of the Enol Ether 19b. A solution of 10.0 g (47.5 mmol) of the acetal **18b** and 100 mg of TsOH in 65 ml of toluene was refluxed for 3 hr and then fractionally distilled through a 40-cm Vigreux column[9] over a period of 3 hr. After the temperature of the distillate had risen from 90° (allyl alcohol–toluene azeotrope) to 110°, the residual toluene solution remaining in the stillpot was washed successively with aqueous 5% $FeSO_4$, with aqueous $NaHCO_3$, and with aqueous NaCl and then dried. Fractional distillation separated a forerun followed by 4.25 g (59%) of the aldehyde **20b** as a colorless liquid, bp 85–90° (15 mm), $n^{25}D$ 1.4700 [lit.[17] bp 105–107° (32 mm), $n^{25}D$ 1.4701]. The product contained (glpc, silicone SE-30 on Chromosorb P) the aldehyde **20b** (retention time 4.2 min) accompanied by minor amounts of toluene (1.6 min) and the aldehyde **17b** (2.4 min). Tlc analysis (silica gel coating with 5% Et_2O in pentane as an eluent) gave the following R_f values: aldehyde **17b,** 0.40; aldehyde **20b,** 0.64; acetal **18b,** 0.64. A pure sample of the aldehyde **20b** was collected as a colorless liquid, $n^{25}D$ 1.4699 [lit.[17] bp 105–107° (32 mm), $n^{25}D$ 1.4701]: ir (CCl_4) 2800, 2700, 2680 (aldehyde CH), 1723 (C=O), 1638 (C=C), 1000, and 928 cm^{-1} (CH=CH_2); uv (95% EtOH) end absorption with ϵ 140 at 210 mμ; nmr (CCl_4) δ 9.50 (1 H, s, CHO), 4.8–6.2 (3 H, m, vinyl CH), 2.20 (2 H, d, J = 7.0 Hz, allylic CH_2), and 1.0–2.1 (10 H, m, aliphatic CH); mass spectrum *m/e* relative intensity) 152 (M^+, 1), 110 (28), 97 (21), 82 (20), 81 (100), 79 (20), 69 (24), 67 (67), 55 (48), 53 (20), 41 (72), and 39 (39).

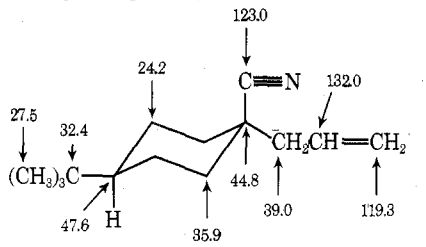
Preparation of the Aldehyde 20b from the Imine Salt 26. A mixture of 5.0 g (45 mmol) of the aldehyde **17b,** 7.0 g (90 mmol) of *t*-$BuNH_2$, 150 ml of PhH, and 10 g of anhydrous K_2CO_2 was stirred at 25° for 65 hr at which time ir analysis indicated conversion to the imine **25** was complete. The mixture was filtered and the filtrate was concentrated under reduced pressure and then distilled to separate 4.12 g (55%) of the crude imine **25** as a colorless liquid, bp 37° (0.55 mm), $n^{25}D$ 1.4511: ir (CCl_4) 1660 cm^{-1} (C=N); nmr (CCl_4) δ 7.45 (1 H, d, J = 4 Hz, CH=N), and 1.1–2.5 (20 H, m, aliphatic CH including a *t*-Bu singlet at 1.10); mass spectrum *m/e* (relative intensity) 167 (M^+, 3), 152 (30), 99 (69), 95 (18), 58 (41), 57 (100), 56 (55), and 41 (39). The imine **25** exhibited a single glpc peak (TCEP on Chromosorb P) with a retention time of 4.8 min; under the same conditions the retention time for the aldehyde **17b** was 6.0 min.

A cold (−38°) solution of (*i*-Pr)$_2$NLi, from 10.2 mmol of CH_3Li, 1.08 g (10.7 mmol) of (*i*-Pr)$_2$NH, and 35 ml of DME, was treated, dropwise and with stirring, with 1.23 g (7.40 mmol) of the imine **25.** The resulting solution of the lithium salt **26** was allowed to warm to 13° over a period of 1 hr and then 1.40 g (11.6 mmol) of freshly distilled allyl bromide was added, dropwise and with stirring. The resulting mixture, which warmed to 24° during the addition, was stirred at 25° for 17 hr during which time some LiBr separated. The mixture was partitioned between Et_2O and saturated aqueous NaCl and the organic layer was dried and concentrated. Distillation of the residual yellow liquid afforded 1.0 g (65%) of the imine **27** as a colorless liquid, bp 51–55° (0.5 mm), $n^{25}D$ 1.4601, that exhibited a single glpc peak (TCEP on Chromosorb P): ir (CCl_4) 1655 (C=N), 1635 (C=C), and 922 cm^{-1} (CH=CH_2); nmr (CCl_4), δ 7.40 (1 H, s, CH=N), 4.6–6.8 (3 H, m, vinyl CH), 2.1 [2 H, doublet (J = 7 Hz) with further partially resolved splitting, allylic CH_2], and 1.0–2.0 (19 H, m, aliphatic CH including a *t*-Bu singlet at 1.15); mass spectrum *m/e* (relative intensity) 207 (M^+, 9), 192 (38), 152 (64), 136 (21), 111 (20), 110 (32), 99 (42), 96 (52), 81 (35), 57 (100), 55 (27), 44 (23), and 41 (63).

Anal. Calcd for $C_{14}H_{25}N$: C, 81.09; H, 12.15; N, 6.76. Found: C, 80.99; H, 12.19; N, 6.76.

A mixture of 0.50 g (2.4 mmol) of the imine **27,** 10 ml (9.2 mmol) of aqueous 0.92 *M* HOAc, and 15 ml of hexane was stirred under N_2 at 25° for 16 hr and then partitioned between Et_2O and saturated aqueous NaCl. The organic layer was washed successively with aqeous $NaHCO_3$ and with aqueous NaCl and then dried and concentrated. Distillation of the residual liquid in a short-path still (0.15 mm and 55° bath) afforded 138 mg (38%) of the aldehyde **20b** as a colorless liquid, $n^{25}D$ 1.4701, that exhibited a single glpc peak (Apiezon L on Chromosorb P) and was identified with the previously described sample by comparison of ir, nmr, and mass spectra.

Alkylation of the Nitrile 28. *Samples of the nitrile* **28** *were obtained either as previously described*[11] or by the low-pressure hydrogenation of an MeOH solution of 4-*tert*-butyl-1-cyclohexenylnitrile[18] over a 5% Pd-on-C catalyst. To a cold (−30°) solution of (*i*-Pr)$_2$N$^-$Li$^+$, from 3.8 g (38 mmol) of (*i*-Pr)$_2$NH and 34 mmol of MeLi in 35 ml of DME, was added a solution of 5.0 g (30 mmol) of the nitrile **28** in 10 ml of DME. The resulting mixture was stirred at 25° for 20 hr, during which time a white solid separated, and then 4.84 g (40.0 mmol) of allyl bromide was added, dropwise with stirring and external cooling to keep the reaction mixture at 25°. *After the reaction mixture had been stirred at* 25° for 16 hr, it was partitioned between H_2O and Et_2O. The Et_2O solution was dried, concentrated, and distilled to separate 4.63 g (75%) of a mixture of nitriles **30** and **31** as a colorless liquid, bp 88° (0.45 mm), $n^{25}D$ 1.4670. The mixture contained (glpc, TCEP on Chromosorb P, instrument calibrated with a known mixture of the two nitriles) 88% of the nitrile **30** (retention time 51.6 min) and 12% of the nitrile **31** (64.8 min) as well as a small amount of the starting nitrile **28** (33.4 min). A collected (glpc) sample of the major component, nitrile **30,** was obtained as a colorless liquid, $n^{25}D$ 1.4670: ir (CCl_4) 2220 (C≡N), 1640 (C=C), 990, and 920 cm^{-1} (CH=CH_2); nmr (CCl_4) δ 4.9–6.4 (3 H, m, CH=CH_2), and 0.9–2.4 [20 H, m, aliphatic CH including a doublet (J = 7 Hz) at 2.26 attributable to an allylic CH_2 and a *t*-Bu singlet at 0.90]; mass spectrum *m/e* (relative intensity) 190 (20), 149 (35), 148 (44), 121 (100), 120 (44), 57 (63), and 41 (56). The natural abundance ^{13}C nmr spectrum of the nitrile **30,** measured in $CDCl_3$ solution with added TMS, is summarized in the accompanying structure.



^{13}C nmr δ values for nitrile **30**

Anal. Calcd for $C_{14}H_{23}N$: C, 81.99; H, 11.29; N, 6.82. Found: C, 81.80; H, 11.31; N, 6.87.

The stereoisomeric nitrile **31** was collected (glpc) as a colorless liquid, $n^{25}D$ 1.4700: ir (CCl_4) 2225 (C≡N), 1640 (C=C), 993, and 920 cm^{-1} (CH=CH_2); nmr (CCl_4) δ 4.8–6.5 (3 H, m, CH=CH_2), 2.35 (2 H, d, J = 7 Hz, allylic CH_2), and 0.8–2.2 (18 H, m, aliphatic CH including a *t*-Bu singlet at 0.87); mass spectrum *m/e* (relative intensity) 205 (M^+, 26), 190 (34), 150 (73), 149 (25), 148 (50), 123 (20), 121 (100), 120 (40), 81 (30), 79 (30), 67 (22), 58 (31), 57 (100), 56 (60), 55 (31), 53 (20), 43 (51), 41 (94), and 39 (34).

Anal. Calcd for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82. Found: C, 81.85; H, 11.27; N, 6.88.

Conversion of the Nitrile 30 to the Aldehyde 20a. To a cold (9°) solution of 210 mg (1.03 mmol) of the nitrile **30** in 10 ml of PhH was added a solution of 2.51 mmol of (*i*-Bu)$_2$AlH in 10 ml of PhH. The resulting solution was stirred at 25° for 3 hr and then cooled to 10° and treated with 10 ml of aqueous NH_4Cl. After the mixture had been stirred for 20 min, 10 ml of aqueous 1 *M* H_2SO_4 was added and the mixture was extracted with Et_2O. The organic phase was dried, concentrated, and distilled under reduced pressure in a short-path still to separate 160 mg (75%) of the aldehyde **20a** as a colorless liquid, $n^{25}D$ 1.4700, that was identified with a subsequently described sample by comparison of glpc retention times and of mass spectra, ir spectra, and proton and ^{13}C nmr spectra.

Preparation of the Aldehyde 17a. Trimethylsulfoxonium iodide (57.8 g or 260 mmol, mp 171–173°, lit.[19] mp 172–174°) was converted to the ylide by reaction with 5.70 g (260 mmol) of NaH (the oil dispersion was washed with petroleum ether, bp 30–60°) in 250 ml of DMSO.[7] Following a previously described procedure,[7] this ylide solution was treated with 28.4 g (184 mmol) of 4-*tert*-butylcyclohexanone and allowed to react for 15 min at 25° and 30

min at 55–60°. The reaction mixture was cooled and partitioned between Et_2O and H_2O. The Et_2O solution was washed with aqueous NaCl, dried, concentrated, and distilled (with extra care because of foaming) to separate 19.24 g (64%) of the epoxide **16**, bp 95–98° (10 mm), $n^{25}D$ 1.4583–1.4584 [lit.[7] bp 110° (13 mm)]: ir (CCl_4) 3040 cm^{-1} (epoxide CH) with no OH or C=O absorption in 3- or 6-μ regions; nmr (CCl_4) δ 2.45 (2 H, s, epoxide CH_2), 1.0–2.1 (9 H, m, aliphatic CH), and 0.90 (9 H, s, *t*-Bu); mass spectrum *m/e* (relative intensity) 168 (M^+, 2), 153 (27), 111 (25), 84 (71), 81 (25), 79 (27), 57 (100), 55 (18), 43 (30), and 41 (44).

Although earlier workers had reported[7] the successful BF_3-catalyzed rearrangement of the epoxide **16** to the aldehyde **17a** when the aldehyde was isolated as its 2,4-dinitrophenylhydrazone, we encountered considerable difficulty in isolating the pure aldehyde **17a** from this reaction because of the predominant formation of high molecular weight by-products when distillation of the crude aldehyde **17a** was attempted. The nmr spectrum (CCl_4) of these by-products had absorption at δ 4.5–4.6 [$CH(OR_2$] suggesting that they were mixtures of stereoisomers of the trimer **22** of aldehyde **17a**. A cold (5–10°) solution of 5.00 g (30 mmol) of the epoxide **16** in 25 ml of PhH was treated with 2.0 ml (15 mmol) of freshly distilled $BF_3 \cdot Et_2O$. After the mixture had been allowed to stand for 1 min at 10°, it was washed with aqueous $NaHCO_3$ and dried. The resulting PhH solution had nmr absorption at δ 9.32 (d, J = 4.5 Hz, CHO) corresponding to about 80% aldehyde **17a** as well as absorption at δ 4.8 corresponding to about 20% of the trimer **22**. Even concentration of this solution under reduced pressure increased the amount of trimer present in the crude product. When various fractions of this crude product were allowed to stand, the crude trimer **22** (a mixture of stereoisomers) separated as a white solid, mp 168–172°. Recrystallization from pentane at Dry Ice temperatures separated one diastereoisomer of the trimer **22** as white plates, mp 210–212°: ir (CCl_4) no absorption in the 3- or 6-μ regions attributable to OH or C=O groups; nmr (CCl_4) δ 4.45 [3 H, broad, $CH(OR)_2$] and 0.7–2.0 (*ca.* 57 H, m, aliphatic CH including a *t*-Bu singlet at 0.78).

Anal. Calcd for $C_{33}H_{60}O_3$: C, 78.51; H, 11.98. Found: C, 78.40; H, 11.97.

A PhH solution of the aldehyde **17a**, formed from the epoxide **16**, exhibited two major glpc peaks (TCEP on Chromosorb P) corresponding to the axial isomer **24** (retention time 24.8 min, *ca.* 23% of the mixture) and the equatorial isomer **23** (30.0 min, *ca.* 77% of the mixture) as well as several minor more rapidly eluted components. A collected (glpc) sample of the mixture of aldehyde epimers **23** (*ca.* 83%) and **24** (*ca.* 17%) was obtained as a colorless liquid, $n^{25}D$ 1.4611 (lit.,[8] aldehyde **24**, $n^{25}D$ 1.4635; aldehyde **23**, $n^{25}D$ 1.4630): ir (CCl_4) 2870, 2805, 2715 (aldehyde CH), and 1724 cm^{-1} (C=O); nmr (CCl_4) δ 9.71 (*ca.* 0.2 H, s, CHO), 9.60 (*ca.* 0.8 H, s, CHO), and 0.8–2.4 [19 H, m, aliphatic CH including *t*-Bu singlets at 0.88 (major) and 0.85 (minor)]; mass spectrum *m/e* (relative intensity), 168 (M^+, 1), 111 (11), 94 (15), 83 (13), 57 (100), 56 (26), and 41 (27). The ^{13}C nmr spectrum ($CDCl_3$) of this mixture of epimers exhibits two low-field peaks at δ 205.6 (*ca.* 25%, axial CHO) and 204.6 (*ca.* 75%, equatorial CHO).

Preparation of the Aldehydes 20a and 21 by a Claisen Rearrangement. Following the previously described procedure, 1.60 g (9.35 mmol) of the epoxide **16** in 35 ml of cold (7°) PhH was rearranged by reaction with 1.27 g (9.0 mmol) of $BF_3 \cdot Et_2O$ for 2 min, and the resulting mixture was washed successively with aqueous NaHCO and aqueous NaCl and then dried. The resulting PhH solution of the crude aldehyde **17a** (*ca.* 9 mmol) was treated with 0.90 g (15 mmol) of allyl alcohol, 100 mg (0.55 mmol) of *p*-TsOH, and 50 ml of PhH and then refluxed for 24 hr with continuous separation of H_2O. The PhH was distilled from the mixture at atmospheric pressure and the residual liquid was heated to 200° until all the allyl alcohol had distilled from the mixture. Distillation of the resulting liquid in a short-path still separated 0.605 g (31%) of a mixture of aldehyde **20a** (77%) and aldehyde **21** (23%). From a comparable reaction using 5.0 g (30 mmol) of the epoxide **16**, 2.5 g (18 mmol) of $BF_3 \cdot Et_2O$, 1.8 g (31 mmol) of allyl alcohol, and 200 mg (1.1 mmol) of *p*-TsOH, the yield of aldehydes was 1.30 g (21%) of a colorless liquid, bp 118–123° (3.5 mm), containing 75% of aldehyde **20a** and 25% of aldehyde **21**. The compositions of the mixtures were determined on glpc equipment (TCEP on Chromosorb P) that have been calibrated with known mixtures prepared from the axial aldehyde **20a** (retention time 43.6 min), the equatorial aldehyde **21** (50.4 min), and an internal standard, 2-methylnaphthalene (61.2 min).

In another experiment the PhH solution of the crude aldehyde **17a** (*ca.* 18 mmol), from 3.0 g (18 mmol) of the epoxide **16** and 1.3 g (9.0 mmol) of $BF_3 \cdot Et_2O$ in 150 ml of PhH, was mixed with 250 ml of PhH, 5.0 g (86 mmol) of allyl alcohol, 100 mg (0.5 mmol) of *p*-TsOH, and 5 mg of 2,5-di-*tert*-butylhydroquinone (a free-radical inhibitor). The resulting solution was refluxed with continuous removal of H_2O for 63 hr and then cooled, washed with aqueous $NaHCO_3$, dried, and concentrated under reduced pressure to leave 3.8 g of pale yellow liquid. Distillation of a 2.0-g portion of this liquid separated 692 mg of fractions of colorless liquid, bp 65–95° (0.55 mm), that contained (glpc, TCEP Chromosorb P) the starting aldehyde **17a** (retention times 13.0 min for axial isomer **24** and 15.8 min for equatorial isomer **23**) and the product aldehydes **20a** (25.3 min, 79% of the product) and **21** (29.4 min, 21% of the product).

A collected (glpc) sample of the more rapidly eluted axial aldehyde **20a** was obtained as a colorless liquid, $n^{25}D$ 1.4700: ir (CCl_4) 2680, 2710, 2810 (aldehyde CH), 1723 (C=O), 1640 (C=C), 1000, and 930 cm^{-1} ($CH=CH_2$); mass spectrum *m/e* (relative intensity), 208 (M^+, 2), 166 (40), 151 (37), 137 (23), 133 (25), 111 (22), 110 (38), 109 (54), 97 (50), 95 (38), 93 (34), 91 (28), 83 (27), 81 (73), 79 (38), 69 (47), 67 (62), 57 (100), 55 (45), 53 (24), 43 (32), 41 (62), and 39 (26); nmr (CCl_4) δ 9.42 (1 H, s, CHO), 4.7–6.0 (3 H, m, vinyl CH), 2.08 (2 H, d, J = 7 Hz, allylic CH_2), 0.82 (9 H, s, *t*-Bu), and 0.7–2.4 (9 H, m, aliphatic CH).

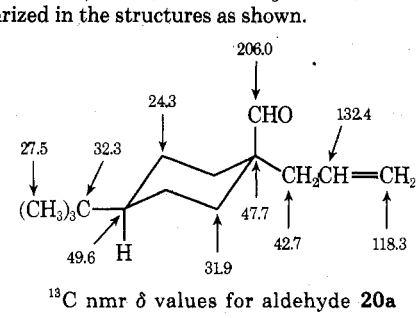
Our efforts to obtain a satisfactory elemental analysis for the aldehyde **20a** were thwarted by the rapidity with which this product reacted with oxygen from the air to form the corresponding acid as a contaminant (ir and mass spectral analyses). Consequently, 12.5 g (0.060 mmol) of the collected (glpc) aldehyde **20a** was added to 1.5 ml of a solution prepared from 218 mg (1.1 mmol) of 2,4-dinitrophenylhydrazine, 0.5 ml of concentrated HCl, and 25 ml of EtOH.[20] The resulting solution was refluxed for 20 min and then cooled to precipitate 15.6 mg (67%) of the crude 2,4-dinitrophenylhydrazone. Recrystallization from EtOH afforded 12.3 mg (53%) of the pure 2,4-dinitrophenylhydrazone of aldehyde **20a** as orange plates, mp 171.5–172.5°: ir (CCl_4) 3288 (NH), 1617 (C=N), 1510, and 1333 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 11.22 (1 H, broad, NH), 7.1–9.3 (4 H, m, aryl CHand CH=N), 4.8–5.8 (3 H, m, vinyl CH), 0.9–2.4 (11 H, m, aliphatic CH), and 0.83 (9 H, s, *t*-Bu).

Anal. Calcd for $C_{20}H_{28}N_4O_4$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.61; H, 7.31; N, 14.36.

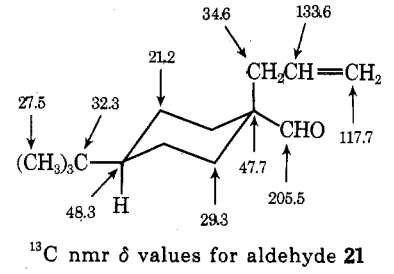
A collected (glpc) sample of the equatorial aldehyde **21** was obtained as a colorless liquid, $n^{25}D$ 1.4740: ir (CCl_4) 2680, 2710, 2820 (aldehyde CH), 1720 (C=O), 1638 (C=C), 1000, and 926 cm^{-1} ($CH=CH_2$); mass spectrum *m/e* (relative intensity), 208 (M^+, 3), 166 (36), 151 (49), 137 (30), 133 (34), 123 (58), 110 (35), 109 (62), 97 (43), 95 (46), 91 (29), 83 (32), 79 (37), 69 (51), 67 (64), 57 (100), 55 (47), 53 (26), 43 (36), 41 (62), and 39 (26); nmr (CCl_4) δ 9.36 (1 H, s, CHO), 4.7–6.0 (3 H, m, vinyl CH), 2.36 (2 H, d, J = 7 Hz, allylic CH_2), 0.88 (9 H, s, *t*-Bu), and 0.8–2.0 (9 H, m, aliphatic CH).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.83; H, 11.83.

The natural-abundance ^{13}C nmr spectra of the isomeric aldehydes **20a** and **21**, measured in $CDCl_3$ solution with added TMS, are summarized in the structures as shown.



^{13}C nmr δ values for aldehyde **20a**



^{13}C nmr δ values for aldehyde **21**

Registry No.—**6**, 13733-50-1; **7**, 41498-18-4; **8**, 78-39-7; **9**, 53260-29-0; **10**, 53188-54-8; **11**, 53188-55-9; **12**, 53188-56-0; **13a**,

53188-57-1; **13b**, 53188-58-2; **14**, 22700-58-9; **15**, 53188-59-3; **16**, 2815-45-4; **17b**, 2043-61-0; **18b**, 53188-60-6; **19b**, 53188-61-7; **20a**, 53188-62-8; **20a** 2,4-DNP, 53188-63-9; **20b**, 29517-58-6; **21**, 53188-64-0; **22**, 53188-65-1; **23**, 15763-62-9; **24**, 15763-61-8; **25**, 53188-66-2; **26**, 53188-67-3; **27**, 53188-68-4; **28**, 31865-37-9; **30**, 53188-69-5; **31**, 53188-70-8; 4-*tert*-butylcyclohexanone, 98-53-3; ethyl cyanoacetate, 105-56-6; allyl alcohol, 107-18-6; 4-*tert*-butyl-1-cyclohexenylnitrile, 7370-14-1.

References and Notes

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Electron Impact Induced Fragmentation of Macrocyclic Polyethers (Crown Ethers)[1]

David A. Jaeger* and Richard R. Whitney

Department of Chemistry, University of Wyoming, Laramie, Wyoming 82071

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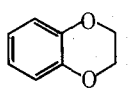
The mass spectra of catechol ethylene diether (1) and a series of macrocyclic polyethers (crown ethers) of the general class benzo-3*n*-crown-*n* (n = 3, 4, 5, 6) were correlated. The molecular ion (M) of benzo-18-crown-6 (**5**) loses C_2H_4O to give a peak at m/e 268. Other important peaks were found at m/e 224, 180, and 136, which formally correspond to the loss of two, three, and four C_2H_4O units, respectively, from M. Mass spectra of **2**, **3**, and **4** also displayed a series of peaks corresponding to the formal loss of C_2H_4O units from M; a peak at m/e 136 was the terminus in this series for each crown ether. Mass spectra of open-chain analogs **6** and **7** were compared with those of **3** and **4**, respectively. Mass spectra of deuterated analogs **4a** and **4b** allowed formulation of plausible fragmentation pathways for **4**.

Macrocyclic polyethers (crown ethers)[2] have unique chemical properties associated with their ability to form complexes with cations[2,3] and with other species.[4] Crown ethers have been employed in mechanistic,[5] physical,[6] and synthetic[7] studies and in chromatographic processes.[8] The chemical importance of crown ethers warranted study of their electron impact induced fragmentation pathways for qualitative identification purposes. Also, it was hoped that the novel chemical properties of crown ethers might be paralleled by unusual mass spectral fragmentation characteristics.

Aliphatic, aryl alkyl, and aromatic ethers have been subjects of numerous mass spectrometry investigations.[9] Several studies have included cyclic ethers,[10] notably catechol polymethylene diether derivatives[10a] and methylene dioxybenzenes.[10c,d] In the present investigation mass spectra of a homologous series of crown ethers were correlated and compared with those of open-chain analogs.

The mass spectra of catechol ethylene diether (**1**),[11,12] benzo-9-crown-3 (**2**),[2a,13] benzo-12-crown-4 (**3**),[2a] and benzo-18-crown-6 (**5**)[2a] are compiled in Table I, and that of benzo-15-crown-5 (**4**)[2a] is given in Figure 1. The mass spectrum of **5** displayed a base peak at m/e 136 and other important peaks at m/e 268, 224, 180, 121, 110, 109, 108, 80, and 52. The elemental compositions of most of the important fragment ions for **5** were determined by high-resolution mass spectrometry and are listed in Table II. The results indicate that the molecular ion (M) of **5** loses C_2H_4O to give the mass 268 ion and that ions of m/e 224, 180, and 136 formally correspond, respectively, to the loss of two, three, and four C_2H_4O units from M. The mass spectra of



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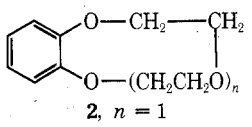

2, $n = 1$
3, $n = 2$
4, $n = 3$
5, $n = 4$