Tricyclic Ketones *via* Cyclodehydration of Bicyclic Unsaturated Acids[1]

ROBERT L. CARGILL,* A. M. FOSTER, JAMES J. GOOD, AND F. KEITH DAVIS[2]

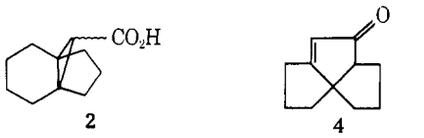
Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

Received May 30, 1973

Cyclodehydration of acids **5** and **8** provides a mixture of ketones **6** and **7** in 30% yield. Acids **14** and **19** provide representatives of the tricyclo[6.2.1.$0^{5,11}$]undecane system. Catalytic hydrogenation of the unsaturated ketones derived from **14** and **19** leads to the corresponding all-cis-saturated derivatives. These and other related transformations are discussed.

In a previous paper[3] we reported that cyclodehydration of acids **1** and **2** gave ketone **4**, probably *via*

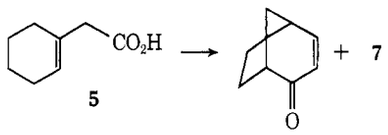
1 **3**



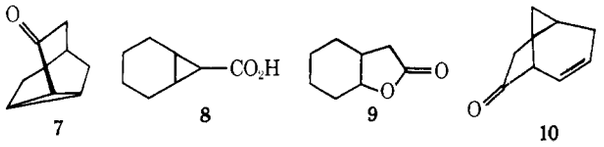
2 **4**

intramolecular acylation of acid **3**[3] and subsequent carbonium ion rearrangements. In this paper we describe the cyclodehydrations of a new series of olefinic acids.

Cyclodehydration of acid **5**[4,5] with polyphosphoric acid (PPA) for 1 hr at 100° gave a mixture of ketones **6** and **7** (ratio 2:1, respectively) in 34% yield. Similar cyclization of the cyclopropyl acid **8**[6] provided an identical mixture of **6** and **7** in 10–20% yield. The lower yield in the latter case appears to result from the lower solubility of the solid isomer **8** in PPA compared with that of the liquid acid **5**. The structures of ketones **6** and **7** were established by comparison of their spectra with those of authentic samples.[7,8] Separate treatment of **6** and **7** with PPA gave only recovered starting material; therefore the mixture



5 **6**

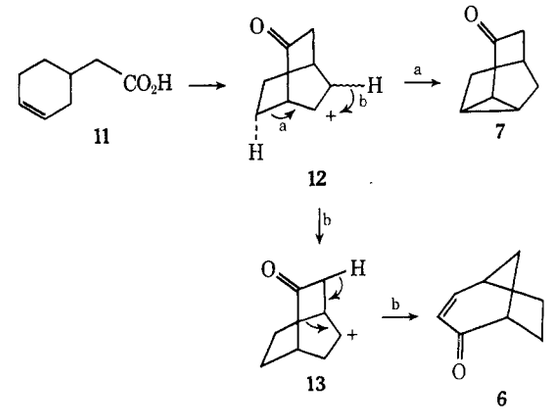


7 **8** **9** **10**

obtained in the cyclodehydration represents a kinetic rather than an equilibrium mixture of ketones.

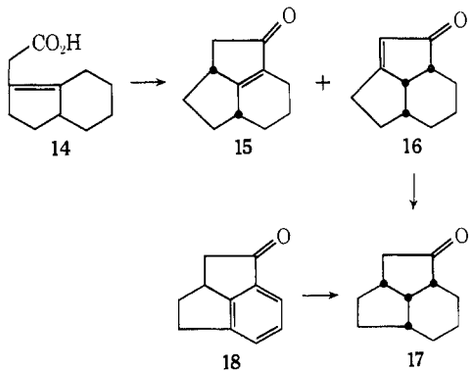
Ketones **6** and **7** presumably arise *via* isomerization of the starting acid to **11** and cyclization of **11** to yield ion **12**. The latter may yield **7** by loss of a proton (path a), or ion **13** *via* the equivalent of a hydride shift (path b). Formation of **6** from **13** by a Wagner–Meerwein shift and proton loss has ample precedent (Scheme I). These results are essentially the same as those reported recently by Ficini and Maujean,[9] who found that lactone **9** gave **6**, **7**, and a β,γ-unsaturated ketone, **10**.

SCHEME I



11 **12** **13** **6** **7**

When acid **14** was heated in PPA for 1 hr at 100°, a mixture of ketones **15** and **16** (ratio 85:15, respectively) was obtained in 30% yield. A similar result was obtained when **14** was stirred in methanesulfonic acid–phosphorus pentoxide[10] for 2 days at 25°. The structures of **15** and **16** were established by catalytic hydrogenation of the mixture of α,β-unsaturated cyclopentenones[11] to yield a single cyclopentanone **17**.



14 **15** **16** **18** **17**

(1) We thank the National Science Foundation for generous support of this research.

(2) NSF Undergraduate Research Participant, summer, 1969; deceased.

(3) R. L. Cargill and A. M. Foster, *J. Org. Chem.*, **35**, 1971 (1970).

(4) A. C. Cope, A. A. D'Addieco, D. E. Whyte, and S. A. Glickman, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 243.

(5) Having concluded earlier[3] that the position of the double bond in the starting acid is unimportant in these PPA cyclodehydrations, we have not separated double-bond isomers of our olefinic acids.

(6) M. Mousseron, R. Jacquier, and R. Fraisse, *C. R. Acad. Sci.*, **243**, 1880 (1956).

(7) H. L. Goering, R. W. Greiner, and M. F. Sloan, *J. Amer. Chem. Soc.*, **83**, 1391 (1961).

(8) W. R. Moore, W. R. Moser, and J. E. LaPrade, *J. Org. Chem.*, **28**, 2200 (1963). We thank Professor Moore for copies of the ir and nmr spectra of **7**.

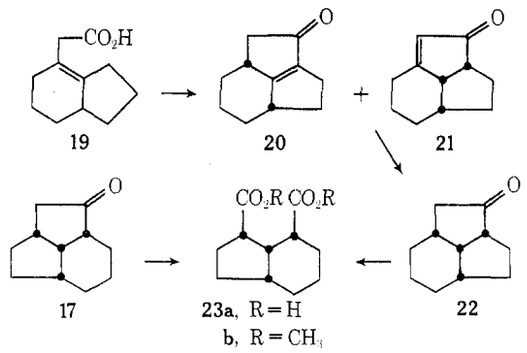
(9) J. Ficini and A. Maujean, *Bull. Soc. Chim. Fr.*, 4395 (1972).

(10) P. E. Eaton and R. H. Mueller, *J. Amer. Chem. Soc.*, **94**, 1014 (1972).

(11) See Experimental Section for spectral data.

The identity of the latter with the saturated ketone obtained from hydrogenation of the strained aromatic ketone **18**[12] confirmed structures **15**, **16**, and **17**.

Cyclization of acid **19** as above again provided a mixture of cyclopentenones[11] for which structures **20** and **21** were assigned. In this case the two new ketones were obtained in almost equal amounts (31% total yield). Catalytic hydrogenation of the mixture of **20** and **21** gave cyclopentanone **22**. Conversion of both **17** and **22** *via* oxidation with nitric acid into diacid **23** es-

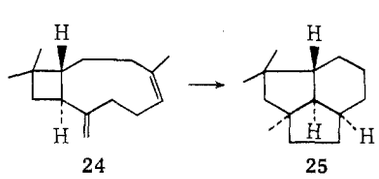


tablished the structural relationship of the two series of tricyclic ketones. The cyclization of both **14** and **19** presumably occur after initial double-bond migration followed by standard acylation processes which need no further elaboration here.

In the mixtures of unsaturated ketones derived from acids **14** and **19** the ratios of trisubstituted *vs.* tetrasubstituted double bonds varied somewhat depending upon the reaction conditions. In each case, the tetrasubstituted isomer may arise directly from deprotonation of the obvious intermediate cation. The trisubstituted isomer must result from isomerization of the initial product(s). If reaction times were sufficiently long, an equilibrium mixture of ketones was produced.

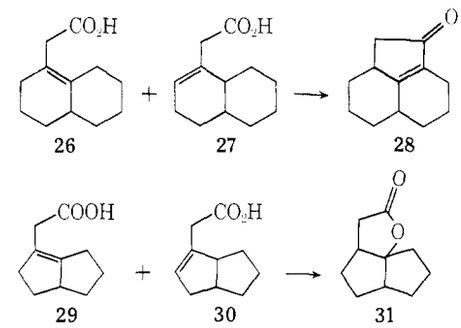
The stereochemical assignments indicated in the structural formulas are based on the reasonable assumption that catalytic hydrogenation of the distorted benzene ring of **18** will occur from the convex face of that molecule, thus providing all-cis **17**. The interrelation of all other tricyclic compounds with **17** confirms that all possess the same relative stereochemistry. Our assumptions were confirmed by a series of lanthanide shift experiments performed with **17**, **22**, and the corresponding alcohols.[13]

The only other known aliphatic tricyclo[6.2.1.$0^{5,11}$]-undecane compound appears to be the product of acid-catalyzed isomerization of isocaryophylene (**24** → **25**). The structure of **25** was determined by X-ray crystallo-



graphic analysis of the corresponding dibromide.[14] In this case, the stereochemistry of **25** reflects the trans ring fusion of the starting material.

Cyclodehydration of the higher and lower homologs of **14** and **19** was carried out with slightly different results. Thus, a mixture of acids **26** and **27** yielded a single cyclopentenone to which structure **28** is assigned, based on spectroscopic analysis[11] and analogy to the previously discussed results. Attempts to cyclodehydrate a mixture of acids **29** and **30** gave only a γ-lactone[11] whose structure is assigned as **31**.



Although the yields of the cyclodehydrations described here are in the 30–40% range, the starting acids are easily prepared; thus the tricyclic systems represented by **17**, **22**, and **28** are now readily available.

Experimental Section

Melting points were determined on a Büchi apparatus and are uncorrected. Ultraviolet spectra were determined on a Perkin-Elmer Model 202 spectrophotometer, infrared spectra with a Perkin-Elmer Model 337 spectrophotometer, and nmr spectra with a Varian A-60 spectrometer using tetramethylsilane as internal reference. Analyses were performed by Bernhardt Microanalytisches Laboratorium, Elbach über Engelskirchen, West Germany. Mass spectra were determined with a Hitachi Perkin-Elmer RMU-6 spectrometer. An Aerograph Model 1200 Hy-Fi was used for analytical glpc and an Aerograph Model A-90-P3 was used for preparative glpc work.

Bicyclo[4.3.0]non-6-ene-7-acetonitrile.—A solution of 13.70 g (0.098 mol) of tetrahydro-1-indanone, 17 g (0.20 mol) of cyanoacetic acid, and 3.85 g (0.05 mol) of dry ammonium acetate in 150 ml of benzene was refluxed for 3 days with removal of water. The mixture was cooled, washed with water, dried ($MgSO_4$), and concentrated at reduced pressure. The residue was then subjected to decarboxylation–distillation to yield two fractions. The first, bp 42–52° (0.8 mm), yielded 4.70 g of the starting ketone, and the second, bp 112° (5.5 mm), yielded 7.12 g (45%) of bicyclo[4.3.0]non-6-en-7-acetonitrile: ir (CCl_4) 2245 cm^{-1}; nmr (CCl_4) δ 3.0 (s, 2, $-C{=}CCH_2CN$).

Anal. Calcd for $C_{11}H_{15}N$: C, 81.93; H, 9.38; N, 8.69. Found: C, 81.83; H, 9.31; N, 8.90.

Bicyclo[4.3.0]nonene-2-acetonitrile and 4-hydrindanylidineacetonitrile were obtained from bicyclo[4.3.0]nonan-2-one according to the general procedure described above in 67% yield: bp 94–96° (0.6 mm); ir (CCl_4) 2240 and 2215 cm^{-1}; nmr (CCl_4) δ 5.70 (br s, 1, $-C{=}CHCN$) and 2.93 (s, 2, $-C{=}CCH_2CN$).

Anal. Calcd for $C_{11}H_{15}N$: C, 81.93; H, 9.38; N, 8.69. Found: C, 81.84; H, 9.07; N, 8.90.

Bicyclo[4.4.0]decene-2-acetonitrile and 1-decalinylideneacetonitrile were obtained from 1-decalone in 71% yield according to the general procedure described above: bp 106–108° (0.65 mm); ir (CCl_4) 2240 and 2210 cm^{-1}; mass spectrum (70 eV) m/e 175 (M^+); glpc (3% SE-30, 8 ft × 0.125 in., 175°, 50 ml/min He) shows two compounds; nmr (CCl_4) δ 5.65 (br s, 1, $-C{=}CHCN$), 2.95 (d, 2, J = 1 Hz, $-C{=}CCH_2CN$).

(12) H. Rapoport and J. Z. Parky, *J. Amer. Chem. Soc.*, **78**, 3788 (1956). We thank Professor Henry Rapoport for a sample of the corresponding alcohol.

(13) M. R. Willcott, R. E. Lenkinski, and R. E. Davis, *J. Amer. Chem. Soc.*, **94**, 1742 (1972); R. E. Davis and M. R. Willcott, *ibid.*, **94**, 1744 (1972). These experiments, which were carried out in the laboratory of Professor Willcott, will be reported in detail separately.

(14) K. Gollnick, G. Schade, A. F. Cameron, C. Hannaway, J. S. Roberts, and J. M. Robertson, *Chem. Commun.*, 248 (1970). See also K. Gollnick, G. Schade, A. F. Cameron, C. Hannaway, and J. M. Robertson, *ibid.*, 46 (1971).

Anal. Calcd for $C_{12}H_{17}N$: C, 82.28; H, 9.72; N, 8.00. Found: C, 82.17; H, 9.57; N, 7.81.

Bicyclo[3.3.0]octene-2-acetonitrile and 1-octahydropentalenylidineacetonitrile were obtained from bicyclo[3.3.0]octan-2-one in 63% yield according to the above procedure: bp 110–114° (5 mm); ir (CCl_4) 2260 and 2220 cm^{-1}; nmr (CCl_4) δ 5.5 (br s, 1, $-C{=}CHCN$), and 3.0 (br s, 2, CH_2CN).

Anal. Calcd for $C_{10}H_{13}N$: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.60; H, 8.83; N, 9.43.

Bicyclo[4.3.0]non-6-ene-7-acetic Acid (14).—A mixture of 10 g (0.062 mol) of bicyclo[4.3.0]non-6-ene-7-acetonitrile and 100 ml of 30% potassium hydroxide was refluxed overnight. The resulting solution was cooled, washed with pentane, and acidified with 1:1 hydrochloric acid. The resulting cream-colored precipitate was filtered and dried *in vacuo* at 40°. Recrystallization from hexane yielded 6.93 g (62%) of fluffy white crystals (mp 74.1–74.9°) of **14**: ir (CCl_4) 3200–2500 and 1705 cm^{-1}; nmr (CCl_4) δ 3.10 (s, 2, $-C{=}CCH_2CO_2H$) and 10.8 (s, 1, $-CO_2H$).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.48; H, 8.90.

Bicyclo[4.3.0]nonene-2-acetic acid (19) was obtained from the appropriate mixture of nitriles in 79% yield according to the general procedure described above: mp 66.3–67.2°; ir (CCl_4) 3300–2500 and 1700 cm^{-1}; nmr (CCl_4) δ 11.4 (s. 1, $-CO_2H$), 2.91 (s, 2, $-C{=}CCH_2CO_2H$).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.20; H, 8.72.

Bicyclo[4.4.0]decene-2-acetic acid (26) and bicyclo[4.4.0]dec-2-ene-2-acetic acid (27) were obtained from the mixture of nitriles in 55% yield according to the general procedure described above: bp 130° (0.30 mm); ir (CCl_4) 3300–2500, 1705, and 1645 cm^{-1}; nmr (CCl_4) δ 5.45 (m, 1, $HC{=}CCH_2CO_2H$), 2.95 (s, 2, $C{=}C-CH_2CO_2H$), 2.88 (br s, 2, $C{=}CCH_2CO_2H$), and 11.00 (s, 1, $-CO_2H$). Treatment of the acid mixture with diazomethane gave the methyl esters: glpc (3% SE-30, 8 ft × 0.125 in., 140°, 50 ml/min He) shows two compounds; ir (CCl_4) 1740 and 1645 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 75.00; H, 9.62. Found: C, 74.82; H, 9.55.

Bicyclo[3.3.0]octene-2-acetic acid (29) and bicyclo[3.3.0]oct-2-ene-2-acetic acid (30) were obtained in 70% yield from the nitriles according to the above procedure: bp (bath temperature) 100° (0.02 mm). Treatment of the acids with diazomethane gave the corresponding methyl esters: ir (CCl_4) 1735 cm^{-1}; nmr (CCl_4) δ 5.25 (br s, 1, $HC{=}CCH_2CO_2CH_3$), 3.55 (s, 3, $-OCH_3$), and 2.90 (br s, 2, $-CH_2CO_2CH_3$).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.53; H, 8.72.

Cyclodehydration of 14.—A mixture of 2 g (11.2 mmol) of **14** and 40 g of PPA was stirred at 120° for 1 hr, cooled, poured onto ice, and extracted with ether. The ether extracts were combined, washed with aqueous Na_2CO_3 and brine, and dried ($MgSO_4$), and the ether was removed under reduced pressure. The residual oil was vacuum distilled [bath temperature 100–150° (0.15 mm)] to yield 0.550 g (30%) of a mixture of **15** and **16**, ratio 85:15, respectively.

Preparative glpc (10% Carbowax 1000, 8 ft × 0.25 in., 132°, 300 ml/min He, followed by 10% SE-30, 10 ft × 0.25 in., 172°, 120 ml/min He) gave a pure sample of **15**: ir (CCl_4) 1710 and 1670 cm^{-1}; uv max (95% C_2H_5OH) 241 nm (ϵ 12,150); mass spectrum (70 eV) *m/e* 162 (M^+); and **16** slightly contaminated with the major component: ir (CCl_4) 3060, 1705, 1670, and 1630 cm^{-1}; nmr (CCl_4) δ 5.60 (m, 1, $-CH{=}C-$); uv max (95% C_2H_5OH) 241 nm (ϵ 12,100); mass spectrum (70 eV) *m/e* 162 (M^+). Elemental analysis was obtained for the mixture of ketones.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.20; H, 8.86.

Tricyclo[6.2.1.0^{4,11}]undec-1(11)-en-2-one (20) and tricyclo[6.2.1.0^{4,11}]undec-3-en-2-one (21) were obtained in 31% yield from **19**, ratio 5:3 (nmr), respectively, by the above procedure: bp (bath temperature) 115–135° (0.37 mm). Preparative separation of **20** and **21** was not practical. Therefore, spectral data were obtained for the mixture: ir (CCl_4) 1700, 1655, and 1620 cm^{-1}; nmr (CCl_4) δ 5.80 (br s, 1, $C{=}CH$); uv max (95% C_2H_5OH) 241 nm (ϵ 13,100); mass spectrum (70 eV) *m/e* 162 (M^+). Elemental analysis was obtained for the mixture of ketones.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.46; H, 8.70.

Tricyclo[7.2.1.0^{5,12}]dodec-9(12)-en-10-one (28) was obtained in 38% yield from a mixture of **26** and **27** by the procedure described above: bp (bath temperature) 115–130° (0.13 mm); ir (CCl_4) 1700 and 1650 cm^{-1}; glpc (10% Carbowax 1000, 6 ft × 0.125 in., 160°, 50 ml/min He) shows a single peak; mass spectrum (70 eV) *m/e* 176 (M^+); uv max (95% C_2H_5OH) 241 nm (ϵ 13,600).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.78; H, 9.00.

Lactone 31 was obtained in 70% yield from a mixture of **29** and **30** as described above: bp (bath temperature) 130° (0.2 mm); ir (CCl_4) 1770 cm^{-1}; mass spectrum (70 eV) *m/e* 166 (M^+).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.18; H, 8.44.

Bicyclo[3.2.1]oct-3-en-2-one (6) and tricyclo[3.2.1.0^{2,7}]octan-3-one (7) were obtained in 34% yield, ratio 2:1, respectively, according to the above procedure from acid **5**: bp (bath temperature) 80° (0.5 mm). Separation of the two compounds was accomplished by preparative glpc (20% DEGS, 5 ft × 0.25 in., 145°, 100 ml/min). The major component was identified as bicyclo[3.2.1]oct-3-en-2-one (**6**): ir (CCl_4) 3025 and 1690 cm^{-1}; nmr (CCl_4) δ 7.07 (m, 1, $-CH{=}CHC{=}O$) and 5.62 (d, 1, J = 9 Hz, $-CH{=}CHC{=}O$); uv max (95% C_2H_5OH) 230 nm (ϵ 10,000). The minor component was identified as tricyclo[3.2.1.0^{2,7}]octan-3-one (**7**), ir (CCl_4) 3040 and 1700 cm^{-1}.

Ketones 6 and 7 were obtained in 11% yield, ratio 2:1, respectively, according to the above procedure from acid **8**.

Hydrogenation of 15 and 16.—A mixture of 0.600 g (37 mmol) of **15** and **16** was hydrogenated over 10% Pd/C at 50 psi in methanol to yield 0.590 g (95%) of **17**. The crude product was sublimed (bath temperature 60°, 0.1 mm) to give white crystals (mp 55.5–58.2°): ir (CCl_4) 1740 cm^{-1}; mass spectrum (70 eV) *m/e* 164 (M^+).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.07; H, 9.55.

Tricyclo[6.2.1.0^{4,11}]undecan-2-one (22) was obtained in quantitative yield from a mixture of **20** and **21** according to the above procedure: bp (bath temperature) 95° (0.15 mm); ir (CCl_4) 1730 cm^{-1}; mass spectrum (70 eV) *m/e* 164 (M^+).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.26; H, 9.94.

Oxidation of 22.—A solution of 35 mg (0.21 mmol) of **22**, 10 ml of 1:1 nitric acid, and 20 mg of vanadium pentoxide was heated at 70° until the brown fumes disappeared. The solution was cooled and extracted with ether; the combined ether extracts were dried ($MgSO_4$); and the ether was removed under reduced pressure. Esterification of the product with diazomethane gave a yellow oil which was vacuum distilled (bath temperature 85°, 0.3 mm) to yield 20 mg (36%) of **23b**: ir (CCl_4) 1730 cm^{-1}; nmr (CCl_4) δ 3.58(s, 3, $-OCH_3$), 3.47 (s, 3, $-OCH_3$); mass spectrum (70 eV) *m/e* 240 (M^+); glpc (10% Carbowax 1000, 6 ft × 0.125 in., 160°, 50 ml/min He) shows a single peak.

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.66; H, 8.21.

Oxidation of 17.—Oxidation of 35 mg of **17** as above, followed by esterification and distillation, gave 18 mg (33%) of ester **23b**. The two samples were shown to be identical by glpc and by comparison of ir and nmr spectra.

Reduction of 28.—A mixture of 0.425 g (2.4 mmol) of **28**, 50 ml of liquid ammonia, and 0.252 g (36 mg-atoms) of lithium was refluxed for 1.5 hr. Ammonium chloride, then water, was added and the excess ammonia was removed. The aqueous layer was extracted with ether, the combined ether extracts were dried ($MgSO_4$), and the ether was removed under reduced pressure. The pure saturated ketone, tricyclo[7.2.1.0^{5,12}]dodecan-10-one, was isolated by column chromatography on neutral alumina using a mixture of hexane and benzene (2:1) as the eluting solvent: ir (CCl_4) 1745 cm^{-1}; mass spectrum (70 eV) *m/e* 178 (M^+); glpc (10% Carbowax 1000, 6 ft × 0.125 in., 165°, 50 ml/min He) shows a single peak.

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.67; H, 10.01.

Reduction of 17.—To a suspension of 77 mg (2 mmol) of lithium aluminum hydride in 50 ml of dry ether was added 600 mg (27.4 mmol) of **17**. After the mixture had been stirred for 2 hr, a solution of 15% potassium hydroxide was added dropwise. The resulting white precipitate was filtered, the ether was removed under reduced pressure, and the residual semisolid was distilled onto a cold finger (bath temperature 100°, 0.45 mm) to give 0.530 g (88%) of tricyclo[6.2.1.0^{4,11}]undecan-3-ol: ir (CCl_4) 3590 and 3350 cm^{-1}; nmr (CCl_4) δ 4.0 (m, 1, HOCH) and 3.40 (s, 1, HOCH); mass spectrum (70 eV) no M^+, peak at *m/e* 148 indicates loss of water from parent ion.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.27; H, 10.81.

Tricyclo[6.2.1.0^{4,11}]undecan-2-ol was obtained from **22** in 89% yield according to the above procedure: mp 97.1–98°; ir (CCl_4) 3590 and 3430 cm^{-1}; nmr ($CDCl_3$) δ 4.32 (m, 1, –CHOH) and 1.72 (br s, 1, –OH); mass spectrum (70 eV) no M^+, *m/e* 148 results from loss of H_2O from parent.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.71; H, 10.69.

Tricyclo[7.2.1.0^{5,12}]dodecan-10-ol was obtained as an oil in quantitative yield from tricyclo[7.2.1.0^{5,12}]dodecan-10-one by the above procedure: bp (bath temperature) 80° (0.3 mm); ir (CCl_4) 3590 and 3350 cm^{-1}; nmr (CCl_4) δ 3.70 (m, 1, –CHOH) and 2.90 (br s, 1, –OH); glpc (10% Carbowax 1000, 6 ft × 0.125 in., 160°, 50 ml/min He) shows a single peak; mass spectrum (70 eV) *m/e* 180 (M^+).

Anal. Calcd for $C_{12}H_{20}O$: C, 79 94; H, 11.18. Found: C, 79.90; H, 11.04.

Registry No.—**5**, 18294-87-6; **6**, 3212-77-9; **7**, 39163-38-7; **8**, 41894-76-2; **14**, 41894-77-3; **15**, 41915-67-7; **16**, 41915-68-8; **17**, 41915-69-9; **19**, 41894-78-4; **20**, 41915-70-2; **21**, 41915-71-3; **22**, 41915-72-4; **23b**, 41915-73-5; **26**, 41894-79-5; **26** methyl ester, 41894-80-8; **27**, 41894-81-9; **27** methyl ester, 41894-82-0; **28**, 41894-83-1; **29**, 41894-84-2; **29** methyl ester, 41894-85-3; **30**, 41894-86-4; **30** methyl ester, 41894-87-5; **31**, 41894-88-6; bicyclo[4.3.0]non-6-ene-7-acetonitrile, 41894-89-7; tetrahydro-1-indanone, 22118-00-9; cyanoacetic acid, 372-09-8; bicyclo[4.3.0]nonene-2-acetonitrile, 41894-91-1; 4-hydrinanylidineacetonitrile, 41894-92-2; bicyclo[4.3.0]nonan-2-one, 5686-83-9; bicyclo[4.4.0]decene-2-acetonitrile, 41894-94-4; 1-decalinylidineacetonitrile, 41894-95-5; 1-decalone, 4832-16-0; bicyclo[3.3.0]-octene-2-acetonitrile, 41894-96-6; 1-octahydropentalenylideneacetonitrile, 41894-97-7; bicyclo[3.3.0]octan-2-one, 28569-63-3; tricyclo[7.2.1.0^{5,12}]dodecan-10-one, 41894-98-8; tricyclo[6.2.1.-0^{4,11}]undecan-3-ol, 41894-99-9; tricyclo[6.2.1.0^{4,11}]undecan-2-ol, 41895-00-5; tricyclo[7.2.1.0^{5,12}]dodecan-10-ol, 41895-01-6.

Thermal Cyclization of Substituted Aryl Propargyl Ethers. The Scope and Regioselectivity of the Reaction in the Synthesis of Substituted 3-Chromenes[1]

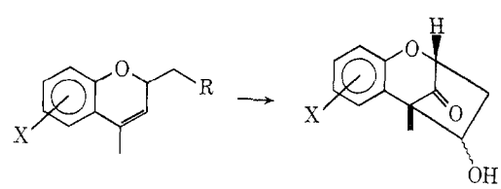
WAYNE K. ANDERSON* AND EDMOND J. LAVOIE

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14214

Received May 16, 1973

The thermal cyclization of substituted aryl propargyl ethers was examined. Simple 3-aryloxypropynes (**12**, **15a–c**) were cyclized to the corresponding chromenes in ~60% yield. The cyclization of **12** was not regiospecific and two isomeric chromenes (**13** and **14**) were obtained. The thermal cyclizations of C-1 and/or C-3 methyl-substituted 3-aryloxypropynes (**16d–g**) have been shown to proceed in a much higher yield than the corresponding unsubstituted compounds. The influence of water, reaction temperature, and solvent on the cyclization was also studied.

During the course of our research directed toward the synthesis of trichothecan mycotoxins and simpler analogs for antitumor evaluation, we required a simple yet flexible method for the synthesis of chromene precursors. Specifically, we required an efficient synthesis of 2,4-disubstituted chromenes (*cf.* eq 1) which



(1)

could incorporate a variety of substituents in the aromatic ring.

A variety of standard methods for the preparation of 3-chromenes have been described in the literature.[2] More recently, new methods have been developed; some of these newer methods include the reaction of vinylphosphonium salts with *o*-hydroxybenzaldehyde,[3] the oxidative cyclization of *o*-allyl phenols,[4] and the partial reduction of a coumarin followed by alkylation and cyclization.[5] None of these methods, however, appear to be broadly applicable and many suffer from the disadvantage of low yields, difficult and/or expensive reagents, and long procedures or difficult work-up.

The thermal cyclization of aryl propargyl ethers has been reported to yield chromenes and related compounds.[6–8] The general utility and scope of a variety of thermal reactions in organic synthesis (*e.g.*, Diels–Alder reaction, Claisen rearrangement, Cope rearrangement, etc.) prompted us to further examine this method for the synthesis of chromenes.

The Claisen rearrangement of propargyl ethers has been reported in both aromatic and nonaromatic systems.[9] Thermal cyclization of aryl propargyl ethers has been used to prepare naphtho[2,1-*b*]- and -[1,2-*b*]-pyrans,[6] pyranoflavones,[7d] pyranocoumarins,[7d,g] pyranoacridones,[7e] chromenes,[7] pyrano[3,2-*d*]pyrimidines,[8a] and furo[3,2-*d*]pyrimidines.[8a]

The mechanism of the thermal cyclization of aryl propargyl ethers has been studied by Zsindely and Schmid.[8b] The proposed mechanism (Scheme I) involves an initial Claisen rearrangement of the aryl propargyl ether **1** to give the allene intermediate **2**. Enolization of **2** followed by a [1,5] sigmatropic hydrogen shift would give **4**, which can undergo an electrocyclic reaction to give 3-chromene (**5**).[8b]

Otter, *et al.*, have proposed a similar mechanism (Scheme II) for the cyclization of uracil propargyl

(1) This research was supported by Grant 1 R01 CA 11880 from the National Cancer Institute, National Institutes of Health.

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