α-Halo Ketones. V.[1] The Synthesis of Some Bicyclic Bridgehead Bromo Ketones[2]

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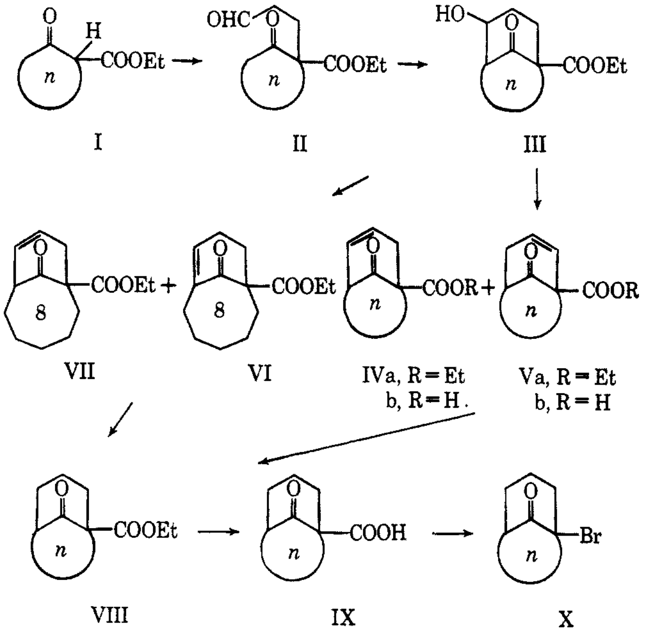
The synthesis of two bicyclic bromo ketones X(7) and X(8) is described and compared with the previously reported synthesis of X(6). Effects of the increasing ring size on the reactions are noted and rationalizations are offered for the differences observed.

For a study of the Favorskii reaction, a series of three bicyclic bridgehead bromo ketones X (n = 6, 7, 8) was needed. The efficient synthesis of the lowest homolog X(6) developed by Cope, Synerholm, and Graham[3,4] was used for the preparation of this compound, and it seemed likely that this same route might serve for the higher homologs X(7) and X(8). However, as the ring size increased, various side reactions were no longer suppressed by the bicyclic structure and difficulties were encountered which required modification of the synthesis. Consequently, the preparation of X(7) and X(8), compared with that of X(6), provides interesting examples of the changing chemical effects of Bredt's rule with increasing ring size.[5]

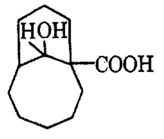
The initial step, a Michael reaction of I(7) and I(8) with acrolein, worked as well as for I(6), but the sulfuric acid catalyzed cyclization of the aldehydes II(7) and II(8) was much less satisfactory than that in the case of II(6). Considerable experimentation was necessary to find conditions that would give 16–23% of cyclization–dehydration product from II(7) compared to 62–69% from II(6). Just as the cyclization–dehydration of II(6) was found to give a mixture of the double-bond isomers IV(6a) and V(6a),[6] so the unsaturated ester produced from II(7) was indicated to be a mixture of IV(7a) and V(7a) by the complex vinyl hydrogen pattern in its nmr spectrum and by the wide melting point range of the acid obtained on saponification. The ultraviolet spectrum of this crystalline acid gave no evidence for any conjugated ketone with a bridgehead double bond.[7] The poor yield of the unsaturated ester was accounted for by several side reaction products of which the major one, 5,6,7,8-tetrahydro-1-naphthoic acid (XI), resulted from a rearrangement first reported by Raphael and co-workers.[9] They found that cyclization of the related compound XVI gave the acid XVIII, presumably *via* XVII. The only difference between the two rearrangements is that no methyl migration is required for aromatization of IV(7a) + V(7a).[10] The sulfuric acid cyclization–dehydration of II(8) gave even



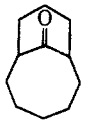
I II III

VII VI IVa, R = Et
b, R = H. Va, R = Et
b, R = H

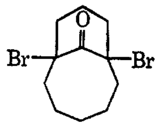
VIII IX X



XII

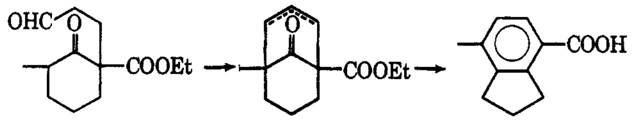


XIII

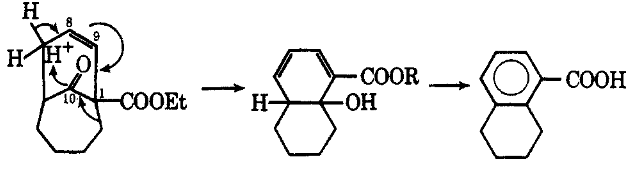


XIV

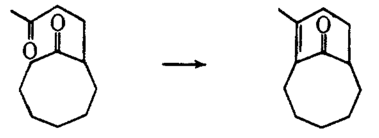
For those formulas with an n inside a ring, ring size is specified by an arabic numeral beside the roman numeral, *e.g.*, I(7).



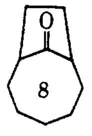
XVI XVII XVIII



(IV7a) XI



XIX XV



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[1] Part IV: E. W. Warnhoff and D. R. Marshall, *J. Org. Chem.*, **32**, 2000 (1967).

[2] Presented in part at the 152nd Meeting of the American Chemical Society, New York, N. Y., Sept 1966.

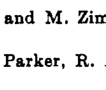
[3] A. C. Cope and M. E. Synerholm, *J. Am. Chem. Soc.*, **72**, 5228 (1950).

[4] A. C. Cope and E. S. Graham, *ibid.*, **73**, 4702 (1951).

[5] In a paper which appeared after the present work on the 7-ring compound was completed (R. D. Sands, *J. Org. Chem.*, **29**, 2488 (1964)), the keto acid IX(7) was prepared by Cope's method as part of a structure proof, but the intermediate compounds were not characterized.

[6] E. W. Colvin and W. Parker, *J. Chem. Soc.*, 5764 (1965).

[7] *Cf.* the case of i[8] which also exhibited no conjugation in its ultraviolet spectrum.



i

[8] V. Prelog, P. Barman, and M. Zimmermann, *Helv. Chim. Acta*, **32**, 1284 (1949).

[9] R. D. H. Murray, W. Parker, R. A. Raphael, and D. B. Jhaveri, *Tetrahedron*, **18**, 55 (1962).

[10] If the rearrangement takes place by the path depicted in IV(7a) → XI, then the increase in this side reaction for IV(7a), relative to that for IV(6a) or XVII, might be rationalized by the closer approach to coplanarity of C-8, C-9, C-1, and C-10 permitted in the transition state for rearrangement of IV(7a), thus allowing greater resonance stabilization of the transition state.

more products from which was isolated a still poorer yield (13%) of unsaturated ester contaminated with aromatic impurities. However, at this ring size a double bond can now be accommodated at the bicyclo[5.3.1] bridgehead without undue strain, as shown by the work of Prelog and co-workers in which XIX was cyclized to XV.[8] Therefore, with II(8) advantage could be taken of a base-catalyzed dehydration of the aldol III(8), whereas with III(6) and III(7) the base-catalyzed elimination of water is doubly forbidden because these smaller bicyclic systems make the ketone α hydrogen much less acidic (decreased resonance stabilization of enolate anion) and a bridgehead double bond very strained.

The aldehyde II(8) was readily cyclized to the aldol III(8) by mild base, but complete dehydration required more vigorous conditions. Treatment of II(8) with N,N-dimethylbenzylamine and oxalic acid at 160–180° for 60 hr gave a 90% yield of almost pure unsaturated ester as a mixture of the α,β-conjugated ketone VI and the β,γ-unsaturated isomer VII. While the double bond can exist at the bridgehead of this ring system, the molecule is somewhat strained since equilibration of the pure crystalline conjugated ketone VI in refluxing triethylamine and acetic acid gave a mixture of VI and VII containing about 10% of the β,γ isomer.[11] Moreover, in the conjugated isomer VI, the double bond and the ketone carbonyl group are not coplanar since the extinction coefficient of pure VI is only 5630 at λ_{max} 240 mμ.

There was a notable difference in the next step of the synthetic sequence, the hydrogenation of the double bond. For the IV(7a) + V(7a) mixture the disubstituted double bonds were reduced in the presence of palladium supported on barium sulfate (ethanol solution, atmospheric pressure) as readily as the IV(6a) + V(6a) mixture. With the trisubstituted conjugated keto ester VI, the same conditions resulted in very slow hydrogen uptake even under 3 atm of pressure. In acetic acid the reduction was faster, but the carbonyl group was partially reduced to yield the hydroxy acid XII on hydrolysis.[12] In ethanol with palladium on a more basic support, barium carbonate, the hydrogenation of VI proceeded at a rate comparable to that for the IV(6a) + V(6a) mixture. Presumably, it was the β,γ-unsaturated isomer VII that was actually being reduced, and the basic barium carbonate accelerated the reduction by catalyzing the VI $\rightleftharpoons$ VII interconversion.

Saponification of VIII(7) and the mixture IV(7a) + V(7a) gave β-keto acids IX(7) and IV(7b) + V(7b) which had no tendency to decarboxylate when heated to their melting points (104 and 109°, respectively).[13] However, the acid IX(8), which can readily support a bridgehead enol, decarboxylated on melting (132°) or during isolation if heated in solution to yield the ketone XIII.[14] Further evidence on the sharp demarcation line between the seven- and eight-membered ring compounds for the applicability of Bredt's rule is provided by the following observations. The keto acid IX(7) did not undergo exchange of the carbonyl α hydrogen on reflux in ethanol-O-d_1 with sodium ethoxide. On the other hand, the ketone XIII was readily converted to the dibromo ketone XIV by bromine in acetic acid on the water bath. Thus, the bicyclo[4.3.1]decan-10-one system (S = 8) is reluctant to accept even the partial bridgehead double-bond character of an enolate anion, whereas the bicyclo[5.3.1]undecan-11-one skeleton (S = 9) allows the establishment of the full bridgehead double bond of an enol. However, it should be noted that the closely related bicyclo[5.2.1]decan-10-one XX (S = 8) does exchange the two bridgehead α-hydrogen atoms when refluxed with sodium deuterioxide in a mixture of methanol-O-d_1 and deuterium oxide.[15] The final step in the synthesis, the Hunsdiecker reaction on the silver salts of the acids IX(7) and IX(8), gave good yields of the crystalline bromo ketones X(7) and X(8) for the proposed study of the Favorskii reaction.[16]

Experimental Section

General.—Melting points were taken on a Reichert microscope hot stage and are corrected. Infrared spectra were recorded on a Beckman IR-5 or IR-5A spectrophotometer. Ultraviolet spectra were taken on a Cary Model 14 spectrophotometer. Nmr spectra were determined with carbon tetrachloride or deuteriochloroform solutions (20–30 mg/0.1 ml) on a Varian A-60 instrument. Camag DF-5 silica gel with calcium sulfate binder was used for tlc analysis. Solutions in organic solvents were dried by washing them with saturated sodium chloride and then allowing them to stand with anhydrous magnesium sulfate. Petroleum ether refers to the fraction boiling at 60–80° unless otherwise specified. Microanalyses were carried out in the laboratories of Dr. A. Bernhardt, Mülheim, Germany.

2-Carbethoxycycloheptanone I(7).—The Claisen condensation procedure and proportions of Ayerst and Schofield[17] were used on 100 g (0.89 mole) of cycloheptanone and 216 g (1.86 moles) of diethyl carbonate except that the sodium hydride was a 48% dispersion in mineral oil and was washed with ether just before use. Saturated sodium chloride solution was used in place of aqueous bicarbonate to wash the ether extract of the product. The crude product was roughly fractionated by distillation at reduced pressure through a 10-cm Claisen head. The β-keto ester fractions were then redistilled through a 1-m Nester and Faust spinning-band column at reduced pressure. There was collected 92.7 g (56%) of pure 2-carbethoxycycloheptanone I(7), bp 111–112° (9 mm), whose infrared and nmr spectra were identical with those of I(7) prepared from the reaction of cyclohexanone and

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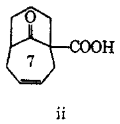
[11] *Cf.* the related 2- and 3-cyclohexenones in which only 1% of the β,γ isomer is present at equilibrium in boiling benzene: N. Heap and G. H. Whitham, *J. Chem. Soc. Sect. B*, 164 (1966).

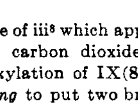
[12] The hydroxy acid XII was not formed by hydride transfer to the keto ester VIII(8) during hydrolysis (*cf.* G. L. Buchanan, A. McKillop, and R. A. Raphael, *J. Chem. Soc.*, 833 (1965)) since pure VIII(8) gave no hydroxy acid on saponification.

[13] However, the IV(7b) + V(7b) acid mixture was decarboxylated by heating in boiling quinoline (see Experimental Section); *cf.* the similar cases of i[7] and ii[5] which exhibited the same behavior.



ii

[14] *Cf.* the related example of iii[8] which apparently did not decarboxylate at mp 175° but did lose carbon dioxide at 245° in quinoline. The difference in ease of decarboxylation of IX(8) and iii reflects the difference between putting one and *trying* to put two bridgehead double bonds in the bicyclo[5.3.1]undecane skeleton. Actually iii may undergo tautomerization to the β,γ-unsaturated isomer before decarboxylation.



iii

[15] C. D. Gutsche and T. D. Smith, *J. Am. Chem. Soc.*, **82**, 4067 (1960).

[16] Although X(8) could have been prepared by monobromination of ketone XIII, the proposed study of the Favorskii reaction required the use of optically active X(8), most easily obtained from the Hunsdiecker reaction on optically active IX(8). Preparation of X(8) by decarboxylation of optically active IX(8) in the presence of bromine might have been complicated by dibromination.

[17] G. G. Ayerst and K. Schofield, *J. Chem. Soc.*, 3445 (1960).

diazoacetic ester.[18] The yield of pure I(7) from that reaction was 79% based on diazoacetic ester or 51% based on the amount of cyclohexanone consumed. The two methods are comparable in yield and convenience.

Michael Reaction Adduct II(7) of 2-Carbethoxycycloheptanone and Acrolein.—A solution of 1.0 g of sodium and 190 mg of hydroquinone in 350 ml of anhydrous ethanol was stirred and cooled to between −60 and −70°. A mixture of 171 g (0.93 mole) of 2-carbethoxycycloheptanone I(7), 60.0 g, (1.18 moles) of freshly distilled acrolein, and 50 mg of hydroquinone was added dropwise to this cold solution during a period of 6 hr. The cooling bath was removed; the reaction mixture was stirred for an additional 30 min and then allowed to stand at room temperature for 3 hr. Glacial acetic acid was added with stirring until the pH was ~7. The bulk of the ethanol was removed on a rotating evaporator at reduced pressure. The viscous residue was dissolved in 500 ml of ether and this solution was washed with water, aqueous sodium bicarbonate, water, and dried. The ether was removed on a rotating evaporator and the residue, to which was added 50 mg of hydroquinone, was distilled through a 10-cm Claisen head at reduced pressure. The crude product distilling below 240° (3.5 mm) amounted to 198 g. Fractional distillation of this material through a 1-m Nester and Faust spinning-band column gave 122 g (55%) of pure Michael reaction adduct II(7): bp 142–145° (1.0 mm); ν^{CCl_4} 2720 (aldehyde CH), 1730, and 1715 cm^{-1} (superimposed aldehyde, ester, and ketone C=O); δ^{CCl_4} 1.25 (3 H, t, J = 7 cps, $CH_3[CH_2O]$), 4.14 (2 H, q, J = 7 cps, $OCH_2[CH_3]$), and 9.64 ppm (1 H, s, CHO).

Anal. Calcd for $C_{13}H_{20}O_4$ (mol wt 240.29): C, 64.97; H, 8.39. Found: C, 64.90; H, 8.33.

Cyclization of Michael Reaction Adduct II(7).—Freshly distilled aldehyde II(7) (25.6 g, 0.107 mole)[19] was added in fine drops during 1 hr to 100 ml of concentrated sulfuric acid maintained at 4–5° and stirred mechanically. The stirring at 4° was continued for 1 hr more and the reaction mixture was then allowed to stand at room temperature for 24 hr. The sulfuric acid solution was allowed to flow through a fine pipet onto 1.5 kg of crushed ice, thus precipitating a brown solid. Extraction with three 400-ml portions of methylene chloride dissolved most of the solid. When these organic solutions were washed with saturated sodium chloride solution, some dark brown material separated and was discarded. Removal of methylene chloride from the dried solution left 19.2 g of dark brown residue which was subjected to a short path distillation at 0.4 mm and an oil-bath temperature of 165–200°. There was collected 5.72 g of a mixture of yellow liquid and white acidic solid. This distillate was dissolved in ether and the solution washed with 5% aqueous sodium carbonate to remove any acid. The ether was removed to leave 4.69 g (19%) of ethyl 10-oxobicyclo[4.3.1]dec-7(and 8)-ene-1-carboxylate IV(7a) + V(7a) as a yellow oil which gave a major spot, R_f 0.56, and a minor contaminant spot ($\lesssim$5%), R_f 0.23, on tlc in petroleum ether–ethyl acetate (1:1). The yield of distilled material from five such reactions varied between 16 and 23%. For analysis, a sample was fractionally distilled through a 20-cm silvered and vacuum-jacketed Nester and Faust spinning-band column and had bp 99–101° (0.15 mm); $\nu_{max}^{CCl_4}$ 3040 (C=CH), 1745 (ester C=O), and 1715 cm^{-1} (ketone C=O); δ^{CCl_4} 1.26 (3 H, t, J = 7 cps, $CH_3[CH_2O]$), 4.15 (2 H, q, J = 7 cps, $OCH_2[CH_3]$), and ~5.17 ppm (2 H, complex pattern, HC=CH).

Anal. Calcd for $C_{13}H_{18}O_3$ (mol wt 222.27): C, 70.24; H, 8.16. Found: C, 69.76; H, 8.22.

Acidification of the sodium carbonate extract yielded 1.03 g (5.5%) of white precipitate. From another reaction 1.97 g (10%) of the white acid was obtained. The two samples were combined and recrystallized from petroleum ether (bp 80–100°) to give 2.54 g of colorless needles of 5,6,7,8-tetrahydro-*1*-naphthoic acid (XI): mp 148–150° (lit.[20] mp 150°); neut equiv 175.8 (calcd value, 176); $\nu_{max}^{CS_2}$ 2500–3500 (broad acid OH), 1692 (aryl acid C=O), and 754 cm^{-1} (three adjacent ArH); δ^{CDCl_3} 1.77 (4 H, bm, CH_2CH_2), 2.65–3.30 (4 H, bm, benzylic CH_2), 7–8 (3 H, m, ArH), and 11.91 ppm (1 H, bs, COOH). The mixture melting point with 5,6,7,8-tetrahydro-*2*-naphthoic acid, mp 153–155°, was depressed to 110–127°. This authentic 5,6,7,8-tetrahydro-2-naphthoic acid was prepared by hypobromite oxidation of 5,6,7,8-tetrahydro-2-acetonaphthone (Eastman). Its infrared spectrum in carbon disulfide differed greatly from that of the 1 acid XI. When the cyclization reaction mixture was extracted with ether instead of methylene chloride and the ether extract washed with sodium bicarbonate solution to remove XI before distillation, the yield of cyclization product IV(7a) + V(7a) was the same.

10-Oxobicyclo[4.3.1]dec-7- (and 8-) ene-1-carboxylic Acid IV(7b) + V(7b).—A mixture of 315 mg (1.42 mmoles) of the unsaturated keto ester and 10 ml of 10% aqueous potassium hydroxide was heated at 85–100° for 10 hr until there was only one phase present. The saponification mixture was washed with ether and acidified with concentrated hydrochloric acid. Extraction of the acidified solution gave, after evaporation of the ether, 260 mg (94%) of an oil which crystallized on standing, mp 90–104°. The product was quantitatively sublimed at 95–100° (0.01 mm) without decarboxylation. Four recrystallizations from chloroform–petroleum ether gave colorless rhombic clusters of IV(7b) + V(7b): mp 105–109°; $\nu_{max}^{CHCl_3}$ 2300–3500 (carboxyl OH) and 1720 cm^{-1} (broad ketone and carboxyl C=O); δ^{CDCl_3} 3.0–3.2 (1 H, bm, ketone α-H), 5.7 (2 H, m, HC=C), 11.91 ppm (1 H, s, COOH). In the ultraviolet region the material had only rising end absorption with ϵ_{210} 400.

Anal. Calcd for $C_{11}H_{14}O_3$ (mol wt, 194.22); C, 68.02; H, 7.26. Found: C, 68.44; H, 7.23.

When 60 mg of the sublimed IV(7b) + V(7b) mixture was refluxed in 1 ml of quinoline for 1 hr, the acid was completely decarboxylated and the product was 36 mg of neutral unsaturated ketone.

Ethyl 10-Oxobicyclo[4.3.1]decane-1-carboxylate VIII(7).—A solution of 17.1 g (0.0771 mole) of the unsaturated keto esters IV(7a) and V(7a) in 150 ml of 95% ethanol was hydrogenated at room temperature and atmospheric pressure over 3.5 g of 5% palladium supported on barium sulfate.[21] After 51 hr hydrogen absorption had ceased with the uptake of 1.94 l. (94%) of gas. Filtration and distillation gave, after a forerun of ethanol, 15.9 g (92%) of colorless liquid VIII(7): bp 105–106° (0.4 mm); $\nu_{max}^{CCl_4}$ 1740 (ester C=O) and 1705 cm^{-1} (ketone C=O); δ^{CCl_4} 1.24 (3 H, t, J = 7 cps, $CH_3[CH_2O]$), 2.5–2.8 (~1 H, bm, ketone α-H), and 4.12 ppm (2 H, q, J = 7 cps, $OCH_2[CH_3]$).

Anal. Calcd for $C_{13}H_{20}O_3$ (mol wt 224.28): C, 69.59; H, 8.99. Found: C, 69.94; H, 9.02.

10-Oxobicyclo[4.3.1]decane-1-carboxylic Acid IX(7).—A mixture of 15.8 g (0.070 mole) of the saturated keto ester VIII(7), 45 ml of 10% aqueous potassium hydroxide solution, and 25 ml of ethanol was heated on the steam bath for 48 hr. The reaction mixture was diluted with 50 ml of water and washed with ether. The aqueous solution was then acidified with concentrated hydrochloric acid and extracted with ether. The dried ether solution was evaporated to leave 11.9 g (86%) of slightly yellow solid, mp 76–106°. Four recrystallizations of a sample from petroleum ether (bp 80–100°) gave colorless prisms of IX(7): mp 102–104° (no decarboxylation) (lit.[5] mp 102–103°); $\nu_{max}^{CHCl_3}$ 2500–3500 (broad acid OH) and 1750–1660 cm^{-1} (broad C=O); δ^{CDCl_3} 2.85 (1 H, bm, ketone α-H) and 11.61 ppm (1 H, s, COOH).

Anal. Calcd for $C_{11}H_{16}O_3$ (mol wt 196.23): C, 67.33; H, 8.22. Found: C, 67.18; H, 8.02.

1-Bromobicyclo[4.3.1]decan-10-one X(7).—A solution of 8.30 g (0.042 mole) of keto acid IX(7) in 25 ml of methanol was titrated to the phenolphthalein end point with a 5% solution of methanolic potassium hydroxide. To this neutral solution was added dropwise with stirring (magnetic bar) a solution of 7.20 g (0.042 mole) of silver nitrate dissolved in a mixture of 8 ml of water and 40 ml of methanol. The precipitate which formed was collected on a filter and dried at 78° (1 mm) for 24 hr to leave 15.2 g of crude silver salt admixed with potassium nitrate. This solid was added slowly with stirring to a solution of 6.78 g (0.042 mole) of bromine (dried by extraction with concentrated sulfuric acid followed by distillation from phosphorus pentoxide) in 35 ml of carbon tetrachloride at such a rate that the evolution of carbon dioxide was not vigorous. When the initial gas evolution was over, the reaction mixture was warmed at 50° for 15 min, filtered to remove salts, and finally concentrated under reduced pressure. An ethereal solution of the residue was washed with aqueous sodium bisulfite, aqueous sodium bicarbonate, and water, and dried. Evaporation of the ether at reduced pressure left 8.33 g (94% with allowance for recovered IX(7)) of clear light brown oil which solidified on chilling, mp ~37°. The crude

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[18] W. T. Tai and E. W. Warnhoff, *Can. J. Chem.*, **42**, 1333 (1964).

[19] In agreement with Cope and Graham,[4] we find that the aldehyde should be used immediately after distillation for the best yield of cyclization product.

[20] J. von Braun, K. Moldaenke, H. Dirlam, and H. Gruber, *Ber.*, **55**, 1700 (1922).

[21] R. Mozingo, *Org. Syn.*, **26**, 77 (1946).

product gave a single spot, R_f 0.59, on tlc in ethyl acetate–petroleum ether (1:1). Several recrystallizations of a portion from petroleum ether (bp 80–100°) gave an analytical sample of X(7): mp 38–40°; $\nu_{\max}^{CCl_4}$ 1725 cm^{-1} (C=O); δ^{CCl_4} 2.75–3.10 ppm (1 H, bm, ketone α-H).

Anal. Calcd for $C_{10}H_{15}OBr$ (mol wt 231.13): C, 51.94; H, 6.54; Br, 34.56. Found: C, 51.84; H, 6.44; Br, 34.43.

The bicarbonate and water washings were acidified with hydrochloric acid and extracted with ether to yield 787 mg (9.5%) of recovered keto acid IX(7), mp 86–100°.

2-Carbethoxycyclooctanone I(8).—A solution of 168 g (1.50 moles) of cycloheptanone (Aldrich) in 210 ml of ether was cooled to −65° by means of a Dry Ice–acetone bath. Freshly distilled boron trifluoride etherate (213 g, 1.50 moles) was added with stirring at −65°. Then a solution of 57 g (0.50 mole) of ethyl diazoacetate in 60 ml of ether was added dropwise over a period of 80 min at −60 to −65°. The nitrogen evolution (12.3 l.) amounted to 96% of theory. After nitrogen evolution had ceased, the reaction mixture was poured into 600 ml of water and the aqueous layer was saturated with sodium chloride. The ether layer was separated and the aqueous layer extracted with five portions of ether. The combined ethereal solutions were washed with aqueous sodium bicarbonate and then with saturated aqueous sodium chloride until the washings were neutral to pH paper. The ether solution was dried over magnesium sulfate, filtered, and distilled. After removal of the ether there was collected 109 g of recovered cycloheptanone, bp 66–72° (8 mm), shown to be pure by infrared and nmr spectra, followed by 50.3 g of 2-carbethoxycyclooctanone I(8) (53% yield based on diazoacetic ester or 48% based on cycloheptanone consumed), bp 102–125° (2.5 mm). There remained 9.7 g of undistilled residue. The infrared and nmr spectra showed the 50.3-g fraction to consist only of the keto and enol forms of the β-keto ester I(8): $\nu_{\max}^{CCl_4}$ 1750 ester (C=O), 1710 (ketone C=O), 1645 (ester C=O of enol), and 1615 cm^{-1} (C=C of enol); δ^{CCl_4} 1.20 (t, *J* = 7 cps) and 1.28 (t, *J* = 7 cps) (3 H total, $CH_3[CH_2O]$, 3.42 (dd, *J* ∼ 6.5, 8 cps, O=CCHC=O), 4.18 (2 H, q, *J* = 7 cps, OCH_2-$[CH_3]$), and 12.08 ppm (s, C=COH).

Anal. Calcd for $C_{11}H_{18}O_3$ (mol wt 198.25): C, 66.63; H, 9.15. Found: C, 66.60; H, 9.07.

Michael Reaction Adduct II(8) of 2-Carbethoxycyclooctanone and Acrolein.—A solution of 0.68 g of sodium and 0.8 g of hydroquinone in 200 ml of absolute ethanol was stirred and cooled to −70° by means of a Dry Ice–acetone bath. A mixture of 91.2 g (0.46 mole) of 2-carbethoxycyclooctanone and 32.3 g (0.57 mole) of redistilled acrolein was added dropwise to the alcoholic base maintained at −70° during a period of 2.3 hr. The cooling bath was removed and the reaction mixture was stirred for 1 hr more. Glacial acetic acid was added dropwise until the reaction mixture had pH ∼7. The bulk of the ethanol was removed on a rotating evaporator at reduced pressure. The viscous residue was dissolved in 300 ml of ether, and the resulting solution was washed with water, aqueous sodium bicarbonate, water, and dried. The ether was removed on the rotating evaporator to leave 112.8 g of crude product which was distilled at reduced pressure. After a forerun of 2.84 g of recovered I(8), the main fraction of 69.6 g (61%), bp 134–149° (0.58 mm), was collected. The infrared and nmr spectra and tlc showed this product to be pure Michael reaction adduct II(8): $\nu_{\max}^{CCl_4}$ 2710 (aldehyde CH), 1730, and 1712 cm^{-1} (superimposed aldehyde, ester, and ketone C=O); δ^{CCl_4} 1.25 (3 H, t, *J* = 7 cps, $CH_3[CH_2O]$), 4.12 (2 H, q, *J* = 7 cps, $OCH_2[CH_3]$), and 9.66 ppm (1 H, t, *J* = 1 cps, CHO).

Anal. Calcd for $C_{14}H_{22}O_4$ (mol wt 254.31): C, 66.13; H, 8.72. Found: C, 66.25; H, 8.68.

Cyclization of Michael Reaction Adduct II(8). A. In Acid.—Since two small-scale sulfuric acid catalyzed cyclizations gave a crude product (exhibiting four tlc spots) of which only about 5% was distillable in the boiling-point range (∼100–120° at 0.1 mm) expected for VI or VII, the following chromatographic procedure was adopted. Freshly prepared II(8) (13.0 g, 0.051 mole) was added dropwise during 1.5 hr with mechanical stirring to 26 ml of concentrated sulfuric acid maintained at 0°. The reaction mixture was allowed to stand for a further 12.5 hr and was then poured onto 600 g of crushed ice. The product was extracted with four 200-ml portions of ether. The combined ethereal extracts were washed with aqueous sodium bicarbonate and dried. Evaporation of the ether at reduced pressure left 8.95 g of viscous reddish orange product which was chromatographed on 80 g of silica gel (BDH). Benzene–petroleum ether mixtures and pure benzene eluted 1.60 g (13%) of impure cyclization product VI + VII which was distilled. The nmr spectrum revealed that one impurity was aromatic. The acid-catalyzed cyclization was not investigated further.

B. In Base.—A solution of 128.3 g (0.50 mole) of the Michael reaction adduct II(8) in 262 ml of N,N-dimethylbenzylamine (Eastman) and 10 ml of glacial acetic acid was heated for 22 hr under nitrogen in an oil bath maintained at a temperature of 170°. The dark brown reaction mixture was dissolved in ether and the N,N-dimethylbenzylamine removed by extraction with eight portions of 5% sulfuric acid. The ether solution was then washed with aqueous sodium bicarbonate and water, and dried. The ether was removed under reduced pressure at the rotating evaporator to leave 117 g (95%) of crude product. Chromatography of aliquots on silicic acid showed it to consist of about equal amounts of ethyl 11-oxobicyclo[5.3.1]undec-7- (and 8-) ene-1-carboxylate VI + VII and ethyl 8-hydroxy-11-oxobicyclo[5.3.1]-undecane-1-carboxylate III(8). For example, chromatography of 10.0 g of the product on 250 g of silica gel (BDH) with development by benzene and benzene–ether mixtures eluted 4.05 g of VI + VII, 1.83 g of about equal amounts of VI and III(8), and 3.30 g of aldol III(8), the composition of fractions being determined by tlc.

The unsaturated ketone VI crystallized on standing. Six recrystallizations from petroleum ether gave colorless crystals: mp 52–54°, $\lambda_{\max}^{EtOH}$ 240 mμ (ϵ 5630); $\nu_{\max}^{CCl_4}$ 1735 (ester C=O) and 1700 cm^{-1} (conjugated ketone C=O); $\delta_{\max}^{CCl_4}$ 1.27 (3 H, t, *J* = 7 cps, $CH_3[CH_2O]$), 4.19 (2 H, q, *J* = 7 cps, $OCH_2[CH_3]$), and 6.22 ppm (1 H, bm, HC=C).

Anal. Calcd for $C_{14}H_{20}O_3$ (mol wt 236.30): C, 71.16; H, 8.53. Found: C, 70.93; H, 8.53.

The hydroxyketo ester III(8) remained a viscous oil after redistillation: $\nu_{\max}^{CCl_4}$ 3610, 3460 (OH), 1735 (ester C=O), and 1705 cm^{-1} (ketone C=O); δ^{CCl_4} 1.26 (3 H, t, *J* = 7 cps, CH_3-$[CH_2O]$), 3.62 (1 H, bs, OH), 4.17 (2 H, q, *J* = 7 cps, OCH_2-$[CH_3]$), and 4.03 ppm (1 H, m, HCO).

Anal. Calcd for $C_{14}H_{22}O_4$ (mol wt 254.14): C, 66.11; H, 8.69. Found: C, 65.61; H, 8.51.

C. Preferred Method in Base.—Freshly prepared Michael reaction adduct II(8) (28.0 g, 0.11 mole) was dissolved in 140 ml of N,N-dimethylbenzylamine (Eastman practical grade) to which 14 g of anhydrous oxalic acid was added. The reaction mixture was heated at 160° for 60 hr, cooled, and diluted with 300 ml of ether. The amine and acid were removed by successive washings with aqueous sulfuric acid, aqueous sodium bicarbonate, and water. The ether was evaporated from the dried organic solutions to leave 23.5 g (90%) of clear brown liquid which from tlc analysis was almost completely VI and VII with only a trace of aldol III(8). The crude product crystallized, and a little remaining liquid was drained off to leave 19.16 g (73%) of yellowish conjugated keto ester VI, mp 38–48°, which gave a single tlc spot and was suitable for hydrogenation to VIII(8).

Dehydration of Aldo III(8).—A solution of 16.4 g (0.064 mole) of the hydroxyketo ester III(8) and 9 g of oxalic acid in 50 ml of N,N-dimethylbenzylamine was refluxed (oil-bath temperature 210°) for 36 hr. The reaction mixture was then dissolved in ether and extracted successively with aqueous sulfuric acid, aqueous sodium bicarbonate, and water. Evaporation of the dried ethereal solution left 11.86 g (78%) of amber liquid which tlc showed to be almost completely dehydrated to a mixture of VI and VII. This product was suitable for hydrogenation to VIII(8).

Equilibration of Unsaturated Keto Esters VI and VII.—Pure α,β-unsaturated keto ester VI (300 mg), mp 52–54°, $\lambda_{\max}$ 240 mμ (ϵ 5630), R_f 0.52, was dissolved in a mixture of 3 ml of glacial acetic acid and 20 ml of triethylamine. The resulting solution was refluxed for 24 hr. The amine and acid were removed by diluting the reaction mixture with ether and extracting successively with 5% aqueous sulfuric acid, 5% aqueous sodium bicarbonate, and finally water. Evaporation of the dried ethereal solution left 283 mg (94% recovery) of isomerized product, $\lambda_{\max}$ 240 mμ (ϵ 5150), which slowly solidified. Tlc analysis in petroleum ether–ethyl acetate (6:1) revealed two spots, R_f 0.52 (VI) and R_f 0.62 (VII). The composition of the mixture calculated from ultraviolet extinction coefficients was 91% VI and 9% VII.

When 267 mg of a mixture of 83% ester VI and 17% ester VII ($\lambda_{\max}^{EtOH}$ 240 mμ, ϵ 4650) was refluxed for 50 hr in a mixture of 10 ml of triethylamine and 1.5 ml of glacial acetic acid, there was recovered 250 mg (94%) of a mixture containing 90% VI and 10% VII ($\lambda_{\max}^{EtOH}$ 240 mμ, ϵ 5050).

Hydrogenation of Unsaturated Keto Ester VI. A. Palladium–Barium Sulfate–95% Ethanol.—A solution of 4.72 g (0.020 mole) of crystalline VI in 50 ml of 95% ethanol was hydrogenated at 3-atm initial pressure and room temperature in a Parr Series 3910 shaker in the presence of 2.5 g of 5% palladium supported on barium sulfate.[21] Hydrogen uptake was slow and finally ceased after 30 hr when the pressure drop was 19 lb (theoretical, 15.9 lb). Filtration and evaporation of solvent left 4.64 g (98%) of colorless ethyl 11-oxobicyclo[5.3.1]undecane-1-carboxylate VIII(8) which solidified on standing, mp 39–43°. The material gave a single spot, R_f 0.59, on a tlc plate on which VI had R_f 0.49 (petroleum ether–ethyl acetate, 6:1). A sample was recrystallized four times from petroleum ether to give colorless prisms: mp 43–45°; $\nu_{\max}^{\mathrm{CCl_4}}$ 1735 (ester C=O) and 1700 cm^{-1} (ketone C=O); $\delta^{\mathrm{CCl_4}}$ 1.26 (3 H, t, J = 7 cps, $CH_3[CH_2O]$), 2.2–2.6 (~1 H, bm, ketone α-H), and 4.12 ppm (2 H, q, J = 7 cps, $OCH_2[CH_3]$).

Anal. Calcd for $C_{14}H_{22}O_3$ (mol wt 238.31): C, 70.56; H, 9.30. Found: C, 70.55; H, 9.05.

B. Palladium–Barium Sulfate–Acetic Acid.—A solution of 2.36 g (0.010 mole) of crystalline VI in 8 ml of glacial acetic acid was hydrogenated at 3-atm initial pressure and room temperature in a Parr Series 1309 shaker in the presence of 1.0 g of 5% palladium supported on barium sulfate. Hydrogen uptake was faster than in (a) and ceased after 12 hr when the pressure drop was 10.2 lb (125% of the theoretical 8 lb). The catalyst was removed by filtration and most of the solvent evaporated. The residue was taken up in ether and washed with sodium hydroxide solution and water. Evaporation of the dried solution left 1.64 g of product in which the ketone carbonyl group was partially reduced: $\nu_{\max}^{\mathrm{CCl_4}}$ 3500 (OH), 1735 (ester C=O), and 1700 cm^{-1} (ketone C=O).

C. Palladium–Barium Carbonate–95% Ethanol.—A solution of 5.0 g (0.0212 mole) of crystalline VI in 20 ml of redistilled 95% ethanol was hydrogenated at 3-atm initial pressure and room temperature on a Parr Series 1309 shaker in the presence of 2.0 g of 5% palladium supported on barium carbonate (Matheson Coleman and Bell). Hydrogen uptake was relatively rapid and ceased within 3 hr (80% of the total amount in 25 min) when the pressure drop was 18 lb (106% of the theoretical 17 lb). Filtration and evaporation of solvent left 4.99 g (99%) of liquid VIII(8) which crystallized on standing. The product gave a single tlc spot and its infrared spectrum was identical with that of the sample prepared in A. Mixtures of VI and VII were also hydrogenated by this procedure to pure VIII(8).

Isolation of 11-Hydroxybicyclo[5.3.1]undecane-1-carboxylic Acid XII.—To the product from hydrogenation B in acetic acid was added enough material from hydrogenation A to give 2.40 g of saturated ester which was dissolved in 15 ml of methanol. After the addition of 8 ml of 10% aqueous potassium hydroxide solution, the reaction mixture was refluxed for 24 hr. The basic solution was diluted with water, washed with ether, and acidified with concentrated hydrochloric acid to pH <2. The acidic solution was extracted with four 50-ml portions of ether. Evaporation of the dried ethereal solution left 1.60 g of yellow mixture of IX(8) and XII, mp 110–120°. Five recrystallizations of a sample from petroleum ether (bp 80–100°) gave colorless needles of XII: mp 115–116°; $\nu_{\max}^{\mathrm{CHCl_3}}$ 3500 (OH), 3500–2300 (carboxyl OH), and 1695 cm^{-1} (carboxyl C=O); $\delta^{\mathrm{CDCl_3}}$ 4.29 (1 H, bd, J ~ 3.5 cps, HCO) and 7.52 ppm (2 H, bs, OH).

Anal. Calcd for $C_{12}H_{20}O_3$ (mol wt 212.28): C, 67.89; H, 9.49. Found: C, 67.90: H, 9.52.

11-Oxobicyclo[5.3.1]undecane-1-carboxylic Acid IX(8).—A solution of 7.32 g (0.0307 mole) of ester VIII(8), prepared by hydrogenation procedure C, in 60 ml of methanol was refluxed with 25 ml of 10% aqueous potassium hydroxide solution for 24 hr. The reaction mixture was diluted with 60 ml of water and extracted with three 50-ml portions of ether. Evaporation of the dried ethereal washes left 0.10 g of neutral material. Acidification of the basic aqueous solution with tartaric acid and extraction with four 60-ml portions of ether yielded, after drying and evaporation, 6.44 g (100%) of crude amber IX(8), mp 109–123°. Six recrystallizations of a sample from ethyl acetate–petroleum ether (bp 80–100°) gave colorless prisms of IX(8): mp 130–132° with decarboxylation; $\nu_{\max}^{\mathrm{CHCl_3}}$ 3500–2600 (carboxyl OH) and 1750–1680 (superimposed carboxyl and ketone C=O).

Anal. Calcd for $C_{12}H_{18}O_3$ (mol wt 210.26): C, 68.54; H, 8.62. Found: C, 68.88; H, 8.96.

1-Bromobicyclo[5.3.1]undecan-11-one X(8).—A solution of 8.40 g (0.040 mole) of pure keto acid IX(8) in 25 ml of methanol was titrated with 5% aqueous potassium hydroxide to the phenolphthalein end point. To this neutral solution of the potassium salt was added dropwise with stirring a solution of 6.80 g (0.040 mole) of silver nitrate dissolved in a mixture of 10 ml of water and 40 ml of methanol. The gray precipitate which formed was collected on a filter, washed with several portions of methanol, and dried at 56° (0.02 mm) for 24 hr to yield 15 g of silver salt containing some potassium nitrate.

The dried silver salt was added in small portions with mechanical stirring to a solution of 6.96 g (0.0435 mole) of bromine (dried by treatment with concentrated sulfuric acid and distillation from phosphorus pentoxide) in 40 ml of reagent grade carbon tetrachloride. After the initial evolution of carbon dioxide, the temperature of the reaction mixture was raised to 50° for 20 min and then briefly to 100° to complete the reaction. The yellow silver bromide was removed by filtration, and the filtrate was concentrated to dryness. The residue was dissolved in 60 ml of ether and the yellow solution was washed successively with sodium bisulfite solution and sodium bicarbonate solution. Acidification of the bicarbonate washings gave 1.206 g of recovered keto acid IX(8). The dried ethereal solution was evaporated to leave 6.96 g (82% taking recovered IX(8) into account) of pale yellow solid bromo ketone X(8) which gave a single tlc spot. One recrystallization from petroleum ether (bp 80–100°) gave almost quantitative recovery of crystalline X(8) mp 59–69°. A sample was recrystallized six times from the same solvent to give colorless prisms: mp 76.5–78.5°; $\nu_{\max}^{\mathrm{CCl_4}}$ 1720 cm^{-1} (ketone C=O); $\delta^{\mathrm{CCl_4}}$ 2.7–2.9 ppm (1 H, bm, ketone α-H).

Anal. Calcd for $C_{11}H_{17}OBr$ (mol wt 245.14): C, 53.89; H, 6.98; Br, 32.59. Found: C, 54.07; H, 7.09; Br, 32.58.

Inadvertent Preparation of Bicyclo[5.3.1]undecan-11-one XIII.—A solution of 10.7 g (0.045 mole) of keto ester VIII(8) in 20 ml of methanol was saponified with 30 ml of 10% aqueous potassium hydroxide as described for the preparation of IX(8), except that the aqueous layer was acidified with hydrochloric acid. When the dried ethereal extract of the acidified solution was evaporated for a prolonged period on the water bath at reduced pressure, the keto acid was partially decarboxylated. The residue (7.2 g) was dissolved in ether and remaining acid removed by extraction with sodium bicarbonate solution. Evaporation of the dried ethereal solution left 2.13 g (29%) of ketone XIII which was distilled at 90–90.5° (1.5 mm): R_f 0.71 (petroleum ether–ethyl acetate, 6:1); $\nu_{\max}^{\mathrm{CCl_4}}$ 1700 cm^{-1} (ketone C=O); $\delta^{\mathrm{CCl_4}}$ ~2.15–2.6 ppm (~2 H, bm, ketone α-H).

Anal. Calcd for $C_{11}H_{18}O$ (mol wt 166.25): C, 79.46; H, 10.91. Found: C, 79.20; H, 10.98.

The **2,4-dinitrophenylhydrazone** was prepared in ethanolic sulfuric acid and was recrystallized from 95% ethanol–ethyl acetate to afford orange prisms, mp 190.5–192°.

Anal. Calcd for $C_{17}H_{22}O_4N_4$ (mol wt 346.36): C, 58.94; H, 6.40. Found: C, 59.03; H, 6.37.

Bromination of Bicyclo[5.3.1]undecan-11-one XIII.—A solution of 366 mg (2.20 mmoles) of ketone XIII in 2 ml of glacial acetic acid was added to a solution of 527 mg (3.3 mmoles) of bromine and two drops of 48% aqueous hydrobromic acid in 1 ml of acetic acid. Since reaction appeared to be negligible at room temperature, the solution was heated on the water bath at ~70° for 6 hr during which time a yellowish precipitate appeared. The cooled reaction mixture was diluted with ether and the resulting solution was washed successively with sodium bisulfite solution and sodium bicarbonate solution. Evaporation of the dried ethereal solution at reduced pressure left 484 mg (90% based on bromine) of long yellowish needles of **1,7-dibromobicyclo[5.3.1]undecan-11-one** XIV which gave a single tlc spot. Five recrystallizations of a sample from petroleum ether gave long colorless blades: mp 183.5–184°; $\nu_{\max}^{\mathrm{CCl_4}}$ 1738 cm^{-1} (ketone C=O).

Anal. Calcd for $C_{11}H_{16}OBr_2$ (mol wt 324.07): C, 40.77; H, 4.97; Br, 48.56. Found: C, 40.45; H, 5.11; Br, 49.00.

Deuterium Exchange Attempts with 10-Oxobicyclo[4.3.1]decane-1-carboxylic Acid IX(7).—In the nmr spectrum of IX(7) the tertiary hydrogen adjacent to the ketone group appears as an almost completely separated lump at 2.85 ppm. There was no detectable change in relative area under this peak after either of the following experiments: (a) acid IX(7) (100 mg, 0.51 mmole) dissolved in 4 ml of deuterium oxide (>99.6% D) containing the sodium deuterioxide from 60 mg (2.6 mg-atoms) of sodium was refluxed for 24 hr and recovered by acidification with deuterium chloride, or (b) acid IX(7) (200 mg, 1.02 mmoles) dissolved in 20 ml of ethanol-O-d_1 (>98% OD) containing the sodium ethoxide from 35 mg (1.5 mg-atoms) of sodium was refluxed for 24 hr and recovered by acidification with deuterium chloride.

Registry No.—I (S = 7), 774-05-0; I (S = 8), 4017-56-5; II (S = 7), 13347-95-0; II (S = 8), 13347-96-1; III (S = 8), 13347-97-2; IVa (S = 7), 13347-98-3; IVb (S = 7), 13347-99-4; Va (S = 7), 13348-00-0; Vb (S = 7), 13348-01-1; VI, 13348-02-2; VIII (S = 7), 13348-03-3; VIII (S = 8), 13348-04-4; IX (S = 7), 13348-05-5; IX (S = 8), 13348-06-6; X (S = 7), 13348-07-7; X (S = 8), 13348-08-8; XI, 4242-18-6; XII, 13348-10-2; XIII, 13348-11-3; XIII (2,4-dinitrophenylhydrazone), 13348-12-4; XIV, 13348-13-5.

Direct Oxidation of Alkenes to Ketones Using Peroxytrifluoroacetic Acid–Boron Fluoride[1,2]

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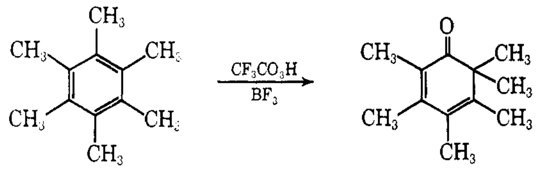
Peroxytrifluoroacetic acid-boron fluoride etherate is shown to be a satisfactory oxidant for effecting a one-step transformation of a number of alkenes to ketones. The products can be explained as the result of attack of positive hydroxyl on the double bond, followed by Wagner-Meerwein rearrangement, to yield the corresponding ketone. The products are shown to be the result of hydrogen, methyl, acyl, chlorine, or bromine migration, as well as of ring contraction.

Previous reports[1] from this laboratory have described the use of peroxytrifluoroacetic acid–boron fluoride as an electrophilic oxidant of substituted aromatic compounds. With hexaalkylbenzenes, hexaalkylcyclohexadienones were obtained in good yields by electrophilic attack of the oxidant, followed by a Wagner–Meerwein rearrangement and proton loss. For example, hexamethylbenzene (**1**) was converted into hexamethyl-2,4-cyclohexadienone (**2**)[3] in 88% yield.



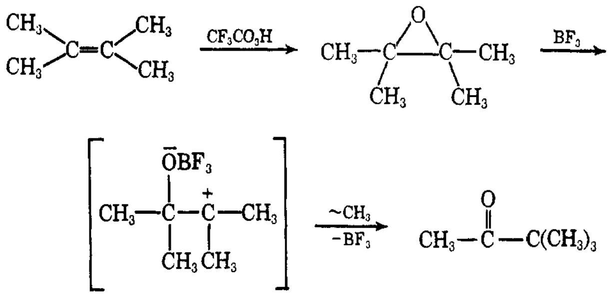
1 **2**

Since epoxidation of olefins by organic per acids is also believed to proceed by attack of "positive hydroxyl," [4] and since boron fluoride catalyzes epoxide ring opening to carbonyl compounds *via* Wagner–Meerwein rearrangements,[5] we believed that the oxidation of alkenes with peroxytrifluoroacetic acid–boron fluoride might combine both reactions in sequence and lead to a one-step synthesis of ketones. This paper reports the results of a number of such oxidations.

Results and Discussion

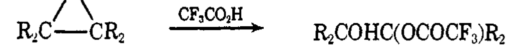
The alkenes investigated were either oxidized at 0–8° or allowed to warm to reflux[6] with peroxytrifluoroacetic acid in methylene chloride. Boron fluoride was most conveniently added in the form of its etherate, concurrent with the addition of the peracid dissolved in methylene chloride. The reactions were complete within 15 min after mixing the reagents. Table I summarizes the results.

Oxidation of 2,3-dimethyl-2-butene was expected to give pinacolone, assuming the oxidation and rearrangement occurs as in eq 1. The major product was



(1)

formed, as predicted, in 75% yield. An intermediate other than the epoxide could be involved since it has been shown by Emmons[7] that the initially formed epoxide, from the oxidation of olefins with peroxytrifluoroacetic acid, further reacts with the trifluoroacetic acid present to give hydroxytrifluoroacetates. To test



whether such a trifluoroacetate might be the precursor of pinacolone, the oxidation was run without boron fluoride. The yield of pinacolone was reduced to 16%, and the major product was the hydroxytrifluoroacetate **3**, which on treatment with boron fluoride gave pinacolone quantitatively, possibly as envisioned in eq 2.

Since even without boron fluoride a 16% yield of pinacolone was found, direct attack of positive hydroxyl on the olefin is a third possibility, where boron fluoride enhances the heterolytic cleavage of peroxytrifluoroacetic acid as in eq 3. Equation 3 is similar

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[1] Paper IX in a series on Oxidations with Peroxytrifluoroacetic Acid-Boron Fluoride; for paper VIII, see H. Hart and R. K. Murray, Jr., *J. Org. Chem.*, in press.

[2] We are grateful to the National Science Foundation and the Army Research Office (Durham) (DA-31-124-ARO-D-157) for financial support of this research.

[3] H. Hart, P. M. Collins, and A. J. Waring, *J. Am. Chem. Soc.*, **88**, 1005 (1966).

[4] For a review, see D. Swern, *Org. Reactions*, **7**, 378 (1953).

[5] For a review, see R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

[6] The yields for oxidations run at reflux were as good as or better than those run at 0–8° for the olefins studied at both temperature ranges. The latter temperature range has been generally used for the oxidation of aromatic compounds (see ref 1).

[7] W. D. Emmons, A. S. Pagano, and J. P. Freeman, *J. Am. Chem. Soc.*, **76**, 3472 (1954); W. D. Emmons and A. S. Pagano, *ibid.*, **77**, 89 (1955).