Allylic Oxidation of Olefins with Chromium Trioxide–Pyridine Complex[1]

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Received March 13, 1969

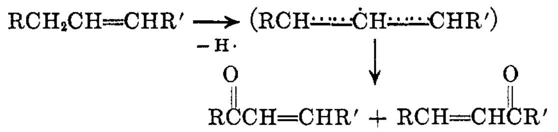
The allylic oxidation of 16 substituted cyclohexenes and steroids with the isolated dry CrO_3–(pyridine)$_2$ complex in methylene chloride at room temperature has been studied. The yield of enones varied from 48 to 95% (based on recovered starting material). The following generalizations were formulated: (1) allylic methyl groups are not readily oxidized; (2) if more than one allylic methylene group is present in a conformationally flexible molecule, enones resulting from attack at both positions are formed; if the molecule is conformationally rigid, like a steroid, a selectivity is found; (3) attack at an allylic methine position yields the isomeric enone where possible; similar rearrangements occur with a methylene system possessing steric hindrance. The advantages and limitations of this oxidation procedure are mentioned and the course of the oxidation is discussed on a mechanistic basis.

The oxidation of an olefin to an α,β-unsaturated ketone has been utilized in the synthesis and in the transformation of natural products. In most cases, chromium(VI) has been the oxidant and varying results have been obtained depending upon the specific chromium(VI) reagent used and the conditions employed.[2–8] The conditions used most often have been chromium(VI) in acetic acid but in recent years *t*-butyl chromate[3–5] has been employed with varying degrees of success. With the latter reagent, the reaction is usually run at an elevated temperature (60–80°) for an extended period of time (10–70 hr), the yields vary greatly, and unreacted starting material can be recovered in small yield. More recently, chromium trioxide in pyridine[7] was employed in one case and the reaction was allowed to proceed for 30 days at room temperature.

It has now been found that many of the difficulties encountered can be overcome by utilization of the isolated dry CrO_3–(pyridine)$_2$ complex in dichloromethane.[9,10] The allylic methylene groups can be oxidized to ketones at room temperature (24 hr) in yields of 48–95% (based upon recovered starting material). In those cases where the yields are low, starting olefins can usually be recovered. In Table I, the results obtained from the oxidation of 17 compounds are reported and where possible compared with the results from other reagents.

Examination of the results permits certain generalizations. Allylic methyl groups are not readily oxidized (see compounds **7, 9, 11, 14, 21, 38**). If more than one allylic methylene group is present in a conformationally flexible molecule, enones resulting from attack at both positions are found (see compounds **11, 14, 24, 31, 38**); if the molecule is conformationally rigid, a selectivity is observed (see compounds **1, 3, 5, 7**). Attack at an allylic methine position yields the isomeric unsaturated ketone when possible (see compound **17**); similar rearrangements occur with a methylene system possessing steric hindrance (see compounds **24, 28, 31**).

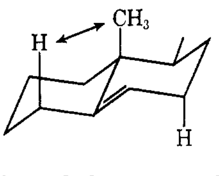
The various selectivities outlined above can best be understood by consideration of the mechanism of allylic oxidation of olefins by chromium(VI). It has been proposed[8,11] that a hydrogen atom (or hydride ion) is first abstracted from an allylic carbon to yield an allylic radical (or carbonium ion). The resulting species then is oxidized at either terminal end of the allylic radical (or ion) to yield an α,β-unsaturated ketone. The



$$RCH_2CH{=}CHR' \xrightarrow[-H\cdot]{} (RCH\cdots\dot{C}H\cdots CHR') \;\downarrow\; R\overset{O}{\overset{\|}{C}}CH{=}CHR' + RCH{=}CH\overset{O}{\overset{\|}{C}}R'$$

products and the ratio of products can reflect a combination of several factors. The steric accessibility of the allylic hydrogens to be abstracted, the relative energies of possible allylic intermediates, and the steric and the electronic control of the oxygen transfer step at competing sites must all be considered. These features can be evaluated by consideration of the following examples.

In 5-cholestene (**5**), there are two conformationally inflexible sites of allylic hydrogens (C-4 and C-7). It is to be expected that axial hydrogens will be preferentially abstracted to equatorial hydrogens because of the more favorable stereoelectronic situation with the developing p-orbital and the π system.[12] In this steroid case, the axial hydrogen on C-4 lies above the plane of the steroid molecule and the approach of the chromium species would be hindered by the angular methyl group at C-10. The axial hydrogen at C-7 being below the plane of the molecule is free from such steric interferences and the reaction proceeds at this position to yield 5-cholesten-7-one (**6**). Similar results are obtained in all related rigid systems; *i.e.*, oxidation occurs in the ring holding the double bond.



Oxidation of 3-methyl-1-cyclohexene (**17**) yields 3-methyl-2-cyclohexen-1-one (**15**) and 4-methyl-2-cy-

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[1] This work was supported, in part, by Grant No. CY-04284, National Cancer Institute, U. S. Public Health Service.

[2] H. E. Stavly and G. N. Bollenback, *J. Amer. Chem. Soc.*, **65**, 1285 (1942).

[3] W. Marshall, R. E. Ray, I. Laos, and B. Riegel, *ibid.*, **79**, 6308 (1957).

[4] R. V. Oppenauer and H. Oberrauch, *Anales Asoc. Quim. Arg.*, **37**, 246 (1949).

[5] K. Heusler and A.Wettstein, *Helv. Chim. Acta*, **35**, 284 (1962).

[6] W. G. Dauben and A. C. Ashcraft, *J. Amer. Chem. Soc.*, **85**, 3673 (1963).

[7] I. Yosioka and T. Kimara, *Chem. Pharm. Bull.* (Tokyo), **13**, 1430 (1965).

[8] For general review, see K. B. Wiberg, "Oxidation in Organic Chemistry," Academic Press Inc., New York, N. Y., 1965, pp 105–109.

[9] H. H. Sisler and C. E. Accountius, *J. Amer. Chem. Soc.*, **70**, 3827 (1948).

[10] This reagent has been reported to be excellent for the oxidation of alcohols, see J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

[11] K. B. Wiberg and S. D. Nielson, *J. Org. Chem.*, **29**, 3353 (1964).

[12] E. J. Corey and R. H. Sneen, *J. Amer. Chem. Soc.*, **78**, 6269 (1956); A. B. Turner and H. L. Ringold, *J. Chem. Soc.*, 1720 (1967).

TABLE I

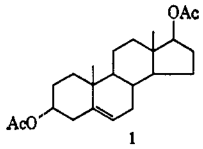
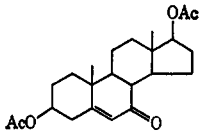
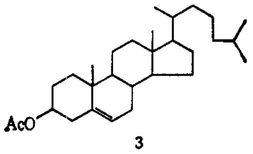
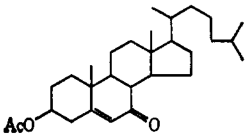
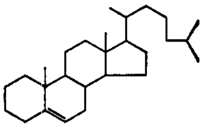
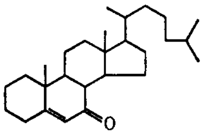
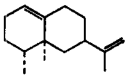
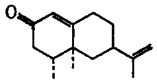
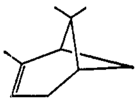
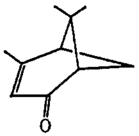
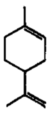
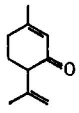
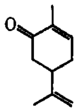
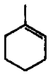
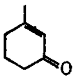
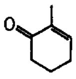
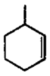
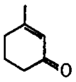
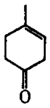
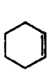
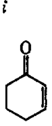
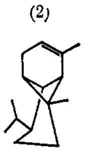
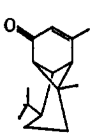
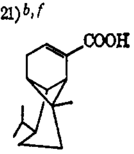
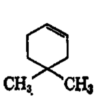
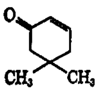
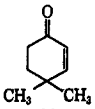
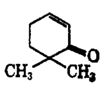
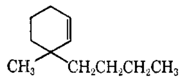
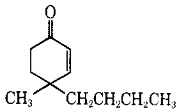
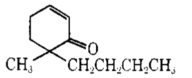
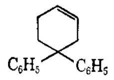
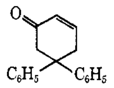
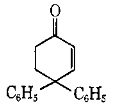
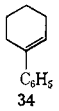
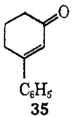
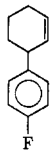
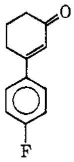
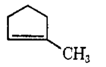
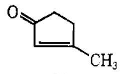
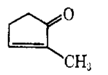
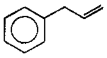
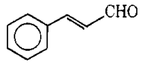
Starting material (% starting material recovered)	Products (yield, %)	—Other allylic oxidations— Reagent	Yield, %
 **1** (0)	 **2** (76)^{a,b}	t-Butylchromate	62^{c}
 **3** (0)	 **4** (74)^{a,b}	t-Butylchromate	60^{d}
 **5** (0)	 **6** (52)^{a,b}	t-Butylchromate	41^{e}
 **7** (15)	 **8** (95)^{a,f}	t-Butylchromate	67^{g} (crude)
 **9** (19)	 **10** (48)^{a,f}	t-Butylchromate	38^{h}
 **11** (16)	 **12** (31)^{f,i}  **13** (36)^{f,i}	t-Butylchromate	12 (13)^{j} 13 (21)^{j}
 **14** (4)	 **15** (60)^{f,i}  **16** (15)^{f,i}	CrO$_3$, HOAc	15 (20)^{k} 16 (2)^{k}
 **17** (14)	 **15** (68)^{f,i}  **18** (10)^{f,i}		
 **19** (2)	 **20** (21)^{b,f}	CrO$_3$, HOAc	20 (37)^{k} adipic acid (25)^{k}
 **21** (3)	 **22** (65)^{a,f}  **23** (2)^{a,f}		
 **24** (12)	 **25** (20)^{f,i}  **26** (50)^{f,i}  **27** (7)^{f,i}		

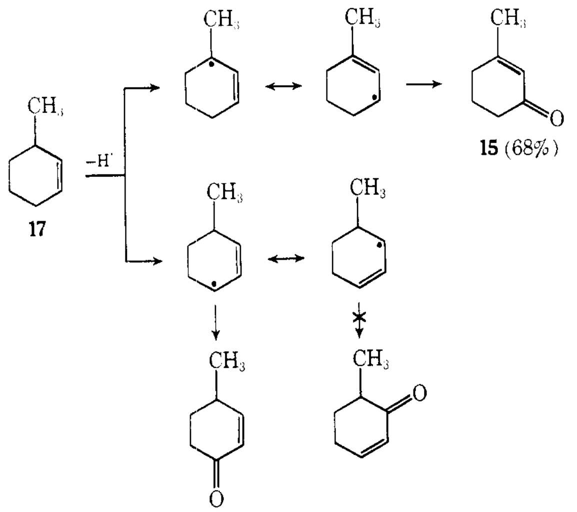
TABLE I (*Continued*)

Starting material (% starting material recovered)	Products (yield, %)	Other allylic oxidations Reagent	Yield, %
 **28** (4)	 **29** (74)^{f,i}  **30** (6)^{f,i}		
 **31** (55)	 **32** (13)^{a,f}  **33** (67)^{a,f}		
 **34** (32)	 **35** (71)^{a,f}	*t*-Butylchromate	22^{l}
 **36** (39)	 **37** (84)^{a,f}		
 **38** (0)	 **39** (41)^{f,i}  **40** (13)^{f,i}		
 **41** (36)	 **42** (63)^{f,i}		

[a] Isolated. [b] Complex added in two portions. [c] CIBA Ltd., Swiss Patent 295,994 (April 1, 1954); *Chem. Abstr.*, **50**, P6518*d* (1956). [d] K. Bloch, *Helv. Chim. Acta*, **36**, 1611 (1953). [e] W. G. Dauben and K. Takemura, *J. Amer. Chem. Soc.*, **75**, 6302 (1953). [f] Complex added all at once. [g] G. L. K. Hunter and W. B. Brogden, Jr., *J. Food Sci.*, **30**, 876 (1965). [h] G. Du Pont, R. Dulov, and O. Murdov, *Bull. Soc. Chim. Fr.*, 433 (1952). [i] Vpc analysis. [j] K. Fujita, *Nippon Kagaku Zasshi*, **81** 1676 (1960); **78**, 1112 (1957). [k] F. C. Whitmore and G. W. Piedlow, *J. Amer. Chem. Soc.*, **63**, 758 (1941). [l] D. Ginsburg and R. Pappo, *J. Chem. Soc.*, 517 (1951).

clohexen-1-one (**18**) in a ratio of 7:1 (Scheme I). It was established that there was no isomerization of **17** into the isomeric **14** prior to the oxidation. Therefore, **15** results from the preference for abstraction of the tertiary allylic hydrogen. This preference stems more from the energy of the intermediate radical (or ionic) species than from the relative C–H bond strengths since nonresonance stabilized allylic tertiary hydrogens on bridgehead positions are not preferentially attacked (see compounds **9** and **21**). Furthermore, it should be noted that a methine hydrogen which is allylic to a side chain double bond is *not* attacked in preference to a methylene group allylic to a double bond contained in the same ring (see compounds **7** and **11**).

SCHEME I



17

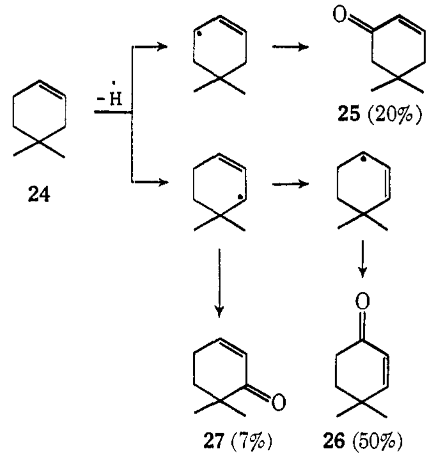
15 (68%)

18 (10%)

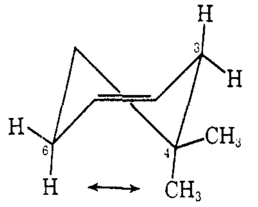
Oxidation of 4,4-dimethyl-1-cyclohexene (**24**) gives 5,5-dimethyl-2-cyclohexen-1-one (**25**), 4,4-dimethyl-2-cyclohexen-1-one (**26**), and 6,6-dimethyl-2-cyclohexen-1-one (**27**) in a ratio of 3:7:1 (Scheme II). The major product **26** arises by hydrogen abstraction at C-3 followed by oxidation at the other lesser hindered end (C-1) of the delocalized intermediate to yield **26**. Evidently oxygen transfer to C-3 is much less facile owing to the steric hindrance afforded by the *gem*-dimethyl group at C-4. The total yield of products arising from hydrogen abstraction at C-3 was 57%.

The singular product **25** which can arise by hydrogen abstraction at C-6 was obtained in 20% yield. Therefore, hydrogen abstraction at C-3 is favored over abstraction at C-6 by a ratio of 3:1. This preference factor can be readily explained by the 1,3-diaxial interaction of an axial hydrogen at C-6 and an axial methyl

Scheme II



group at C-4. No such steric factor hinders abstraction of the axial hydrogen at C-3.



These steric factors affecting the oxidation of the resonance hybrid intermediate are clearly accentuated in 3-methyl-3-n-butylcyclohexene (**28**). The preference for oxidation at the lesser hindered C-1 to C-3 rose to 13:1 compared with 7:1 in the dimethyl series. Consideration of the foregoing mechanistic and steric aspects of the allylic oxidation reaction permits prediction of the major oxidation product.

The use of CrO_3-(pyridine)$_2$ complex in methylene chloride offers two distinct advantages over other reagents used for allylic oxidation. In all cases where comparison could be made, the yields were higher and the amount of over oxidation was less. The reaction conditions are mild and the work-up of the reaction mixture is easy. The greatest synthetic utilization for allylic oxidation is with compounds which possess only one allylic methylene group, such as α-pinene (**9**) and copaene (**21**) and with rigid compounds which have one of their two axial hydrogen atoms sterically blocked, such as Δ^5 steroids (**1**, **3**, **5**) and valencene (**7**).

Optimum conditions were not evaluated for each compound but only with **1** and **17**. From this study best yields of product with minimum recovery of starting material were obtained by stirring the olefin at room temperature for 24 hr with a 15:1 molar ratio of complex to substrate. The large molar excess of complex required, *i.e.*, 15:1 compared with 3-6:1 with other reagents,[2,3] was not unexpected since it has been reported that reduced chromium by-products react with the complex.[10]

A few compounds have been found which are not attacked by the complex under the above conditions. For example, methylenecyclohexanes, 6-methoxytetralin, and thujopsene are found to be attacked slowly and, though reaction occurred at the boiling point of the solvent, the process offers no advantages. The reasons for this unreactivity are not apparent at this time. As with cyclohexene, the CrO_3-(pyridine)$_2$ complex appears to offer little advantage with a simple, unsubstituted cycloalkene such as 1,5-cyclooctadiene.

Experimental Section

Unless specified, all vpc analyses of C-5-C-8 enones were done on a 10 ft × 0.125 in. column of 10% SE-30 on Chromosorb W at 100° and of C-9-C-15 enones on a 10 ft × 0.125 in. column of XF-1150 column on Chromosorb G at 150°. In all analyses either measured samples of starting olefin or enone were used as quantitative standards. Preparative vpc isolations were done on a 5 ft × 0.25 in. column of SF-30. All column chromatographies were done on Woelm neutral alumina (activity III) unless otherwise specified.

Except where noted, the starting materials and products were obtained from Eastman Chemical or Aldrich Co. The starting materials **3**, **9**, **11**, **14**, **17**, **19**, **24**, **34**, **38**, and **41** were obtained from commercial sources and used directly. Authentic samples of products **8**, **10**, **13**, **15**, **16**, **18**, **20**, **22**, **23**, **25**, **26**, **27**, **33**, **39**, **40**, and **42** were used for identification by comparison of vpc retention times, and spectral data. When authentic samples were not available or when a product was a new compound, the data used for its identification are given in the Experimental Section.

Preparation of CrO_3-(Pyridine)$_2$ Complex.[9]—The complex was formed in a 3-l. three-necked flask which was cooled in an acetone-ice bath and equipped with a sealed mechanical stirrer. Through one neck of the flask was added 946 ml of dry reagent pyridine. A drying tube containing indicating Drierite was inserted in this neck. To the cold (−15 to −18°), rapidly stirred pyridine[13] was added 90 g (0.9 mol) of CrO_3 (dried over P_2O_5 under reduced pressure for 12 hr) over a period of 5 min, through a glassine paper cone inserted in the dry neck of the flask. The glassine paper cone was frequently replaced with a new cone. With these precautions fires were avoided. It must be emphasized that *pyridine should never be added to CrO_3* or else the pyridine will ignite. After addition of the CrO_3, the neck was stoppered. Stirring was continued for 6 hr, during which time no further ice was added to the bath. In the course of the stirring the initially formed, bright yellow, viscous mixture turned into a bright red, crystalline slurry in pyridine.

The complex was rapidly suction filtered on a sintered-glass funnel and then washed immediately with 300 ml of dry reagent petroleum ether. The wet complex was immediately placed in a desiccator over P_2O_5 and stored under vacuum of 15-30 mm. The entire filtration, washing, and placing under vacuum was performed in less than 3 min to minimize hydration of the complex. The dry complex weighed 180 g (80%).

When stored under 15-30-mm pressure over P_2O_5, the complex was still active after 10 days. The dry complex did not cause any fires. However, the usual precautions for avoiding the inhalation of pyridine must be taken.

The red anhydrous complex was found to be extremely hydroscopic, and the use of the complex was done very rapidly in order to minimize exposure to moisture. Furthermore, the yellow hydrated complex was relatively insoluble in methylene chloride and therefore assumed to be less effective in the oxidation procedure.

5-Androsten-7-one-3β,17β-diol Diacetate (**2**).—In 300 ml of methylene chloride at room temperature and under a nitrogen atmosphere 5.5 g (0.015 mol) of 5-androstene-3β,17β-diol diacetate (**1**)[14] was dissolved. To the mechanically stirred[15] solution was added 35 g (0.135 mol) of CrO_3-(pyridine)$_2$ complex as a slurry in 75 ml of methylene chloride.[16] The mixture immedi-

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(13) Violent flash fires which immediately extinguished themselves were found to occur during addition of CrO_3 to the cold pyridine if stirring was inefficient. Therefore, if the reaction mixture became too viscous for good stirring, addition of CrO_3 was terminated. The activity of CrO_3-(pyridine)$_2$ obtained by addition of less than 90 g of CrO_3 to 946 ml of pyridine was equal to the activity of the CrO_3-(pyridine)$_2$ obtained when a full 90 g of CrO_3 was added.

(14) L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, **18**, 1264 (1935).

(15) Because of the tarry precipitate formed in the reaction, magnetic stir bars could not be used for agitation.

(16) A slurry or a solution of the complex in methylene chloride is deep red in color. A yellow color indicates that the complex has hydrated. A mixture which rapidly turns brown-black to black indicates that the methylene chloride contains oxidizable impurities.

ately began turning brown and depositing a tarry precipitate on the sides and bottom of the flask. (It was necessary to have the stirrer paddles near the surface of the solution to avoid clogging the paddles with the precipitate.) After 17 hr of stirring at room temperature, an additional 11.0 g (0.042 mol) of CrO_3–(pyridine)$_2$ complex was added to the reaction mixture. Seven hours later, the reaction mixture was poured from the flask. The precipitate remaining in the flask was rinsed with three 100-ml portions of ether. The washings and an additional 400 ml of ether were added to the methylene chloride solution. (No improvement in yield was found when the tarry precipitate was dissolved in saturated $NaHCO_3$ and then extracted with ether.) The resulting solution was washed six times with 50 ml of saturated $NaHCO_3$. The washings were extracted once with 100 ml of ether, and the ether extract added to the original ether solution. This solution was washed three times with 50 ml of 5% HCl, once with 5% $NaHCO_3$, and once with saturated salt and then dried over $MgSO_4$. The solvents were rotary evaporated to give 5.8 g of a yellow solid. Crystallization from methanol gave 4.7 g (82%) of 5-androsten-7-one-3β,17β-diol diacetate (**2**): mp 214–218°; λ_{max}^{EtOH} 236 mμ (ε 12,600). Recrystallization of the product from hexane yielded 4.37 g (76%) of needles: mp 218–221°; λ_{max}^{EtOH} 236 mμ (ε 13,350)[lit.[5,17] mp 224–226°; λ_{max}^{EtOH} 236 mμ (ε 13,800)]. Thin layer analysis of the recrystallized product showed the presence of a trace of starting material. Longer oxidation periods did not eliminate this contaminant.

5-Cholesten-7-one-3β-ol Acetate (**4**).—A solution of 5.0 g (0.012 mol) of cholesteryl acetate (**3**) in 300 ml of methylene chloride was oxidized, as described above using 30- and 20-g portions of CrO_3–(pyridine)$_2$ complex (0.194 mol, total). The reaction mixture was processed in the usual manner and the yellow residue was first crystallized from methanol and then from hexane: yield 3.75 g (74%); mp 161–163°; λ_{max}^{EtOH} 236 mμ (ε 12,400) [lit.[18] mp 157–159°; λ_{max}^{EtOH} 237 mμ (ε 12,400)]. Thin layer analysis showed the presence of a trace of starting material.

To test the stability of the product to the oxidation conditions, 2.0 g of **4** was stirred for 24 hr with 20 g of complex in 100 ml of methylene chloride and 1.70 g was recovered. About 100 mg of acidic material was obtained.

5-Cholesten-7-one (**6**).—A solution of 1.0 g (0.003 mol) of 5-cholestene (**5**)[19] in 200 ml of methylene chloride was treated in the usual manner with 10-g and 5-g portions of CrO_3–(pyridine)$_2$ complex (0.058 mol, total) to give 915 mg of a crude product which was recrystallized from methanol, yield 510 mg (50%), mp 131–132° (lit.[20] mp 130.0–130.5°). Thin layer analysis of the mother liquor revealed at least three more polar substances.

Nootkatone (**8**).—To a solution of 2.0 g (0.01 mol) of valencene (**7**, 85% purity)[21] in 300 ml of methylene chloride at room temperature was added, in one portion, a slurry of 39 g (0.15 mol) of CrO_3–(pyridine)$_2$ complex in 75 ml of methylene chloride. After stirring for 25 hr and work-up, there was obtained 2.0 g of a yellow oil with a strong grapefruit odor. Chromatography on silica gel (10% H_2O) gave 1.6 g of nootkatone[22] (90% pure by vpc analysis) and 300 mg of valencene. The yield of **8**, allowing for the 15% impurity in valencene, was 81%, or 95% allowing for recovered valencene.

Verbenone (**10**).—A slurry of 35 g (0.135 mol) of CrO_3–(pyridine)$_2$ complex in 400 ml of methylene chloride was stirred for 5 min, a solution of 2.7 g (0.02 mol) of α-pinene (**9**) added, and the mixture stirred 24 hr. The usual work-up gave 2.4 g of a dark brown liquid. A vpc analysis showed the material was 64% verbenone,[23] 25% starting material **9**, and 11% other products. Column chromatography gave 0.5 g of starting material and 1.19 g of verbenone (90% pure by vpc analysis), yield 48%.

Oxidation of Limonene (**11**).—Following the procedure used for **7**, 3.0 g (0.02 mol) of limonene (**11**, 99% pure by vpc) and 85 g (0.33 mol) of CrO_3–(pyridine)$_2$ complex yielded 2.6 g of a yellow oil. Analysis by vpc showed the oil to contain 18% limonene, 39% carvone (**13**), and 33% isopiperitenone[24] (**12**). This corresponds to yields of 36% carvone and 31% isopiperitenone.

The spectra properties of isopiperitenone were as follows: mass spectrum, parent peak 150; $\nu_{max}^{CCl_4}$ 1585, 1640, 895 cm^{-1}; nmr (δ, ppm), 6.6 (1 H, multiplet), 4.75 (2 H, multiplet), 2.4 (4 H, multiplet), 2.2 (1 H, multiplet), 1.77 (6 H, multiplet).

Oxidation of 1-Methyl-1-cyclohexene (**14**).—Following the procedure used for **9**, 2.0 g (0.02 mol) of 1-methyl-1-cyclohexene (**14**) and 55 g (0.21 mol) of CrO_3–(pyridine)$_2$ gave 1.81 g of a dark oil. Analysis by vpc showed the presence of 4% starting material, 76% 3-methyl-2-cyclohexen-1-one (**15**, yield 60%), and 19% 2-methyl-2-cyclohexen-1-one[25] (**16**, yield 15%).

Oxidation of 3-Methyl-1-cyclohexene (**17**).—Following the procedure used for **7**, 2.0 (0.02 mol) of 3-methyl-1-cyclohexene (**17**) and 77 g (0.30 mol) of CrO_3–(pyridine)$_2$ complex yielded 1.8 g of a yellow oil. Analysis by vpc showed the presence of 15% starting olefin, 74% 3-methyl-2-cyclohexen-1-one (**15**, yield 68%) and 11% 4-methyl-2-cyclohexen-1-one[26] (**18**, yield 10%). The use of less oxidant led to poorer yields.

Stopping the reaction at 2 min, 17 min, 1 hr, and 2 hr did not reveal any **14** on careful vpc analysis. If **14** was formed and immediately oxidized, **16** would be formed along with **15**. However, **16** was not found in these studies.

Oxidation of Cyclohexene (**19**).—Following the procedure used for **7**, 5.0 g (0.06 mol) of cyclohexene (**19**) and 120 g (0.47 mol) of CrO_3–(pyridine)$_2$ complex gave 2.0 g of a yellow oil. Analysis by vpc showed the presence of less than 5% starting material, 60% 2-cyclohexene-1-one (**20**, yield 21%), and 35% more polar material.

To determine the stability of the product, 2.0 g of 2-cyclohexene-1-one and 52 g of CrO_3–(pyridine)$_2$ complex in 450 ml of methylene chloride were allowed to react for 24 hr. There was obtained 1.0 g of neutral material (80% cyclohexenone, 40% recovery).

Oxidation of Copaene (**21**).[27]—Following the procedure used for **9**, 2.0 g (0.0098 mol) of copaene (**21**) and 30 g (0.115 mol) of CrO_3–(pyridine)$_2$ complex yielded 1.41 g of yellow oil. Chromatography over Silicar yielded 172 mg of a mixture of four compounds (30% unreacted **21**) in the *n*-pentane fraction and 1.33 g (65%) of mustakone (**22**), of 90% purity in 50:50 pentane–chloroform fraction. In addition, 24 mg (2%) of copaenic acid (**23**) was obtained.

Oxidation of 4,4-Dimethyl-1-cyclohexene (**24**).—Following the procedure used for **9**, 1.1 g (0.01 mol) of 4,4-dimethyl-1-cyclohexene (**24**)[28] and 35 g (0.135 mol) of CrO_3–(pyridine)$_2$ complex afforded 0.98 g of a yellow liquid. Column chromatography gave 0.13 g of starting olefin and 0.82 g of a mixture of unsaturated ketones. Analysis by vpc on a 500 ft × 0.03 in. stainless steel open tubular column coated with OV-101 and run at 70° showed three ketones in a ratio of 3:7:1; the compounds were shown to be 5,5-dimethyl-2-cyclohexen-1-one[29] (**25**, yield 20%), 4,4-dimethyl-2-cyclohexen-1-one[30] (**26**, yield 50%), and 6,6-dimethyl-2-cyclohexen-1-one[31] (**27**, yield 7%).

Oxidation of 3-Methyl-3-*n*-butyl-1-cyclohexene (**28**).—Following the procedure used for **9**, 1.5 g (0.01 mol) of 3-methyl-3-*n*-butyl-1-cyclohexene (**28**)[32] and 35 g (0.135 mol) of CrO_3–(pyridine)$_2$ complex yielded 1.32 g of a dark oil. Analysis by vpc showed the presence of 5% starting olefin, 89% 4-methyl-4-*n*-

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(22) A sample of authentic nootkatone was kindly provided by Dr. R. Teranishi, USDA Western Regional Laboratory, Albany, Calif.

(23) Generously provided by Roure-Bertrand Fils and J. DuPont, France.

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(27) The starting material and authentic product samples were kindly supplied by C. Heathcock and J. E. Ellis who performed the experiment.

(28) The starting olefin was prepared following a synthetic procedure previously reported [*J. Amer. Chem. Soc.*, **90**, 4762 (1968)], by reaction of 2 equiv of methyllithium with the *p*-toluenesulfonyhydrazone of 4,4-dimethyl-1-cyclohexanone. Its properties were in agreement with published data [see H. Pines, F. J. Paulic and V. N. I. Putieff, *ibid.*, **73**, 5738 (1951)].

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(32) The starring olefin was prepared following a synthetic procedure previously reported [*J. Amer. Chem. Soc.*, **90**, 4762 (1968)], by reaction of 2 equiv of methyllithium with the *p*-toluenesulfonhydrazone of 2-*n*-butyl-2-methyl-1-cyclohexanone: mol wt 152 (mass spectrum); nmr (δ, ppm), 5.4 (2 H, multiplet), 1.2–2.0 (13 H, complex, sharp band at 1.3), 1.0 (6 H, multiplet with sharp band).

Anal. Calcd for $C_{11}H_{20}$: C, 86.76; H, 13.24. Found: C, 86.48; H, 13.31.

butyl-2-cyclohexen-1-one (**29**),[33] and 6% 6-methyl-6-*n*-butyl-2-cyclohexen-1-one (**30**).[34] Column chromatography gave 1.2 g of a mixture of the two enones; this corresponds to a yield of 74% **29** and 6% **30**.

Oxidation of 4,4-Diphenyl-1-cyclohexene (31).—Following the procedure used for **9**, 4.5 g (0.02 mol) of 4,4-diphenyl-1-cyclohexene (**31**)[35] and 35 g (0.135 mol) of CrO_3–(pyridine)$_2$ complex gave 4.38 g of a viscous oil. Chromatography on silica gel yielded 2.46 g of starting olefin, 1.46 g (67%) of 4,4-diphenyl-2-cyclohexen-1-one[36] (**33**), and 0.27 g (13%) of 5,5-diphenyl-2-cyclohexen-1-one[37] (**32**).

Oxidation of 1-Phenyl-1-cyclohexene (34).—Following the procedure used for **9**, 3.12 g (0.02 mol) of 1-phenyl-1-cyclohexene (**34**) and 55 g (0.21 mol) of CrO_3–(pyridine)$_2$ complex afforded 2.82 g of a viscous brown oil. Column chromatography gave 1.0 g of starting olefin and 1.65 g (71%) of 3-phenyl-2-cyclohexen-1-one (**35**) which was recrystallized from ethanol, mp 61–64° (lit.[38] mp 61–62°).

Oxidation of 3-(*p*-Fluorophenyl)-1-cyclohexene (36).—Following the procedure used for **9**, 1.75 g (0.01 mol) of 3-(*p*-fluorophenyl)-1-cyclohexene (**36**)[39] and 55 g (0.21 mol) of CrO_3–(pyridine)$_2$ complex gave 1.43 g of a brown oil. Column chromatography afforded 0.68 g of starting material and 0.97 g (84%) of 3-(*p*-fluorophenyl)-2-cyclohexen-1-one (**37**): nmr (δ, ppm), 7.5 (2 H, multiplet), 7.0 (2 H, multiplet), 6.1 (1 H, triplet, J = 1 cps), 2.65 (2 H, multiplet), 2.25 (4 H, multiplet); mass spectrum, 190 (parent peak).

Oxidation of 1-Methyl-1-cyclopentene (38).—Following the procedure used for **9**, 2.46 g (0.03 mol) of 1-methyl-1-cyclopentene (**38**) and 55 g (0.21 mol) of CrO_3–(pyridine)$_2$ complex afforded 1.73 g of a yellow liquid. Column chromatography gave 1.52 g of a mixture of two unsaturated ketones, shown by vpc analysis to be present in the ratio of 3.5:1. These values correspond to a yield of 41% 3-methyl-2-cyclopenten-1-one (**39**)[40] and 12% 2-methyl-2-cyclopenten-1-one (**40**).[41]

Oxidation of Allylbenzene (41).—Following the procedure used for **9**, 2.4 g (0.02 mol) of allylbenzene and 35 g (0.135 mol) of CrO_3–(pyridine)$_2$ complex gave 1.95 g of a crude reaction product. Analysis by vpc showed the presence of 45% starting material and 55% cinnamaldehyde (63%).

Registry No.—**1**, 2099-26-5; **3**, 604-35-3; **5**, 570-74-1; **7**, 20479-02-1; **9**, 80-56-8; **11**, 138-86-3; **14**, 591-49-1; **17**, 591-48-0; **19**, 110-83-8; **21**, 3856-25-5; **24**, 14072-86-7; **28**, 21544-97-8; **31**, 21544-98-9; **34**, 771-98-2; **36**, 21545-08-4; **38**, 693-89-0; **41**, 300-57-2; chromium trioxide–pyridine complex, 20492-50-6.

Acknowledgment.—The authors are indebted to Dr. R. Teranishi for his interest and assistance in this study.

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[33] The spectral properties were as follows: mass spectrum 166 (parent peak); ν_{max} 1680, 1625 cm^{-1}; nmr (δ, ppm), 6.28 (1 H, doublet, J = 10 cps), 5.85 (1 H, doublet, J = 10 cps), 1.3–2.3 (4 H, multiplet), 1.2 (6 H, broad peak), 1.1 (3 H, singlet), 1.0 (3 H, multiplet).

[34] The spectral properties were as follows: mass spectrum, 166 (parent peak); ν_{max} 1682 cm^{-1}.

[35] The starting olefin was prepared by Wolff–Kishner reduction of 4,4-diphenyl-2-cyclohexen-1-one (W. A. Spitzer, unpublished results).

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[37] The spectral properties were as follows: ν_{max} 1665, 1559 cm^{-1}; mass spectrum, 248 (parent peak); nmr (δ, ppm), 7.15 (10 H, singlet), 6.75 (1 H, multiplet), 5.9 (1 H, doublet of triplets), 3.1 (4 H, multiplet).

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[39] The olefin was kindly supplied by Richard J. Shavitz and was prepared by coupling of *p*-fluorobromobenzene and 3-cyclohexenyl-1-magnesium bromide [A. Berlande, *Compt. Rend.*, **213**, 437 (1941)].

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The Condensation of Internal Olefins with Paraformaldehyde and Hydrogen Chloride

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Received December 3, 1968

The condensation of *cis*- and *trans*-2-butene with paraformaldehyde and hydrogen chloride at −65° gives predominantly the diastereomeric and chloro alcohols, *threo*-3-chloro-2-methyl-1-butanol and *erythro*-3-chloro-2-methyl-1-butanol, respectively, with 80–90% isomeric purity. The structures of the products were established by a nuclear magnetic resonance study.

In a previous article[1] we have described a novel modification of the Prins reaction in which 1 olefins are condensed with paraformaldehyde and hydrogen halides at low temperatures to give good yields of 3-alkyl-4-halotetrahydropyrans. Extension of this modified Prins reaction to include the condensation of 2-butenes with paraformaldehyde and hydrogen chloride at −65° is described in this report. In contrast to the 1-olefin reactions, the principal products were found to be a mixture of chloro alcohols and their formals (45–60% yield). Small amounts of alkylchlorotetrahydropyrans and uncharacterized 1,3-dioxanes were formed as by-products.

It has been previously demonstrated that conventional Prins reactions of cyclohexenes proceed exclusively with *trans*[2,3] diaxial[4] addition, but condensation of *trans*- and *cis*-4-octene with formaldehyde was stereoselective only for the *trans* isomer under the conditions employed.[5] To determine the stereochemistry in our modification of the Prins reaction, *trans*- and *cis*-2-butene were condensed separately with paraformaldehyde and hydrogen chloride at −65°. Distillation of the reaction mixtures gave, after removal of the lower boiling dioxanes and chlorotetrahydropyrans, mixtures of chloro alcohols and formals in proportions dependent on the olefin/formaldehyde molar ratio. Treatment of these mixtures with methanol and hydrochloric acid to hydrolyze the formals produced two diastereomeric chloro alcohols which were indistinguishable by glpc, but which were determined to be of high isomeric purity by nuclear magnetic resonance (nmr) analysis (Chart I). If the chloro alcohols are formed by *trans* addition in this system, then *trans*-2-butene would produce *erythro*-3-chloro-2-methyl-1-butanol and

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