THE JOURNAL OF Organic Chemistry®

VOLUME 30, NUMBER 7 JULY 12, 1965

Cycloalk-2-enones and $\alpha,\beta,\alpha',\beta'$-Cycloalkadienones. A. Synthesis. B. On the Direction of Bromination of 2-Substituted Cycloalkanones and Their Ketals

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Received November 11, 1964

A convenient synthesis of cycloalk-2-enones and $\alpha,\beta,\alpha',\beta'$-cycloalkadienones, which utilizes direct brominations of cycloalkanones in alcohol and cycloalkanone ketals in ether, is described and discussed. The directions of brominations of several cyclic ketones and corresponding ketals are found to differ markedly in a consistent manner. An inquiry into those factors which may affect the directions of brominations is made, and the problem is discussed in some detail along with supporting experimental results.

An interest in the chemical and spectral properties of cycloalk-2-enones and $\alpha,\beta,\alpha',\beta'$-cycloalkadienones has led to a search for a simple and possibly general route to their syntheses. Preparations of cycloalk-2-enones by a variety of approaches have been described[2–4]; however, stable unsubstituted $\alpha,\beta,\alpha',\beta'$-cycloalkadienones do not appear to have been synthesized. In this paper, a synthetically direct approach to a number of both of these classes of compounds will be described and a discussion apropos to the direction of brominations of 2-substituted cycloalkanones and their ketals will be given.

Results

Synthetic.—Direct brominations of cyclopentanone (**1**), cyclohexanone (**2**), 4,4-dimethylcyclohexanone (**3**), 4-*t*-butylcyclohexanone (**4**), cycloheptanone (**5**), and cyclooctanone (**6**) in either methanol or ethylene glycol solvent under mild conditions (15–20°) are found to lead to respectable yields of the 2-bromocycloalkanone ketals. After one equivalent of bromine has reacted, further reaction with bromine is visibly much slower; however, if the reaction temperature is raised by about 30° (*ca.* 40–60°), the reaction proceeds at a convenient rate to give predominantly the α,α'-dibromocycloalkanone ketals. It was found, though, that cleaner conversions to the dibromocycloalkanone ethylene ketals were effected if the ethylene ketals of the cycloalkanones were dibrominated directly in ethereal solution.[5]

The ketals of the 2-bromocycloalkanones cleanly dehydrobrominate in refluxing alcoholic alkali or more rapidly in potassium *t*-butoxide– (or sodium methoxide–) dimethyl sulfoxide solution to give cycloalk-2-enone ketals (**7–13**). These ketals were hydrolyzed readily in dilute aqueous acid[6] to the known cycloalk-2-enones (**14–19**) (Scheme I).

Ketals of 2,7-dibromocycloheptanone and 2,8-dibromocyclooctanone dehydrobrominate in refluxing methanolic alkali to give cyclohepta-2,6-dienone ketals (**21** and **22**) and cycloocta-2,7-dienone ketal (**23**), respectively, with no detectable isomeric contaminants (*via* n.m.r.). Dehydrobrominations using sodium methoxide in DMSO are more rapid than in alcoholic alkali; however, the initial dienone ketal products are susceptible to further reactions (see later). Ketals **21–23** hydrolyze rapidly in dilute aqueous acid to dienones **25** and **26**.

The structures of **25** and **26** are substantiated by their n.m.r. spectra. Figure 1 (top) shows the spectrum of **25**. Spin decoupling[7] (Figure 1, bottom) of the low-field vinyl protons from the aliphatic protons led to an "apparent"[7,8] AB resonance for the four vinyl protons. This decoupled spectrum is consistent only with the symmetrical dienone **25**. The n.m.r. spectrum of the vinyl protons of **26** is shown in Figure 2 (left). Spin decoupling[7] (Figure 2, right) of the vinyl protons

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(1) Part of this work was initiated at the University of Chicago.

(2) (a) K. Alder and F. H. Flock, *Chem. Ber.*, **89**, 1732 (1956); (b) W. F. Gannon and H. O. House, *Org. Syn.*, **40**, 14 (1960); (c) K. L. Williamson, R. T. Keller, G. S. Fonken, J. Szmuszkovicz, and W. S. Johnson, *J. Org. Chem.*, **27**, 1612 (1962).

(3) E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 607 (1954).

(4) A. C. Cope, M. R. Kinter, and R. T. Keller, *J. Am. Chem. Soc.*, **76**, 2757 (1954).

(5) A. Marquet, M. Dvolaitzky, H. B. Kagan, L. Mamlok, C. Ouannes, and J. Jacques, *Bull. soc. chim. France*, 1822 (1961); A. Marquet and J. Jacques, *ibid.*, 90 (1962).

(6) H. W. Wanzlick, G. Gollman, and H. Milz, *Chem. Ber.*, **88**, 69 (1955).

(7) See E. W. Garbisch, Jr., *Chem. Ind.* (London), **41**, 1715 (1964), for a description of the decoupling experiments.

(8) Actually, an A_2B_2 resonance is recorded[7] and each component of the doublet of doublets shown in Figure 1 (bottom) is split further into triplets.

SCHEME I

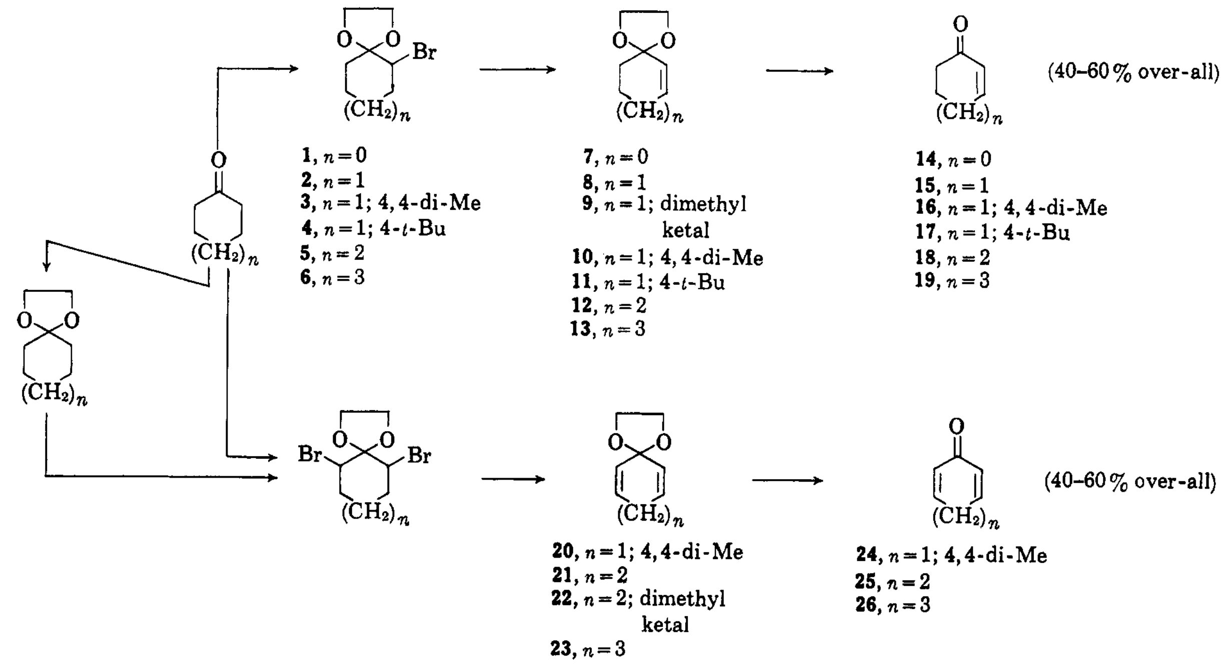
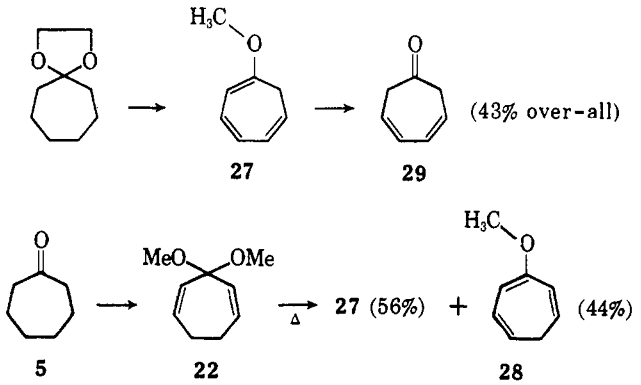


Figure 1.—N.m.r. spectrum of **25** (top) and of decoupled H-3,H-6 and H-4,H-5 (bottom).

from the allylic protons (centered at about τ 7.64) led to an "apparent" AB resonance[9] for the four vinyl protons. Again, the decoupled spectrum is consistent only with the symmetrical dienone **26**.

Table I summarizes the ultraviolet and infrared spectral data for the cycloalk-2-enones **16**, **18**, and **19**, the cycloalkadienones **24**–**26**, cyclohepta-2,4-dienone, and cyclohepta-3,5-dienone (**29**). A pronounced red shift in the $\pi \rightarrow \pi^*$ (cycloalk-2-enones and $\alpha,\beta,\alpha',\beta'$-cycloalkadienones) and $n \rightarrow \pi^*$ ($\alpha,\beta,\alpha',\beta'$-cycloalkadienones) transitions and a shift to lower wave numbers for the carbonyl stretching vibration are observed as the ring size is increased. A reverse trend was expected, as molecular models suggest that the conformations of the seven- and eight-membered rings may encompass minimum torsional and angle strains when the olefinic and carbonyl carbon p-orbitals have been rotated appreciably from maximum overlap.[10]



Dibromination of the ethylene ketal of **5** in methanol with molecular bromine followed by dehydrobromination using sodium methoxide in DMSO led to 1-methoxy-1,3,5-cycloheptatriene [**27**, $\lambda_{\max}^{\mathrm{EtOH}}$ 285 mμ (ε 4520)] in 53% conversion. The product was characterized by a doublet aliphatic proton resonance ($J_{6,7} \cong 7.1$ c.p.s.) at $\tau^{\mathrm{CCl_4}}$ 7.55[11] and was contaminated by less than 5% of 3-methoxy-1,3,5-cycloheptatriene (**28**), which exhibits a triplet ($J_{7,6} \cong J_{7,1} \cong 6.8$ c.p.s.) aliphatic proton resonance at $\tau^{\mathrm{CCl_4}}$ 7.76.[11] Hydrolysis of **27** in dilute sulfuric acid led to cyclohepta-3,5-dienone (**29**) of greater than 95% purity. Characterization of **29** was affected through its ultraviolet (Table I) and n.m.r. spectra (aliphatic proton resonance appears as a doublet, $J_{2,3} \cong J_{7,6} \cong 5.7$ c.p.s., at $\tau^{\mathrm{CCl_4}}$ 7.02). Dibromination of **5** in methanol followed by dehydrobromination of the resulting dibromo ketal in alcoholic alkali led to 46% of **22** contaminated with about 5%

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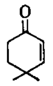
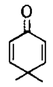
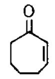
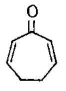
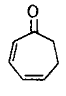
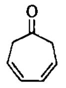
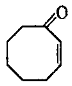
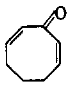
[9] In this instance, since no long-range coupling is apparent, the A_2B_2 resonance appears as a typical AB resonance with no further splittings.[7]

[10] Discussions of the spectral properties of the cycloalk-2-enones and the $\alpha,\beta,\alpha',\beta'$-cycloalkadienones will be given in subsequent reports.

[11] E. Weth and A. S. Dreiding, *Proc. Chem. Soc.*, 59 (1964). The n.m.r. parameters determined for **27** and **28** coincide with those reported by these authors. Thermal equilibration (150°) of **27**, **28**, and 2-methoxy-1,3,5-cycloheptatriene reportedly leads to about 1% of the latter and about 9% of **28**.

TABLE I

ULTRAVIOLET AND INFRARED SPECTRAL DATA[a]

Compd.	$\lambda_{\pi \rightarrow \pi^*}^{EtOH}$ mμ (log ε)	$\lambda_{n \rightarrow \pi^*}^{EtOH}$ mμ (log ε)	$\lambda_{C=O}^{CCl_4}$ cm.$^{-1}$	$\lambda_{C=C}^{CCl_4}$ cm.$^{-1}$
	224 (4.20)^b		1680^b	
	234.5 (4.16) [224.5 (4.17), 229 (4.14)^c 237 (3.96),^{c} 246 (3.59)^c]^d	323 (1.38) [319 (0.9), 332 (1.0) 345 (1.14), 360 (1.08) 370 (0.8), 385 (0.6)]^d	1665	1630
	227 (4.01) 227^e	317 (1.72)	1665	
	235 (4.03), 266 (3.40)^c [226 (4.04, 235 (3.92)^c 244 (3.66),^{c} 258 (3.37)^c]^d	339 (1.52) [357 (1.28), 366 (1.32) 384 (1.11)]^d	1647	1613
	292 (3.79)^f			
	213–214 (3.74)^g 211 (3.76),^{c} 232 (3.69)^c	290 (2.75)^g 282 (2.85)	1709^g	1595^g
	230 (3.87) 230 (3.89)^h	310 (1.86) 310 (1.90)^h	1664	
	243.5 (4.03) [236 (4.03)]^d	346.5 (1.98) [339 (1.62), 353 (1.79), 366 (1.90) 383 (1.84), 398 (1.53)]^d	1640	1613

[a] The ultraviolet and infrared spectra were determined using Beckman DK and Unicam spectrometers. [b] Ref. 39. Infrared spectrum was run in CS_2. [c] Shoulder. [d] Isooctane solvent. [e] Ref. 3. Spectrum was determined on a mixture of cyclohept-2-enone and cyclohept-3-enone. [f] E. E. Van Tamelen and G. T. Heldahl, *J. Am. Chem. Soc.*, **78**, 4405 (1955). [g] J. Meinwald, S. L. Emerman, N. C. Yang, and G. Büchi, *ibid.*, **77**, 4401 (1955). [h] Ref. 4.

of **27** and **28** in the ratio of about 1:2. Thermal (gas chromatographic) decomposition of **22** at 165° gave a mixture of 44% of **28** and 56% of **27**.

cis-2,6-Dibromo-4,4-dimethylcyclohexanone ethylene ketal (**30**) undergoes reductive dehydrobromination cleanly in refluxing methanol to give **10** with no indication of the presence of **20**. After partial reaction, n.m.r. analysis of the product indicated the presence of 12% of **30**, 46% of 2-bromo-4,4-dimethylcyclohexanone ethylene ketal (**31**), 42% of **10**, and no indication of 6-bromo-4,4-dimethylcyclohex-2-enone ethylene ketal. Apparently, nucleophilic reaction at the bromine of **30** precedes dehydrohalogenation and leads to a carbanion intermediate **32**, which becomes protonated by solvent giving **31**. Presumably, **31** more readily adopts the conformation containing the axial bromine, which then is situated for facile dehydrobromination, than does **30**. Employing the strongly basic medium of potassium *t*-butoxide in DMSO, **30** reacts to give a mixture of **20** and **10** in the ratio of about 4:1.

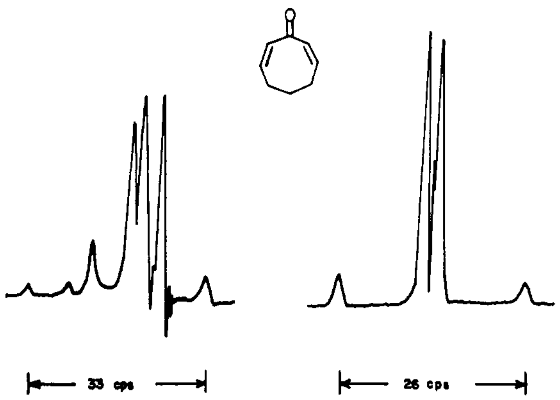
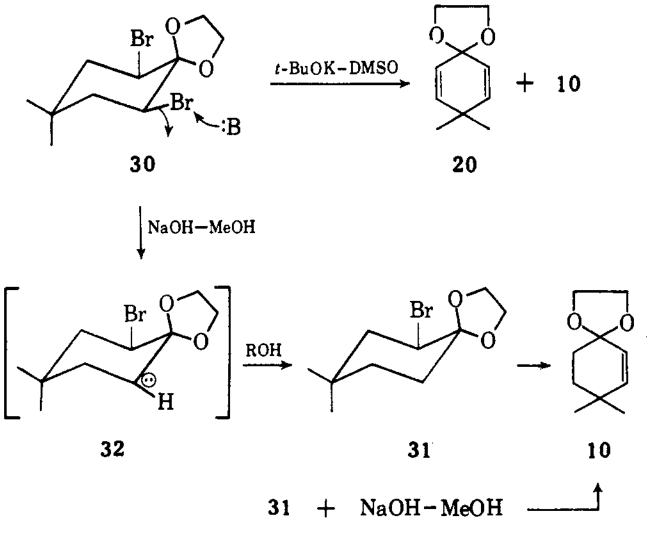


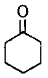
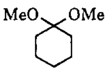
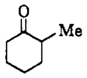
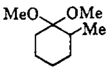
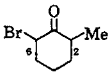
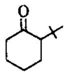
Figure 2.—N.m.r. spectrum of the vinyl protons of **26** (left) and of the vinyl protons upon decoupling from the allylic protons (right).



On the Direction of Acid-Catalyzed Bromination of 2-Substituted Cycloalkanones.—The success of the approach described in this paper for the synthesis of cycloalk-2-enones and $\alpha,\beta,\alpha',\beta'$-cycloalkadienones relies on (1) the ease of selectively monobrominating the

TABLE II

DIRECTIONS OF BROMINATIONS OF SEVERAL CYCLIC KETONES AND KETALS

	 **2**	 **33**	 **34**	 **46**	 **36 + 37**	 **40**
% substitution on C-6[a]						
Monobromination in Et_2O	. . .	. . .	4	. . .	9	61
Monobromination in MeOH	. . .	. . .	67	78	. . .	97
% 2,6-disubstitution[b]						
Dibromination in Et_2O	67	. . .	100	. . .	. . .	. . .
Dibromination in MeOH	. . .	>97	. . .	100	. . .	. . .

[a] Subtraction from 100 gives the % substitution at C-2. [b] Subtraction from 100 gives the % α,α disubstitution.

TABLE III

BROMINATIONS OF SEVERAL CYCLIC KETONES AND KETALS

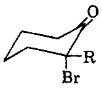
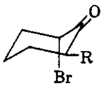
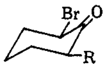
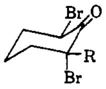
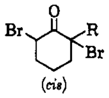
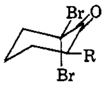
Expt.	Description of bromination	Breakdown, % (monobromination, %)[a]			Breakdown, % (dibromination, %)[a]			Unreacted, %
								
	R = H							
1	**2** in Et_2O; 2-equiv. Br_2; −10°[c]	. . .	. . .	. . .	67[b]		33 (100)	. . .
1a	Product (expt. 1) equilibration in Et_2O–HBr; 25°	. . .	. . .	. . .	84[b]		16 (100)	. . .
1b	*cis*-2,6-Dibromocyclohexanone equilibration in Et_2O–HBr; 25°	. . .	. . .	. . .	85[b]		15	. . .
2	**33** in CH_3OH; 2-equiv. Br_2; 40–60°	. . .	. . .	. . . (8)	>97[c]		<3[c] (92)	0
	R = CH_3	**35**	**36**	**37**	**38**	*cis*	**39**	**34**
3	**34** in Et_2O; 1-equiv. Br_2; −40 to −50°	96	3	1 (87)	13	0	0 (13)	*d*
3a	Product (expt. 3) equilibration in Et_2O–HBr; 25°	86	9	5 (90)	10	0	0 (10)	*d*
4	**34** in Et_2O; 2-equiv. Br_2; −10°			(0)	100	0	0 (100)	0
4a	Equilibration of 86% of **39** + 14% of **38** in Et_2O–HBr; 25°			(0)	100	0	0	
5	**36** + **37** in Et_2O; 1-equiv. Br_2; 10°				91	0	9 (100)	(Trace)
6	0.0025 *M* of 65% of **39** + 35% of **38** and 0.0100 *M* of **34** in Et_2O; 0.020 *M* Br_2; 10°	. . .	. . .	. . . (0)	89	0	11 (100)	*d*
7	**34** in MeOH; 1-equiv. Br_2; 20–25°[e]	33[f]	34	33 (93)	7[g]		0 (7)[g]	*d*
7a	Equilibration of product of expt. 7 (neat) with HBr; 25° (see expt. 3a)	85	9	6	*g, h*	*g, h*	*g, h*	
8	**46** in MeOH; 1-equiv. Br_2; 20°[e]	22[f]	38	40 (90)	10[g]		0 (10)[g]	*d*
9	0.05 *M* of 95% of **35** + 5% of (**36** + **37**) and 0.05 *M* of **34** in MeOH containing 0.05 *M* of HBr; 0.05 *M* Br_2; 20°	67	18	15 (93)	7[g]		0 (4)[g]	*d*
10	**46** in MeOH; 2-equiv. Br_2; 30–40°	. . .	. . .	. . . (0)	100[g]		0 (100)[g]	0
11	0.0025 *M* of 65% of **39** + 35% of **38** and 0.0100 *M* of **46** in MeOH; 0.020 *M* Br_2; 30–40°	. . .	. . .	. . . (0)	87[g]		13 (100)[g]	0

TABLE III (*Continued*)

	R = *t*-Butyl	**41**	**42**	**43**	**44**	**45**	—	**40**
12	**40** in Et_2O; 1-equiv. Br_2 at −10°	39	43	18 (70)	57	43[i]	0[j] (18)	12
12a	Product (expt. 12) partial equilibration (neat) with HBr; 25°	21	47	32 (72)	~100	. . .	0[j] (16)	12
13	**40** in MeOH; 1-equiv. Br_2 at 20°[e]	3	77	20 (72)			(6)[k]	22
13a	Product (expt. 13) partial equilibration (neat) with HBr; 25°	7	56	37		*h*		

[a] Percentages are thought to be reliable to within ±5%. [b] The overlapping of the H-2 and H-6 magnetic resonances of the *cis*- and *trans*-2,6-dibromocyclohexanones precludes an accurate estimation of the isomer composition. It may be concluded, though, that the *trans* isomer predominates at equilibrium. [c] Analyses were performed on the dibromo ketals dissolved in carbon tetrachloride and in benzene. The *trans*-2,6-dibromocyclohexanone dimethyl ketal was tentatively associated with the lowest field α-proton resonance (see footnote *e* of Table IV). Analysis gave 92% of dibromination consisting of 59% of *cis*-2,6-dibromocyclohexanone dimethyl ketal which apparently is not in the ideal chair conformation as judged by the small $J^0_{\alpha\text{-H}}$ value and the magnetically nonequivalent methoxyl protons ($\tau^{CCl_4}_{\alpha\text{-H}}$ 5.77, $\tau^{C_6H_6}_{\alpha\text{-H}}$ 6.03, $\tau^{CCl_4}_{OCH_3}$ 6.51 and 6.69, $\tau^{C_6H_6}_{OCH_3}$ 6.52 and 7.00, and $J^0_{\alpha\text{-H}} \cong 10.9$ c.p.s.[18]), 41% of *trans*-2,6-dibromocyclohexanone dimethyl ketal ($\tau^{CCl_4}_{\alpha\text{-H}}$ 5.50, $\tau^{C_6H_6}_{\alpha\text{-H}}$ 5.57, $\tau^{CCl_4}_{OCH_3}$ 6.51, $\tau^{C_6H_6}_{OCH_3}$ 6.69, and $J^0_{\alpha\text{-H}} \cong 11.7$ c.p.s.[18]), and 8% of 2-bromocy clohexanone dimethyl ketal ($\tau^{CCl_4}_{\alpha\text{-H}}$ 5.69, $\tau^{C_6H_6}_{\alpha\text{-H}}$ 5.70, $\tau^{CCl_4}_{OCH_3}$ 6.80, $\tau^{C_6H_6}_{OCHO_3}$ 6.89 and 6.99, and $J^0_{\alpha\text{-H}} \cong 6.5$ c.p.s.[18]). The low J^0 value for the latter compound shows that the bromine is almost exclusively in the axial conformation.[18] Less than 3% of α,α dibromination resulted judged by the relative areas of the α-H and the methoxyl proton resonances. [d] The unreacted ketone, if any, is removed from the product as a result of the experimental procedure (see Experimental). [e] Mild hydrolysis of the bromo ketal product followed bromination. [f] The greater amount of **35** found in this experiment compared with that found in expt. 8 is thought to arise from the bromination of ketone. About 10% of bromo ketone generally is present when the reaction solution is worked up under nonhydrolyzing conditions for the bromoketals. [g] Analyses was performed on the dibromo ketals which do not hydrolyze under the conditions employed. The dimethyl ketal of **38** (τ^{CCl}_{Me} 8.18, $\tau^{C_6H_6}_{CH_3}$ 8.18, $\tau^{CCl_4}_{OCH_3}$ 6.21 and 6.43, and $\tau_{H\text{-}6}$ 5.20 with $J^0 \cong 16$ c.p.s.) and of *cis*-2,6-dibromo-2-methylcyclohexanone ($\tau^{CCl_4}_{CH_3}$ 8.13, $\tau^{C_6H_6}_{CH_3}$ 8.38, $J^4_{CH_3,H3} = 0.4$ c.p.s., $\tau^{CCl_4}_{OCH_3}$ 6.32 and 6.35, and $\tau_{H\text{-}6}$ 5.73 with $J^0 \cong 15.5$ c.p.s.) are formed in the ratio of 1.4:1. The high values of J^0 for both isomers suggests that their C-6 hydrogens are predominantly axial.[18] The stereochemical assignment is based upon the low τ value for H-6 or **38** compared with that for the *cis* stereoisomer owing to the deshielding effect of the axial (assumed) bromine of **38** (see text), and upon the long-range coupling in the *cis* isomer in which the axial methyl protons and axial proton on C-3 are expected to couple, and the absence of such coupling in **38** in which the methyl protons and both of the C-3 protons bear the wrong stereo relationship for expected coupling [see S. Sternhell, *Rev. Pure Appl. Chem.*, **14,** 15 (1964)]. [h] Bromo ketals do not withstand equilibration and appear to be converted to enol ethers. [i] Tentative assignment. See footnote *g* of Table IV. [j] The chemical shifts of the *t*-butyl proton and CBr–H magnetic resonances in carbon tetrachloride and in benzene solutions differ markedly. The number of *t*-butyl resonances and the analysis of the product composition in both of these solvents is the same and gives no indication of the presence of 2,2-dibromo-6-*t*-butylcyclohexanone. [k] The percentage is derived from the low-field *t*-butyl resonances all of which were not characterized because of incomplete hydrolysis of the dibromo ketals under the hydrolysis conditions employed.

parent ketones[12] in ethylene glycol (or methanol) and on (2) dibrominating these ketones in methanol (or preferably their ethylene ketals in ether) largely in the α and α' positions. The acid-catalyzed brominations of ketones[13] and of ketals[5] probably proceed similarly, ionization of the protonated substrate leading to the enol or enol ether being the rate-controlling process, followed by bromination. The decreased reactivities of the α-bromo relative to the unsubstituted ketones or ketals toward bromination, which contributes to the ease of selective monobromination, is predicted by analogy to the decreased solvolysis rate (by a factor of about 10) of *trans*-2-bromocyclohexyl *p*-bromobenzenesulfonate relative to that for cyclohexyl *p*-bromobenzenesulfonate.[14]

Somewhat surprising are the high conversions of cyclic ketones (or dimethyl ketals) in methanol and their ethylene ketals in ether to the respective ketals of the α,α'-dibromo ketones *via* direct bromination. The crude dibromination products generally were dehydrobrominated to **21**–**23** with no indication of the presence of 2-bromocycloalk-2-enones, and dibromination of the ethylene ketal of cyclooctanone led to an 87% isolation of a purified configurationally homogeneous 2,8-dibromocyclooctanone ethylene ketal.

Acid-catalyzed brominations of 2-bromocycloalkanones under a variety of conditions have been observed to lead to appreciable amounts of α,α' dibrominations[15]; however, estimations of the extents of α,α dibrominations apparently have not been made. Conversely, 2-methylcyclohexanone (**34**)[16] and 2-methylcyclopentanones[5] are reported to be brominated under acidic conditions predominantly at C-2.

Directions of brominations of several α-substituted cyclohexanones and corresponding dimethyl ketals in ether and methanol solvents have been estimated by n.m.r. The results are summarized in Table II. Table III summarizes in greater detail the results of the experiments performed.

Estimation of the composition of the product from the dibromination of **2** in ether was accomplished from the areas[17] of the H-2 plus H-6 resonances relative to the remaining proton magnetic resonances. Relative areas of the H-2 plus H-6 and the methoxyl proton magnetic resonances were used to approximate the composition of product arising from the dibromination of **33** in methanol. The relative areas of the methyl

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[12] The brominations carried out on ketones in methanol or ethylene glycol solvents probably involve brominations of the ketals and ketones which are in equilibrium. Whereas the products are predominantly the ketals of the bromo ketones, minor amounts of ketones are evident from the infrared spectra of the crude reaction products.

[13] H. Shechter, M. J. Collis, R. Dessy, Y. Okuzumi, and A. Chen, *J. Am. Chem. Soc.*, **84,** 2905 (1962).

[14] S. Winstein, E. Grunwald, and L. L. Ingraham, *ibid.*, **70,** 821 (1948).

[15] E. J. Corey, *ibid.*, **75,** 3297 (1953); G. Hesse and F. Urbank, *Chem. Ber.*, **91,** 2733 (1958); D. Lloyd, D. R. Marshall, and M. Randall, *Chem. Ind.* (London), 1132 (1950).

[16] E. J. Corey, T. H. Topie, and W. A. Wozniak, *J. Am. Chem. Soc.*, **77,** 5415 (1955).

[17] Varian Associates, "NMR and EPR Spectroscopy," Pergamon Press Inc., New York, N. Y., 1960, Chapter 8.

proton resonances of the various brominated 2-methylcyclohexanones (**35–39**, Table III) arising from the mono- and dibrominations of **34** in ether were employed for estimations of product compositions. Authentic samples of **35**, **36** + **37**, **38**, and **39** were synthesized in order to obtain the necessary n.m.r. parameters for the analyses. The configurational assignments of **36** and **37** were made assuming that **37** will be homogeneous in the conformation shown (Table III) giving an expected value of about 18 c.p.s. for $J^0_{\text{H-6a}}$.[18] On the basis of deductions made by Corey[16] that **35** has the structure shown (Table III), **36** likewise is expected to entertain predominantly an axial bromine giving an expected value for $J^0_{\text{H-6e}}$ of about 6 c.p.s.[18] In addition, the τ value for H-6e of **36** is expected to be somewhat higher than that for H-6a of **37**.[18,19] The n.m.r. parameters for **35–39** are given in Table IV and substantiate fully the assignments made.

The products resulting from the monobromination of **34** and **46** in methanol were hydrolyzed under mild conditions to mixtures of **35**, **36**, and **37** which were analyzed; however, the dibromination products resulting from the monobromination of **34** and the dibromination of **46** resisted hydrolysis under the mild conditions employed. No attempt was made to assign unambiguously the configurations of the dimethyl ketals of **38** and of the *cis* stereoisomer which are formed in nearly equal amounts upon dibromination of **46** in methanol (see footnote *e* of Table III for a tentative assignment). Identification of the dimethyl ketal of **39** among the reaction product is made by the presence of a high-field methyl proton doublet resonance ($J \sim 7$ c.p.s.).

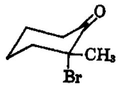
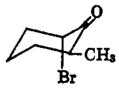
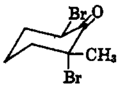
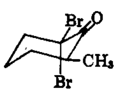
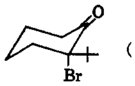
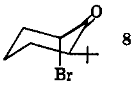
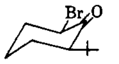
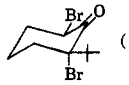
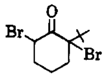
Analysis of the product composition arising from the monobromination of **40** in ether and in methanol (followed by mild hydrolysis) was accomplished by characterizing the products by means of interrelation of the CBr–H and *t*-butyl proton magnetic resonances followed by composition estimation from the relative areas of the respective *t*-butyl resonances. The assignments made are entirely compatible with the observed n.m.r. parameters (see Table IV and compare with the parameters for the brominated 2-methylcyclohexanones). The results were substantiated and the absence of degenerate *t*-butyl resonances made less probable by conducting analyses of the products in carbon tetrachloride and in benzene solvents. The chemical shifts of these resonances are different markedly in the two solvents.

Discussion

An understanding of those factors that influence the directions of brominations of 2-substituted cycloalkanones and their dimethyl or ethylene ketals requires an explanation of the following salient features (*cf.* Tables II and III) of these reactions. (1) Acid-catalyzed brominations of the dimethyl or ethylene ketals of 2-bromocycloalkanones (in methanol and in ether, respectively) lead almost exclusively to α,α'-dibrominated products, whereas similar bromination of 2-bromocyclohexanone (and probably other 2-bromocycloalkanones) in ether leads to product containing appreciable quantities of 2,2-dibromocyclohexanone. (2) Acid-catalyzed brominations in methanol of 2-alkylcyclohexanones or their dimethyl ketals lead to predominant substitution at C-6, whereas similar brominations of the ketones in ether lead to substitution

TABLE IV

N.M.R. PARAMETERS FOR SOME BROMINATED 2-ALKYLCYCLOHEXANONES[a]

Compd.		τ_{alkyl}	J_{alkyl},[b] c.p.s.	$\tau_{\text{H-6}}$	$J^0_{\text{H-6}}$,[c] c.p.s.
34		9.02	6.5	...	...
35		8.20	...	...	...
36		8.99	6.8	5.57	5.8[d]
37		8.92	6.5	5.19	18.2[e]
38		8.06	...	4.30[f]	18.0[e]
39		8.86	6.8	...	...
40		(+1.35)[g]	...	...	...
41		(−13.6)[g]	...	...	...
42		8.99 (0.0)[g]	...	5.66	5.6[d]
43		(−0.9)[g]	...	5.27	17.8[e]
44		(−15.7)[g]	...	4.21[d]	17.8[e]
45	 (*cis*)	(−12.4)[g]	...	(5.2–5.5)[a]	*h*

[a] At 60 Mc. and 30–40% (v./v.) in CCl_4. τ values are reproducible to ±0.02 p.p.m. [b] Apparent CH_3, *t*-H coupling: see F. A. L. Anet, *Can. J. Chem.*, **39**, 2262 (1961). [c] See ref. 18. [d] Poorly resolved six-peak resonance arising possibly from a long-range coupling (*ca.* 1.3 c.p.s.) between H-6e and H-4e in addition to nearly equal couplings between H-6e and H-5e and H-6e and H-7a.[7,18] [e] Complex resonance consisting of four major bands. The nonideal X part of an ABX system arises probably from long-range virtual couplings. The resonance simplifies somewhat, without altering J^0, when benzene solvent is employed. [f] The low τ values for H-6a of **38** and **44** relative to those for **37** and **43** is attributed to a magnetic anisotropic deshielding from the axial C-2–Br bond. This matter will be discussed further in a subsequent paper. [g] Chemical shifts (60 Mc.) in c.p.s. relative to that of the *t*-butyl proton resonance of **42**. [h] This assignment is tentative. From spectra integrals, the H-6 resonance from small amounts of **45** that appear to be present in the bromination products is between τ 5.2 and 5.5. In time, **45** isomerizes to **44**.

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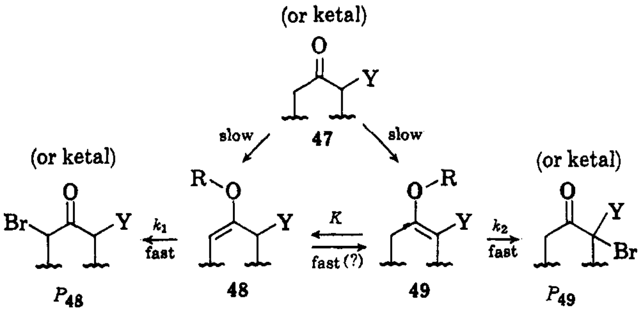
[18] J^0 is equal to the frequency separation between the strong terminal lines of the X resonances of the ABX system in question and is equal to $J_{AX} + J_{BX}$: see E. W. Garbisch, Jr., *J. Am. Chem. Soc.*, **86**, 1780 (1964).

[19] K. M. Wellman and F. G. Bordwell, *Tetrahedron Letters*, 1703 (1963); A. Nickon, M. A. Castle, R. Harada, C. E. Berkoff, and R. O. Williams, *J. Am. Chem. Soc.*, **85**, 2185 (1963).

largely at C-2 when the alkyl substituent is methyl and to roughly comparable substitution at C-2 and C-6 when the alkyl substituent is *t*-butyl. (3) Acid-catalyzed dibrominations of the dimethyl ketal of 2-methylcyclohexanone in methanol and of 2-methylcyclohexanone in ether lead to quantitative 2,6 disubstitutions. Bromination of 2-bromo-6-methylcyclohexanone in ether leads to about 10% substitution at C-2, whereas a mixture consisting of about 78% of 2-bromo-6-methyl- and 22% of 2-bromo-2-methylcyclohexanone dimethyl ketals gives quantitatively 2,6-dibromo product.

Several possibilities may be considered in developing explanations for the experimental results outlined above. (A) Product equilibrations may be competative with brominations. In this event, the product compositions would approach those observed at thermodynamic equilibria. (B) Directions of brominations may be governed by directions of enolizations of ketones (**47**) or eliminations of alcohol from ketals (**47**) to give **48** and **49**.[20] If brominations of **48** and **49** are fast relative to the rates of their equilibrations, the product compositions should represent the compositions of **48** and **49** that result directly from **47**. Should the equilibrations of **48** and **49** be fast relative to (or competative with) the rates of their brominations, the product composition P_{49}/P_{48} will approach Kk_2/k_1.[20]



The product equilibration process that would affect the conclusions regarding the directions of brominations of 2-substituted cycloalkanones may be one that involves an $\alpha \leftrightarrows \alpha'$ bromine equilibration. Equilibrations of this type are known in steroidal systems[21,22] and appear to be catalyzed specifically by hydrogen bromide. Perchloric acid and hydrogen chloride reportedly are ineffective as catalysts.[22] Such equilibrations occur often at appreciably slower rates than the rates of brominations so that kinetically controlled products may be isolated.[21,22] Under $\alpha \leftrightarrows \alpha'$ equilibrating conditions, β-naphthol is found to intercept bromine. Consequently, these equilibrations may proceed *via* a debromination–bromination pathway[22] rather than by an allylic bromine rearrangement of the enol ($C{=}COHCBr_2 \leftrightarrows CBrCOH{=}CBr$).[21,23]

Experiments 3, 3a, 4a, 6, 7a, 9, and 11 in Table III demonstrate, it is felt, that $\alpha \leftrightarrows \alpha'$ bromine equilibrations do not compete seriously with the brominations discussed in this paper. It is concluded, therefore, that the directions of brominations summarized in Tables II and III are qualitatively representative of those expected from kinetic control. Experiments 3, 3a, and 7a show that at least 96% of bromination must occur initially at C-2 of **34,** since product equilibration leads to only 86% of bromine at this position. Experiment 4a shows that the equilibrium **39** $\rightleftarrows$ **38** ($\rightleftarrows$ *cis* stereoisomer) lies entirely on the side of **38** within the limits (<0.5%) of experimental detection of **39** (or the *cis* stereoisomer), whereas expt. 6 shows that **39** does not undergo appreciable $\alpha \rightleftarrows \alpha'$ equilibration during the course of the dibromination of **34** in ether. The expected percentages of **38** and **39** (based upon the results of expt. 4) in the absence of equilibration is 87 and 13, respectively, and those found are 89 and 11, respectively. In a similar manner, expt. 9 and 11 demonstrate that **35** and **39** (or more likely their dimethyl ketals) do not undergo significant $\alpha \rightleftarrows \alpha'$ bromine equilibration during the course of monobromination of **34** and dibromination of the dimethyl ketal of cyclohexanone (**46,** see Table II) in methanol. Assuming no $\alpha \rightleftarrows \alpha'$ equilibrations, the expected percentage of **35** in expt. 9 (based upon the results of expt. 7) is 64 and that found was 67; and the expected percentage of **39** in expt. 11 (based upon the results of expt. 10) is 13 and that found was 13. It is not possible to determine equilibrium compositions of the mono- and dibrominated products of **46** in methanol owing to rather facile methanolysis of the dimethyl ketals of **35** and **38.** This methanolysis did not occur significantly during the bromination reactions (see Experimental).

In view of the results discussed above, it appears likely that the directions of brominations in some way reflect the compositions of **48** and **49** obtained from **47.** The simplest expectation is that they may reflect closely the equilibrium compositions of **48** and **49.** This would imply (1) that ketones or ketals, **47,** are converted directly to equilibrium mixtures of **48** and **49** followed by their rapid brominations and that the equilibrations of **48** and **49** are either slow relative to the rates of their brominations or competative with these rates with $k_1 \cong k_2$; or (2) that ketones or ketals (**47**) are converted to nonequilibrium mixtures of **48** and **49** which are rapidly equilibrated followed by relatively slower brominations with $k_1 \cong k_2$.

Equilibrations of vinyl ethers **50** and **51, 52** and **53,** and **54** and **55** were accomplished so as to determine if the products resulting from the brominations of the corresponding ketals reflect the equilibrium composition of the intermediate enol ethers. Table V summarizes the results of these equilibrations.

The acid-catalyzed elimination of methanol from 2-bromocyclohexanone dimethyl ketal gives 6-bromo-1-methoxycyclohexene (**50**). The n.m.r. spectrum of **50** exhibits a single methoxyl resonance in carbon tetrachloride and in benzene solvents and is split into a doublet through long-range coupling over five bonds with the vinyl proton (J = 0.3 c.p.s.). The relative areas of the methoxyl and vinyl plus C-6 proton resonances suggest that, if 1-bromo-2-methoxycyclohexene is

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(20) It is well understood (see, for example, ref. 13) that the enolization process (**47** → **48** + **49**) is rate controlling for the acid-catalyzed brominations of ketones (and probably ketals). Equilibrations of **48** and **49** and their brominations then are of no kinetic significance. However, these processes may combine to govern product compositions, if the rate of equilibrations of **48** and **49** approach or exceed those of their brominations.

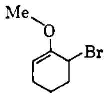
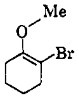
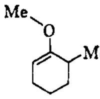
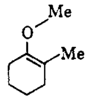
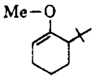
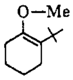
(21) H. H. Inhoffen, *Chem. Ber.*, **70**, 1695 (1937); H. H. Inhoffen and R. Zuhlsdorff, *ibid.*, **76**, 233 (1943); C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, **69**, 2404 (1947); E. J. Corey, *ibid.*, **76**, 175 (1954).

(22) C. W. P. Crowne, R. M. Evans, G. F. H. Green, and A. G. Long, *J. Chem. Soc.*, 4351 (1956).

(23) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, Chapter 8.

TABLE V

N.M.R. DATA AND EQUILIBRIUM COMPOSITION OF SOME ENOL METHYL ETHERS

Compd.	$\tau_{OCH_3}^{CCl_4}$	$\tau_R^{CCl_4}$ (*J*, c.p.s.)	$\tau_{vinyl\ H}^{CCl_4}$ (*J*, c.p.s.)	*J* (OCH$_3$, vinyl H), c.p.s.	Equil. compn. (25°), %	% bromination at C-6	
						Corres. dimethyl ketal	Corres. ketone
 **50**	6.48	...	5.22 (3.5)^{a,b}	0.3	98 ± 2 (of **50**)	>96	67
 **51**	...	...	...	...			
 **52**	5.57^c	8.97 (6.7)	5.49 (3.8)^a	0.3	65 ± 2 (of **52**)	78	4
 **53**	5.57^c	8.43	...	...			
 **54**	6.50	9.03	5.26 (3.9)^a	0.4	93 ± 2 (of **54**)	97	61
 **55**	6.52	8.89	...	...			

^{a} Broadened triplet resonance. ^{b} C-3 H resonance appears at τ 5.47. The low J^0 value of *ca.* 6.0 c.p.s. ($w_H \cong 7$ c.p.s.) shows that the bromine is confined to the quasi-axial conformation: see E. W. Garbisch, Jr., *J. Org. Chem.*, **27**, 4249 (1962). ^{c} In benzene solution, the methoxyl proton resonances are separated by 1.2 c.p.s.

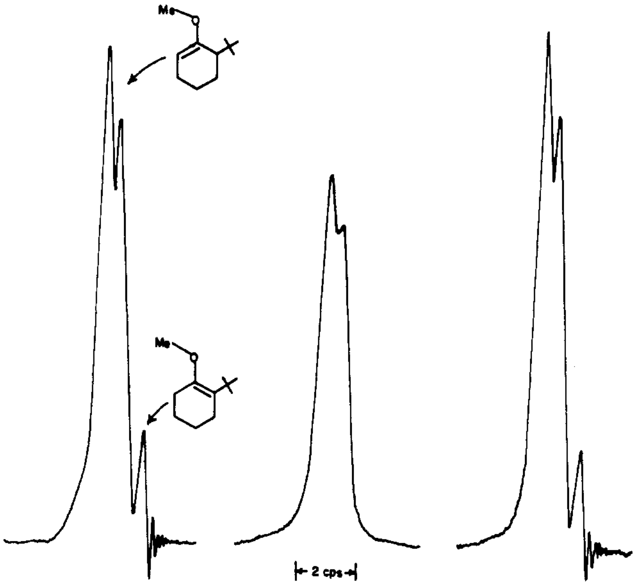


Figure 3.—N.m.r. spectra of the methoxyl protons of **54** and **55** in carbon tetrachloride (left), in the presence of 10 mole % of trifluoroacetic acid (center), and after neutralization of acid with triethylamine (right).

present, it must be so to an extent of less than 5%. No indication of **51** resulted after subjecting **50** in carbon tetrachloride to 200 mole % of trifluoroacetic acid for 1 day at about 30°. Pyrolytic (gas chromatographic) elimination of methanol from **46** at 190° leads to a mixture of about 53% of **52** and 48% of **53**. In carbon tetrachloride and in the presence of 10 mole % of trifluoroacetic acid, an equilibrium mixture consisting of 65 ± 2% of **52** is obtained within the period (<2 min.) of recording the n.m.r. spectrum. The conditions under which **46** was synthesized from **34** led to a mixture of about 92% of **54** and 8% of **55** from **40**. Equilibration of **54** and **55** in carbon tetrachloride and in the presence of 10 mole % of trifluoroacetic acid did not alter significantly the composition of this mixture.

The equilibration of **52** and **53** in carbon tetrachloride containing about 50 mole % of trifluoroacetic acid at 35° must be fairly rapid as evidenced by the broadening of the vinyl proton resonance almost beyond detection and the nearly complete loss of fine structural detail in the remainder of the spectrum. In carbon tetrachloride at about 35° and in the presence of 10 mole % of trifluoroacetic acid, **54** and **55** exchange at a frequency of greater than 1 c.p.s. but less than 8 c.p.s., since their methoxyl proton resonances ($\Delta\nu \cong 1.0$ c.p.s.) are found to coellesce under these conditions, whereas their *t*-butyl proton resonances ($\Delta\nu \cong 8.5$ c.p.s.) remain separated. When the acid concentration is increased to about 50 mole %, the *t*-butyl proton resonances are found to coellesce (see Figure 3).[24] Spectral line broadening was not observed for **50** and **51**, as the equilibrium mixture lies almost completely on the side of the trisubstituted olefin.

Comparing the data on the directions of brominatons of dimethyl ketals **33** and **46** and ketone **40** in methanol and the data on the methyl vinyl ether equilibrium

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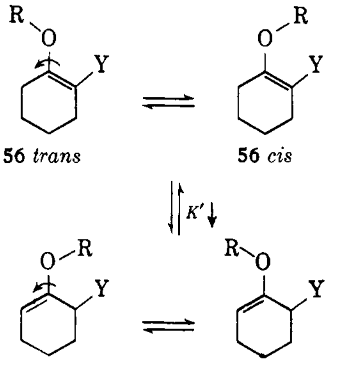
(24) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956).

compositions (see Table V), it is seen that $K' \cong$ per cent bromination at C-6 (ketal)/per cent bromination at C-2 (ketal), where K' = (trisubstituted enol ether)/(tetrasubstituted enol ether) at equilibrium. These results show that the directions of brominations of the cyclic ketals and probably the corresponding ketones[25] closely correspond to the equilibrium compositions of **48** and **49.**

Interpretation

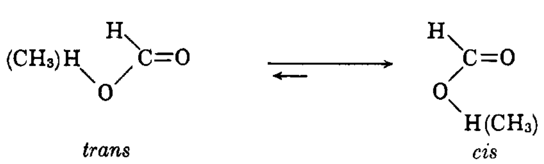
There remains for consideration a more comprehensive explanation of the quite marked differences between the directions of brominations of ketones in ether and dimethyl ketals (or ketones) in methanol. Apparently, the directions of brominations of the systems investigated approximately correspond to those expected from brominations of equilibrium compositions of nonequilibrating enol ethers and enols. Consequently, it seems appropriate to center attention on those factors that influence the equilibrium compositions of the enol ethers and enols. From the bromination results, it appears that the tetrasubstituted relative to the trisubstituted enols are more stable than the corresponding enol methyl ethers by about 1–2 kcal./mole (compare $\Delta\Delta G$ values for the equilibria derived from the directions of brominations summarized in Table V). This instability of the tetrasubstituted enol methyl ethers relative to the corresponding enols may be understood if there exists a pronounced conformational preference for the enol and enol methyl ether groups in these systems.

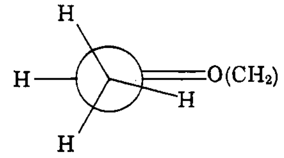


56 *trans* **56** *cis*

57 *trans* **57** *cis*

Spectroscopic investigations on the rotational isomerism of monomeric formic acid[26] and methyl formate[27] in the gas phase show the coplanar systems to be at energy minima (as in phenol[28]) with the *cis* isomers favored over the *trans* isomers by about 2 kcal./mole and >0.8 kcal./mole, respectively. Also, the potential functions for rotation in acetaldehyde[29] and propene[30] exhibit energy minima (ΔE_V = 1.2 and 2 kcal./mole, respectively) in the eclipsed conformation (**58**). It may be expected, consequently, that the rotational isomerism of the enol and enol methyl ether of acetaldehyde will favor also the *cis* isomer to extents roughly comparable with those observed for formic acid and methyl formate. Assuming that in the absence of other effects[31] the minimum energy conformations of the O–H and O–CH_3 groups in the systems investigated are those in which these groups are coplanar and eclipsed with the carbon–carbon double bonds, it becomes predictable that **56** (R = CH_3) will become decreasingly favored relative to **56** (R = H) as the size of the Y substituent is increased. The controlling factors that influence these relative values of K' are presumably the destabilizing R–Y ($\neq$ H) interactions in **56** *cis.* These interactions (Y $\neq$ H), which are undoubtedly more serious when R = CH_3 than when R = H, serve to offset the low torsional strain which has been associated with this rotational conformation relative to **56** *trans* and offer the impetus for isomerization to **57** *cis* where minimal torsional strain is preserved and R–Y nonbonded interactions are eliminated.





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Finally, results show the absence of alkene-stabilizing influences of vinyl bromine atoms in contrast to the well-known stabilizing effects of vinyl alkyl groups. For example, 2-bromo-6-methylcyclohexanone (**36** and **37**) is brominated at C-6 to the extent of 91% (expt. 5, Table III) and 2-methylcyclohexanone (**34**) is brominated to the extent of 96% at C-2 (expt. 3, Table III). Consequently, if brominations take place as thought on near-equilibrium mixtures of enols and the products are indicative roughly of the equilibrium compositions, the results show that a vinyl bromine is ineffective as an olefinic stabilizing group[31] (steric repulsions between O and Br and between O and Me in the intermediate enols are expected to be roughly the same[32]). In addition, the dibromination of cyclohexanone which is found to give about 30% 2,2-dibromocyclohexanone (expt. 1, Table III) and the equilibrium data on **50** and **51** *vs.* **52** and **53** in Table V substantiate further this conclusion. Simple Hückel MO theory predicts also the absence of significant electronic stabilization of **51** over **50**. Taking $\alpha_{\dot{O}} = \alpha + \beta$, $\alpha_{Br} = \alpha + 1.5\beta$, $\beta_{C-O} = 0.8\beta$, and $\beta_{C-Br} = 0.3\beta$,[33a] and neglecting the contributions from the vinyl carbon

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(25) For **34**, where bromination occurs almost entirely at C-2 to give **35**, enolization appears to lead directly to the most stable enol **49** (Y = Me and R = H), or rapid acid-catalyzed equilibration between **48** and **49** preceeds bromination (with $k_1 \cong k_2$). It is difficult, otherwise, to visualize almost complete enolization to **49** in the absence of thermodynamic control.

(26) T. Miyazawa and K. S. Pitzer, *J. Chem. Phys.*, **30**, 1076 (1959).

(27) D. Tabuchi, *ibid.*, **28**, 1014 (1958).

(28) T. Kojima, *J. Phys. Soc. Japan*, **15**, 284 (1960).

(29) R. W. Kilb, C. C. Lin, and E. B. Wilson, *J. Chem. Phys.*, **26**, 1695 (1957).

(30) D. R. Lide and E. E. Mann, *ibid.*, **27**, 868 (1957); D. R. Herschback and L. C. Krisher, *ibid.*, **28**, 728 (1958).

(31) Hydrogen bonding between the enol hydrogen and the vinyl bromine of *cis* **56** (R = H and Y = Br) and the allylic bromine of *trans* **57** (R = H and Y = Br) may be significant energetically under the bromination conditions employed: see E. A. Allan and L. W. Reeves, *J. Phys. Chem.*, **66**, 613 (1962); **67**, 591 (1963).

(32) L. Pauling, "The Nature of The Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960, p. 260.

(33) (a) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, Chapter 5. (b) E_D is delocalization energy.

groupings and methoxyl methyl group which should cancel nearly in **50** and **51**, $E^{50}{}_{\mathrm{D}}$ is found to be 0.32β compared with 0.34β for $E^{51}{}_{\mathrm{D}}$.[33b]

Summary

A convenient and expedient synthesis of many cycloalk-2-enones and $\alpha,\beta,\alpha',\beta'$-cycloalkadienones may be accomplished by monobrominating cyclic ketones in methanol or ethylene glycol, or dibrominating the ethylene ketals of cyclic ketones in ether followed by dehydrobromination and finally by ketal hydrolysis. Dibrominations of cycloalkanone ketals proceed to give essentially complete α,α' substitution and monobrominations of dimethyl ketals of 2-alkylcyclohexanones occur with predominant substitution at C-6. On the other hand, brominations of 2-substituted cyclohexanones in ether lead to appreciable and sometimes predominant substitution at C-2. Consequently, directions of brominations may be controlled often by simple variation of conditions. Brominations are completed with minimal $\alpha \rightleftarrows \alpha'$ bromine equilibrations of the products. The directions of brominations correspond closely to those expected for brominations of equilibrium mixtures of nonequilibrating enols and enol ethers. The equilibrium compositions of the enols and enol methyl ethers of 2-substituted cyclohexanones are influenced by the nature of the substituent and appear to range from near-quantitative favoring of the tetrasubstituted enol to mixtures consisting of appreciable quantities of tri- and tetrasubstituted enols, whereas the trisubstituted enol ethers always predominate. These differences in equilibrium compositions of enols relative to enol ethers appear to derive from the preference of the O–H and O–CH_3 bonds for the coplanar and double-bond eclipsed rotational conformation.

Experimental[34]

Brominations. General Procedure.—To a stirred solution of 0.4 mole of cycloalkanone or its dimethyl or ethylene ketal in 500 ml. of anhydrous methanol or ethylene glycol at room temperature was added a small portion of bromine. If, after a short period, uptake of the bromine was not complete, the solution was warmed until the reaction was initiated. The remainder of 64 g. of bromine was added generally at 15–20° at such a rate so as to maintain a faint coloration of bromine at all times. If at the end of the bromine addition the bromine color did not persist for several minutes at *ca.* 10°, additional bromine was added until this condition was realized. The reaction mixture[35] then was poured into a stirred mixture of 100 g. of anhydrous sodium carbonate and 400 ml. of pentane (hydrogen bromide may be neutralized with an excess of sodium methoxide for brominations carried out in methanol, followed by pouring into water and extraction of product). After continuing the stirring for several minutes, about 500 ml. of water was added, the pentane extract separated and dried, and the pentane was evaporated under reduced pressure. Occasionally the residue was distilled; however, significant fractions distilling before or after the monobromo ketal were seldom encountered and it was found advantageous often to proceed directly to the dehydrobromination.[36]

The crude or distilled reaction product was refluxed with 200 ml. of methanol and 50 g. of sodium hydroxide for 2–3 days. Reaction periods of less than 24 hr. were sufficient for the five- and six-membered rings and it appears (see later) that sodium methoxide in DMSO affects dehydrohalogenation within much shorter periods. The reaction mixture was poured into 400 ml. of water saturated with sodium chloride and the product was extracted with two 400-ml. portions of pentane. The extracts were combined and dried, and the pentane was evaporated under atmospheric pressure. The residue was distilled to give the ketal of the corresponding cycloalk-2-enone. The ketal product was shaken with an equal volume of 3% sulfuric acid for 5 min. The product was extracted with several portions of ether, the combined extracts were washed with dilute sodium bicarbonate and dried, and the ether was evaporated under atmospheric pressure. The residue was distilled to give the cycloalk-2-enone in 40–60% over-all yield.

It is considered important, particularly for dibrominations of cycloalkanones in methanol, to ensure that a slight excess of bromine is maintained in the reaction mixture during the course of the bromination. Elimination of alcohol from the monobromo ketal product leads predominantly to the enol ether containing an allylic bromine (see text) which reacts rapidly in the presence of bromine to give the α,α'-dibromo ketal. In the absence of bromine, methanolysis of the allylic bromine of the enol ether, which occurs apparently at a slower rate than that of bromine reaction, may result. For example, monobromination of 2-methylcyclohexanone in methanol which takes about 25 min. at 20° leads to a mixture of 2- and 6-bromo ketals (see text) with no indication of methanolysis products. If the reaction solution is left after completion of bromination, within 10 min. nearly all of the 2-bromo ketal and possibly some of the 6-bromo ketal has solvolyzed to the corresponding methoxy ketal (followed by n.m.r.), and, within 1 hr., no brominated products remain. Yet, if 2-methylcyclohexanone dimethyl ketal is dibrominated in methanol at 20° higher temperature and about 10 min. longer reaction time than required for monobromination, the n.m.r. of the product indicates that bromination was accompanied by less than 5% of methanolysis.

Cyclopent-2-enone (**14**).[37]—Following the general procedure, bromination of **1** in ethylene glycol followed by dehydrobromination for a period of 3 hr. gave 58% of **7**, b.p. 64–65.5° (22 mm.), $n^{28}{}_{\mathrm{D}}$ 1.4646, lit.[6] $n^{18}{}_{\mathrm{D}}$ 1.4675. The hydrolysis of **7** led to 65% of **14**, b.p. 68.5–69° (23 mm.), $n^{29}{}_{\mathrm{D}}$ 1.4739, lit.[2a] $n^{20}{}_{\mathrm{D}}$ 1.4814.

Cyclohex-2-enone (**15**).[37]—Bromination of **2** in ethylene glycol at 35–40° gave 78% of 2-bromocyclohexanone ethylene ketal, b.p. 90.5–92.5° (5 mm.), which upon dehydrobromination for 18 hr. was converted in 75% yield (based upon 79% reaction of bromo ketal) to **8**, b.p. 86.5–88.5° (23 mm.), $n^{26}{}_{\mathrm{D}}$ 1.4775, lit.[6] $n^{20}{}_{\mathrm{D}}$ 1.4768. Hydrolysis of **8** gave 75% of **15**, b.p. 68.5–69° (23 mm.), $n^{27}{}_{\mathrm{D}}$ 1.4838, lit.[2b] $n^{27}{}_{\mathrm{D}}$ 1.4858.

Carrying out the bromination of **2** in methanol at 15–20° led to 78% of 2-bromocyclohexanone dimethyl ketal, b.p. 78° (3.2 mm.).

Anal. Calcd. for $C_8H_{15}BrO_2$: C, 43.06; H, 6.78. Found: C, 43.11; H, 6.62.

Dehydrobromination of 2-bromocyclohexanone dimethyl ketal for 24 hr. following the general procedure gave 80% of **9**, b.p. 66.5–67° (21 mm.). Alternatively, 22.3 g. of bromo ketal in 50 ml. of dry dimethyl sulfoxide[38] was treated with 16 g. of sodium methoxide. Cooling was required to maintain the initial reaction temperature below 50°. After the initial reaction had subsided, the reaction mixture was left at room temperature for 3 hr. Proceeding as described in the general procedure led to 11.6 g. (82%) of **9**.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.29; H, 9.74.

4,4-Dimethylcyclohex-2-enone Ethylene Ketal (**10**).—Bromination of **3**[39] was carried out[37] in ethylene glycol at 50–55°. The crude product was crystallized from methanol to give 81% of **31**, m.p. 63°.

Anal. Calcd. for $C_{10}H_{17}BrO_2$: C, 48.20; H, 6.88. Found: C, 48.33; H, 6.83.

Dehydrobromination of **31** (24-hr. reaction time) afforded 81% of **10** (based upon 67% reaction of bromo ketal), b.p. 69° (4 mm.).

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[34] Spectral data given in the tables or in the text are not repeated in the Experimental. N.m.r. spectral data on **7–26** will be discussed in subsequent articles; see ref. 7.

[35] During brominations in ethylene glycol, the bromo ketal product separated generally from solution. Consequently, dibrominations in ethylene glycol are difficult to accomplish, even at increased temperatures.

[36] The brominations of ketones in alcohol generally led to small amounts (*ca.* 10%) of unketalized bromocycloalkanone.[12] Under the dehydrobromination conditions and subsequent work-up, products arising from the Favorsky rearrangement are thought to be removed from the major reaction products.

[37] The general procedure was followed unless stated otherwise.

[38] The dimethyl sulfoxide was dried over Linde 3A Molecular Sieves.

[39] F. G. Bordwell and K. M. Wellman, *J. Org. Chem.*, **28**, 1347(1963).

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.35; H, 9.89.

The hydrolysis of **10** to give **16**, the precursor of **3**, was not performed.

4-*t*-Butylcyclohex-2-enone (**17**).—4-*t*-Butylcyclohexanone[40] (0.1 mole) was monobrominated at 50–55° in 200 ml. of ethylene glycol containing 8.1 g. of anhydrous hydrogen bromide.[37] The bromo ketal product (24.0 g., 87%) distilled between 94 and 96° at 0.05 mm. The bromo ketal (24.0 g.), DMSO[38] (100 ml.), and sodium methoxide (16.2 g.) were mixed and the resulting mixture was kept at 80° for 2.5 hr. The mixture was poured into water, and the product was extracted with pentane. The pentane extract was separated and dried, and the pentane was evaporated. The residue was distilled to give 8.7 g. (72% based upon bromo ketal reacted) of **11**, b.p. 76–78° (0.5 mm.), and 7.0 g. (29%) of recovered bromo ketal, b.p. 95–100° (0.5 mm.).

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.76; H, 10.30.

A mixture of 4.2 g. of **11**, 15 ml. of 15% sulfuric acid, and 10 ml. of dioxane was stirred at room temperature for 15 min. Work-up[37] led to 2.3 g. (71%) of **17**, b.p. 88–89° (4.6 mm.).[34]

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.91; H, 10.92.

Cyclohept-2-enone (**18**).[37]—Cycloheptanone (**5**) was brominated in ethylene glycol between 25 and 30° and the 2-bromocycloheptanone ethylene ketal, b.p. 79–83° (0.5 mm.), was obtained in 81% yield. Dehydrobromination of the bromo ketal for 72 hr. led to 78% of **12**, b.p. 67° (2.4 mm.).

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.40; H, 9.39.

The hydrolysis of **12** gave 87% of **18**, b.p. 52–52.5° (2.4 mm.).

Cyclooct-2-enone (**19**).[37]—The bromination of **6** in ethylene glycol at 5 to 10° followed by dehydrobromination of the crude bromo ketal for 64 hr. led to 59% of **13**, b.p. 67–69° (1.4 mm.).

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.16; H, 9.45.

The hydrolysis of **13** gave 88% of **19**, b.p. 70–71.5° (2.8 mm.).

4,4-Dimethylcyclohexa-2,5-dienone (**24**).—To a stirred solution of 9.4 g. of 4,4-dimethylcyclohexanone ethylene ketal in 100 ml. of anhydrous ether was added 18 g. of bromine dropwise at such a rate so as to maintain a gentle reflux. After 1 equiv. of bromine had reacted, further reaction proceeded relatively slowly. The remainder of the bromine was added over a period of several minutes, and the resulting mixture stirred for 15 min. at room temperature. A cooled solution of monosodium ethylene glycolate prepared from 2.6 g. of sodium and 70 ml. of ethylene glycol at 70–100° was added slowly, and the resulting mixture was poured into water. The ether layer was separated and dried, and the ether was evaporated under reduced pressure. The residue was crystallized from methanol, and 8.4 g. (47%) of **30**, m.p. 123–124°, was collected by filtration. The *cis* (diequatorial) bromine configuration of **30** follows from a single sharp methylene proton magnetic resonance of the ketal function (τ^{CCl_4} 5.71) and a four-peak resonance for the two axial C-2 and C-6 hydrogens displaying a large value of J^0 of 18.1 c.p.s.[18] at τ^{CCl_4} 7.54.

Anal. Calcd. for $C_{10}H_{16}Br_2O_2$: C, 36.61; H, 4.92. Found: C, 36.80; H, 4.84.

A solution of 8.2 g. of **30** in 50 ml. of dry[38] DMSO was treated with 11.5 g. of potassium *t*-butoxide. The mixture slowly warmed to 75° and, after standing at room temperature for 1.5 hr., was poured into 100 ml. of saturated salt solution. The product was extracted with two 100-ml. portions of pentane, and the extracts were combined and dried. The pentane was evaporated under reduced pressure and the residue was distilled to give 2.2 g. (53%) of a mixture of about 80% of **20** and 20% of **10**, b.p. 70–73° (1.8 mm.), and 1.3 g. of unidentified products, b.p. 95–100 (1.8 mm.).

Hydrolysis[37] of 1.5 g. of the mixture of **20** and **10** gave 1.0 g. of product analyzed by g.l.c. to consist of about 80% of **24** and 20% of **16**. Pure **24** was collected by g.l.c. and its n.m.r. spectrum[34] was identical with that of **24** prepared by a different route.[41]

Refluxing a mixture of 8.2 g. of **30** and 2 g. of sodium hydroxide in 75 ml. of methanol for 66 hr. gave, after work-up (general procedure), 3.2 g. (76%) of **10**, b.p. 61.5–63° (2.0 mm.), containing no detectable amount of **20**, and 1.5 g. of a mixture of **30** and **31**. After a mixture of 1.1 g. of **30**, 2 g. of sodium hydroxide, and 10 ml. of methanol was refluxed for 18 hr., the product was analyzed by n.m.r.[42] and found to consist of 12% of **30**, 46% of **31**, and 42% of **10**.

Cyclohepta-2,6-dienone (**25**).—To a solution of 15.6 g. of cycloheptanone ethylene ketal in 150 ml. of anhydrous ether was added 32 g. of bromine at such a rate so as to maintain a gentle reflux of the ether. Extra bromine (several drops) was added until the bromine color persisted for several minutes. A solution of monosodium ethylene glycolate prepared from 5 g. of sodium and 75 ml. of ethylene glycol was added slowly. The resulting mixture was worked up as described for **24**. The crude dibromo ketal product was added to a mixture of 22 g. of sodium hydroxide and 100 ml. of methanol and the mixture refluxed for 48 hr. Proceeding as described in the general procedure, 9.7 g. (64%) of **21**, b.p. 58° (0.75 mm.), was obtained.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.53; H, 8.11.

The hydrolysis of **21** as described in the general procedure gave 72% of **25**, b.p. 50.5–51° (1.0 mm.).[34]

Anal. Calcd. for C_7H_8O: C, 77.75; H, 7.45. Found: C, 77.43; H, 7.70.

Bromination[37] of 0.2 mole of cycloheptanone in 500 ml. of absolute methanol using 2 equiv. of bromine and adding the first equivalent at 25° and the second at 40°, followed by dehydrobromination of the crude product using 32 g. of sodium hydroxide and 100 ml. of methanol for 66 hr., yielded 46% of **22** distilling between 63 and 67° at 3.8 mm.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.35; H, 9.45.

Cyclohept-3,5-dienone (**29**).—Cycloheptanone ethylene ketal (15.6 g.) in 250 ml. of absolute methanol was brominated with 32 g. of bromine as described for the above synthesis of **22**. The crude product dissolved in 100 ml. of dry DMSO[38,41] was treated with 26 g. of sodium methoxide (cooling is required to maintain the initial reaction temperature below 60°), and the mixture was left at room temperature for 16 hr. Proceeding as described in the general procedure, 6.4 g. (53%) of **27**[11] (containing <5% of **28**[11]), b.p. 54.5–55.5° (5.4 mm.), was obtained.

Anal. Calcd. for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.40; H, 8.49.

Pyrolysis of **22** on a 15-ft. QF-1-on-firebrick column at 165° afforded a mixture of about 56% of **27** and 44% of **28**, determined by n.m.r.

A mixture of 4.5 g. of **27** and 10 ml. of 10% sulfuric acid was stirred at room temperature for 15 hr. The product was extracted with pentane. The pentane extract was washed with dilute sodium bicarbonate and dried, and the pentane was evaporated. Distillation of the residue gave 3.2 g. (81%) of **29**, b.p. 54° (5.4 mm.).

Cycloocta-2,7-dienone (**26**).—Cyclooctanone ethylene ketal, 17.0 g., was dibrominated following the directions described for the synthesis of **25**. The crude product was crystallized from methanol and 28.4 g. (87%) of 2,8-dibromocyclooctanone ethylene ketal, m.p. 74–75°, was collected by filtration. Recrystallizations from methanol raised the melting point to 78°. The configurationally homogeneous dibromo ketal exhibits a four-peak H-2, H-8 magnetic resonance at τ^{CCl_4} 5.43 with J^0 = 11.8 c.p.s.[18]

Anal. Calcd. for $C_{10}H_{16}Br_2O_2$: C, 36.61; H, 4.92. Found: C, 36.80; H, 4.84.

A mixture of 20 g. of dibromo ketal, 20 g. of sodium hydroxide, and 100 ml. of methanol was refluxed for 66 hr. Proceeding as described in the general procedure, 8.8 g. (87%) of **23**, b.p. 65° (0.3 mm.), was obtained.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.47; H, 8.64.

The hydrolysis of **23** as described in the general procedure afforded 75% of **26**, b.p. 44° (0.5 mm.).[34]

Anal. Calcd. for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.41; H, 8.40.

3-Bromo-2-methoxycyclohexene (**50**).—To a solution of 11.1 g. of 2-bromocyclohexanone dimethyl ketal (see above) in 25 ml. of anhydrous ether containing 5.1 g. of acetic anhydride was

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[40] The author is grateful to the Dow Chemical Co. for providing a generous sample of this material.

[41] F. G. Bordwell and K. M. Wellman, *J. Org. Chem.*, **28**, 2544 (1963).

[42] In benzene solution the chemical shifts of the methyl proton resonances of **30** (two), **31** (two), and **10** (one) are all different and are appreciably concentration dependent.

added 15 drops of sulfuric acid. The solution was left at room temperature for 15 hr. and then poured onto 20 g. of anhydrous sodium carbonate. Ether (75 ml.) was added, and the mixture was stirred for several minutes and then filtered. The ether of the filtrate was evaporated under reduced pressure, and the residue was distilled giving 8.5 g. (89%) of **50**, b.p. 49° (0.2 mm.).

Anal. Calcd. for $C_7H_{11}BrO$: C, 44.00; H, 5.81. Found: C, 43.98; H, 5.89.

2-Methoxy-3-methylcyclohexene (52) and 1-Methoxy-2-methylcyclohexene (53).—The acid-catalyzed elimination of methanol from 2-methylcyclohexanone dimethyl ketal (**46**) according to the procedure described for the synthesis of **50** was not straightforward. Pyrolytic decomposition of **46** to **52** and **53** was affected on a 15-ft. QF-1-on-firebrick g.l.c. column at 190°. The product was collected and distilled, b.p. 65° (23 mm.), and consisted of 53% of **52** and 48% of **53** by n.m.r. analysis (see Table V and text).

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.40; H, 11.48.

3-*t*-Butyl-2-methoxycyclohexene (54) and 1-*t*-Butyl-2-methoxycyclohexene (55).—The approach for the preparation of 2-*t*-butylcyclohexanone dimethyl ketal was exactly that used for the preparation of **46**. A solution of 15.4 g. of 2-*t*-butylcyclohexanone,[43] 21 g. of trimethyl orthoformate, 6.4 g. of anhydrous methanol, and 1.0 g. of *p*-toluenesulfonic acid was refluxed until the required quantity of methyl formate was collected. Sodium methoxide (1.5 g.) was added, and the mixture was filtered. The methanol and excess orthoformate were evaporated under reduced pressure and the residue was distilled to give 13 g. (77%) of a mixture of 92% of **54** and 8% of **55** distilling at 48° (0.75 mm.).

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.75; H, 11.90.

Brominated 2-Methylcyclohexanones.—Table III shows that mono- and dibrominations of **34** in ether led almost exclusively to **35**, b.p. 46–48° (0.5 mm.), and **38**, m.p. 39°, respectively, as concluded by Corey, Topie, and Wozniak.[16] No *cis*-2,6-dibromo-2-methylcyclohexanone could be detected from the dibromination of **34**; n.m.r. spectra of the product dissolved in carbon tetrachloride or benzene exhibited single sharp methyl resonances and single H-6 resonances.

2-Bromo-6-methylcyclohexanone (**36** and **37**) was prepared by brominating at 20° and with 3.52 g. of bromine 3.43 g. of 3-methylcyclohexan-2-one carboxylic acid[16] in 80 ml. of water containing 11 g. of sodium acetate trihydrate. After the bromine was absorbed, the solution was warmed to 50° and maintained at this temperature for 10 min. The product was extracted with ether. The ether extract was dried, and the ether was evaporated. Distillation of the residue gave 2.3 g., b.p. 56–76° (0.25 mm.), of a mixture consisting of 77% of **36** and 23% of **37** and no detectable **35** or dibromination product (by n.m.r.). **37** distils at the higher temperature and should be separated readily from **36** if desired.

The preparation of **39** was accomplished according to the directions of Corey, *et al.*[16] The procedure is essentially the same as for the synthesis of **36** and **37**; however, decarboxylation was affected in the presence of a second equivalent of bromine. The first attempt gave a mixture of dibromo ketones, b.p. 85–87° (0.5 mm.), consisting of 86% of **39** and 14% of **38**. The second attempt, which differed from the first insofar as the decarboxylation temperature was about 60° compared with 50° and the second equivalent of bromine was added more rapidly, gave a product that analyzed for 65% of **39** and 35% of **38**.

Brominations of 2, 33, 34, 40, and 46 (Table III).—The essential conditions for each experiment reported are listed in Table III. Further details are given as footnotes when necessary. For brominations conducted in methanol, it is important to ensure that a small excess of bromine is maintained in the reaction mixture during the course of the bromination (see general procedure). Immediately after the completion of each bromination the reaction mixture was processed. For mono- and dibrominations in ether, the reaction mixture was poured into water and the ether layer was washed with water and dilute sodium bicarbonate, and finally dried. For monobrominations in methanol, cold water was added slowly to the reaction mixture until the point of turbidity. The mixture was stirred for 3–5 min. at room temperature followed by adding an excess of water and extraction with ether. The ether layer was washed with water and dilute sodium bicarbonate and finally dried. This procedure was found to lead to complete hydrolysis of the monobromo ketals, but negligible hydrolysis of the dibromo ketals. For dibrominations in methanol, the reaction mixtures were added to an excess of anhydrous sodium carbonate, and the resulting mixture was stirred for several minutes. Water was added then and the dimethyl ketal products were extracted with pentane. In all instances, the solvent of the dried extracts was evaporated under reduced pressure and the residue were placed under 0.5-mm. pressure at room temperature for 5 min. N.m.r. analyses were performed then on samples of the crude products.

The bromination and equilibration results listed in Table II and III were found to be reproducible well within ±5%.

N.m.r.—The n.m.r. spectra were determined using a Varian A-60 spectrometer. Double resonance experiments were performed using a Varian DP-60 spectrometer and have been described in part.[7] Composition analyses were accomplished on mixtures containing **34–45** by planimeter integration of the methyl and *t*-butyl proton magnetic resonances recorded under slow-sweep conditions so as to minimize peak-shape distortions, or by measuring peak heights under normal-sweep conditions. Both procedures afforded closely comparable results. Other analyses were performed by electronic integration.

Acknowledgment.—The author is appreciative of support from the Petroleum Research Fund (Grant No. 1536) of the American Chemical Society.

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