Relative Rates and Stereochemistry of the Iodozincmethyl Iodide Methylenation of Some Hydroxy- and Methoxy-Substituted Cyclic Olefins

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Abstract: Relative rates were determined for methylenation of the following compounds: 2-cyclohexenol (**1**), 1.00; 2-cyclohexenyl methyl ether (**2**), 0.50; 1-cyclohexenylmethanol (**3**), 0.46; *cis*-5-methylcyclohexenol (**4**), 1.54; *trans*-5-methylcyclohexenol (**5**), 0.46; 3-cyclohexenol (**6**), 0.091; 1-methoxycyclohexene (**7**), 0.059. The reactions of **1**, **4**, **5**, and **6** were shown to occur with high stereospecificity. In contrast, 3-cyclohexenylmethanol (**8**) undergoes methylenation at a much slower rate (comparable to cyclohexene itself), and yields a mixture of *cis* and *trans* products. No directive influence can be ascribed to the hydroxyl function in this system. *endo*- and *exo*-bicyclo[2.2.1]-hept-5-en-2-ol and *endo*- and *exo*-2-hydroxymethylenebicyclo[2.2.1]hept-5-ene were briefly examined, and no significant rate increase associated with the hydroxyl function was observed. From the rate data, it can be concluded that the reaction of allylic cyclohexenols occurs through the quasi-equatorial hydroxyl conformation.

The important cyclopropane-forming reaction evolved by Simmons and Smith[2] has found wide application in organic synthesis. A particularly interesting aspect of this methylenation reaction is the stereoelectronic control, or *cis* directive influence, of a nearby hydroxyl group. First observed by Winstein and his coworkers[3] in the conversion of homoallylic 3-cyclopentenol to the corresponding *cis*-cyclopropane derivative, others have subsequently shown that the effect is operative also in the allylic alcohols 2-cyclopentenol[4] and 2-cyclohexenol.[5] There is some ambiguity concerning the specificity of reaction of the latter compound—Dauben and Berezin[5] found exclusive *cis* product, while Cope and his coworkers[6] obtained from a number of experiments mixtures containing 75–88% of the *cis* isomer. Similarly, 2-cycloheptenol has been reported to give a mixture (91% *cis*) of cyclopropane derivatives.[7] In more complex molecules, the directing influence of a hydroxyl group has been used to effect stereoselective syntheses.[5,8-11]

The present study was directed at determining the limitations of the directive influence in terms of substrate structure and position of hydroxyl substitution, and also the effect of structure on the rate of methylenation.

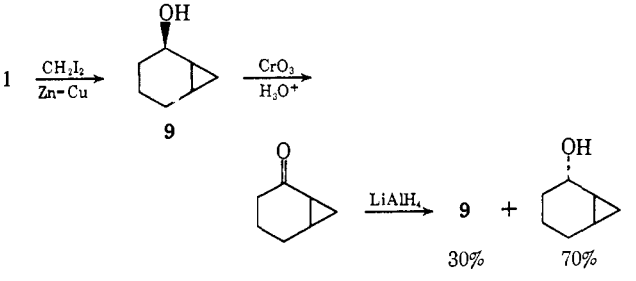
Results and Discussion

The Simmons–Smith reaction does not lend itself readily to the determination of absolute rate constants, due to the instability of the organometallic reagent, and difficulties in accurately determining the concentration of this reactive species.[12,13] Relative rates, however, may be obtained using the competitive kinetic technique.[11] We have recently used this approach in a study of the effects of ring size and alkyl substitution on the methylenation of cyclic olefins.[14] The same experimental procedure was used in the present work, except that formation of zinc salts of the hydroxyolefins and cyclopropanes necessitated an aqueous wash and extraction prior to vapor phase chromatography (vpc) analysis.

Blanchard and Simmons[12] have shown that the methylenation reaction (using cyclohexene) is kinetically first order in olefin and in organometallic reagent. Although the competition method furnishes no information regarding the order in organometallic (as this concentration term is cancelled), the possibility that a different mechanism operates with hydroxy-substituted olefins required that the order in these materials be determined. Different initial concentrations of 2-cyclohexenol (**1**) and *cis*-5-methyl-2-cyclohexenol were used, and, as shown in the Experimental Section, reproducible constants were obtained only when the data were treated according to the usual first-order rate law.

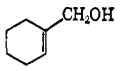
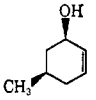
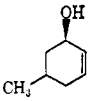
Relative rate values obtained in this manner are shown in Table I.

As noted previously, the literature[5,6] is not in accord regarding the degree of *cis* specificity in the methylenation of **1**. Consequently, we have reexamined this reaction, using chromic acid oxidation of the cyclopropane derivative **9** and subsequent lithium aluminum



(1) Alfred P. Sloan Foundation Fellow, 1967–1969.
(2) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, 80, 5323 (1958); 81, 4256 (1959).
(3) S. Winstein, J. Sonnenberg, and L. DeVries, *ibid.*, 81, 6523 (1959); S. Winstein and J. Sonnenberg, *ibid.*, 83, 3235 (1961).
(4) E. J. Corey and R. L. Dawson, *ibid.*, 85, 1782 (1963).
(5) W. G. Dauben and G. H. Berezin, *ibid.*, 85, 468 (1963).
(6) A. C. Cope, C. H. Park, and P. Scheiner, *ibid.*, 84, 4862 (1962).
(7) A. C. Cope, S. Moon, and C. H. Park, *ibid.*, 84, 4843 (1962).
(8) W. G. Dauben and A. C. Ashcraft, *ibid.*, 85, 3673 (1963).
(9) P. Radlick and S. Winstein, *ibid.*, 86, 1866 (1964).
(10) R. Ginsig and A. D. Cross, *ibid.*, 87, 4629 (1965).
(11) J. J. Sims, *J. Org. Chem.*, 32, 1751 (1967).
(12) E. P. Blanchard and H. E. Simmons, *J. Amer. Chem. Soc.*, 86, 1337 (1964).
(13) P. Turnbull, K. Syhora, and J. H. Fried, *ibid.*, 88, 4764 (1966).
(14) B. Rickborn and J. H. Chan, *J. Org. Chem.*, 32, 3576 (1967).

Table I. Relative Rates and Stereochemistry of Methylenation

Olefin	*k*(rel)	Stereochemistry
 1	1.00	100% *cis*
 2	0.50 ± 0.05	100% *cis*[c]
 3	0.46 ± 0.05	
 4	1.54 ± 0.1	100% *cis*[a]
 5	0.46 ± 0.05	100% *cis*[a,b]
 6	0.091 ± 0.012	100% *cis*
 7	0.059 ± 0.006	
 8	Very slow	55% *trans*, 45% *cis*[a]

[a] See Discussion. [b] Relative to hydroxy group. [c] See ref 5.

hydride reduction to give a mixture[5] of *cis*- and *trans*-alcohols. Our results are in agreement with those of Dauben and Berezin,[5] *i.e.*, no detectable (by vpc) *trans* product is formed in the methylenation of **1**.[15]

Two possible mechanisms have been suggested to account for the *cis*-directing function of a hydroxyl group in the Simmons–Smith reaction. Blanchard and Simmons,[12] noting the nearly equal amounts of methyl iodide and cyclopropane formed in the reaction of 3-cyclopentenol, have argued that the organometallic species contains two Zn–C bonds, one of which suffers rapid alcoholysis to give methyl iodide and a Zn–O derivative which subsequently yields *cis*-cyclopropane. Other authors[3,5] have suggested simple complex formation, with alcoholysis and methylenation occurring as two competing subsequent reactions.[5] Dauben and Berezin[5] found that mixing equivalent amounts of the organozinc reagent (determined by iodimetry) and 2-cyclopentenol gave cyclopropyl derivative in 80% yield. Clearly rapid prior alcoholysis is precluded by this result. Further, 2-cyclohexenyl methyl ether (**2**) was also found[5] to react readily to give exclusively the *cis*-cyclopropane derivative in good yield. This stereochemical result could of course obtain if **1** and **2** reacted by different mechanisms. However, in competition **1** is methylenated only twice as fast as **2** (Table I); a larger difference might have been anticipated if a particularly facile reaction route were available to **1** *via* alcoholysis.

Data supporting alcoholysis have been obtained from homoallylic systems, and it may be, as pointed out in later discussion, that a different mechanism prevails for methylenation of allylic and homoallylic alcohols.

We have previously shown[14] that 1-methylcyclohexene reacts somewhat faster than cyclohexene (factor of 2.1) in the Simmons–Smith methylenation. Conversely, 1-cyclohexenylmethanol (**3**) reacts only half as fast as **1**. It is apparent that the degree of alkyl substitution in either the hydroxylic or the simple olefin series does not greatly alter the rate of reaction. On the basis of the 1-methylcyclohexene–cyclohexene ratio, it might have been anticipated that **3** would undergo methylenation somewhat faster than **1**; the opposite experimental result may be associated with the slightly different geometries of this pair, or simply a function of the facility of zinc coordination with a primary as opposed to a secondary alcohol.

Although there is no direct evidence bearing on this question in the literature, it has been suggested[5] that stereospecific methylenation of allylic alcohols in the cyclohexyl series involves reaction through the axial-hydroxyl conformation. The relative rates of the isomeric compounds **4** and **5** were determined to clarify this point.

Earlier work has shown that an axial 4-methyl group exhibits a substantial rate-retarding effect in both epoxidation[16] and in Simmons–Smith methylenation[14] of cyclohexene. Both *cis*-4,5-dimethylcyclohexene and 4,4-dimethylcyclohexene, in which one methyl group must assume the axial position, react at rates approximately one-half that of the unsubstituted olefin.

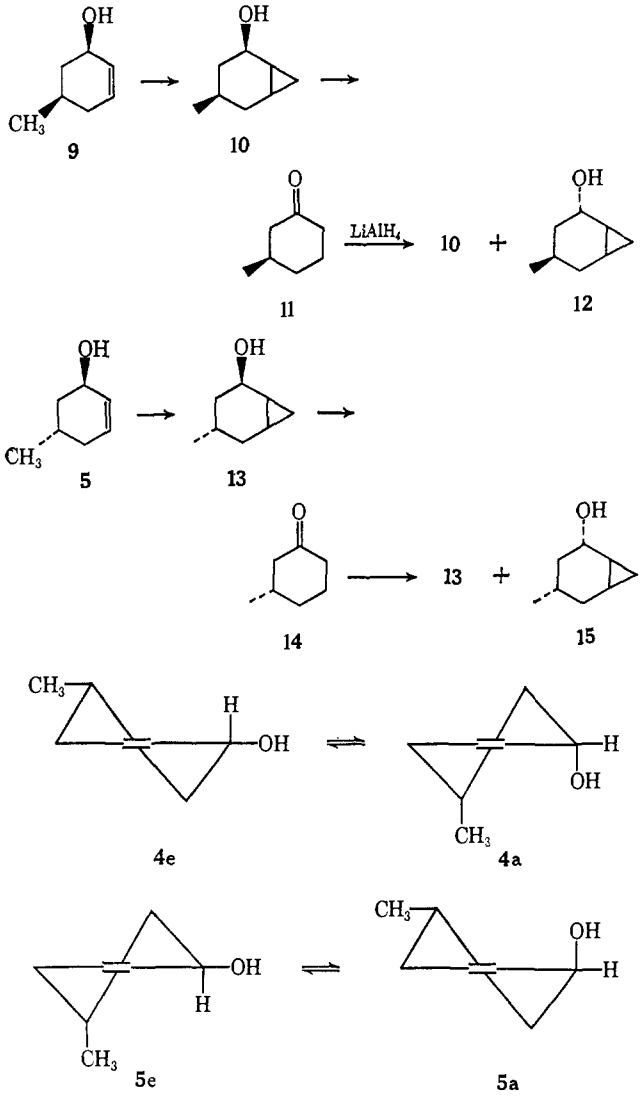
cis-5-Methyl-2-cyclohexenol (**4**) reacts readily with the organozinc reagent to give a single cyclopropane adduct **10**; oxidation of **10** gave a single ketone (**11**) which was subsequently reduced to a mixture of **10** and one other isomeric alcohol (**12**). These results, in conjunction with those obtained by similar treatment of the adduct from **5**, show that both **4** and **5** react in a completely stereospecific manner; by analogy with the reaction of **1** and other allylic systems, the methylenation is presumed to occur *cis* to the hydroxyl group.[17]

Two half-chair conformers may be drawn for both the *cis* (**4e**, **4a**) and *trans* (**5e**, **5a**) alcohols. If the methylenation reaction occurs through the quasi-axial hydroxyl organometallic complex (*i.e.*, with conformers **4a** and **5a** giving the observed stereospecific

(15) (a) The experimental evidence for a mixture of isomers given in ref 6 appears to be quite strong. Although there are no obvious differences in the experimental conditions employed, it may be that the mixture results from subsequent partial equilibration, perhaps due to the presence of some ketone and Oppenauer-type oxidation–reduction. It should be noted that this problem may also have arisen in the reaction of 2-cycloheptenol.[7] (b) After this paper was submitted, S. Sawada, K. Takehana, and Y. Inouye [*J. Org. Chem.*, 33, 1767 (1968)] reported that methylenation of **1** occurs with 97% stereospecificity.

(16) B. Rickborn and S. Lwo, *J. Org. Chem.*, 39, 2212 (1965).

(17) Compound **10** has been converted (tosylation and hydride reduction) to a single (presumed *cis*) 3-methylnorcarane, which has been catalytically reduced to a mixture of dimethylcyclohexanes. Unfortunately, our capillary vpc columns will not separate all four of the isomeric 1,3- and 1,4-dimethylcyclohexanes.

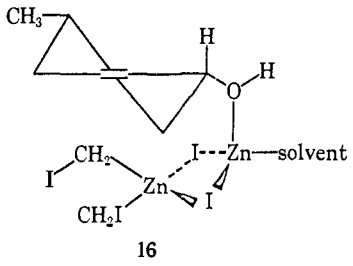


reaction), the axial 4-methyl group in **4a** should inhibit the rate such that $k(5) > k(4)$.

In fact, the opposite result is observed, with $k(4) = 3.3k(5)$. The relative rate constants for these isomers bracket the value for 2-cyclohexenol (**1**), supporting the suggestion that *stereospecific methylenation of allylic cyclohexenols occurs through the quasi-equatorial hydroxyl conformation.*

Application of the Winstein–Holness treatment[18] to the rate constants for **1**, **4**, and **5**, using the previously determined[19] conformational preference of the 4-methyl group (1.0 kcal/mol), leads to a value of 0.4 kcal/mol for the allylic hydroxyl group (quasi-equatorial conformation favored). Ferrier and Prasad[19] recently reported a comparable value of 0.4 kcal/mol obtained by equilibration of *cis*- and *trans*-5-*t*-butyl-2-cyclohexenol in aqueous acetone.[20,21]

Reaction of 2-cyclohexenol (and its alkyl derivatives) through the quasi-equatorial hydroxyl conformation seems unlikely for monomeric ICH_2ZnI. Models suggest that such a monomer, even with a relatively long Zn–O bond, would not allow centrosymmetric approach of the methylene group to the double bond. A dimeric organometallic species, on the other hand, may be sufficiently flexible to allow this preferred geometry and account for *cis* stereospecificity. A possible dimer–alcohol structure is illustrated (**16**).



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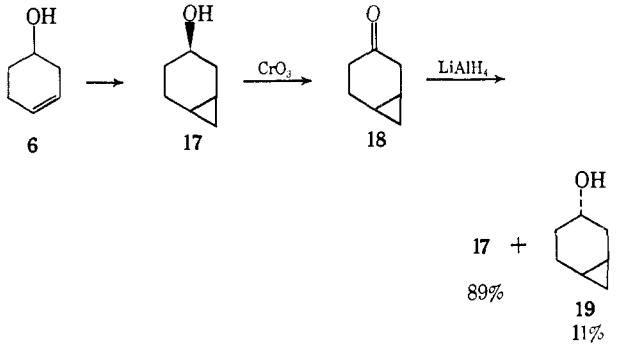
It should be noted that cancellation of the organometallic reagent concentration term occurs in the relative rate treatment used in this study, and consequently requiring a dimer for reaction need not imply that this is the major species in solution.

The homoallylic alcohols 3-cyclopentenol[3] and 3-cycloheptenol[7] have been reported to undergo methylenation with very high *cis* specificity. The six-membered homoallylic analog, 3-cyclohexenol (**6**), has not been previously examined. Although **6** reacts



about a factor of 10 slower than the allylic alcohol **1**, the product **17** is formed stereospecifically, as shown by oxidation to the ketone **18**, followed by hydride reduction to a mixture of **17** and the isomeric alcohol **19**. Again the *cis* structure of **17** is assumed by analogy with results from other homoallylic systems.[22]

While **6** is less reactive than **1**, it is methylenated immeasurably faster than a nonhydroxylic olefin, as shown by competition with 4-*t*-butylcyclohexene.[23] Thus stereospecificity is anticipated on the basis of kinetics. It is interesting that the rate factor separating **1** from **6** is similar for both methylenation and epoxidation by perbenzoic acid,[24] although the latter reaction is reported to show *cis* specificity only for the allylic alcohol.[24–27]

(18) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, 77, 5562 (1955); for the present calculation, it was assumed that 4 very strongly prefers the diequatorial conformation.

(19) R. J. Ferrier and N. Prasad, *J. Chem. Soc., C*, 1417 (1967).

(20) However, the equilibration of 4 and 5 has been reported[21] to favor 5 (55 ± 1%) under similar conditions. This unusual result has not been adequately rationalized (*cf.* discussion in ref 19).

(21) H. L. Goering and R. R. Josephson, *J. Amer. Chem. Soc.*, 84, 2779 (1962).

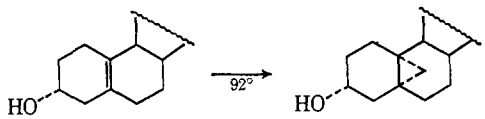
(22) The most obvious and direct method to demonstrate the stereochemistry of **17** would be hydrogenolysis to give 3- and 4-methylcyclohexanols; unfortunately, we have been unable to separate by vpc the four possible isomers involved in this analysis.

(23) This olefin, which reacts only slightly slower (~10%) than cyclohexene itself,[14] was used to facilitate analysis.

(24) (a) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957); (b) H. B. Henbest and B. Nicholls, *ibid.*, 4608 (1957).

(25) The generality of a *cis*-directing influence, even in allylic alcohols, is open to question. For example, Cope and his coworkers have reported that peracid epoxidation of 2-cycloheptenol yields a mixture of isomers (mainly *cis*),[26] while 2-cyclooctenol gives the *trans* epoxide.[21]

A striking example of *cis* methylenation in the very slow reaction of estr-5(10)-ene-3α,17β-diol (partial structure **20**) has been described by Ginsig and Cross.[10] Under the usual Simmons–Smith conditions (refluxing ether), **20** was recovered unchanged; higher temperature (92°, sealed tube) was required for reaction. The



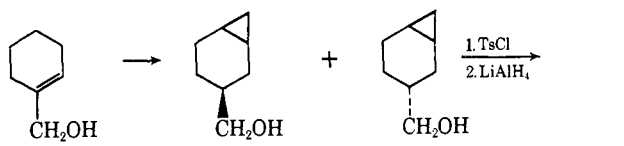
20 **21**

product, obtained in high yield, was the α, or *cis*, methylenated material **21**. It is significant that alcoholysis occurred in this system prior to methylenation; coupled with the observed *cis* specificity, this suggests that the reaction takes place according to the mechanism proposed by Blanchard and Simmons.[12]

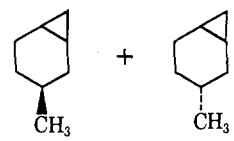
In the absence of a directing group, the steroid 5(10) double bond is usually attacked at the β face by electrophiles. For example, the analogous 3-one in reaction with peracid is reported to give the β-5(10)-epoxide.[28] Further, the 3-β-ol epimer of **20** undergoes *cis* methylenation readily under normal Simmons–Smith conditions.[10] A convincing argument has been presented[29] that the preferred ring A half-chair conformation is such that the 3-α-hydroxyl will be predominantly equatorial; conversely the 3-β-hydroxyl should exist preferentially in the axial conformation.

If the observed epimer rate difference is in fact due to the conformational preference of the hydroxyl group, it would appear that there is a fundamental difference in the mechanism of methylenation of allylic and homoallylic alcohols, namely, reaction through the equatorial and axial conformations, respectively. Prior alcoholysis may also be a general feature of the methylenation of homoallylic alcohols.

Interestingly, when the hydroxyl group is one carbon further removed from the double bond, as in 4-hydroxymethylenecyclohexane (**8**), the rate of methylenation becomes too slow to measure in competition with an allylic or homoallylic alcohol. In fact, **8** proved to be only slightly more reactive than 4-*t*-butyl-



8 **22** **23**

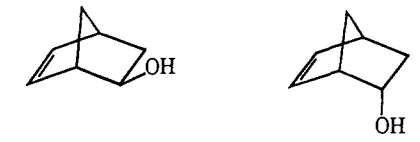


24 **25**

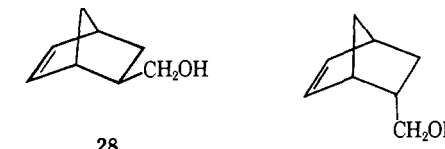
cyclohexene,[23] with k(**8**)/k(4-*t*-butylcyclohexene) = 1.6 ± 0.3. Furthermore, **8** gave rise to a mixture of isomers, **22** (45%) and **23** (55%); these in turn were converted to the tosylates, which on lithium aluminum hydride reduction gave a mixture of **24** (45%) and **25** (55%). The *cis* configuration of **24** (and hence **22**) was assigned by tosylation and subsequent hydride reduction of **10**.

The effective total absence of an hydroxyl directive influence in the methylenation of **8** is emphasized by comparison with the stereochemical results obtained with 4-methylcyclohexene, which gave 43% *cis*- and 57% *trans*-3-methylnorcaranes (**24** and **25**).[30] Hence, both kinetically and stereochemically the hydroxymethylene group in **8** is equivalent to a methyl group, with deviations from complete nonselectivity in both being associated with steric interactions of the axial conformer.[14,16]

In this connection some preliminary results with bicyclic systems are worth mentioning. Although product analyses have not been carried out, the compounds **26**–**29** are comparable in reactivity. Specifically,



26 **27**



28 **29**

it was found that **28** and **29** undergo methylenation at essentially the same rate (±10%) as **8**. Thus differences in rate in comparison with norbornene are small or negligible.[14] It appears that rate enhancement due to hydroxy participation is subject to very specific geometric constraints.

Finally, the relative rate of the vinyl ether **7** was determined (Table I). Systems of this sort are of particular interest from the synthetic viewpoint, as acid cleavage leads to the corresponding α-methyl ketone. The utility of this sequence for angular methylation has already been demonstrated.[31] Although **7** proved to be the slowest of the "fast" systems examined, its relative rate is still much greater than that of, *e.g.*, cyclohexene. Since inductive and resonance effects appear to have only a small influence on the Simmons–Smith reaction,[12,14] it is suggested that the rate enhancement observed with **7** is again associated with a specific interaction of the vinyl ether oxygen with the organozinc reagent.

Experimental Section

2-Cyclohexenol (1). Commercial material (Aldrich) was dried over 4A Molecular Sieves and distilled through a 15-cm Vigreux column, bp 164–164.5°.[32]

3-Methoxycyclohexene (2). Similar drying and distillation of commercial material (K & K) gave the ether with bp 138–139°.[33]

(26) A. C. Cope, J. K. Heeren, and V. Seeman, *J. Org. Chem.*, 28, 516 (1963).

(27) A. C. Cope, A. H. Keough, P. E. Peterson, H. E. Simmons, Jr., and G. W. Wood, *J. Amer. Chem. Soc.*, 79, 3900 (1957).

(28) J. P. Ruelas, J. Iriarte, F. Kinci, and C. Djerassi, *J. Org. Chem.*, 23, 1744 (1958).

(29) (a) S. G. Levine, N. H. Eudy, and E. C. Farthing, *Tetrahedron Lett.*, 1517 (1963); (b) S. G. Levine, D. M. Feigl, and N. H. Eudy, *ibid.*, 4615 (1967).

(30) Kinetic analogies between methylenation and epoxidation have been discussed in a previous paper;[14] epoxidation of 4-methylcyclohexene also leads to a predominance of *trans* products (54%).

(31) E. Wenkert and D. A. Berges, *J. Amer. Chem. Soc.*, 89, 2507 (1967).

(32) R. Willstätter and E. Sonnenfeld, *Chem. Ber.*, 46, 2952 (1913).

(33) A. Berlande, *Bull. Soc. Chim. Fr.*, 9, 644 (1942).

1-Cyclohexenylmethanol (3). To a 500-ml flask fitted with a condenser, thermometer, and dropping funnel was added 100 g (0.78 mol) of cyclohexanecarboxylic acid and 1.8 ml of phosphorus pentachloride. The magnetically stirred mixture was heated to 90–95° and bromine, 150 g (0.94 mol), was added through the dropping funnel. The mixture was stirred for 12 hr at 70–80°, after which it was cooled and taken up in ether. Addition of 10% sodium bicarbonate gave the solid sodium salt, which was filtered, washed with ether, then treated with 3 *N* acid. The ether extract was dried with magnesium sulfate and evaporated to give a viscous oil residue of 1-bromocyclohexanecarboxylic acid.

The acid was converted to the methyl ester using methanol and sulfuric acid catalyst. The ester was taken up in pentane and washed with dilute bicarbonate solution and water. Evaporation of the solvent gave an oily residue which was added to 600 ml of dry 2,6-lutidine; this mixture was refluxed for 24 hr, taken up in pentane, and washed repeatedly with dilute acid to remove the lutidine. Evaporation of the solvent and distillation gave 80 g (73%) of the unsaturated ester, bp 80–81° (13 mm).

The ester was reduced using excess lithium aluminum hydride in ether. After quenching with dilute acid, the aqueous phase was saturated with salt and extracted with ether. After drying, the solvent was evaporated and the residue distilled to give 42 g (65%) of a clear colorless oil, bp 185–186°.[34] Vpc analysis using a 3.2 mm × 3 m diisodecylphthalate column indicated a purity of >99%; the integrated nmr spectrum was consistent with the structure of 1-cyclohexenylmethanol.

***cis*- (4) and *trans*-5-Methyl-2-cyclohexenols (5).** The 5-methyl-2-cyclohexenone was prepared by the method of Blanchard and Goering.[35] Using a slight excess of lithium aluminum hydride, 112 g (1.02 mol) of the ketone was reduced to give 107 g (94%) of material with bp 60–61° (5–6 mm). Vpc analysis showed this material to consist of 8% of **5** and 92% of **4**, in good agreement with the results of Goering.[36]

Substantial fractionation of this isomeric pair was accomplished by careful distillation through a Nestor–Faust Teflon annular spinning-band column. Pure **4** and **5** were then obtained by preparative vpc using a 6.4 mm × 8 mm 10% Carbowax 20M column at 160°. Samples were hydrogenated to the corresponding *trans*- and *cis*-3-methylcyclohexanols to verify the earlier configurational assignments.[36]

3-Cyclohexenol (6). Benzene was reduced by sodium in methanol–ammonia to 1,4-cyclohexadiene.[37] Purification was effected by distillation through the Teflon annular band column, bp 86.5–87.5°.

The diene, 30 g (0.38 mol), was treated with 1 equiv of *m*-chloroperbenzoic acid in ether for several hours at 0–5°. The ethereal solution was washed with dilute base and bisulfite solution, then dried and evaporated. Distillation of the residue gave 14.5 g (40%) of the monoepoxide, bp 41–43° (14 mm).[38] Lithium aluminum hydride reduction of 12.3 g (0.13 mol) afforded 11.8 g (94%) of 3-cyclohexenol, bp 164–165°.[39]

1-Methoxycyclohexene (7). Cyclohexanone was converted to the dimethyl ketal, bp 63–64° (30 mm), using trimethyl orthoformate and *p*-toluenesulfonic acid catalyst. The isolated ketal was heated with a small amount of concentrated sulfuric acid, and the methanol removed as it was formed. Distillation gave a nearly quantitative yield of the vinyl ether, bp 67–68° (57 mm).[40]

3-Cyclohexenylmethanol (8) was prepared in 71% yield by lithium aluminum hydride reduction of commercial 3-cyclohexene-1-carboxaldehyde. The product had bp 99–100° (25 mm),[41] gave only one peak on different vpc columns, and exhibited the anticipated nmr spectrum.

Cyclopropanes. The methylenation reaction was carried out using the procedure of Simmons and Smith[2] in ether solution with zinc–copper couple prepared by LeGoff's method.[42] Excess methylene iodide was added in portions to assure complete reaction; the reaction was followed by withdrawing aliquots for vpc analysis. The mixtures were hydrolyzed with 10% sodium hydroxide solution on completion to avoid losses in the gelatinous zinc hydroxide which otherwise precipitates when water is added. The aqueous phase was extracted with ether and the combined ethereal solutions were dried over potassium carbonate and evaporated. Very high crude yields were obtained.

The residues were used directly for stereochemical examination, as described below, or, for use as kinetic standards, purification (mainly removal of solvent and excess methylene iodide) was effected either by distillation or, more generally, by preparative vpc. All cyclopropane derivatives exhibited the expected nmr spectra.

Kinetics. The competitive kinetic technique was used, with approximately equal amounts of the two olefins to facilitate analysis by vpc. Standards were prepared using accurately weighed samples of the two purified olefins and their methylenated derivatives, and the vpc trace areas corrected by the factors obtained from the known mixtures. At least three runs were made for each olefin pair examined. Aliquots were hydrolyzed with base prior to analysis.

The question of kinetic order was explored using the allylic alcohols 2-cyclohexenol (A) and *cis*-5-methyl-2-cyclohexenol (B). Three runs were made with $A_0 = B_0$, $0.5B_0$, and $2B_0$, respectively. Calculated rate ratios using the usual first-order expression $k_B/k_A = [\ln (B/B_0)]/[\ln (A/A_0)]$ were 1.65, 1.8, and 1.55, identical within experimental uncertainty (material balances[14] were ≥90%). Values calculated using the zero-order expression $k_B/k_A = (B_0 - B)/(A_0 - A)$ were 1.6, 3.5, and 0.76. Treatment by the second-order expression $k_B/k_A = [(1/B) - (1/B_0)]/[(1/A) - (1/A_0)]$ led to values of 1.6, 0.97, and 3.0, respectively.

The competitive kinetic method used here does not furnish accurate data unless olefins of similar reactivity are used; data were thus obtained using the following pairs of olefins with the vpc column indicated in parentheses:[43] **1** and **2** (a); **1** and **3** (b); **1** and **4** (c); **4** and **5** (a) at 135°; **1** and **6** (c); **6** and 4-*t*-butylcyclohexene (c); **8** and 4-*t*-butylcyclohexene (c); **2** and **7** (a) at 90°; **8** and **28** (a) at 160°; **8** and **29** (a) at 160°. Material balances[14] were good in all kinetic runs, and in general exceeded 95%.

***cis*-2-Norcaranol (9).** The residue obtained from methylenation of **1** showed only one peak by vpc analysis, using column a.[43] A small amount was treated with excess Jones' oxidant[44] in acetone to give 2-norcaranone, a single peak by vpc analysis. The crude ketone was reduced directly by excess lithium aluminum hydride in ether to give a mixture of **9** (30%), RT (retention time in minutes) 22.1, and *trans*-2-norcaranol (70%), RT 26.2 using column a[43] at 140°. These results are in excellent agreement with those reported by Dauben and Berezin.[5]

***cis*-3-Norcaranol (17).** The residue obtained from methylenation of **6** gave a single peak on column c.[44] Oxidation as above gave alcohol-free ketone **18**, which was reduced to a mixture of **19** (11.4%), RT 22.0, and **17** (88.6%), RT 23.8; the above column was used at 145°.

***cis,cis*-4-Methyl-2-norcaranol (10).** Methylenation of **4** gave a single product, **10**; oxidation gave **11**, which was then reduced to a mixture of **10** (74.7%) and **12** (25.3%). Analytical conditions are described below.

***cis,trans*-4-Methyl-2-norcaranol (13).** Methylenation of **5** again gave a single product **13.** Oxidation to **14** followed by hydride reduction gave a mixture of **13** (5.6%) and **15** (94.4%).

Analyses were carried out on column a[43] at 132°; all stereoisomeric alcohols and ketones were mutually separable, with RT's as follows: **13**, 26.9; **10**, 29.2; **12**, 31.6; **11**, 34.8; **15**, 36.3; **14**, 38.8.

***cis*-3-Methylnorcarane.** A small sample of **10** was treated with tosyl chloride in pyridine at 5°. After standing overnight, the mixture was taken up in ether and washed with dilute acid, water, and bicarbonate solution. After drying, the solution was concentrated somewhat by rotary evaporation, and the tosylate was then reduced directly by adding lithium aluminum hydride.

The product obtained in this manner was compared with the methylenation product of 4-methylcyclohexene,[14] which showed two imperfectly separated peaks (43 and 57% in order of RT) on a 46-m Apiezon L capillary column at 65°. The hydrocarbon

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obtained by reduction of the tosylate exhibited only the shorter RT peak (*cis*).

3-Hydroxymethylenenorcarane (22, 23). The residue from methylenation of **8** gave only one peak on the vpc column used for kinetic analysis, but on an 8 m × 1.6 mm Carbowax 4M column at 150° showed two imperfectly separated peaks with areas of 45 and 55% (in order of RT). The tosylate prepared from a sample of this mixture was reduced by lithium aluminum hydride to give a mixture of *cis*- (45%) and *trans*-3-methylnorcarane (55%), analyzed on the capillary column described above.

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Rates and Salt Effects in the Reactions of Phenacyl Bromide with N-Ethylaniline and Triethylamine in Chloroform

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Abstract: Measurements of the rate of reaction of phenacyl bromide and N-ethylaniline in chloroform are fitted best by a rate equation involving two terms, one first order in amine and first order in bromide and the other second order in amine and first order in bromide. The reaction is subject to a strong, positive, neutral salt effect, and with a neutral salt added the reaction is bimolecular. The reaction of phenacyl bromide with triethylamine in chloroform also shows a positive salt effect and is bimolecular even in the absence of the neutral salt. The significance of these observations has been discussed.

The remarkable ease with which α-halo ketones undergo SN2 displacements was reported as early as 1909 by Slator and Twiss[1] and has been a subject of active investigation ever since. This enhanced reactivity has been attributed to inductive electron withdrawal by the carbonyl group,[2] to a mechanism involving an intermediate in which the nucleophile is covalently bonded to the carbonyl carbon,[3] to the electrostatic effect exerted by the carbonyl group on the approaching nucleophile,[4] and to orbital overlap with the nucleophile, either by the π-molecular orbital of the C–C–O system[5] or the p orbital of the carbonyl carbon.[6] The stereochemical implications of this last proposal have been explored in a well-designed experiment by Bartlett and Trachtenberg.[7] Although the results strongly support the orbital-overlap mechanism, they do not eliminate Pearson's[4] hypothesis.

The rates of reaction of phenacyl halides with amines are of special interest because of the many perturbations of second-order kinetics that are potentially possible. With strongly basic amines some of the diphenacyl halide formation observed in the reaction with ethoxide ion becomes possible.[8] With a primary amine competing azine formation has been observed in the reaction of 2-(bromoacetyl) naphthalene with isopropylamine.[9] In this same study it was found that the data were fitted best by eq 1

$$\frac{dx}{dt} = k(A_0 - X)(B_0 - nX) \qquad (1)$$

where A_0 is the initial halide concentration, B_0 the initial amine concentration, and n has a value intermediate between 1 and 2 rather than the expected value of 2. In reactions with amines the starting materials are neutral molecules, but the product includes a salt, either an amine hydrohalide or a quaternary ammonium salt. The transition state might, therefore, be expected to show extensive charge separation and to have ionic or zwitterionic characteristics. This could manifest itself in the observation of significant neutral salt effects. Finally, in the reactions with primary and secondary amines the transition from reactants to products necessarily involves a proton transfer at some stage of the process. The implications of this proton transfer step, even if not rate determining, are important in rate studies but have not been fully explored.

In the present study the rates of reaction of phenacyl bromide with N-ethylaniline were measured in methanol, in chloroform, and in 50% chloroform–50% carbon tetrachloride at 24.6 ± 0.1°. For purposes of comparison measurements were also made of the rates of reaction of phenacyl bromide with triethylamine and of benzyl bromide with N-ethylaniline and with triethylamine, all in chloroform. In addition the effect of added neutral salts on these reaction rates was investigated.

Results

The rate of reaction of phenacyl bromide and N-ethylaniline in chloroform, stabilized with 0.75% eth-

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