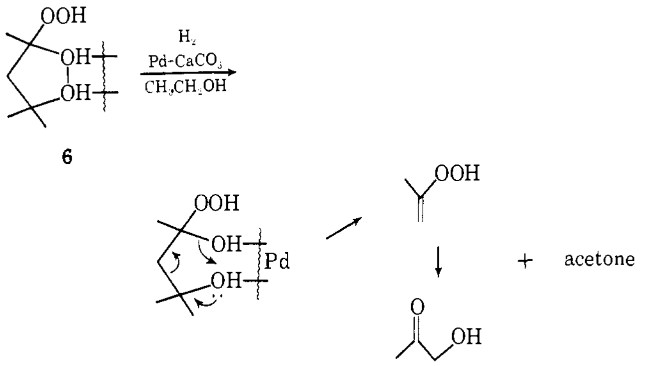
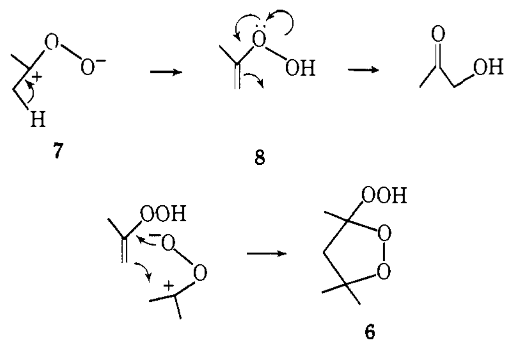
function.[12] Quantitative catalytic hydrogenation resulted in the uptake of approximately 1.5 mole equiv of hydrogen to yield acetone and hydroxyacetone, as identified by nmr and infrared analysis. These products are understandable in terms of, again, a retroaldol-type cleavage of the intermediate, as illustrated



The data outlined here constitute an unequivocal structure proof for the peroxy hydroperoxide **6**. We further submit that the most reasonable interpretation of the mechanism of formation of **6** is through a 1,3-dipolar addition of the dimethyl carbonyl oxide **7** to the vinyl hydroperoxide **8** which, we propose, is formed in the reaction by tautomerization of the carbonyl oxide **7**. The vinyl hydroperoxide **8** would be expected to isomerize to hydroxyacetone, as apparently observed in hydrogenation of **6**. Therefore, if the proposed mechanistic scheme is correct, the ozonolysis reaction mixture would be expected to contain some hydroxyacetone. We have established that the other, minor product (~1% yield) isolated from the ozonolysis is indeed hydroxyacetone. Taken together, the isolation of hydroxyacetone and **6** constitutes excellent evidence for the tautomerization and subsequent rearrangement of the carbonyl oxide **7**. This work constitutes the first observation of such a rearrangement of carbonyl oxides and suggests that this type of reaction should be given serious consideration in accounting for abnormal ozonolyses. In addition, the isolation of **6** provides the first concrete evidence for a 1,3-dipolar addition of a carbonyl oxide to an olefin. An obvious extension of the observed reaction is the addition of carbonyl oxides to vinyl ethers; this investigation is in progress.



It is interesting that the zwitterion **7** is sufficiently reactive toward the vinyl hydroperoxide **8** to intercept it efficiently before isomerization to hydroxyacetone. Even though hydroxyacetone is present in the ozonolysis mixture and might be expected to yield ozonides, we have not yet detected the hydroxy ozonide which would result from its 1,3-dipolar condensation with the carbonyl oxide **7**.

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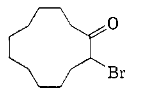
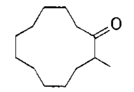
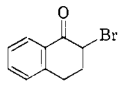
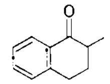
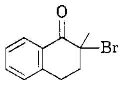
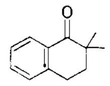
Chemistry of Enolates from Zinc Reduction of α-Bromo Ketones. A New Method of Substitution α to Carbonyl Groups

Sir:

Treatment of α-bromo ketones with zinc in 10:1 benzene–dimethyl sulfoxide generates species, presumably zinc enolates, which react with electrophiles to form carbon–carbon bonds at the original site of the bromine. This procedure, which has its origins in the classical Reformatsky reaction[1] and in zinc–acetic acid reductions,[2] represents a potentially useful alternative method for introduction of substituents at a specific position adjacent to a carbonyl group.[3]

When 0.01 mole of 2-bromocyclododecanone in 50 ml of benzene and 5 ml of dimethyl sulfoxide was treated with 0.1 g-mole of zinc powder and 0.02 mole of methyl iodide and stirred under nitrogen at room temperature for 8 hr, an essentially quantitative yield of 2-methylcyclododecanone was obtained.[4] This and other examples of methylation are given in Table I.

Table I. Methylation *via* Zinc Reduction of α-Bromo Ketones[a]

Substrate	Product	% yield[b]
		>99
		85
		57
6-Bromo-7-tridecanone	6-Methyl-7-tridecanone	66[c]
4α-Bromo-3-cholestanone	4α-Methyl-3-cholestanone	40[d]

[a] Reaction conditions like those described in the text for 2-bromocyclododecanone, unless otherwise specified. [b] Determined by vpc with calibration using an authentic sample, unless otherwise specified. [c] Run with lower concentration of bromo ketone; *cf.* Table III. [d] Determined by isolation of product. The only other compound found was 3-cholestanone (40%).

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(12) R. Criegee in "Oxidation in Organic Chemistry," K. B. Wiberg' Ed., Academic Press Inc., New York, N. Y., 1965, p 302.

(1) R. L. Shriner, *Org. Reactions*, 1, 1 (1942); *cf.* W. R. Vaughan, S. C. Bernstein, and M. E. Lorber, *J. Org. Chem.*, 30, 1790 (1965), for a recent discussion of the nature of the Reformatsky reagent.

(2) *E.g.*, H. E. Zimmerman and A. Mais, *J. Am. Chem. Soc.*, **81**, 3644 (1959).

(3) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, Chapters 7–9, gives a general review of methods for carbon–carbon bond formation adjacent to carbonyl groups.

Table II. Methylation *vs.* Furan Formation as a Function of Ring Size[a]

2-Bromocycloalkanone ring size	Products, % yield[b] 2-Methylcycloalkanone	Cycloalkanone	Dicycloalkenofuran
12	>99	<1	0
8	66	7	0
7	6	8	58 (**1**)
6	0	8	62 (**2**)

[a] Reaction conditions like those described in the text for 2-bromocyclododecanone. [b] Determined by vpc; yields of furans checked by ultraviolet spectroscopy.

Table III. Effect of Concentration on Methylation *vs.* Furan Formation

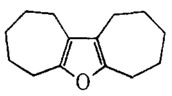
2-Bromocycloheptanone, *M*	% yield[a] of 2-methylcycloheptanone	% yield[b] of dicyclohepteno-furan (**1**)
0.28	6	58
0.060	23	..[c]
0.016	43	<2
6-Bromo-7-tridecanone, *M*	**% yield[a] of 6-methyl-7-tridecanone**	**% yield[b] of furan[d]**
0.18	33	30
0.051	61	2
0.013	67	<2

[a] Determined by vpc. [b] Determined by vpc and/or ultraviolet spectroscopy. [c] Furan decomposed before mixture was analyzed. [d] Furan assigned unproved structure 2,4-di-*n*-pentyl-3,5-di-*n*-hexylfuran by analogy to isolation of **3**.

Methylation occurs at the original site of the bromine even when that position corresponds to the less stable of the two possible enolate anions, as shown by the isolation of 4α-methyl-3-cholestanone as the only methylation product from 4α-bromo-3-cholestanone.

Conditions have not yet been found under which other saturated alkyl halides (*e.g.*, ethyl or *n*-hexyl) can be made to react sufficiently rapidly with these zinc enolates.[5] Allyl bromide is effective as electrophile, serving to convert 2-bromo-5-methoxy-1-tetralone to 2-allyl-5-methoxy-1-tetralone in 75% yield when 1 equiv of allyl bromide was used. With 2 equiv further reaction of (presumably) an allylzinc species at the carbonyl group occurred to afford the 1,2-diallyl-1-hydroxy compound in high yield.[6]

With many α-bromo ketones, however, self-condensation to afford predominantly furans such as **1**[7] and **2**[8] overshadows alkylation. In Table II are given the yields of 2-methylcycloalkanones *vs.* the yields of furans for various ring sizes. This self-condensation can be suppressed by lowering the concentration of α-bromo ketone in an otherwise identical reaction mixture, as shown for 2-bromocycloheptanone and 6-bromo-7-tridecanone in Table III. The course of furan formation was clarified by the nearly quantitative (98%) yield of 2,4-dimethyl-3,5-diethylfuran (**3**) obtained from an attempted methylation of 2-bromo-3-pentanone. The unsymmetrical furan must arise *via* aldol condensation between zinc enolate and α-bromo ketone[9] rather than *via* nucleophilic displacement or free-radical coupling to give the 1,4-dione.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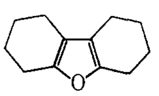
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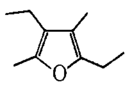
3

Table IV. Aldol Condensation *via* Zinc Reduction of α-Bromo Ketones[a]

Substrate	Electrophile	Product	% yield[b]
2-Bromocyclododecanone	Acetaldehyde	2-Ethylidenecyclododecanone	70
2-Bromocyclododecanone	Propionaldehyde	2-Propylidenecyclododecanone	85
2-Bromocyclooctanone	Acetaldehyde	2-Ethylidenecyclooctanone	57
2-Bromocyclohexanone	Acetaldehyde	2-Ethylidenecyclohexanone	57
2-Bromocyclohexanone	Propionaldehyde	2-Propylidenecyclohexanone	67
2-Bromo-5-methoxy-1-tetralone	Propionaldehyde	2-Propylidene-5-methoxy-1-tetralone	95
2α-Bromo-3-cholestanone	Acetaldehyde	2-Ethylidene-3-chlolestanone	90[c]

[a] Reaction conditions like those for methylation, except that 3 to 4 equiv of aldehyde was used and the reactions were allowed to proceed for 24 hr, or longer in some cases. [b] Determined by vpc and/or ultraviolet spectroscopy. [c] Column chromatography on alumina of the initially isolated condensation product afforded 78% 2-ethylidene-3-cholestanone after recrystallization.

This propensity for aldol condensation is useful synthetically. Even α-bromo ketones which have not been successfully methylated by our procedure, such as 2-bromocyclohexanone, afford good yields of aldol products when aldehydes are used as electrophiles.[10] As in the Reformatsky reaction, the β-hydroxy carbonyl compound is the product initially obtained. In order to facilitate analysis of products by vpc or ultraviolet spectroscopy, the crude ketols were dehydrated to the α,β-unsaturated ketones with *p*-toluenesulfonic acid in benzene. The figures reported in Table IV for the resulting α-alkylidene ketones therefore represent minimum yields for the initial aldol condensation.[11]

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(4) H. E. Zimmerman, D. Döpp, and P. S. Huyffer, *J. Am. Chem. Soc.*, **88**, 5352 (1966), report the apparent generation of an enolate by zinc reduction of an α-bromo ketone in dry dioxane. Attempts in this laboratory to effect α-methylation in dioxane or several other different aprotic solvents have not been successful. That methyl iodide (not dimethyl sulfoxide) was the sole source of the methyl groups introduced by our procedure has been demonstrated by isotopic labeling experiments.

(5) Ethylation of 2-bromocyclododecanone has been achieved (13% yield) only with ethyl tosylate as electrophile in a 336-hr reaction.

(6) Consistent with this interpretation is the observation that 1-tetralone yielded 93% 1-allyl-1-hydroxytetralin upon treatment with allyl bromide and zinc in benzene–dimethyl sulfoxide.

(7) W. Treibs, *Ann.*, **630**, 120 (1960).

(8) W. Treibs and M. Weissenfels, *Ber.*, **93**, 1374 (1960).

(9) J. E. Dubois and J. Itzkowitch, *Tetrahedron Letters*, 2839 (1965), report isolation of **3** from an analogous reaction of 2-bromo-3-pentanone with magnesium.

(10) J. Colonge and J. Gremet, *Bull. Soc. Chim. France*, **21**, 1304 (1954), report the reaction of several α-bromo ketones with magnesium and carbonyl compounds (Grignard-type reaction) to afford analogous products of aldol condensation.

(11) In a few preliminary runs using ketones as electrophiles, the yields of α-alkylidene ketones were much lower; *e.g.*, 2-bromocycloheptanone afforded 16% 2-isopropylidenecycloheptanone with acetone as the electrophile.

Among the further possible conversions of the α-alkylidene ketones is reduction of the double bond, which should lead to over-all α-alkylation in good yield. Further investigations into the generation and chemistry of zinc enolates are in progress.[12]

Acknowledgment. Early experiments by Dr. Albert J. Fritsch, S.J., contributed importantly to the development of the procedure for generation of zinc enolates.

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[12] The authors are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

[13] Alfred P. Sloan Foundation Research Fellow.

[14] Goodyear Foundation Fellow, 1966–1967.

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Steric Factors in the Rates of Solvolysis of *exo*- and *endo*-2- and 3-Bicyclo[3.3.1]nonyl Brosylates. Evidence for Steric Hindrance to Ionization in a Bicyclic System

Sir:

In the solvolysis of many bridged bicyclic compounds, the concurrent possibility of neighboring group participation hinders the assessment of the relative importance of steric effects as driving forces for reaction. We wish to report the results of an investigation of the solvolysis of *exo*- and *endo*-2- and -3-bicyclo[3.3.1]nonyl brosylates (Table I) in which steric factors are clearly responsible for the observed solvolytic activity.

Table I. Acetolysis of Brosylates[a]

Brosylate	Temp, °C	$k \times 10^5$, sec^{-1}	k_{rel}	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
Cyclohexyl	65.00	5.64			
	25.00	0.0229	1.00	27.4	1.6
endo-2	85.00	44.7			
	65.00	4.93			
	25.00	0.0240	1.05	26.6	−0.9
exo-2	45.00	31.7			
	25.00	1.81	79.1	26.9	−8.5
exo-3	25.00	21.7	948	23.2	−1.1
	17.00	7.45			
endo-3	25.00	22.5	973	24.2	−4.3
	17.00	6.87			

[a] Rates were measured titrimetrically. The solvent was glacial acetic acid containing about 2% acetic anhydride and was 0.09 *M* in sodium acetate.

Crystallographic investigations[1–4] have indicated that the preferred conformation of the bicyclo[3.3.1]nonane skeleton is the chair–chair form. However, interactions between C_3 and C_7 are sufficiently severe to cause a partial flattening of both rings and to increase the average bond angles (C_1–C_2–C_3, C_2–C_3–C_4, C_3–C_4–C_5) to a value of 114°. If the C_3 (or C_7) *endo* hydrogen is replaced by an atom such as oxygen, the magnitude of this repulsion is increased and spectral evidence indicates that the substituted ring assumes the boat conformation.[5–7] The strain attending these conformations is reflected in the reactivity of the 3-brosylates and by the fate of the cations which are formed.

The *exo*-3-brosylate solvolyzes at a rate which is 948 times greater than that of cyclohexyl brosylate; more than 90% of the product of acetolysis is bicyclo[3.3.1]-nonene. The driving force for this reaction must have its source in the strain which is relieved as the reacting carbon atom undergoes rehybridization from an sp^3 to an sp^2 center, thereby minimizing the "bowsprit" interaction between C_3 and C_7. The high percentage of elimination which occurs is probably a further indication of the strained nature of the parent ring system, since reaction of the cation with solvent to form an ester would reestablish the unfavorable transannular interaction which formerly existed.[8,12]

The *endo*-3-brosylate is 973 times more reactive than cyclohexyl brosylate, and the major product of solvolysis (>90%) is again the olefin. The reactivity of this isomer is consistent with what would be expected from relief of the strain inherent in the rigid-boat conformational modification of the cyclohexane ring. It is interesting to note that, on the basis of the carbonyl frequency (1717 cm^{-1}, CCl_4), the *exo*-3- and *endo*-3-brosylates exhibit a log (rate enhancement) of 2.58 and 2.59, respectively, if bond angle strain, torsional strain, and nonbonded interaction strain terms are omitted from the Foote–Schleyer correlations.[14,15] Since the possibilities for anchimeric assistance seem remote, it is reasonable to conclude that the major fraction of these enhancements arise from the three steric factors mentioned above.

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[1] M. Dobler and J. D. Dunitz, *Helv. Chim. Acta*, **47**, 695 (1964).

[2] W. A. C. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc.*, 1844 (1965).

[3] W. A. C. Brown, G. Eglinton, J. Martin, W. Parker, and G. A. Sim, *Proc. Chem. Soc.*, 57 (1964).

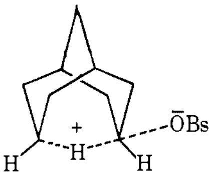
[4] I. Laszlo, *Rec. Trav. Chim.*, **84**, 251 (1965).

[5] W. D. Macrosson, J. Martin, and W. Parker, *Tetrahedron Letters*, 2589 (1965).

[6] C. Y. Chen and R. J. W. LeFèvre, *J. Chem. Soc.*, 539 (1966).

[7] J. P. Schaefer, J. C. Lark, C. A. Flegal, and L. M. Honig, *J. Org. Chem.*, **32**, 1372 (1967).

[8] It is conceivable that a portion of the observed rate enhancement may result from transannular participation by hydrogen during the rate-determining step. Transannular hydride shifts between C_3 and C_7 have been observed[9] in this system as well as in reactions of medium-sized rings,[10] but attempts to detect hydrogen participation in the latter systems have been unsuccessful.[11] Since stereoelectronic factors offer an ideal opportunity for hydrogen participation in reactions of 3-substituted bicyclo[3.3.1]nonanes, we have initiated studies on appropriate deuterated compounds in an attempt to evaluate this possibility.



[9] R. A. Appleton, J. R. Dixon, J. M. Evans, and S. H. Graham, *Tetrahedron*, **23**, 805 (1967).

[10] A. C. Cope, S. W. Fenton, and C. F. Spencer, *J. Am. Chem. Soc.*, **74**, 5884 (1952), and subsequent papers in this series.

[11] V. Prelog, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **18**, 247 (1957).

[12] A rate enhancement of 948 relative to cyclohexane corresponds to a $\Delta\Delta F$ of 4.05 kcal/mole. Since the ΔF for the chair–boat equilibrium of cyclohexane is approximately 6 kcal/mole,[13] it seems reasonable to conclude that the energy difference between the chair–chair and the chair–boat conformations of the bicyclo[3.3.1]nonane skeleton is approximately 2 kcal/mole. The same figure may be obtained from a consideration of the reactivity of the 3-*endo*-brosylate (Table I).

[13] A comprehensive discussion of the energetics of this system can be found in E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

[14] C. S. Foote, *J. Am. Chem. Soc.*, **86**, 1853 (1964).

[15] P. von R. Schleyer, *ibid.*, **86**, 1855, 1856 (1964).