137.5–138.5°, lit.[6] m.p. 136.5–137.5°). The n.m.r. and infrared spectra were consistent with the structural features of (β-methylallyl)acetone.

A *cis* relationship between the carbonyl and alkyl groups in the cyclopropyl carbonyl compound is inherent in the intramolecular mechanism proposed for these rearrangements.[2,3] To test the applicability of this requirement to the rearrangement of substituted acetylcyclopropanes, the *cis* and *trans* isomers of 1-acetyl-2-methylcyclopropane were prepared and subjected to rearrangement conditions. Infrared, n.m.r., and mass spectral analyses of the starting materials were indicative of their isomeric relationship. At 160° the *cis* isomer (VI, R = H) rearranged almost entirely in 12 hr. to allylacetone (VII, R = H), identified by comparison with v.p.c. retention time and infrared spectrum of the authentic material. The *trans* compound was stable under these conditions.[7] Over a period of 24 hr. at 180°, the *trans* isomer decomposed slightly, but no allylacetone was formed. All rearrangements were carried out on samples sealed in Pyrex tubes at 0.1 mm.

Brown[8] has described a similar rearrangement under photolytic conditions, obtaining (β-methylallyl)acetophenone from 1-benzoyl-2,2-dimethylcyclopropane. We found that 1-acetyl-2,2-dimethylcyclopropane rearranged to (β-methylallyl)acetone under irradiation at room temperature.[9] Experiments are in progress to determine if steric factors are determinative for the photolytic process.

Acknowledgments. We gratefully acknowledge assistance from the Robert A. Welch Foundation, the National Science Foundation, and the University of Texas Research Institute.

(6) W. Kimel and A. C. Cope, *J. Am. Chem. Soc.*, **65**, 1992 (1943).
(7) Chemical proof of the geometric configuration of the *cis* and *trans* isomers is in progress. There seems no doubt as to which isomer rearranged and which did not, however, and the nearly identical mass spectrometric fragmentation patterns of the two show them unequivocally to be stereoisomers.
(8) W. G. Brown, *U. S. Govt. Res. Rept.*, **38**, (22) 25 (1963).
(9) Irradiation by a high-pressure Hg arc lamp in a Pyrex flask.
(10) University of Texas Fellow, 1964–1965.

Royston M. Roberts, Robert G. Landolt[10]
Department of Chemistry, University of Texas
Austin, Texas 78712
Received March 13, 1965

Reversible Intramolecular Hydrogen Transfers between Allylic Enol and Cyclopropyl Carbonyl Systems

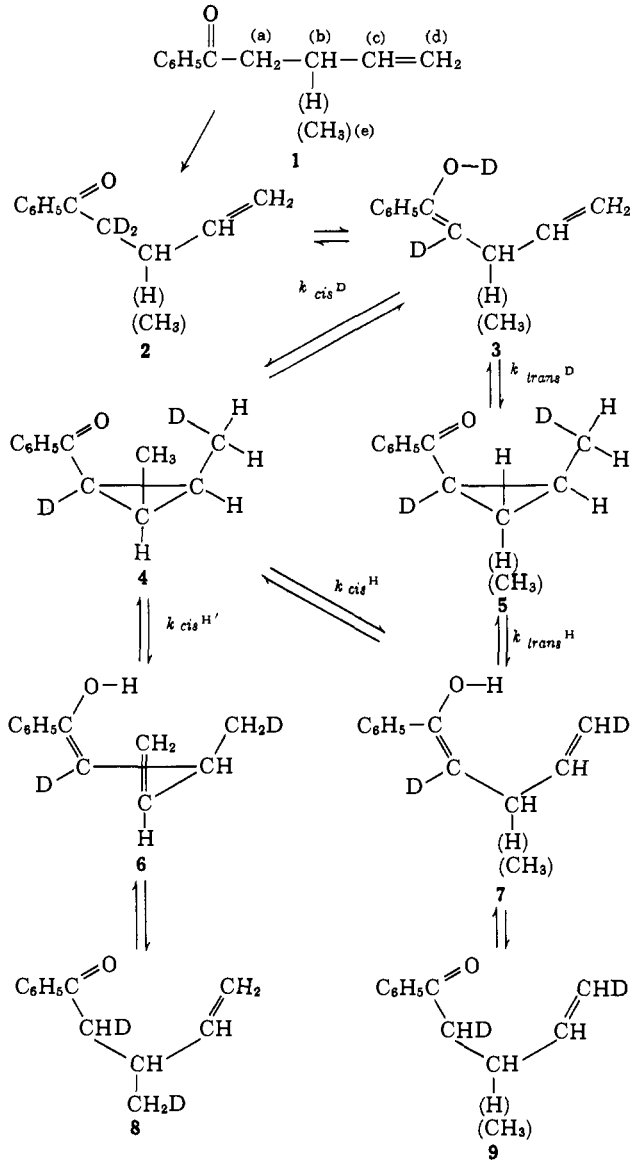
Sir:

In the preceding communication[1] we reported examples of a thermal rearrangement in which transfer of hydrogen from a methyl group to a *cis*-carbonyl oxygen of a ketone occurs, concerted with the opening of a cyclopropane ring. In order to substantiate a rearrangement mechanism in an aliphatic system analogous to the allylic phenol rearrangement of the "abnormal Claisen rearrangement," we must demonstrate the reversibility of this reaction, *i.e.*, the formation of a cyclopropyl carbonyl compound from an allylic enol, with concerted hydrogen transfer.

(1) R. M. Roberts and R. G. Landolt, *J. Am. Chem. Soc.*, **87**, 2281 (1965).

For the initial test of such a process, we chose a technique that is a modification of the elegant deuterium tracer experiments of Schmid.[2]

Allylacetophenone (**1**, H)[3] is ideally suited for this study because of the good separation of the n.m.r. absorptions of its hydrogens: C_6H_5, 2 H(*o*) multiplet, τ 2.1, 3 H(*m,p*) multiplet, 2.6; CH_2(a) triplet, 7.1; CH_2-(b) multiplet, 7.6; CH(c) multiplet, 4.1; CH_2(d) triplet, 5.0. It was deuterated by base-catalyzed exchange with D_2O[4] to yield **2** (H) (n.m.r. identical with that of **1** (H) except for disappearance of the CH_2(a) triplet and replacement of the CH_2(b) multiplet by a doublet, J = 8 c.p.s.). Intramolecular hydrogen exchange according to the scheme shown for **2** (H) ⇄ **9** (H) could be followed by appearance of H n.m.r. absorption at τ 7.1 and decrease at τ 5.0. If equilibrium were reached, absorption at these regions should become equal.



The deuterated allylacetophenone (**2**, H) was heated at 200 ± 5° (sealed tubes evacuated to <0.1 mm.) for

(2) H. Schmid, *Oesterr. Chemiker-Ztg.*, **65** (4), 109 (1964); *Chem. Abstr.*, **61**, 2999 (1964); and private communication.
(3) (a) A. C. Cope, K. E. Hoyle, and D. R. Heyl, *J. Am. Chem. Soc.*, **63**, 1843 (1941); (b) prepared by the method of W. Kimel and A. C. Cope, *ibid.*, **65**, 1992 (1943).
(4) Professor V. J. Shiner, private communication.

17, 41, 72, and 145 hr. After heating, the samples were shown to have unchanged v.p.c. retention times and infrared and mass spectra consistent with deuterated allylacetophenone. N.m.r. analysis showed the D distributions listed in Table I.

Table I. Deuterium Distributions in Allylacetophenone

Time, hr.	CH_2(a)	CH_2(b)	CH(c)	CH_2(d)
17	1.73	0.00	0.00	0.20
41	1.37	0.00	0.00	0.56
72	1.23	0.00	0.00	0.74
145	0.97	0.00	0.00	0.90

(α-Methylallyl)acetophenone (**1**, CH_3) was prepared.[3b] The H n.m.r. absorptions of this compound are also nicely separated, except for one overlap that was not troublesome[5]: C_6H_5, 2 H(*o*) multiplet, τ 2.1, 3 H(*m*,*p*) multiplet, 2.6; CH_2(a) + CH(b) multiplet, 7.1; CH(c) multiplet, 4.1; CH_2(d) triplet, 5.0; CH_3(e) doublet, 8.9, J = 7 c.p.s. The hydrogens on the α-carbon of **1** (CH_3) were exchanged for D as before.[4] The n.m.r. spectrum of **2** (CH_3) was identical with that of **1** (CH_3) except for the much-reduced absorption centered at τ 7.1.[6] Intramolecular hydrogen exchange in this molecule according to the scheme **2** (CH_3) $\rightleftarrows$ **8** $\rightleftarrows$ **9** (CH_3) may be seen to correspond to the allylic phenol rearrangements demonstrated with deuterium labeling[2] and C^{14}-labeling,[7,8] and to be strictly analogous to those in which chemically different molecules are produced.[9,10] The expected equilibrium distribution of the two D's would be CH_2(a) 0.57, CH_2(d) 0.57, and CH_3(e) 0.86.

The deuterated compound **2** (CH_3) was heated at 200 ± 5° for 12, 48, and 121 hr. After heating, the samples were shown to have unchanged v.p.c. retention times and infrared and mass spectra consistent with the structure of deuterated (α-methylallyl)acetophenone. N.m.r. analysis showed the D distributions given in Table II.

Table II. Deuterium Distributions in (α-Methylallyl)acetophenone

Time, hr.	CH_2(a)	CH(c)	CH_2(d)	CH_3(e)
12	1.27	0.00	0.60	0.12
48	0.83	0.00	0.63	0.52
121	0.58	0.00	0.63	0.66

A direct comparison of our results with those of Schmid[2] cannot be made, since the experimental conditions were quite different. However, it is clear that D is transferred from the α-carbon methylene [CH_2(a)] exclusively to the terminal methylene groups [CH_2(d)] and to the methyl group [CH_3(e)], and that the rate of incorporation of D into CH_2(d) is much faster than into CH_3(e), as Schmid found.

Interestingly, there is a greater difference in the rates of D-methylene and D-methyl incorporation in our aliphatic system than in the phenol system: *e.g.*, in our 48-hr. experiment, with 59% migration of D from the α-carbon, $3n/2m$ = 1.82, while in the phenol system, with only 49% migration of D, $3n/2m$ = 1.78.[2] This is nicely explicable in terms of nonbonded interactions in the transition states for D-methyl incorporation into the two systems. Similar explanations can be offered for the slower rate of D transfer in allylacetophenone than in (α-methylallyl)acetophenone. These topics will be discussed in detail in the complete paper to be published later.

These preliminary results show clearly that reversible intramolecular hydrogen transfers are thermally induced between aliphatic allylic enol and cyclopropyl carbonyl systems. Among the topics of interest to us in our continuing study of these systems are the relationship of keto–enol equilibria and of steric and conformational effects to the rearrangements.

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(11) University of Texas Fellow, 1964–1965.

Royston M. Roberts, Robin N. Greene,[11] Robert G. Landolt,[11] Ernest W. Heyer
Department of Chemistry, University of Texas
Austin, Texas 78712
Received March 13, 1965

(5) Since no D was found to migrate to the CH_2(b) in allylacetophenone, we felt justified in assuming no migration to the CH(b) in (α-methylallyl)acetophenone; one H was subtracted from the integrated signal from the CH_2(a) + CH(b) multiplet to give the H integral for CH_2(a).

(6) The H for D exchange was not complete. The n.m.r. spectrum of 2 (CH_3) showed 1.67 D and 0.33 H on the α-carbon[5] (mass spectrometry indicated 1.71 D). For simplicity, the numbers of D and H in various positions in the molecule after rearrangement, calculated from n.m.r. H integrals, were corrected to the values expected from 2.00 D originally on the α-carbon.

(7) (a) W. M. Lauer, G. A. Doldouras, R. E. Hileman, and R. Liepins, *J. Org. Chem.*, **26**, 4785 (1961); (b) W. M. Lauer and T. A. Johnson, *ibid.*, **28**, 2913 (1963).

(8) A. Habich, R. Barner, R. M. Roberts, and H. Schmid, *Helv. Chim. Acta*, **45**, 1943 (1962).

(9) W. M. Lauer and W. F. Filbert, *J. Am. Chem. Soc.*, **58**, 1388 (1936), and later papers.

(10) E. N. Marvell, D. R. Anderson, and J. Ong, *J. Org. Chem.*, **27**, 1110 (1962).

A Correlation between the Biological Activity of Alkyltrimethylammonium Ions and Their Mode of Interaction with Acetylcholinesterase

Sir:

The transition from stimulant activity to antagonism attending the molecular modification of drugs is a phenomenon of considerable importance in medicinal chemistry. The physicochemical and biochemical parameters intervening in such transitions must be elucidated in order that structure–activity relationships among drugs may be interpreted. As a step in this direction we wish to report on the observation of a chain length dependent transition in the mode of binding of alkyltrimethylammonium ions on acetylcholinesterase (AChE), a phenomenon which has its counterpart in the qualitative physiological properties of these ions.[1,2]

Using AChE, Bergmann and Segal[3] have reported the 50% inhibition indices (pI_{50}) for the series methyl- to *n*-heptyltrimethylammonium ions and showed that a roughly linear relationship exists between the pI_{50} values and the number of carbon atoms in the alkyl chains. For our purposes, it was essential to evaluate

(1) E. J. Ariëns, J. M. van Rossum, and A. M. Simonis, *Pharmacol. Rev.*, **9**, 226 (1957).
(2) R. P. Stephenson, *Brit. J. Pharmacol.*, **11**, 379 (1956).
(3) F. Bergmann and R. Segal, *Biochem. J.*, **58**, 692 (1954).