relatively more reactive basic groups. The predominant basic group in proteins is $-NH_3^+$; therefore, this suggests that the initial reaction in molecular inclusion involves the formation of ionic bonds between the amine groups of the protein and the dissociated silanol (SiO^-) groups of the porous glass. Support for this hypothesis may be derived from the studies of reactions of soluble silicic acid with heptadecylamine and with proteins performed by Holt and Bowcott.[1]

The protein–glass bond formed during the molecular inclusion process is so strong that the protein cannot be released subsequently by strong acids, ammonium hydroxide, or by a variety of ionic-strength buffer solutions. This indicates that the ionic amine silicate cannot be the sole mechanism involved in the molecular inclusion process.

Weldes'[2] investigations of the interactions of alkali-metal silicates with amino acids, peptides, and proteins suggested that hydrogen bonding might be responsible for the adherence of the protein to the glass. However, attempts to remove the included protein with urea were unsuccessful, thus indicating that hydrogen bonding was not the sole mechanism. However, when the tubes were extracted with urea in either dilute or concentrated acid solutions, the protein was rapidly and quantitatively released from the glass. The acid probably protonated the silanol group, thus releasing the protein amine, while urea broke the hydrogen bonds formed between the protein and glass surface.

The three apparent forces involved in the reaction of proteins with porous glass are ionic amine silanol bonding, hydrogen bonding, and diffusion.

Acknowledgments. I thank Dr. Leroy S. Hersh for his discussion and his advice with respect to surface charge reactions and Thomas H. Elmer and Raymond B. Forker for the porous glass membranes and for their technical advice.

(1) P. Holt and J. Bowcott, *Biochem. J.*, 57, 471 (1954).
(2) H. Weldes, *Adhesives Age*, 10, 32 (1967).

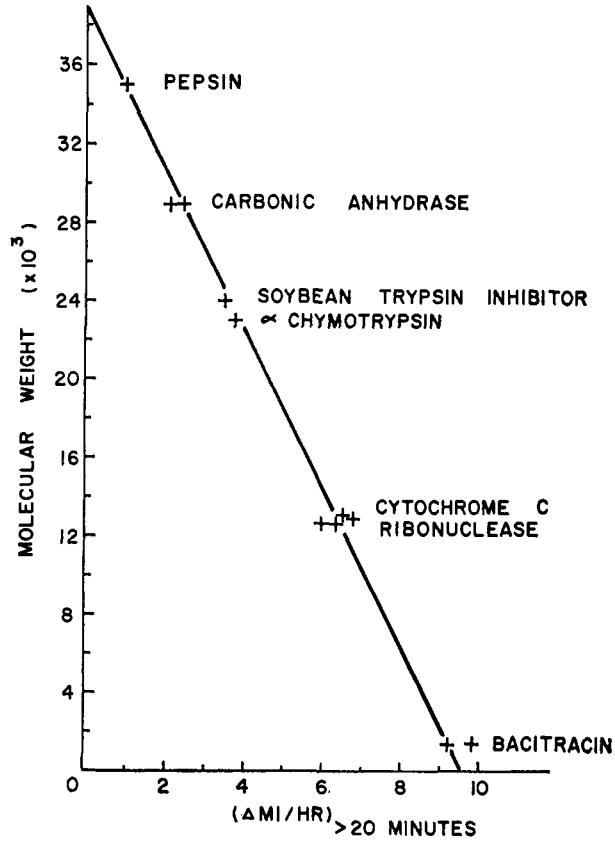


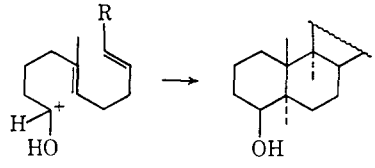
Figure 2. Molecular weight *vs.* molecular inclusion rate after 20 min.

Communications to the Editor

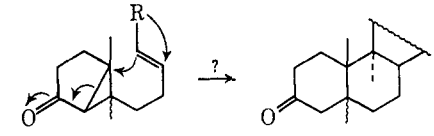
Six-Membered Rings *via* Olefin Participation in the Opening of Acylcyclopropanes

Sir:

Impressive success has recently been achieved by Johnson and his collaborators in the synthesis of polycyclic systems with natural steroid stereochemistry *via* cyclization of properly constituted acyclic polyenes in which the initiating cation is the conjugate acid of an aldehyde.[1] We have been interested for some time



in the possibility of initiating such cyclization *via* acid-catalyzed opening of cyclopropyl ketones which, if successful, would result in the direct formation of polycyclic systems with a keto group at the position

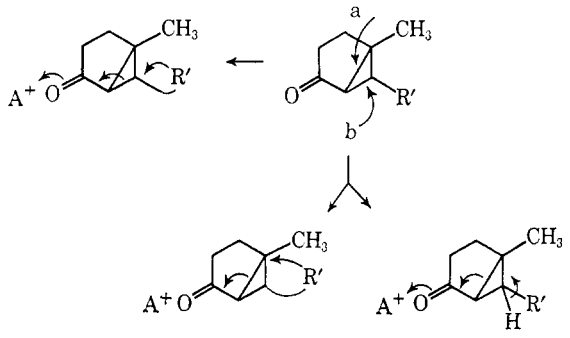


(C_8) where it is normally found in natural steroids. The use of cyclopropyl ketones such as I was especially interesting to us because of their expected easy accessibility *via* the internal diazo ketone insertion method which we introduced some years ago.[2] We report

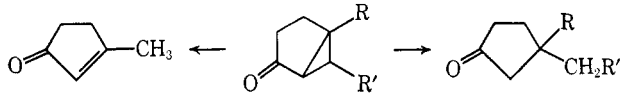
(1) For a recent review, *cf.* W. S. Johnson, *Accounts Chem. Res.*, 1, 1 (1968).
(2) G. Stork and J. Ficini, *J. Am. Chem. Soc.*, 83, 4678 (1961).

here on the initial results which show the feasibility and some limitations of this approach.

Two questions were considered at the outset. Which of the bonds marked a and b would cleave under acid conditions? In the event that the desired cleavage of bond a takes place, would a suitably placed double bond become involved (thus forming a bicyclic system), or would the system merely undergo isomerization to the corresponding cyclohexenone?



The first question is more complex than it appears at first sight because overlap of bond b with the p orbitals of the carbonyl is clearly more favorable than that of bond a. Indeed, cleavage of bond b is the normal

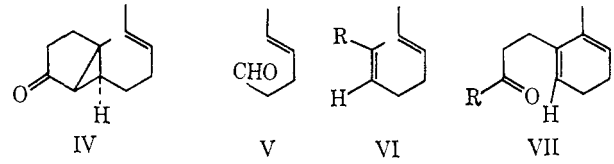


III I II

result of either electron addition[3] to the system (*cf.* I → II) or of photoexcitation[4] (*cf.* I, R = R′ = H, → III). Results of acid-catalyzed opening reactions of related systems have been few and confusing,[5] but it seemed possible that enough overlap with the (bent) bond a might be available so that when R (*cf.* I) is alkyl enough tertiary carbonium ion character might be involved in the transition state to favor the desired opening.

We chose to test this possibility by studying the acid-catalyzed opening of the specific ketone IV. The synthesis of the latter was carried out starting with *trans*-4-hexen-1-ol which was oxidized by the method of Barton[6] to the corresponding aldehyde V (60% yield; bp 42–44° (~15 mm), 2,4-dinitrophenylhydrazone mp 119–120°[7]).

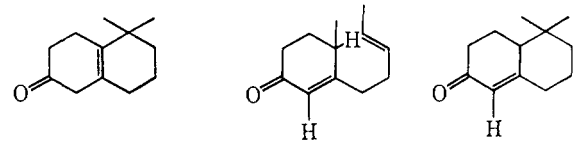
Condensation with ethyl α-diethylphosphonopropionate gave (64%) a 10:1 mixture (bp 98–104° (5 mm)) of VI, R = CO_2Et, and the corresponding geometric isomer VIa (separated by vpc on SF 96 at 120°; the *trans* isomer VI had the longer retention time). The structures were established by nmr analysis which showed the expected characteristics (vinyl hydrogen at C_3: 1 H multiplet centered at δ 6.72 for VI and δ 5.95 for VIa). Conversion to the alcohol VI, R = CH_2OH ($LiAlH_4$–ether, 88%; bp 86–93° (4–5 mm); α-naphthylurethan[7] mp 97–98°), and the corresponding chloride VI, R = CH_2Cl (90%, bp 82–88° (15 mm)), was followed by transformation in 53% yield into 4-methyl-*trans*,*trans*-deca-4,8-dienoic acid (VII, R = OH) (bp 105–108° (0.3 mm); S-benzylthiuronium salt[7] mp 143–144°) *via* alkylation and deacetylation of ethyl acetoacetate, followed by hydrolysis (ethanolic sodium hydroxide).



IV V VI VII

The diazo ketone derived from VII by way of the acid chloride (bp 65° (0.3 mm) (thionyl chloride–ether, trace of pyridine)) smoothly underwent intramolecular insertion in 80% yield to IV (λ 5.78, 10.34 μ; nmr δ 5.46 (multiplet, two olefinic protons), 1.31 (angular methyl); 2,4-dinitrophenylhydrazone mp 102–105°).[7]

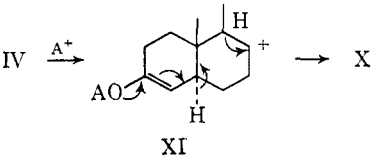
Treatment of IV with stannic chloride in benzene containing a trace of water gave after *ca.* a day at room temperature a mixture of three substances, VIII, IX, and X, separated by preparative vpc (retention times 10.5, 15, and 25 min,[8] respectively, in a ratio of ~1:5:3). The structure of IX, the product of opening without cyclization, followed from its spectral properties (λ_{max}^{EtOH} 237 mμ (ε 10,900); δ 5.68 (1 H, s), 1.20 (3 H, d, $J \sim 7$ cps), 1.65 (3 H, m); *trans*-vinyl absorption in ir and nmr). It gave a 2,4-dinitrophenylhydrazone, mp 114–115°.[7]



VIII IX X

The relationship of VIII as the β,γ isomer of X followed from the isomerization of isolated VIII (λ 5.82 μ; nmr: no vinyl absorption, δ 1.03 (6 H, s), 2.63 (s, broad, 2 H)) on reinjection to a mixture of VIII and X. The latter was identified as 5,5-dimethyl-$\Delta^{1(9)}$-2-octalone; λ_{max}^{EtOH} 240 mμ (ε 10,000); λ_{max}^{film} 5.98, 6.18 μ (*cf.* ref 9); no *trans* olefin; nmr (CCl_4) δ 5.76 (1 H, s), 1.06 (3 H, s), 0.84 (3 H, s); 2,4-dinitrophenylhydrazone mp 111–112° (lit.[9] 109–112°).

We have shown that X is not formed by way of IX, as the latter did not form either VIII or X when submitted to the cyclization conditions. The formation of VIII and X shows that an external double bond can become involved in the cyclopropane opening of IV since the rearranged structure X can only arise from the initial cation XI as shown, but the above does not answer whether the involvement of the external double



XI

(3) *Cf.* H. E. Zimmerman, R. D. Rieke, and J. R. Scheffer, *J. Am. Chem. Soc.*, **89**, 2033 (1967), and references cited therein.

(4) *Cf.* P. J. Kropp and H. J. Krauss, *J. Org. Chem.*, **32**, 4118 (1967).

(5) For two cases related to I which give different results on acid-catalyzed opening, *cf.* W. W. Kwie, B. A. Shoulders, and P. D. Gardner, *J. Am. Chem. Soc.*, **84**, 2268 (1962); D. H. R. Barton, P. de Mayo, and M. Shafiq, *J. Chem. Soc.*, 140 (1958).

(6) D. H. R. Barton, B. J. Garner, and R. H. Wightman, *ibid.*, 1855 (1964).

(7) Satisfactory analytical data were obtained for this substance.

(8) DEGS column at 190°.

(9) A. G. Armour, G. Büchi, A. Eschenmoser, and A. Storni, *Helv. Chim. Acta*, **42**, 2233 (1959).

bond is *concerted* with the cyclopropane opening. This question is considered in the following communication.[10]

Acknowledgment. The support of this work by the National Science Foundation is gratefully acknowledged.

(10) G. Stork and M. Gregson, *J. Am. Chem. Soc.*, **91**, 2373 (1969).

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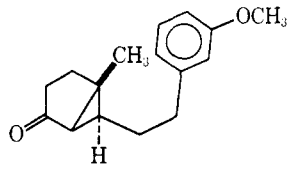
Received February 19, 1969

Aryl Participation in Concerted Cyclization of Cyclopropyl Ketones

Sir:

We have shown in the preceding communication[1] that a double bond may become involved in the acid-catalyzed opening of a suitably constituted cyclopropyl ketone. We now present evidence that this involvement is *concerted* with the breaking of the cyclopropyl bond.

In order to investigate this important mechanistic point, we chose a system which would lead to a bicyclic cation which would not be expected to become involved in structural rearrangements. The systems I and II appeared ideally suited to this purpose, especially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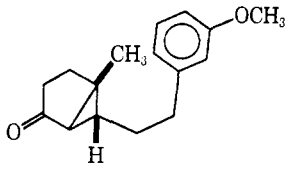
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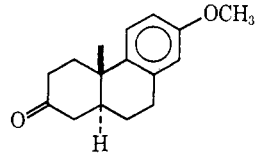
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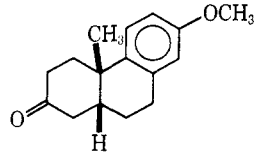
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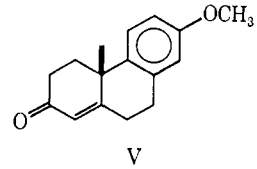
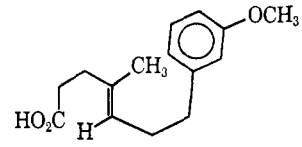
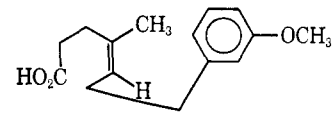
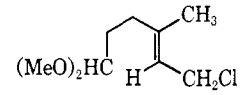

V

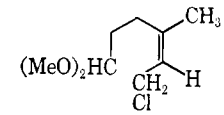
since the two most informative products (III and IV) from their cyclization were readily available from the well-known tricyclic ketone V.[2]

The preparation of I and II by the internal diazo ketone addition[3] required the pure geometric isomers VI and VII. These were prepared from geraniol and nerol, respectively, by the general synthesis we have described elsewhere involving the coupling of *m*-methoxybenzylmagnesium bromide with the chlorides VIII and IX[4] derived from geraniol and nerol, respectively,[5] followed by hydrolysis (20 ml of acetic acid, 15 ml of


VI

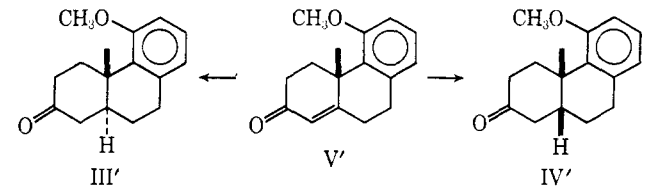

VII


VIII


IX

water, and 1.2 g of sodium acetate; 0.5 hr on a steam bath) and oxidation (silver nitrate in aqueous ethanol; slow addition of 1 *N* sodium hydroxide to pH 9; 60–70°; 1 hr). The two acids were converted to the cyclopropyl ketones I and II in the usual way.[1] The two cyclopropyl ketones I and II, obtained essentially pure after chromatography on silica gel, had very similar spectral characteristics but could readily be differentiated by vpc: the retention time of I was about 1 min longer (co-injection) than that of II on SF 96 at 210°. The homogeneity of I and II also follows from the results of acid cyclization, below.[6] Cyclization of I and II was carried out by allowing each isomer (200 mg) to stand at room temperature overnight with 3 ml of benzene containing 0.1 ml of stannic chloride and 10 μl of water. No starting material was left and the products (~80% yield) from I turned out to be a mixture of III and III′ (~5:1), while from II only IV and IV′ were obtained. The identity of these substances was established as follows.

The mixture from the cyclization of I was resolved by vpc on SF 96 into two components which were separately collected. The lower retention time (minor) substance proved to be III′ by comparison of spectral properties and vpc behavior (co-injection) with the lithium–ammonia reduction product of V′.[7] The


III′ V′ IV′

longer retention isomer was identical with the known ketone III from the lithium–ammonia reduction of V.[8]

Similar separation of the two components obtained from II also gave a lower retention component (minor) which proved to be IV′ (identical with the catalytic hydrogenation product from V′), while the second isomer turned out to be IV (also formed by catalytic hydrogenation of V).

The important fact is that the *cis*-cyclopropyl ketone II gave only *cis*, and the *trans*-cyclopropyl ketone I only *trans* cyclized products. To the extent that cyclization accompanies cyclopropyl ring opening it is, therefore, a concerted reaction.

(1) G. Stork and M. Marx, *J. Am. Chem. Soc.*, **91**, 2371 (1969).
(2) G. Stork, A. Meisels, and J. Davies, *ibid.*, **85**, 3419 (1963).
(3) G. Stork and J. Ficini, *ibid.*, **83**, 4678 (1961).
(4) G. Stork, P. A. Grieco, and M. Gregson, *Tetrahedron Letters*, in press.
(5) G. Stork, M. Gregson, and P. A. Grieco, *ibid.*, in press.
(6) It is worth noting that the fact that the internal diazo ketone addition[3] gives two different cyclopropyl ketones from the two isomeric diazo ketones derived from VI and VII demonstrates the (expected) stereospecificity of this reaction.
(7) D. A. H. Taylor, *W. African J. Biol. Appl. Chem.*, **7**, 14 (1963).
(8) M. E. Kuehne, *J. Am. Chem. Soc.*, **83**, 1492 (1961).