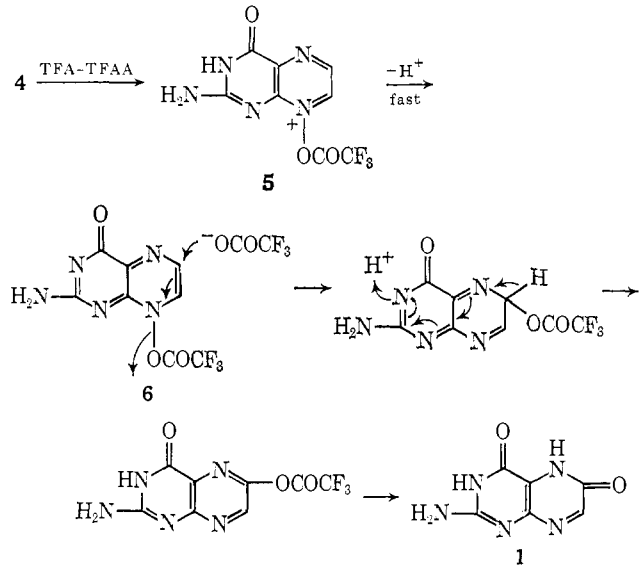
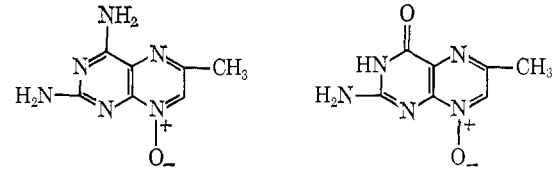
Scheme II



comitant introduction of oxygen (as an acyloxy grouping, subsequently hydrolyzed to a cyclic amide) α to the ring nitrogen.[11] However, in initial experiments with **4** we were unable to induce reaction either with neat acetic anhydride or with mixtures of acetic acid–acetic anhydride even on prolonged (48 hr) reflux. Additionally, no reaction could be detected with acetyl chloride, dichloroacetyl chloride, or benzoyl chloride in DMF or pyridine at temperatures ranging from ambient to 100°. Somewhat surprised at this apparent lack of reactivity of **4**, we turned our attention to the use of trifluoroacetic acid–trifluoroacetic anhydride (TFA–TFAA). This reagent mixture has been used in the past to effect rearrangement of relatively unreactive (nonbasic) *N*-oxides,[11] and in addition was expected to facilitate detection of any resultant molecular transformations by periodic nmr inspection of reaction mixture aliquots (**4** shows two well resolved doublets at δ 8.35 and 8.50 (J = 4.5 Hz) in TFA; any rearrangement product should exhibit only a single C–H proton absorption). Indeed, **4** dissolved almost immediately in 50:50 TFA–TFAA at 50° to give a bright yellow solution, an aliquot of which showed no trace of starting material, and a sharp singlet at δ 8.60. When **4** was dissolved in TFA–TFAA at room temperature, the initial nmr spectrum of the mixture showed the presence of starting material (**4**) (resolved doublets) as well as rearrangement product (sharp singlet). During the course of 3–4 hr, all absorptions due to **4** slowly disappeared with concurrent strengthening of the singlet at δ 8.60; the final spectrum was identical with that obtained from reaction at 50°. To our surprise, however, following the usual work-up (evaporation of solvents and basic hydrolysis), the only product isolated, with no detectable contaminants (tlc), was *xanthopterin* (**1**). Although *N*-oxide rearrangements to a position β to the ring nitrogen are occasionally observed in heterocyclic chemistry, mixtures of products are usually obtained. The above extremely facile rearrangement of pterin 8-oxide (**4**) to xanthopterin (**1**) (consistently in 95–100% yield) may well be unique in its homogeneity.

We suggest that this conversion probably proceeds as shown in Scheme II;[12] the usual α rearrangement is apparently blocked by very rapid deprotonation of the intermediate acyloxypteridinium salt **5**. 2,4-Diaminopteridine 8-oxide (**3**) could be rearranged analogously to 2,4-diamino-6(5*H*)-pteridinone but only under forcing conditions (refluxing TFA–TFAA, 5 hr).[13] Neither 2,4-diamino-6-methylpteridine 8-oxide (**7**) nor 6-methylpterin 8-oxide (**8**) (in which the position to which β rearrangement would occur is effectively blocked by methyl substitution) could be induced to rearrange under any conditions.



More detailed mechanistic studies of these transformations are in progress, and the inherent synthetic potentialities involved are currently under active exploration.[14]

(12) This pathway is analogous in principle to those proposed previously for β rearrangement reactions of aromatic *N*-oxides (see ref 11, pp 287–288).

(13) Alkaline hydrolysis of 2,4-diamino-6(5*H*)-pteridinone provided an alternate, although far less satisfactory, route to **1**.

(14) This investigation was supported by a grant (CA-12876) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.

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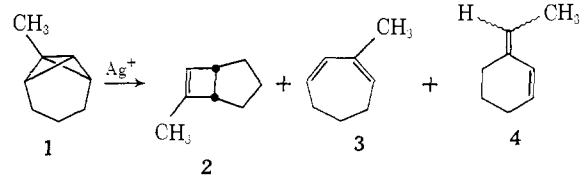
Stereospecificity, Regioselectivity, and Kinetic Deuterium Isotope Effects in the Silver(I)-Catalyzed Isomerizations of 1-Methyltricyclo[4.1.0.0^{2,7}]heptanes to Bicyclo[3.2.0]hept-6-enes[1]

Sir:

Wide variations in kinetic response and product distributions are now recognized to accompany minor substituent changes in bicyclo[1.1.0]butanes and tricyclo[4.1.0.0^{2,7}]heptanes when these are subjected to transition metal catalyzed rearrangement. An enduring significant problem concerns the detailed nature of the mechanistic changeover which operates under conditions of Ag^+ catalysis to divert, for example, the behavior of tricyclo[4.1.0.0^{2,7}]heptane which gives only 1,3-cycloheptadiene to that exhibited by **1** ($k_{Ag}^{40°}$ = 5.10 × 10^{-3} M^{-1} sec^{-1}) which affords chiefly **2** (44%) together with **3** (26%) and **4** (29%, syn:anti = 4:1)



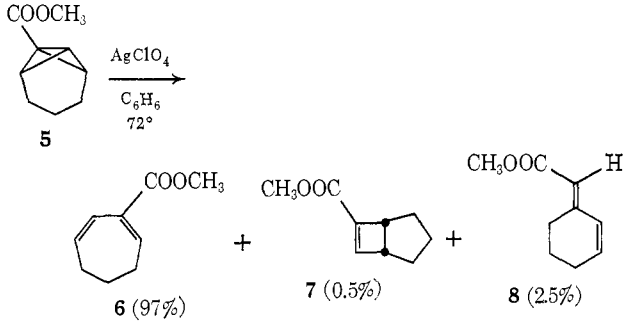
under the identical conditions.[2] Although extensive

(1) Silver(I) Ion Catalyzed Rearrangements of Strained σ Bonds. XVIII. For part XVII, see L. A. Paquette, S. E. Wilson, G. Zon, and J. A. Schwartz, *J. Amer. Chem. Soc.*, 94, 9222 (1972).

(2) (a) L. A. Paquette, R. P. Henzel, and S. E. Wilson, *ibid.*, **93**, 2335 (1971); (b) L. A. Paquette, S. E. Wilson, R. P. Henzel, and G. R. Allen, Jr., *ibid.*, **94**, 7761 (1972).

recent work has elucidated the mechanistic pathways involved in 1,3-cycloheptadiene and alkylidenecyclohexene formation,[3,4] the initial and ensuing stages of that rearrangement which provides bicycloheptene product have remained speculative.[3b,5] We now report experimental evidence which reveals the complete stereoselectivity and moderate regioselectivity of this isomerization.

The significant role played by the electronic nature of the 1 substituent was tested by the rearrangement of **5**. This ester exhibited not only a markedly slower rate of bond relocation ($k_{Ag}^{72°} = 8 \times 10^{-5}\ M^{-1}$ sec^{-1}), but the product mixture now consisted almost exclusively of 2-carbomethoxy-1,3-cycloheptadiene (**6**).[6] The failure of **5** to isomerize in significant amounts to **7** denotes

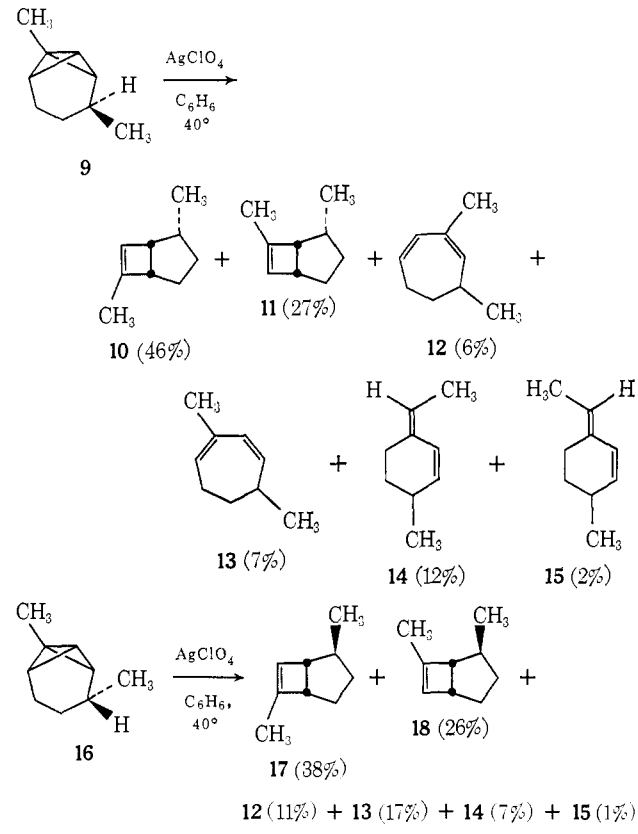


that an electronegative group at C_1 can effectively deter operation of that pathway which is preferred in the case of electron-releasing substituents.

When the stereodistal 1,3-dimethyltricycloheptane **9** was exposed to catalytic quantities of silver perchlorate in anhydrous benzene at 40° ($k_{Ag} = 3.31 \times 10^{-3}\ M^{-1}$ sec^{-1}), six new hydrocarbons were formed, the two major components of which were identified as **10** and **11** on the basis of comparisons of their nmr spectra and vpc retention times with those of authentic samples prepared by independent photolysis of **13** and **12**.[7] No detectable amounts of exo isomers **17** and **18** were seen. The pair of ethylidenecyclohexenes were likewise characterized by spectral means and alternative synthesis from 4-methyl-2-cyclohexenone and ethylidenetriphenylphosphorane (Scheme I).

Treatment of stereoproximally disubstituted hydrocarbon **16** with $AgClO_4$ ($k_{Ag}^{40°} = 7.25 \times 10^{-3}\ M^{-1}$ sec^{-1}) also gave a six-component mixture. In contrast to the behavior of **9**, however, major amounts of **17** and **18** were present and no **10** or **11** was produced within detectable limits. This remarkably high level of stereospecificity is evidently a general feature of the 1-alkyltricycloheptane → bicyclohept-6-ene rearrangement since both **19** ($k_{Ag}^{40°} = 0.23 \times 10^{-3}\ M^{-1}$ sec^{-1})

Scheme I



and **24** ($k_{Ag}^{40°} = 0.59 \times 10^{-3}\ M^{-1}$ sec^{-1}) similarly afforded epimerically pure bicycloheptenes[8-11] (Scheme II).

The overall rates of disappearance of **16**, **1**, **9**, **24**, and **19** show a relative reactivity order of 32:22:14:2.6:1.0 indicating that methoxyl substitution at C_3 exerts a small rate-retarding effect on the total rearrangement and that somewhat faster rates are encountered when the C_3 substituent is stereoproximal to the angular methyl group.

Under identical conditions, **27** was found to exhibit a marked sensitivity to C_7 deuterium substitution which proved identical for conversion to both **28** and **29**. These kinetic decelerations were not shared by the subsidiary conversions of **27** to its 1,3-cycloheptadiene ($k_H/k_D = 0.85 \pm 0.08$) and ethylidenecyclohexene isomers ($k_H/k_D = 0.86 \pm 0.06$), where inverse isotope effects were anticipated on the basis of previously established mechanisms.[2] When isotopic substitution was made at C_2 as in **30**, the conversions to **31** and **32**

(3) (a) L. A. Paquette and S. E. Wilson, *J. Amer. Chem. Soc.*, **93**, 5934 (1971); (b) L. A. Paquette, S. E. Wilson, and R. P. Henzel, *ibid.*, **94**, 7771 (1972).

(4) (a) M. Sakai and S. Masamune, *ibid.*, **93**, 4610 (1971); (b) M. Sakai, H. H. Westberg, H. Yamaguchi, and S. Masamune, *ibid.*, **93**, 4611 (1971).

(5) P. G. Gassman and T. J. Atkins, *ibid.*, **94**, 7748 (1972).

(6) All new compounds reported herein gave correct combustion data or (in the case of deuterium-labeled materials) appropriate accurate mass analyses. The nmr spectra supported all structural assignments.

(7) A detailed description of the spectral basis for the stereochemical assignments will be presented in a full paper on this subject. As expected from steric considerations, the photoisomerizations of **12** and **13** give rise predominantly to exo products **18** and **17**, respectively. Dienes **12** and **13** were independently prepared by the thermally promoted 1,5 sigmatropic hydrogen shift of 1,3- and 1,4-dimethyl-1,3-cycloheptadienes.[3]

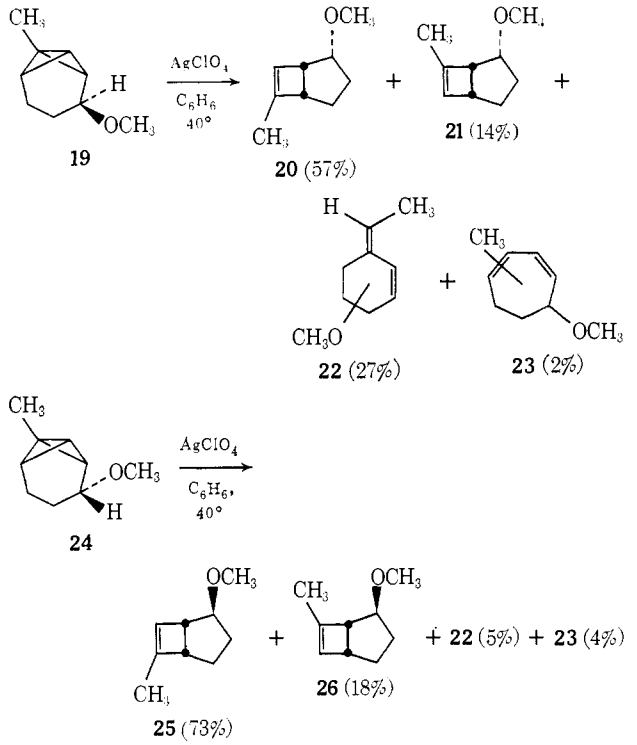
(8) Characterization of **20**, **21**, **25**, and **26** was accomplished by independent synthesis of each isomer. This involved sequential photocycloaddition of propyne to 2-cyclopentenone,[9] lithium aluminum hydride reduction of the individual adducts, and O-methylation. To obtain adequate quantities of the exo alcohols, epimerization of the endo isomers (preferentially formed in the hydride reduction) was accomplished with aluminum isopropoxide in isopropyl alcohol–acetone.

(9) (a) P. E. Eaton, *Accounts Chem. Res.*, 1, 50 (1968). (b) The initial photocycloadditions had been performed earlier by Professor Eaton and we thank him for his helpful comments regarding the structural assignments. (c) See also K. E. Hine and R. F. Childs, *Chem. Commun.*, 145 (1972).

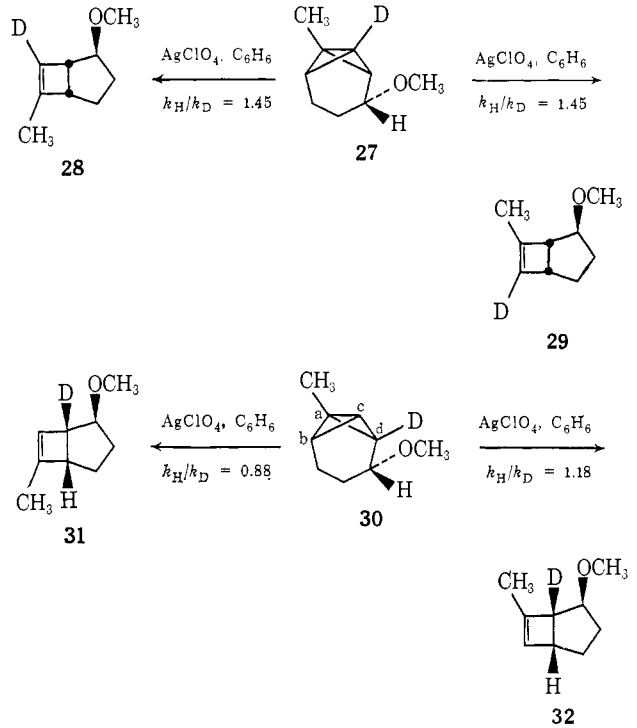
(10) To establish that no Ag(I)-assisted methoxyl group ionization[11] was operating in these examples, **24-3-*d*** was prepared and similarly isomerized. In all the products, the methoxyl substituent had remained bonded to the isotopically labeled carbon.

(11) L. A. Paquette and G. Zon, *J. Amer. Chem. Soc.*, **94**, 5096 (1972).

Scheme II



were again significantly influenced, but in *opposite* directions.



The stereospecificity exhibited by **9**, **16**, **19**, and **24** demonstrates that the 1,3-hydride shift of H_7 to C_1 in the rate-determining step[3] (or at another time during reaction) is not operative, since this pathway would uniquely provide bicycloheptenes of configuration opposite to that observed. Formal cleavage of the a–b or a–d bonds (*cf.* **30**) at the onset of rearrangement likewise cannot account for the combined experimental evidence. Under the terms of this mechanistic option, not only would improper C_2 stereochemistry again be realized, but argento carbonium ion intervention would have to be bypassed despite the presence of an electron-donating bridgehead substituent which favors generation of such a species.[2-4] A mechanism[5] involving edge attack at bonds b–c or c–d followed by 1,2-carbon shift accounts for the above stereospecificity and production of **6**; however, because the combined kinetic, multiple substituent,[3b] and isotope effect data are not readily accommodated by this pathway, concurrent weakening of side bond b–c or c–d and the central bond must be considered as a viable alternative. A full discussion of this point is deferred to our full paper on this subject.

In either case, rupture of the b–c linkage is kinetically preferred to a small degree in the present systems (6-methyl-/7-methylbicycloheptenes = 1.5–4.0) owing to steric congestion engendered by the C_3 group which perturbs what otherwise would be isoenergetic reaction modes. The propensity of the tricycloheptanes to rearrange more rapidly to bicycloheptenes when substituted in stereoproximal fashion is explainable in terms of steric accessibility to that surface of the molecule containing C_7. Since the C_3–R group in stereoproximal systems presumably commands equatorial orientation and consequently forces the C_4 methylene flap to the opposite side of the structure, approach by the exceedingly bulky Ag^+ is facilitated. Similar considerations in stereodistal systems force the C_4 methylene group to adopt a relative orientation which shields this general area of attack.

The direction and magnitude of the isotope effects in the reaction **27** → **28** + **29** and **1-7-*d*** → **2-7-*d***[3] remain difficult to fully comprehend. The C_7–H(D) bond in the reactant, characterized by a high level of s character ($sp^{1.58}$), must experience a substantial influx of p character. Analogy with solvolytic reactions is clearly not valid here, since this change should lead to an inverse isotope effect. Apart from contributions arising from major alterations in C_7–H(D) hybridization, the sizable positive fractionation factors also arise partly from extensive movement of this bond in the rate-determining transition state and possibly to some degree from bonding of Ag^+ to this carbon atom.

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Conformations of Five-Membered Rings. Limitations on the *R*-Value Method

Sir:

In the conformational analysis of six-membered rings, the *R*-value method has served as an important source of structural data for molecules in solution.[1] Analysis of the vicinal coupling constants in a $-CH_2-CH_2-$ fragment within a ring gives a ratio ($R = J_{trans}/$

(1) J. B. Lambert, *Accounts Chem. Res.*, 4, 87 (1971).