Photoirradiation of Steroid 5-En-7-one Systems and a Mutual Exchange of C_4 and C_6 in 3β-Acetoxycholest-5-en-7-one

Sir:

Irradiation of 3β-acetoxycholest-5-en-7-one (**1**)[1,2] afforded a 1:1 mixture of **2** and **3** which was separated by preparative tlc. The structure of the bridged compound **3**,[3] mp 151–152°, was established from the following data: M^+ 442; uv (EtOH) 280 mμ (ε 304); ir (KBr) 1735, 1712, 1648, and 890 cm^{-1}; nmr ($CDCl_3$)[4] 5.20 (m, H-3), 4.95 (d, J = 1 cps, H_β-6[5]), 4.83 (d, J = 1 cps, H_α-6[5]), 3.25 ppm (d, J = 4 cps, H-4). Although the other product, **2**,[6] changed to dienone **4** (compared with authentic sample) during the process of isolation from tlc plates, the following nmr data leave no doubt regarding its structure. Thus, the spectrum of a photostationary *ca.* 1:1 mixture of **2** and **3**, which was obtained by irradiating pure **3** for 2 hr, clearly showed signals which were absent in the spectra of **3**, *i.e.*, an AB pattern[4] (J = 14 cps) at 3.25 (br, d) and 2.80 ppm (d) assignable to H_β-6 and H_α-6, respectively, and a multiplet at 5.50 ppm due to H-3 and H-4. Moreover, it has been possible to isolate and characterize the analogous compounds **8** and **11** in related experiments (see Scheme I).

Irradiation[2] of the deuterated compound **1d** (70% D at C_6)[7,8] afforded **3d** containing the labeling exclusively[8] at the exocyclic methylenes (68% D and none at the bridgehead methine shown in **3'**. This clarifies that the bridged compound is not formed directly from **1** by fission of the C_3–C_4 bond ($\mathbf{1} \not\rightarrow \mathbf{3'}$), but instead *through the route:* $\mathbf{1} \rightarrow \mathbf{2} \rightleftarrows \mathbf{3}$. Presence of all the original D at H_β-6 and H_α-6 in **3d** clearly showed that C_4 had become linked to C_7 in a facile and unique manner. Treatment of **3** with 10% KOH–MeOH eventually gave the dienone **4** in almost quantitative yield. The intermediates in this reaction have been isolated and fully characterized by spectroscopic data and/or comparisons with authentic specimen. Namely, the first product was the β-ketol **5**; this underwent retroaldol cleavage and subsequent aldol cyclization to give a *ca,* 1:1 mixture of the 3β- and 3α-ols **6**, which were separated after acetylation. Similar base treatment of **3d** now afforded the dienone **4d** with the labeling (30% D) only at C_4. Hence, photoirradiation of **1** followed by base treatment of the bridged compound **3** affords the steroid **4** in which *the carbon atoms at C_4 and C_6 in the original nucleus have been exchanged.*

Similar irradiation[2] of cholest-5-en-7-one (**7**) yielded a 1:1 mixture of **8**, mp 106–108°, ORD a = −84° (n–π*), and **9**, mp 108°, ORD a = +48°, which were easily separated by tlc and characterized spectroscopically.[9] The labeled bridged compound **9d** derived from **7d** again had the D atoms distributed in H_β-6 and H_α-6 in the ratio of *ca.* 2:1, as shown. Finally, irradiation of 3β-methoxycholest-5-en-7-one (**10**) gave the deconjugated **11**, mp 81–84°, and bridged **12**, mp 110–112°,[10] which were separated by tlc.

The bridged compound **3** resulting from irradiation[2] of 4β-deuterio-3β-acetoxycholest-5-en-7-one (**13**)[11] (90%

(1) Supported by the National Institutes of Health, Public Health Service Research Grant No. CA08394. The present work is an extension of our studies on photooxygenation of steroidal β,γ-unsaturated enones (*Chem. Commun.*, in press).

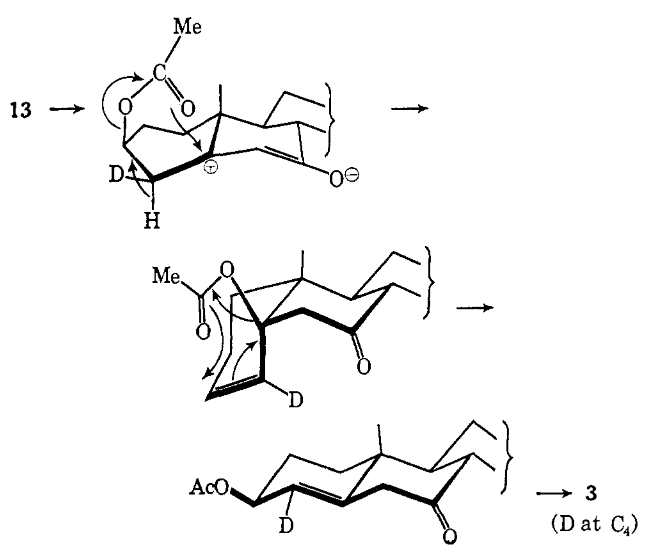
(2) Unless otherwise stated, the following reaction conditions were employed: 450-W high-pressure Hg lamp, N_2 atmosphere, Pyrex filter, 0.015 *M* solution of starting material in *t*-BuOH; in order to prevent formation of products other than the two major ones, the irradiation was stopped after 12 hr; this resulted in *ca.* 60% conversion of starting material.

(3) The C_4–C_6 exchange has been taken into consideration in the numbering system of the bridged compounds and **6**.

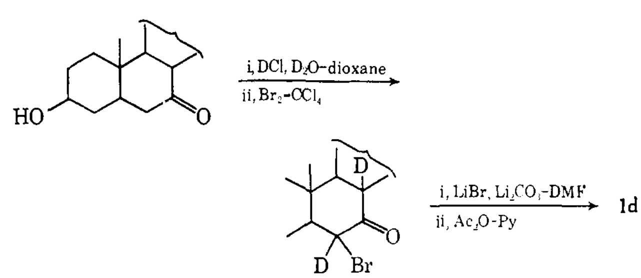
(4) The proton signals have been interrelated by double-resonance experiments.

(5) The exocyclic methylene protons have been designated β and α as depicted on the basis of their genesis, the former and latter originating, respectively, from the 6β and 6α hydrogens (see **2D**, **3D**). The nmr assignments rest on NOE measurements; *i.e.*, irradiation of the 19-Me and H-4 signals, respectively, caused an increase in the integrated intensity of the 4.95- and 4.83-ppm signals: *cf.* F. A. L. Anet and A. J. R. Bourn, *J. Am. Chem. Soc.*, **87**, 5250 (1965); M. C. Woods, I. Miura, Y. Nakadaira, A. Terahara, M. Maruyama, and K. Nakanishi, *Tetrahedron Letters*, 321 (1967). A detailed account of the NOE measurements will be published shortly.

(6) Irradiation of 1 has been reported to afford an equilibrium mixture of 5β-acetoxycholest-3-en-7-one and **2**, which by chromatography were easily separated from each other: P. D. Gardner and H. F. Hamil, *J. Am. Chem. Soc.*, **83**, 3531 (1961). In the present studies, however, **2** could not be isolated without being converted into **4**, and, moreover, no trace of the former compound could be detected. The results described here, *inter alia* those of labeling experiments employing **13**, exclude participation of 5β-acetoxycholest-3-en-7-one; as depicted below, if this were the case, the 4β-D would be retained in the bridged compound, which is against fact.



(7) Prepared in the following manner:

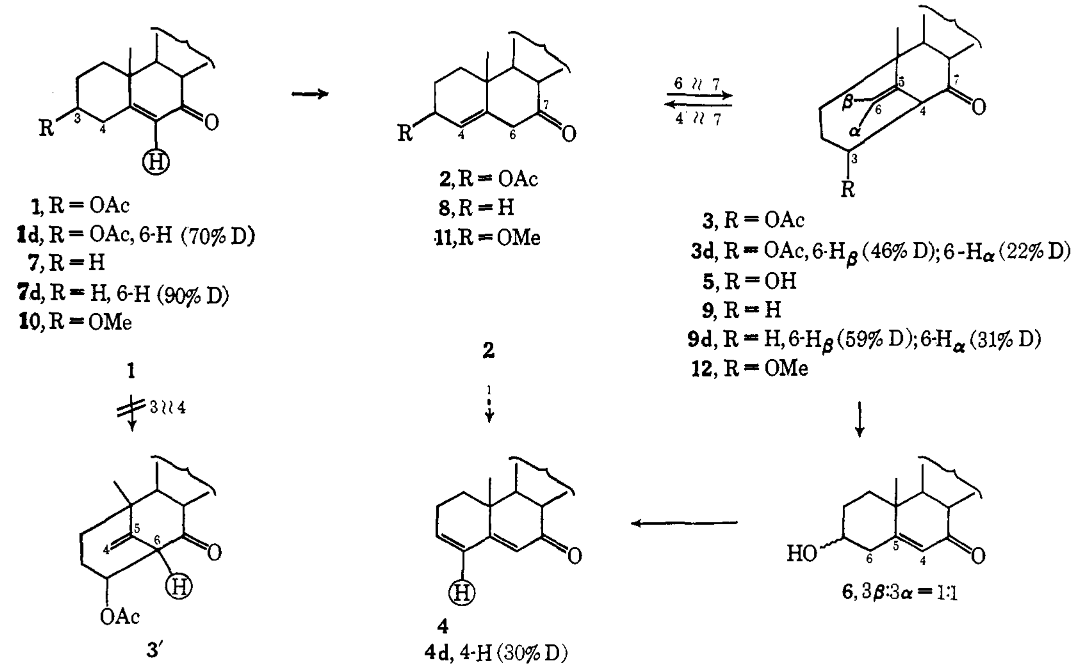


(8) Distribution and content of D are based on nmr and mass spectra data.

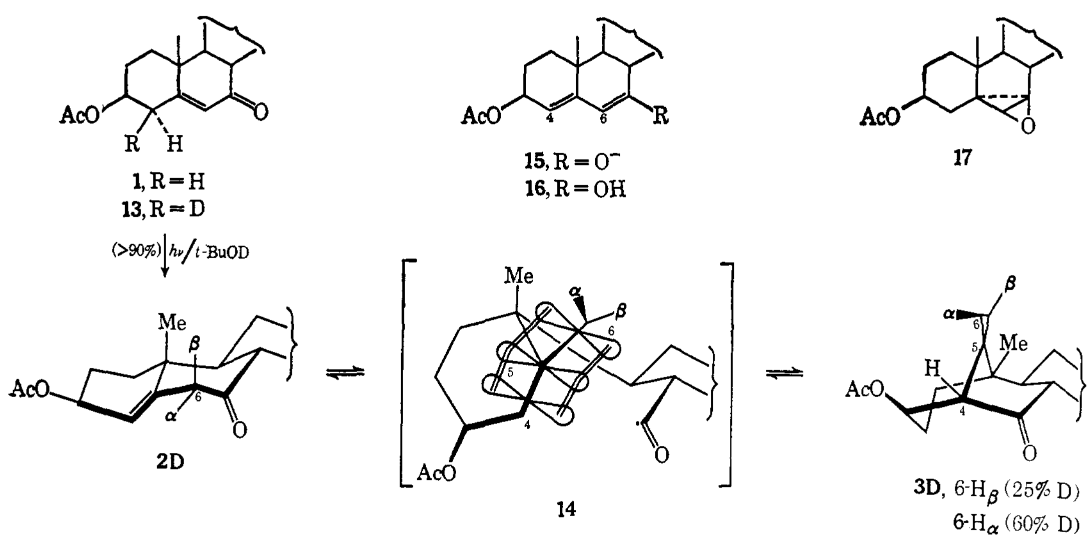
(9) **8**: uv (EtOH) 290 mμ (ε 240); ir (KBr) 1711 cm^{-1}; nmr ($CDCl_3$) 5.35 (m, H-4), 3.26 (br d, J = 13 cps, H_β-6), 2.72 ppm (d, J = 13 cps, H_α-6); **9**: uv (EtOH) 297 mμ (ε 48); ir (KBr) 1710, 1645, 885 cm^{-1}; nmr (C_6D_6) 4.72 (d, J = 1 cps, H_β-6[5]), 4.65 (d, J = 1 cps, H_α-6[5]), 2.79 ppm (m, H-4).

(10) Data for **11**: ir 1715 cm^{-1}; nmr ($CDCl_3$) 5.36 (s, H-4), 3.65 (m, H_α-3), 3.33 (OMe), 3.26 (br d, J = 13.5 cps, H_β-6), 2.77 ppm (d, J = 13.5 cps, H_α-6); data for **12**: ir (KBr) 1711, 1650, 882 cm^{-1}; nmr ($CDCl_3$) 4.94 (d, J = 1 cps, H_β-6[5]), 4.85 (d, J = 1 cps, H_α-6[5]), 3.74 (m, H_α-3), 3.30 (OMe), 3.21 ppm (d, J = 3 cps, H-4).

Scheme I



Scheme II



D content) contained no deuterium, and therefore an intramolecular four-centered mechanism for the production of **2** from **1** is ruled out; the fact that the 4β-axial H (or D) and not the 4α-equatorial H is removed selectively can be ascribed to the favored orientation of the former bond for overlap with the C_5–C_6 π orbital.

On the other hand, when the irradiation was run in *t*-BuOD (Scheme II) the bridged compound **3D** now contained the deuterium only in the exocyclic methylene, *i.e., the deuterium from the solvent had been introduced exclusively at* C_6. Moreover, the nmr pattern of the deuterated exocyclic methylene group (25% D and 60% D in H_β-6 and H_α-6, respectively) was unaffected by the irradiation period, so that in spite of the photoequilibrium between **2D** and **3D**, the D content remains unchanged. From this we conclude that, in the allylic radical **14** resulting from a Norish-type α fission of **2D** or **3D**, *identity of the 6β and 6α hydrogen atoms are preserved* (rotation around C_5–C_6 is hindered) by virtue of orbital overlap of the double-bond electrons and free-radical electron. It should also be noted that the deuterium distribution in **3D** is the reverse of that in **3d** or **9d**; the larger D content in H_α-6 indicates that protonation from the solvent has preferentially occurred from the α side of the molecule.[12]

(11) Prepared by acetylation and Na_2CrO_4 oxidation of 4β-deuteriocholesterol: N. W. Atwater, *J. Am. Chem. Soc.*, **83**, 3071 (1961).

(12) Molecular models indicate that ring B in **2D** must adopt a chair conformation in order that the H_β-6 in **2D** becomes the hydrogen which is closer to the 19-Me in **3D** (assignments based on NOE[5]). A boat conformation would result in scrambling of the D content in the "equilibrium **2D** ⇄ **14** ⇄ **3D**." The chair conformation of ring B is corroborated by the rotatory dispersion data of **8** (negative Cotton effect; *cf.* A. Moscowitz, K. Mislow, M. A. W. Glass, and C. Djerassi, *ibid.*, **84**, 1945 (1962)) and the broad nmr doublet assigned to H_β-6 (axial), in **2**, **8**, and **11**.

Of the conceivable intermediates involved in the photoisomerization of **1** to **2**, the enolate **15** is favored over the enol **16**. If **16** were the intermediate, it would be protonated more readily at C_4 (giving **1**) than at C_6 (giving **2**),[13] and thus the equilibrium **1** $\rightleftarrows$ **16** would be present. However, this possibility can be excluded on grounds of the fact that when irradiation of the 4β-deuterated **13** was stopped after the reaction had proceeded more than 50%, the D content of recovered starting material was unchanged. Intermediate **17**, similar to that encountered in transoid dienes,[14] is also conceivable. Studies are being continued to characterize the intermediate and to clarify the excited species of this photochemical reaction.

(13) H. J. Ringold and S. K. Malhotra, *Tetrahedron Letters*, 669 (1962); S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, **85**, 1538 (1963); 87, 3228 (1965).

(14) W. G. Dauben and W. A. Spitzer, *ibid.*, **90**, 802 (1968); *cf.* also ref 26 in E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *ibid.*, **86**, 5570 (1964).

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Molecular Orbital Symmetry Restrictions on Transition Metal Catalyzed Bis(acetylene)–Cyclobutadiene Interconversion

Sir:

The concerted fusion of two olefins to a cyclobutane ring is a symmetry-forbidden process.[1] We have recently proposed that transformations of this kind can be rendered allowed by an appropriate transition metal system through a unique catalytic process in which the metal and fusing olefin ligands exchange electron pairs as the reaction proceeds across the reaction coordinate.[2] Highly selective and unusually facile transition metal catalyzed valence isomerizations[3] support this hypothesis, and a new catalytic process—olefin metathesis[4]—involving the smooth disproportionation of olefins through interchanging alkylidene groups has been interpreted in terms of this mechanism. The ease with which simple olefins undergo transformations in these catalytic processes is not paralleled in acetylene chemistry. Transition metal catalyzed π-bond fusion of acetylene ligands to the cyclobutadiene ligand would seem to be a relatively low-energy process due to the comparative stability[5] of the cyclobutadiene ligand. The metal-catalyzed concerted cycloaddition would, conceivably, be assisted by the ligand-to-metal π bonding generated along the reaction coordinate with incipient cyclobutadiene formation. An examination of the molecular orbital symmetry conservation aspects of this transformation, however, reveals that such is not the case. Unlike the simple olefin transformation, the concerted transition metal catalyzed interconversion of bis(acetylene) (C_{2v}) and cyclobutadiene (C_{4v}) is not a ground-state process.

The ligand orbitals in both the bis(acetylene)metal complex **1** (C_{2v}) and cyclobutadienemetal complex **2** (C_{4v}) can be treated as two sets, one (Ω) containing orbitals positioned parallel to the X axis (*e.g.*, the p_x orbitals) and the other ($\bar{\Omega}$) parallel to the Z axis (*e.g.*, p_z orbitals) (molecular orbitals in $\bar{\Omega}$ are denoted with a bar, $-$). The elements of symmetry for the concerted transformation **1** $\rightarrow$ **2** are the ZY and ZX planes. The π-orbital combinations in Ω for **1** are described relative to these elements SS (a_1) and AS (b_2) (where A = antisymmetric to ZY and S = symmetric to ZX) and the π^* combinations SA (b_1) and AA (a_2); the corresponding orbitals in $\bar{\Omega}$ are similarly described $\overline{\text{SS}}$, $\overline{\text{AS}}$, $\overline{\text{SA}}$, and $\overline{\text{AA}}$. In **2**, the π combinations are $\overline{\text{SS}}$ (a), $\overline{\text{AS}}$ (e), $\overline{\text{SA}}$ (e), and $\overline{\text{AA}}$ (b); the σ bonds are SS and SA. Metal complex molecular orbitals are constructed from combinations of metal atomic orbitals of the appropriate symmetry with the members of both sets.

The concerted fusion of the Ω–π bonds in **1** to the σ bonds in **2** necessarily effects an exchange of electron pairs between the transforming ligands and the metal.[2] An electron pair moves from the metal d_{yz} orbital into the incipient cyclobutadiene SA σ orbital, while a pair of ligand electrons passes from the AS π combination into the metal d_{zx} orbital. This process can be envisaged as proceeding smoothly across the reaction coordinate. The net result of metal-catalyzed cycloaddition is the relocation of an electron pair from one metal d orbital to another, *i.e.*, from d_{yz} to d_{zx} in **1** $\rightarrow$ **2**.

The second set ($\bar{\Omega}$) of π bonds in **1** interacts negatively with the metal as it undergoes electronic relocalization across the reaction coordinate. The populated $\overline{\text{AS}}$ π combination interacts with the growing electron density in the metal d_{zx} while the unoccupied $\overline{\text{SA}}$ π^* combination interacts with the diminishing density in the metal d_{yz}. Metal-assisted cycloaddition of the Ω–π bonds, therefore, imparts an electronic ordering on the metal which is essentially antibonding with respect to the $\bar{\Omega}$–π bonds. The result is a crossing of bonding and antibonding molecular orbitals across the reaction coordinate. In **1**, the $\overline{\text{AS}}$ π combination is populated and correlates with the π $\overline{\text{AS}}$ (e) orbital in **2**. AS, also populated in **1**, is consequently correlated with the ligand-to-metal antibonding combination of that symmetry. The $\overline{\text{SA}}$ π orbital in **2** (e) is similarly correlated with an unoccupied π^* combination in **1**.

The correlation diagram in Figure 1[6] was constructed from extended Hückel[7] molecular orbital calculations

(1) R. Hoffmann and R. B. Woodward, *J. Am. Chem. Soc.*, **87**, 2046 (1965).

(2) F. D. Mango and J. H. Schachtschneider, *ibid.*, **89**, 2483 (1967).

(3) H. Hogeveen and H. C. Volger, *ibid.*, **89**, 2486 (1967); *Chem. Commun.*, 1133 (1967).

(4) N. Calderon, E. A. Ofstead, J. P. Ward, W. A. Judy, and K. W. Scott, *J. Am. Chem. Soc.*, 90, 4133 (1968).

(5) (a) H. C. Longuet-Higgens and L. E. Orgel, *J. Chem. Soc.*, 1956 (1959); (b) see also W. Hubel in "Organic Synthesis via Metal Carbonyls," Vol. I, I. Wender and P. Pino, Ed., Interscience Publishers, New York, N. Y., 1968.

(6) Figure 1 contains only those molecular orbitals critical to the ligand transformation. Since the molecular orbitals listed are actually mixtures of orbitals of the two sets and metal atomic orbitals of the same symmetry, clear set assignments cannot always be made and have not been attempted in the diagram. Symmetry assignments were made for all the molecular orbitals in the two models. The number of occupied orbitals of the various symmetry classifications for 1 are six SS, four AS, two SA, and two AA; for 2, six SS, three AS, three SA, and two AA.

(7) R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963).