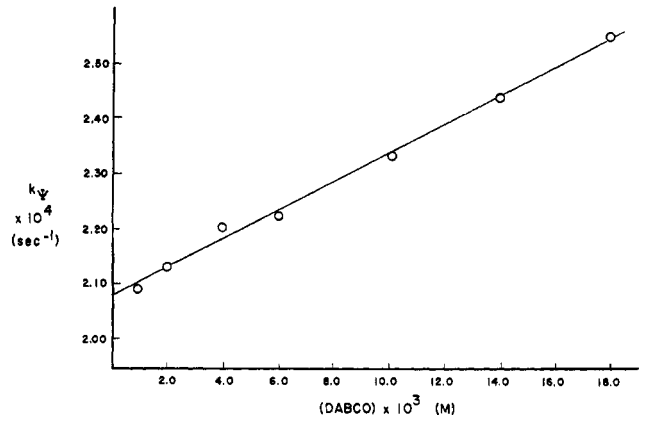

Figure 1. Dependence of the observed pseudo-first-order rate constant on amine concentration for the reaction of Malachite Green with water.

In our earlier work,[1] we utilized triethylamine–triethylammonium ion buffers at concentrations of less than 10^{-3} *M*. We remarked that the observed rates appeared to depend on buffer concentration at higher concentrations than those reported, but attributed the effect to primary and secondary amine impurities in the buffer. The recent work by Bruice[2] and experiments with reactions of ethylamine and diethylamine in our laboratories[3] show that the equilibrium constants for the reactions of Malachite Green with amines are so small that even substantial amounts of such impurities in the buffers would cause negligible effects on the rates of the reactions. A reexamination of our data at relatively high buffer concentrations (10^{-2}–10^{-1} *M*) gives a value of 3×10^{-2} M^{-1} sec^{-1} for the second-order rate constant for catalysis of the reaction by triethylamine.

Table I. Reaction of Malachite Green with Water at 25.0 ± 0.1°[a]

[Dabco], *M*	pH[b]	k_{obsd}[c] × 10^4
1.0×10^{-3}	8.767	2.09
2.0×10^{-3}	8.775	2.13
4.0×10^{-3}	8.789	2.20
6.0×10^{-3}	8.803	2.22
1.0×10^{-2}	8.783	2.33
1.4×10^{-2}	8.778	2.44
1.8×10^{-2}	8.776	2.55

[a] The initial concentration of Malachite Green fluoroborate was 1.23×10^{-6} *M* in all experiments. Ionic strength was maintained constant at 1.8×10^{-2} *M* by addition of the required amount of potassium perchlorate. Buffers were prepared by half-neutralization of Dabco with perchloric acid. [b] The pH of the reaction solution was measured at the beginning and end of each kinetic run with a Beckman Model 1019 pH meter standardized with a commercial pH 6.865 buffer. [c] Pseudo-first-order rate constant in units of sec^{-1}.

The p*K* values of the conjugate acids of Dabco and triethylamine are 8.8[4] and 10.8,[5] respectively. The rate constants given above lead to a Brønsted coefficient of *ca.* 0.5 for the base catalysis. Use of the p*K* value of 15.74 for water leads us to expect the rate constant for catalysis by hydroxide ion to be *ca.* 5 M^{-1} sec^{-1}, in good agreement with the observed value of 2.18 M^{-1} sec^{-1}. It thus appears that hydroxide ion is acting as a general base catalyst in the reaction with Malachite Green.

The reaction of tri-*p*-anisylmethyl cation with water was studied by Hill,[6] who concluded, on the basis of solvent isotope effects, that the reaction is not subject to general base catalysis. Hill found an equilibrium solvent isotope effect, K_{H_2O}/K_{D_2O}, of 2.7, and a kinetic solvent isotope effect of 1.2. We previously reported a kinetic solvent isotope effect of unity for the reaction of Crystal Violet cation with water. The reverse reactions, formation of carbonium ion from alcohol, must then have a kinetic solvent isotope effect of *ca.* 0.44 (*i.e.* 1.2/2.7), which is in the range commonly associated with specific acid catalysis.[7] The present results, of course, show that these reactions involve general acid catalysis.

The situation appears to be quite similar to that encountered in the hydrolysis of ortho esters where solvent isotope effects indicated specific acid catalysis (*i.e.* k_{H_2O}/k_{D_2O} ranges from 0.4 to 0.7) while more recent results clearly indicate general acid catalysis.[8] It is also worth noting that recent studies have shown that the hydrolyses of some acetals and ketals involve general acid catalysis.[9]

The implications of the present results on the interpretation of experiments involving the trapping of carbonium ions in solvolysis reactions[10] are obvious and are the subject of work underway in our laboratories.

Acknowledgment. This work was supported by Grant No. GM-12832 from the National Institutes of Health, PHS.

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(3) This work by Dr. P. O. Virtanen is the subject of a paper in preparation.
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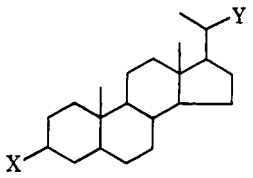
Calvin D. Ritchie
Department of Chemistry, State University of New York at Buffalo
Buffalo, New York 14214
Received January 20, 1972

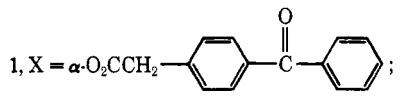
Introduction of a 9(11) Double Bond into Steroids by Selective Free-Radical Halogenation

Sir:

In the course of our studies[1] on remote oxidation, involving the functionalization of steroids by the use of oriented reagents, we came across indications[2] that certain simple free-radical halogenations with selective reagents could also be used to achieve the synthetically important introduction of a 9(11) double bond into steroids. Unsaturation at 9(11) provides an entry into the medicinally useful corticosteroid series.

(1) (a) R. Breslow and M. A. Winnik, *J. Amer. Chem. Soc.*, **91**, 3083 (1969); (b) R. Breslow and S. W. Baldwin, *ibid.*, **92**, 732 (1970); (c) R. Breslow and P. C. Scholl, *ibid.*, **93**, 2331 (1971); (d) R. Breslow and P. Kalicky, *ibid.*, **93**, 3540 (1971).
(2) *Cf.* Ph.D. Thesis, W. N. Washburn, Columbia University, 1971. Some of these observations have been described in public lectures as early as June 1970.



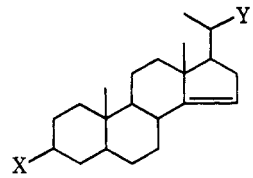


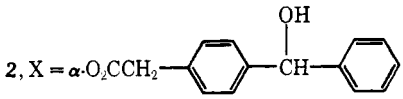
1, X = α-O_2CCH_2—C(=O)—; Y = $CH_2CH_2CH_2CH(CH_3)_2$

4, X = α-OAc; Y = $CH_2CH_2CH_2CH(CH_3)_2$

6, X = β-OAc; Y = OAc

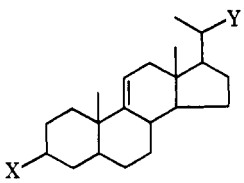
9, X = (O=); Y = (O=)





2, X = α-O_2CCH_2—CH(OH)—; Y = $CH_2CH_2CH_2CH(CH_3)_2$

8, X = β-OAc; Y = OAc



3, X = α-OH; Y = $CH_2CH_2CH_2CH(CH_3)_2$

5, X = α-OAc; Y = $CH_2CH_2CH_2CH(CH_3)_2$

7, X = β-OAc; Y = OAc

We had early observed[1b] that when photochemical remote oxidation of steroids was carried out in CCl_4 solution, some chlorination of the steroid occurred. In an attempt to explore this further, and to divert the course of remote oxidation by interception of an intermediate steroid radical, we irradiated compounds such as **1** in the presence of 0.1 *M* $BrCCl_3$. In the absence of $BrCCl_3$, the simple irradiation of **1** leads to the production of a 55% yield of the Δ^{14} steroid **2** by abstraction of the 14-H and transfer of the 15-H to the benzhydryl carbon. In the presence of $BrCCl_3$ this same irradiation affords no detectable steroidal olefin; instead the product is a bromosteroid and $HCCl_3$, and the benzophenone carbonyl is unchanged. On treatment with base the bromosteroid affords cholestenols in which the predominant isomer, 66% of the product mixture, is 9(11)-cholesten-3α-ol (**3**),[3] mp 155–157°.

(3) The structure of such compounds is indicated by the characteristic nmr shifts of the C-18 and C-19 methyl groups and vinyl hydrogens when the double bond is introduced. In this key case the compound was also identified by an authentic synthesis[2] of **3**, starting with 5α-cholesta-7,9-dien-3β-ol.

Various controls quickly established that this occurs by bromination of C-9 in an independent free-radical process, and it can be conveniently carried out by simple irradiation of steroids with $BrCCl_3$ in solvents such as benzene without the necessity of attached (or unattached) benzophenone. Thus, if a 10^{-3} *M* solution of 3α-cholestanyl acetate (**4**) in benzene with 0.1 *M* $BrCCl_3$ is irradiated with a Hanovia 450-W medium-pressure uv lamp through quartz for 30 min, followed by silica gel chromatography, 75% of the starting material is recovered and the only unsaturated steroid, in 48% yield, is the $\Delta^{9(11)}$ acetate **5**.[3] Application of the same process to pregnane 3β,20-diacetate (**6**) affords an olefin mixture, in 60% yield and 15% conversion, consisting of a 4:1 ratio of the $\Delta^{9(11)}$ product **7** and the Δ^{14} product **8**.[4] With androstane the olefinic products are again the 9(11)- and 14-androstenes,[4] but in a ratio of 1:4. Cholestane affords a 31% yield of 9(11)-cholestene and a 31% yield of 5-cholestene (28% conversion).[4]

Although this process has attractive selectivity for C-9, particularly in the case of compounds **4** and **6**, it is not completely practical synthetically. Reasonable yields of olefins can be obtained only when the reaction is carried out to low conversion, since the products undergo further complex changes with $BrCCl_3$. Furthermore, work-up and isolation of the olefins are somewhat tedious due to the presence of tarry materials derived from the reaction of $BrCCl_3$ with solvent. These difficulties are overcome with a different selective radical halogenation process, which appears to be a practical method for the selective functionalization of steroids. Thus, when a 0.06 *M* solution of **6** with 0.12 *M* $C_6H_5ICl_2$[6] in benzene is irradiated in a Pyrex vessel with a simple 275-W sun lamp for 10 min, followed by treatment with $AgClO_4$ in aqueous acetone, a 75% yield of monoolefins derived from **6** is obtained with no recovered starting material. The olefins produced[4] are an approximately 1:1 mixture of **7** and **8**, with only minor traces of other materials. Other steroids also show good selectivity and convenient conversion to high yields of olefinic products. 3β-Cholestanyl acetate affords a 1:1 mixture of the $\Delta^{9(11)}$- and Δ^{14}-cholestanol acetates,[4] and even 3β-cholestanol gives the mixture of these two olefins in competition with oxidation of the hydroxyl to a carbonyl. With 3,20-diketopregnane (**9**) carried to 89% conversion there is a 22% yield of the conjugated 4-enone, but the other products are 50% of the 14-enone and 28% of the 9(11)-enone.[4] In general, these olefins can be separated chromatographically, and a chemical separation may even be possible since we find that elimination of HCl occurs much more readily with the 14-chlorosteroids than with the 9-chlorosteroids.

(4) These identifications are by mass spectra and the completely characteristic[5] nmr shifts for vinyl and methyl protons. Thus, in 3-α-cholestanol the C-18 signal moves upfield by 0.07 ppm, and the C-19 signal downfield by 0.13 ppm, on introduction of the 9(11) double bond; by contrast, on introduction of the 14, 15 double bond the C-18 signal moves downfield by 0.25 ppm, and the C-19 signal downfield by 0.01 ppm. In the 9(11)-cholestenol the vinyl signal is at δ 5.28 while in the 14-3α-cholestenol it is at δ 5.13. Similar patterns are found in the other steroid series.

(5) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 19–24.

(6) H. J. Lucas and E. R. Kennedy, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 482.

These functionalizations are free-radical chain processes, involving CCl_3 radical[7] or C_6H_5ICl radicals[8] as the hydrogen abstractors. Both of these species are known[7,8] to be highly selective for tertiary hydrogens; they also are clearly both rather bulky radicals. Under the circumstances, it is not surprising that they tend to attack on the less hindered α side of a steroid such as **6**, and that they attack tertiary axial hydrogens which are at the same time the most reactive and the most accessible.[9] Only hydrogens at positions 5, 9, and 14 are at the same time tertiary, α, and axial to a cyclohexane ring; in compounds such as **4** or **6** the hydrogen at C-5 may have decreased reactivity because of polar effects in the hydrogen abstraction transition state. Thus, it does seem that only[10] normal chemical factors are involved in the selectivity of this process, in contrast to the orientation factors involved in our remote oxidation methods. However, these highly selective reactions, in particular the reaction with $C_6H_5ICl_2$, may prove to be useful in steroid functionalization and related practical processes.[11]

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(10) Although the ability of a *flat* reagent to pack on the *flat* side of the steroid so as to produce an activated complex with minimum volume may also be involved here.
(11) Support of this work by the National Institutes of Health is gratefully acknowledged.

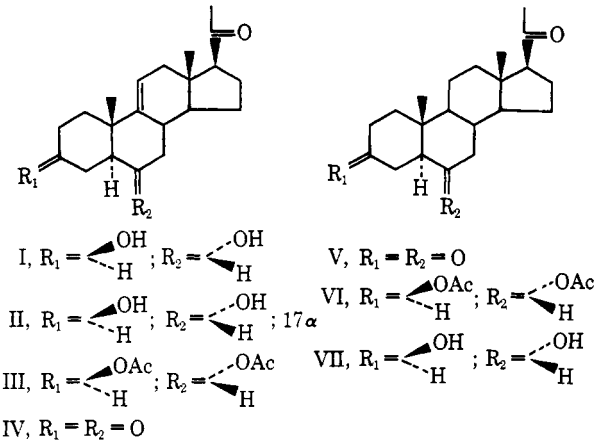
Ronald Breslow,* James A. Dale, Paul Kalicky
Sophia Y. Liu, William N. Washburn
Department of Chemistry, Columbia University
New York, New York 10027
Received February 17, 1972

5α-Pregn-9(11)-ene-3β,6α-diol-20-one and 5α-Cholesta-9(11),20(22)-diene-3β,6α-diol-23-one. Two Novel Steroids from the Starfish *Acanthaster planci*

Sir:

In continuation of our work[1] on novel steroids from marine sources, we report the isolation of the hitherto unknown 5α-pregn-9(11)-ene-3β,6α-diol-20-one (I) and 5α-cholesta-9(11),20(22)-diene-3β,6α-diol-23-one (VIII) from the sapogenin portion (0.15% on dry basis) of *Acanthaster planci* Linn., a starfish threatening many of the Pacific coral reefs. The existence of the rare $\Delta^{9(11)}$ double bond, notably in the pregnene I, makes these compounds potentially interesting marine sources for corticosteroid syntheses.

Genin I [mp 162–163°, M^+ 332.23510, $C_{21}H_{32}O_3$ (required 332.23513); di-*p*-bromobenzoate, mp 198–200°] depicted a single positive Cotton effect [ORD, $\phi_{305} = +5199$, $\phi_{265} = -3812$; CD, $\theta_{287} = +7380$].



Its nmr spectrum (100 MHz, $CDCl_3$) depicted two quaternary methyl (δ 0.57, 0.95, s, 3 H each), an acetyl (2.11, s, 3 H), an acetyl methine (3.09, t, J = 9.5 Hz, 1 H, C-17α H), two secondary carbinol methine (3.57, m, 2 H, which are shifted in the noncrystalline diacetate III to 4.80 (m, 2 H)), and an olefinic proton (5.37, dt (distorted triplet), 1 H, J = 5.5 Hz) signal.

The skeleton and position of all three oxygens were established by hydrogenation of I followed by oxidation to the known triketone V[2] (identified by mixture melting point and comparison of ir, CD, and mass spectrum). Oxidation of I led to the triketone IV [mp 182–184°; M^+ 328; nmr ($CDCl_3$, benzene-d_6) C-18 CH_3 (0.63; 0.45, s, 3 H), C-19 CH_3 (1.01; 0.61, s, 3 H), CH_3CO (2.13; 1.75, s, 3 H), >C=C*H*CH_2 (5.60; 5.10, dt, 1 H)], which was essentially transparent in the uv (neutral or basic solution) and hence could not be an α,β- or β,γ-unsaturated ketone. Of the two possible alternative locations for the double bond (Δ^{14} or $\Delta^{9(11)}$), the former was excluded by the mass spectrum of IV which exhibited an important peak at *m/e* 243 (ring D cleavage)[3] thus indicating the presence of two oxygen atoms and the double bond in rings A, B, and C.

The stereochemistry of the two hydroxyl groups at positions 3 and 6 in I was established by hydrogenation of III followed by reoxidation (at C-20) to VI [$\theta_{292.5}$ = +5857] and saponification to the known[4] 5α-pregnane-3β,6α-diol-20-one (VII) [mp 201–204°[4] (acetone–ether), 171–172° (acetone–hexane), M^+ 334].

In addition to I, there was isolated also a small amount of its 17α isomer 5α,17α-pregn-9(11)-ene-3β,6α-diol-20-one (II) [CD[5] of diacetate $\theta_{290} = -1541$, nmr and mass spectra very similar to that of I], but it is likely that it is an artifact produced during the acid hydrolysis of the glycoside rather than naturally occurring.

Genin VIII was isolated as a noncrystalline diacetate IX [λ_{max} (MeOH) 246.5 nm (ε 13,000); λ_{max}($CHCl_3$) 1735, 1685 cm^{-1}); CD(MeOH) $\theta_{247.5} = -12{,}000$; all spectral properties consistent with an α,β-unsaturated ketone]. The mass spectrum of IX showed the loss of two molecules of acetic acid (*m/e* 438, 378) and significant peaks at *m/e* 441 ($M^+ - C_4H_9$), 311 (438$^+$ –

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