Recently Kirby has postulated that the hydrolysis of aromatic phosphate dianions appears to proceed *via* formation of free monomeric metaphosphate.[29] It is important to note that the dianions in methanol–water mixtures yield consistently a product composition favoring methyl phosphate, whereas the monoanionic species more closely approximates the solvent composition. The authors rationalize this on the basis of selective solvation of the dianion. An alternate explanation is the possibility that the transition state does not involve free metaphosphate, although predominantly unimolecular in character. Treatment of the reported data in terms of the plot of Figure 5 reveals that 2,4-dinitrophenyl phosphate dianion is *ca.* fourfold more reactive with methanol than with water, consistent with considerable P–O fission in the transition state. Selective solvation cannot be completely eliminated nevertheless as a competing factor in the above and present study. It appears, however, that the nonselectivity criterion for metaphosphate is only satisfied at present in the solvolysis of phosphate monoester monoanions in methanol–water mixtures where there exists in addition a considerable body of data supporting the metaphosphate hypothesis. In conclusion it should also be noted that the zwitterionic intermediates in phosphate monoester monoanion hydrolysis constitute the best leaving groups in terms of pK_a' arguments and probably delineate one end of the scale from bimolecular to unimolecular hydrolysis in phosphorus-containing esters. Moreover, in phosphoramidate hydrolysis in particular, one definitely appears to encounter transition states in which the extent of bond formation and fission are not directly proportional, which suggests that pentacovalent intermediates may be important in the hydrolysis of several of these species. From a biological standpoint the lability of phosphoramidates and their selectivity toward hydroxylic nucleophiles other than water indicate their utility as biochemical phosphorylating agents.

Acknowledgment. This research was supported by Public Health Research Grant GM 13306-02. The assistance of Mr. Dennis Kotchmar in formulating a computer program for the pH–rate profiles is gratefully appreciated.

Chromic Acid Oxidation of Allyl Alcohols[1]

Sumner H. Burstein and Howard J. Ringold

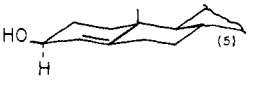
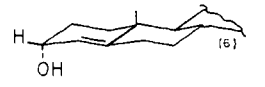
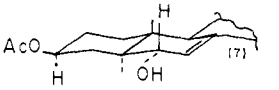
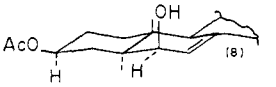
Contribution from the Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts 01545. *Received March 6, 1967*

Abstract: The rate-limiting step in the chromic acid oxidation of allyl alcohols is the cleavage of the carbon–hydrogen bond. In the absence of substantial strain factors equatorial alcohols are oxidized faster than the axial isomer, which may be rationalized on the basis of better overlap of the departing axial hydrogen. The rapid oxidation rate of unsaturated alcohols indicates a substantial contribution from α,β-unsaturated ketone resonance in the transition state.

In a previous publication,[2] evidence was presented that the conversion of allyl alcohols to the corresponding α,β-unsaturated ketones by dichlorodicyanoquinone (DDQ) oxidation proceeds *via* a rate-determining abstraction of hydride ion from carbon. In the case of a sterically compressed axial allyl alcohol, for example, the Δ^7-6β-ol **8**, DDQ oxidation of the axial alcohol was faster than oxidation of the equatorial counterpart **7**. However, the situation was reversed when the alcohols were relatively unhindered such as the Δ^4-3-ols **5** and **6** (Table I). These findings prompted us to determine the effect of unsaturation on chromic acid oxidation rates with these two isomeric alcohol pairs.

It has been demonstrated quite conclusively[3] that saturated secondary axial alcohols are oxidized more rapidly by chromic acid than the equatorial isomers and that these differences are magnified in sterically crowded situations. It is generally accepted[3,4] that rate enhancement in the latter case is due primarily to strain relief in the transition state which proceeds concomitantly with the development of carbonyl (trigonal) character. The primary deuterium isotope effect with

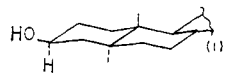
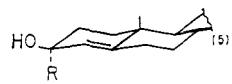
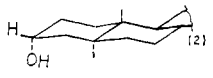
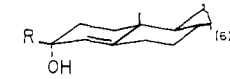
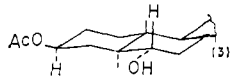
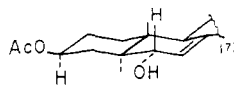
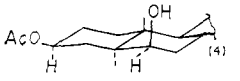
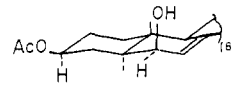
Table I. Relative Oxidation Rates of Allyl Alcohols with Dichlorodicyanoquinone[a]

	k_{rel}	$\frac{k_{eq}}{k_{ax}}$
	33.7	
		6.4
	5.2	
	1.0	
		0.086
	11.7	

[a] Reported in ref 2.

(1) Supported in part by Grant T-185, American Cancer Society.
(2) S. H. Burstein and H. J. Ringold, *J. Am. Chem. Soc.*, 86, 1952 (1964).
(3) J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, 38, 1529 (1955).
(4) *Cf.* J. C. Richer, L. A. Pilato, and E. L. Eliel, *Chem. Ind.* (London), 2007 (1961).

Table II. Relative Oxidation Rates of Saturated and Unsaturated Alcohols with CrO_3 in 90% Acetic Acid–Sodium Acetate[a]

	k_{rel}	$\frac{k_{eq}}{k_{ax}}$		k_{rel}		$\frac{k_{eq}}{k_{ax}}$	$\frac{k_{unsatd}}{k_{satd}}$
	1.0			R = H 310	R = D 45		310
		0.25				5.7	
	4.0			54	11		13.5
	1.4			130			93
		0.024				0.34	
	58.0			380			6.6

[a] The kinetic procedure is detailed in the Experimental Section.

saturated carbinols is well known,[5] and together with other studies[6–8] has led to the formulation of an oxidation mechanism consisting of the reversible formation of a chromate ester which decomposes to the ketone plus a reduced form of chromium.[9] Usually, decomposition of the chromate ester has been found to be the slow step in the over-all reaction. However, in one instance,[8] a very severely hindered alcohol exhibited no isotope effect which indicated that it is possible for ester formation to become the rate-determining step.

Although it is well known[10] that allyl alcohols are rapidly oxidized by chromic acid, little study has been made of the effect, on reaction rate, of conformational and strain factors. One example of considerable interest was the finding that the 3β-equatorial alcohol of 3β,6β-dihydroxycholest-4-ene was oxidized more rapidly than the hindered axial 6β-ol.[11] This prompted the suggestion that the rate-determining step in the oxidation of allyl alcohols is the formation of an allyl carbonium ion rather than the cleavage of a carbon–hydrogen bond.

Table II lists the relative chromic acid oxidation rates for the Δ^4-3-ols and their 3-deuterated analogs **5** and **6**, the Δ^7-6-ols **7** and **8**, and the corresponding saturated compounds **1–4** which have been included for reference.[12] The oxidation rates were studied spectrophotometrically at 27° by following the disappearance of Cr^{VI} in 90% acetic acid which was 0.02 *M* in sodium acetate. The system was a pseudo-first-order one with steroid present in excess. The two saturated equatorial alcohols **1** (3β-hydroxy-5α-androstan-17-one) and **3** (3β-acetoxy-6α-hydroxy-5α-cholestane) exhibited very similar oxidation rates of 1.0 and 1.4, respectively. The saturated axial 3α-hydroxy compound **2** (3α-hydroxy-5α-androstan-17-one) with two diaxial hydrogen–hydroxyl interactions gave a relative oxidation rate of 4.0 while the 6β-hydroxy compound **4** (3β-acetoxy-6β-hydroxy-5α-cholestane) with a methyl–hydroxyl interaction in addition to two hydrogen–hydroxyl interactions reacted much faster (relative rate = 54).

Turning to the allyl alcohols, the equatorial 3β-ol **5** (3β-hydroxyandrost-4-ene) exhibited a rate of 310 times the saturated reference compound. The axial Δ^4-3α-ol **6** (3α-hydroxyandrost-4-ene), with a single hydrogen–hydroxyl interaction, had a relative rate of 54 and therefore was oxidized only 13.5 times faster than the saturated 3α-ol **2**. Thus, just as in the DDQ reaction, chromic acid oxidation of the equatorial isomer proceeds faster than the axial isomer when the latter is relatively unhindered. The C-deuterated analogs of **5** and **6** were also studied and gave substantial isotope effects: k_H/k_D (eq) = 6.9; k_H/k_D (ax) = 4.9. On the basis of the isotope effect, it is clear that the rate-limiting step in the chromic acid oxidation of allyl alcohols is indeed the cleavage of the carbon–hydrogen bond. Also, there is no reason to doubt that the general mechanism involving the prior formation of a chromate ester applies for unsaturated as well as saturated alcohols.

Introduction of a 7,8 double bond into the 6-hydroxy compounds gave rate increases that were not so pronounced as with the 3-alcohols, although a similar equatorial–axial pattern was maintained. The equatorial alcohol **7** (3β-acetoxy-6α-hydroxy-5α-cholest-7-ene) had a relative rate of 130 which was 93 times the saturated analog **3**. The axial isomer **8** (3β-acetoxy-6β-hydroxy-5α-cholest-7-ene) with one methyl–hydroxyl and one hydrogen–hydroxyl interaction exhibited a rate of 380 for an enhancement of 6.6 times the saturated compound **4**. By comparing **8** *vs.* **6**, it is obvious that the introduction of steric strain into the allylic alcohols leads to an enhanced chromic acid oxidation rate. However the strain factor is considerably more important in the saturated substances **4** *vs.* **2**.

The most striking effect in the unsaturated alcohols is the great oxidation rate of the equatorial isomers which is completely unrelated to strain or strain release. The explanation which was invoked[2] to explain similar

(5) F. H. Westheimer and N. Nicolaides, *J. Am. Chem. Soc.*, **71**, 25 (1949).
(6) F. H. Westheimer and A. Novick, *J. Chem. Phys.*, **11**, 506 (1943).
(7) F. Holloway, M. Cohen, and F. H. Westheimer, *ibid.*, **73**, 65 (1951).
(8) J. Rocek, F. H. Westheimer, A. Eschenmoser, L. Moldovanyi, and J. Schreiber, *Helv. Chim. Acta*, **45**, 2554 (1962).
(9) K. B. Wiberg and H. Schafer, *J. Am. Chem. Soc.*, **89**, 455 (1967).
(10) G. Grimmer, *Ann. Chem.*, **636**, 42 (1960).
(11) L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4377 (1953); L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp 203, 225.
(12) Our results for the saturated carbinols agree qualitatively with those reported by Schreiber and Eschenmoser,[8] who report relative rates of 1.0, 3.0, 2.0, and 36 for compounds **1–4**. Numerical differences may be due to the fact that our runs were made in the presence of sodium acetate while the others were unbuffered.

effects in the DDQ oxidation of allyl alcohols may be applied to the chromic acid oxidation. We believe the important factor is not that the alcohol is equatorial but rather that the hydrogen being removed in the rate-determining step is axial, which permits continuous overlap with the π electrons of the adjacent double bond (*i.e.*, the resonance interaction between the incipient carbonyl group and the double bond is maximal). Although it is not known in the chromic acid case whether hydrogen is removed from carbon as a proton or as hydride, the same steric requirements for overlap pertain in either case. The general similarity of k_{eq}/k_{ax} ratios in the DDQ oxidation (Table I) and chromic acid (Table II) is consistent with hydride loss in chromic acid oxidation but does not permit exclusion of a proton abstraction mechanism, in particular, if the reaction is a concerted cyclic process.

The Eschenmoser steric-strain relief hypothesis has been challenged[13] in the past on the grounds that in the transition state almost a fully developed carbonyl would be required to explain some of the observed rate accelerations. While better overlap explains the difference between equatorial and axial allyl alcohol oxidation rates, it must be recognized that the basic factor in the rapid oxidation of the allyl alcohols is the resonance contribution of the incipient α,β-unsaturated ketone.[14] Obviously this requires significant ketonic character in the transition state and may be cited in support of the Eschenmoser hypothesis. Also, based on these principles, it may be anticipated that unsaturated alcohols which yield *S-trans*-unsaturated ketones will be oxidized more readily than those which lead to *S-cis*-unsaturated ketones due to the more favorable resonance contribution of the former. It is probable that the selective oxidation of the 3β-alcohol of 3β,6β-dihydroxycholest-4-ene[11] stems primarily from this latter factor.

Experimental Section

A. Materials. Glacial acetic acid, chromium trioxide, and sodium acetate were commercially available analytical grade substances and were not purified further. 3β-Hydroxy-5α-androstan-17-one (**1**) and 3α-hydroxy-5α-androstan-17-one (**2**) were obtained from commercial sources and their melting point and chromatographic homogeneity used as criteria of purity. Preparation of the Δ^4-3-ols **5** and **6** has been previously described.[2]

3β-Acetoxy-6α-hydroxy-5α-cholestane (3). The procedure was a slight modification of the preparation reported by Nussim, *et al.*[15] Cholesterol acetate (1 g) was dissolved in dry ether and a 25-fold excess of gaseous diborane was passed into the solution at 0° for a period of 30 min. The diborane was generated in a separate vessel by the slow addition of sodium borohydride in diglyme to a diglyme solution of boron trifluoride etherate. The steroid reaction mixture was allowed to warm to room temperature over a 30-min period, and the organoborane then cleaved by shaking the ethereal solution with 1% sodium hydroxide containing hydrogen peroxide and separating the phases as soon as possible. The ether extract was washed with water and ferrous sulfate solution, dried over sodium sulfate, and evaporated. Chromatography of the residue on neutral alumina (15 g, activity III) gave the desired compound in the benzene–cyclohexane (1:1) eluate. Crystallization from aqueous acetone gave 130 mg of pure material, mp 138–139°, which was homogeneous on thin layer silica gel chromatography. In the infrared ($CHCl_3$), the compound showed acetate bands at 5.81 and 8.03 μ. Saponification for 1 hr with 1% potassium hydroxide in hot methanol gave the authentic diol, mp 220° (lit.[15] mp 217°).

3β-Acetoxy-6β-hydroxy-5α-cholestane (4). A cold solution of 1 g of 3β-acetoxy-5α-cholestan-6-one in 50 ml of tetrahydrofuran was treated with a solution of 1 g of sodium borohydride in 5 ml of water. The mixture was stirred for 16 hr at room temperature and then added with stirring to an ice-cold solution of dilute hydrochloric acid. The precipitate was filtered, washed, dried, and twice crystallized from aqueous acetone to yield 500 mg of desired monoacetate, mp 156–158°. In the infrared, acetate bands were visible at 5.81 and 7.95 μ. Thin layer chromatography on silica gel (ethyl acetate–benzene 1:9) showed only a single spot. Acetylation with acetic anhydride–pyridine gave the diacetate, mp 135–137° (lit.[16] mp 139°), and saponification as described above gave the free diol, mp 190° (lit.[17] mp 192°). On silica gel thin layer plates, **3** and **4** exhibited R_f values of 0.56 and 0.64, respectively (hexane–acetone 3:2).

3β-Acetoxy-6α-hydroxy-5α-cholest-7-ene (7). 7-Dehydrocholesterol acetate (1 g) was hydroborated by the procedure described above except that the total reaction time was 45 min at 0°. The crude product was chromatographed on 15 g of neutral alumina and the desired product eluted with benzene–methanol (98:2). Crystallization from aqueous acetone gave 240 mg of **7**, mp 143–144°, homogeneous on silica gel thin layer chromatography. The compound had acetate bands at 5.81 and 7.9 μ in the infrared. In the nmr,[18] the C-7 vinylic proton was unsplit by the C-6 proton and appeared as a singlet at 311 cps, consistent with a dihedral angle of approximately 90°. The acetate methyl was at 122 cps and the 19-methyl group at 52 cps. Saponification of **7** gave the known diol of mp 192°.[19]

3β-Acetoxy-5α-cholest-7-en-6-one. A solution of **6** (500 mg) in acetone (100 ml) was cooled to 15° and treated dropwise with 1.1 equiv of chromic acid in sulfuric acid. Methanol was added to destroy excess chromic acid and water added to precipitate the product. The solid was crystallized from aqueous methanol to yield 420 mg of 6-ketone, mp 148–150° (lit.[20] mp 151°); λ_{max}^{EtOH} 244 mμ (ϵ 12,700); ν_{max}^{KBr} 5.79, 6.01, 6.19, and 8.08 μ.

3β-Acetoxy-6β-hydroxy-5α-cholest-7-ene (8). The 6-keto compound (above) was reduced with sodium borohydride as described for the preparation of **4** and gave after crystallization from aqueous acetone a 78% yield of the desired 6β-ol, mp 156–157°. On silica gel thin layer chromatography (hexane–acetone 3:2), compound **8** was homogeneous and slightly less polar than the equatorial isomer; ν_{max}^{KBr} 2.84, 5.76, 5.83, and 7.97 μ; nmr doublet 324, 328.5 cps (C-7 H), 122 cps (acetate CH_3), 60 cps (19-CH_3).

B. Kinetic Determinations. The rates of oxidation were measured at 27° and followed spectrophotometrically as described in the literature.[3,10,13] Reactions were carried out directly in a 3-ml cuvette which was maintained at the required temperature by means of a thermostated cell compartment. The disappearance of the Cr^{VI} maximum at 340 mμ was used to follow the course of reaction and measurements were made on a Zeiss PMQ-II instrument. The medium was 90% acetic acid which was 0.02 *M* in sodium acetate. Reactions were run as "pseudo first order"[13] by using steroid concentrations in the ratio of 10 moles to 1 mole of chromium trioxide.

Rate curves were plotted as log optical density *vs.* time and the best straight line was drawn through the series of observed points. From these curves, second-order rate constants were calculated by substitution into the equation

$$k = \frac{1}{(a-b)t} \ln \left[\frac{b(a-x)}{a(b-x)}\right] \cong \frac{1}{(a-b)t} \ln \left(\frac{b}{b-x}\right)$$

where a = initial steroid concentration, b = initial CrO_3 concentra-

(13) H. Kwart and P. S. Francis, *J. Am. Chem. Soc.*, **81**, 2116 (1959); H. Kwart, *Chem. Ind.* (London), 610 (1962).

(14) Although higher steady-state concentration of the chromate ester would also lead to a faster over-all rate, there is no reason to believe that the equilibrium position for ester formation would markedly differ in the saturated and unsaturated compounds.

(15) M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **29**, 1121 (1964).

(16) Pl. A. Plattner, Th. Petrzilka, and W. Lang, *Helv. Chim. Acta*, **27**, 513 (1944).

(17) R. E. Marker and J. Kreuger, *J. Am. Chem. Soc.*, **62**, 79 (1940).

(18) The nmr spectra were obtained on a Varian Model A-60 spectrophotometer at 60 Mcps. All spectra were run in deuteriochloroform with tetramethylsilane as internal standard and are reported as cps downfield from the reference compound.

(19) L. Caglioti, G. Cainelli, and G. Maina, *Tetrahedron*, **19**, 1057 (1963).

(20) C. Djerassi, J. C. Knight, and H. Brockman, Jr., *Chem. Ber.*, **97**, 3118 (1964).

tion, and x = the amount of CrO_3 reacted at time t. All rates are expressed in Table II relative to 3β-hydroxy-5α-androstan-3-one (**1**) which had a second-order rate constant of 2.80×10^{-3} l. mole^{-1} sec^{-1}.

The reactions were initiated by mixing nine parts of a freshly prepared solution of the steroid in glacial acetic acid with one part of an aqueous solution of chromium trioxide which was 0.20 *M* in sodium acetate. In the case of the slower reactions, the steroid was 30.9×10^{-3} *M* and chromic acid 3.09×10^{-3} *M*. In the faster reactions, the concentrations were 30.9×10^{-4} and 3.09×10^{-4} *M*, respectively. All reactions were allowed to proceed for at least one half-life. With one exception the steroidal substrates were stable in acetic acid over the period of measurement and no side reaction would be detected by product analysis. In the case of 3α-hydroxyandrost-4-ene (**6**) and the corresponding deuterio compound, a small amount of dehydration was noted. However, this side reaction was insufficient to cause noticeable deviation in the pseudo-first-order plot. All substrates were run in duplicate or triplicate.

Sulfoxide–Carbodiimide Reactions. V.[1] Reactions of 2,6-Disubstituted Phenols

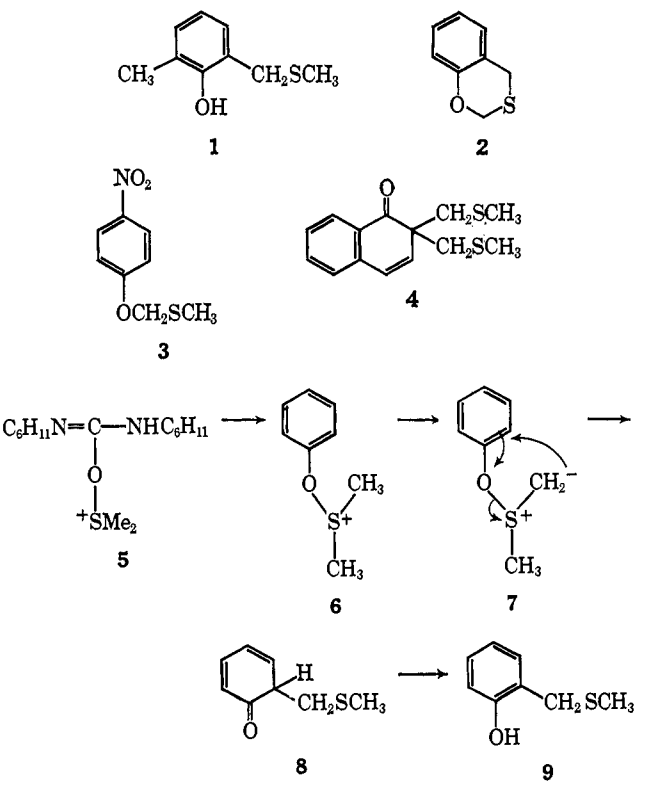
M. G. Burdon[2] and J. G. Moffatt

Contribution No. 38 from the Institute of Molecular Biology, Syntex Research, Palo Alto, California. *Received March 29, 1967*

Abstract: Phenols substituted in the 2 and 6 positions with alkyl groups react with dimethyl sulfoxide and dicyclohexylcarbodiimide in the presence of anhydrous phosphoric acid to give 2,6-disubstituted 6-(thiomethoxymethyl)cyclohexa-2,4-dien-1-ones. These dienones tend to rearrange to thiomethoxymethylphenols during silica chromatography or upon addition of acids, and studies designed to elucidate the mechanism of these rearrangements are described. Under suitable conditions the thiomethoxymethyl group can be efficiently transferred from a suitably substituted dienone to another acceptor molecule. *o*-Chlorophenols behave unusually and lead primarily to 1,3-benzoxathians.

Following the development of the mild, but efficient, dimethyl sulfoxide–dicyclohexylcarbodiimide (DMSO–DCC) method for the oxidation of hydroxyl groups[3] we have undertaken a general program studying the reactions of these reagents with other functional groups. In part IV of this series[1] we have described the mild, acid-catalyzed reactions of DMSO and DCC with a variety of phenols containing unsubstituted *ortho* positions. Such reactions led to a number of different types of products depending upon the nature of the starting material. The principal products were usually phenols substituted in one or both of the available *ortho* positions by thiomethoxymethyl groups (*e.g.*, **1**), and frequently low yields of products containing the previously undescribed 1,3-benzoxathian ring system (*e.g.*, **2**) were also isolated. More strongly acidic phenols, such as nitrophenols, gave rise to aryl thiomethoxymethyl ethers (*e.g.*, **3**), while thiophenols and naphthols were anomalous and gave diaryl disulfides and bis(thiomethoxymethyl)dihydronaphthalenones (*e.g.*, **4**), respectively. Comparable products were also found using sulfoxides other than DMSO.

Mechanisms were proposed for these various reactions[1] involving initial attack of the phenolic oxygen upon the DMSO–DCC adduct **5** which has been shown by isotopic experiments[3d] to be the first intermediate during oxidation of alcohols. The *ortho*-alkylation reaction then proceeds *via* the aryloxysulfonium salt **6** and the sulfonium ylide **7**, the carbanion of which intramolecularly alkylates the available *ortho* position, giving the phenol **9** *via* the dienone **8**.



(1) For part IV see M. G. Burdon and J. G. Moffatt, *J. Am. Chem. Soc.*, **88**, 5855 (1966).

(2) Syntex Postdoctoral Fellow, 1964–1965, and recipient of a Wellcome Trust travel grant, for which we express our thanks.

(3) (a) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem, Soc.*, **85**, 3027 (1963); (b) K. E. Pfitzner and J. G. Moffatt, *ibid.*, **87**, 5661 (1965); (c) K. E. Pfitzner and J. G. Moffatt, *ibid.*, **87**, 5670 (1965); (d) A. H. Fenselau and J. G. Moffatt, *ibid.*, **88**, 1762 (1966).