TABLE I

CATALYTIC EFFECT OF $HgBr_2$ ON THE RATE OF REARRANGEMENT OF 5α,6β-DIBROMOCHOLESTERYL BENZOATE TO 5β,6α-DIBROMOCHOLESTERYL BENZOATE IN BENZENE AT 40.30 ± 0.05°

| Run | Vol of soln, ml | Dibromide 3 | | $HgBr_2$ | | | $k_1 - k_{-1}$, $sec^{-1}$ |
|---|---|---|---|---|---|---|---|
| | | g | mol × $10^{-3}$ | g | mol | mol % | |
| 1 | 100 | 1.00 | 1.53 | 0.020 | $5.55 \times 10^{-5}$ | 3.6 | $3.0 \times 10^{-6}$ |
| 2 | 100 | 1.00 | 1.53 | 0.050 | $1.38 \times 10^{-4}$ | 9.0 | $4.4 \times 10^{-6}$ |
| 3 | 100 | 1.00 | 1.53 | 0.080 | $2.22 \times 10^{-4}$ | 14.5 | $7.4 \times 10^{-6}$ |
| 4 | 100 | 1.00 | 1.53 | | | | $1.0 \times 10^{-6}$ |

propose for this rearrangement the merged ion-pair cyclic-concerted mechanism. This concept has been recently supported by the extensive work of King, *et al.*[4] Both groups found the rearrangement rate to be solvent dependent and, in broad terms, increasing with solvent polarity. Kwart and Weisfeld[5] found that organic acids and phenols enhanced the rate of rearrangement through general acid catalysis.

In practical terms a reaction time of *ca.* 5 hr is necessary to complete the rearrangement **3** → **4** in benzene at the boiling point.[6] The rearrangement **1** → **2** requires about 10 hr in boiling heptane.[3] We were concerned with reducing this time span without resorting to the use of either organic acids and phenols[5] or polar solvents like ethanol in which substantial solvolysis takes place.[7] Concurring with the opinion of Kirk and Hartshorn[2] that the reaction may be viewed in simple terms as an internal concerted nucleophilic substitution, we were inclined to think that it could be catalyzed by metal salts, particularly $Hg^{2+}$ salts like other nucleophilic reactions are.[8] We indeed found that in benzene solutions the rate of rearrangement of 5α,6β-dibromocholesteryl benzoate (**3**) to the 5β,6α isomer **4** is increased by the addition of $HgBr_2$. Some representative runs are summarized in Table I. The rearrangement was followed polarimetrically and the reaction constants were established graphically from first-order linear plots of the logarithm of concentration of the disappearing 5α,6β-dibromocholesteryl benzoate *vs.* time. In accordance with previous work,[3] the reaction constant is expressed as the sum of two constants corresponding to the forward and retroreaction. Viewing $HgBr_2$ as a Lewis acid permits[9] the present observation to be brought into perspective with previous work, particularly that of Kwart and Weisfeld.[5] Our data give a reasonable agreement with the acid catalysis equation $K = K_0 + K_c[HgBr_2]$ and $K_c \simeq 2.8 \times 10^{-3}\ M^{-1}\ sec^{-1}$. This catalytic constant is then in the same range of magnitude as that found by Kwart, *et al.*, for the strongest acid they studied *viz.* trichloroacetic acid. Due to our limited interest in this area we do not attempt to accommodate our results with any detailed mechanism.

(4) J. F. King and R. G. Pews, *Can. J. Chem.*, **43**, 847 (1965).

(5) H. Kwart and J. B. Weisfeld, *J. Amer. Chem. Soc.*, **78**, 635 (1956).

(6) H. Bretschneider, Z. Földi, F. Galinowski, and G. von Fodor, *Chem. Ber.*, **74**, 1451 (1941).

(7) Exploratory work in this direction was carried out by Mr. J. Hjort. In simple primary and secondary alcohols (MeOH, EtOH, *n*-PrOH, *n*-BuOH, *sec*-PrOH, *sec*-BuOH, and cyclohexanol) complete debromination of selected steroidal 5,6-dibromides took place either at reflux temperature or at 100° in higher boiling alcohols. The reaction was completed in several hours; invariably dibromides with a free 3β-OH group showed the highest rate of debromination. However, in *tert*-BuOH this solvolytic debromination was extremely slow.

(8) (a) C. K. Ingold "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1969, p 480 ff; (b) C. A. Bunton, "Nucleophilic Substitution," Elsevier, Amsterdam, 1963, p 154 ff.

(9) Thanks are due to Professor J. F. King, University of Western Ontario, for his valuable comments on our results.

### Experimental Section

**General.**—Uncorrected melting points were taken on a Kofler hot stage. Optical rotations were measured in 0.5- or 1-dm tubes using a Carl Zeiss polarimeter whose accuracy was not less than 0.05°.

**Materials.**—5α,6β-Dibromocholesteryl benzoate (**3**) was prepared according to literature[6,10,11] and recrystallized from $C_6H_6$–$CH_3OH$ at room temperature, mp 135–137°, $[\alpha]^{24}D$ −39° (*c* 1, $C_6H_6$) [lit.[10,11] mp 135–136°, $[\alpha]D$ −40° ($C_6H_6$)]. 5β,6α-Dibromocholesteryl benzoate (**4**) was prepared according to the literature,[6,10] and recrystallized from $C_6H_6$–$CH_3OH$, mp 162–164°, $[\alpha]^{24}D$ +100° (*c* 1, $C_6H_6$) [lit.[6,10] mp 163–164°, $[\alpha]D$ +102° ($C_6H_6$)]. Reagent grade thiophene-free benzene and mercuric dibromide (Fisher) were used directly.

**Kinetic Runs.**—These were carried out in volumetric flasks placed in an automatic thermoelectric water bath. Runs were followed for 50–75 hr to 30–60% completion of full rearrangement *i.e.*, to 50–80% attainment of equilibrium by the two isomers. Usually 6–8 samples per run were withdrawn at intervals of several hours and their rotation measured at 25 ± 2°. The measurement, average of eight readings, took about 5 min and we considered this time negligible in relation to the above-mentioned overall reaction time. Excellent agreement was found between runs repeated after several days. The reaction constants were established graphically using common procedures.[12] The solutions from kinetic runs with $HgBr_2$ were kept at 40° until the rearrangement equilibrium was reached and subsequently they were evaporated *in vacuo* at room temperature to dryness. The dark residue was in each case treated with cold methanol and the tan solid which separated was filtered off and recrystallized from benzene–methanol to give pure **4**, identical (melting point, ir, $[\alpha]D$, elemental analysis) with samples of **4** prepared as given above. The yields in these recoveries averaged about 80% thus indicating absence of appreciable side reactions, particularly dehalogenation, during the kinetic runs.

**Registry No.**—**3**, 6213-04-3; **4**, 5863-62-7.

**Acknowledgment.**—The technical assistance of Mrs. E. C. Fryberg is appreciated.

(10) D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.*, **72**, 1066 (1950).

(11) S. P. J. Maas, M. J. D. VanDam, J. G. De Heus, and D. Mulder, *Bull. Soc. Chem. Belg.*, **72**, 239 (1963).

(12) R. Livingston in "Techniques of Organic Chemistry," Vol. VIII, 2nd ed, part 2, S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Interscience, New York, N. Y., 1961, pp 126, 127. The usual "best fit" lines were drawn. In most runs the scattering of values plotted was negligible.

## Selective Degradation of Guaiol. The Synthesis of 7-Epiguaiol

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In connection with a current project dealing with the total synthesis of the hydroazulenic sesquiterpene alco-

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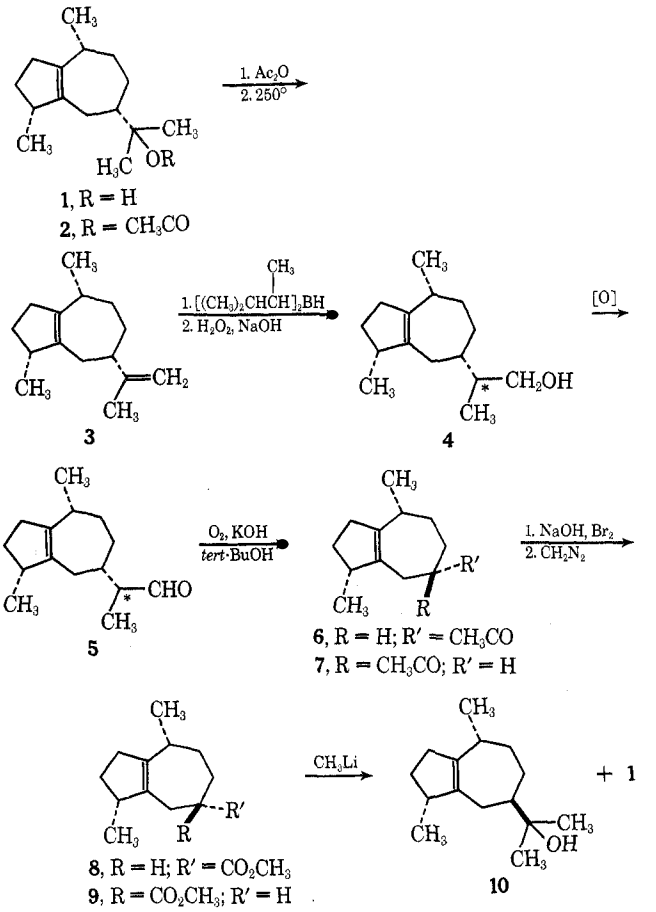
hol guaiol (**1**),[2] it became necessary to gain some information regarding the relative configurational stabilities of epimerizable guaiane derivatives such as the ketones **6** and **7** and the related esters **8** and **9**. We also hoped to work out an effective means for separating these epimers in the event that our synthetic route would lead to the racemic counterparts of such mixtures. These goals have been achieved and the details are described herein.

Pyrolysis of guaiyl acetate (**2**) at 250° as described by Slagel[3] afforded a mixture of dienes composed principally of α-guaiene (**3**).[4] Selective hydroboration of this mixture proceeded smoothly with disiamylborane[5] and, after oxidation with alkaline hydrogen peroxide, alcohol **4** was secured in high yield. This alcohol is undoubtedly a roughly 1:1 mixture of diasterioisomers at the methine center attached to C-7 (asterisk in structure **4**). Oxidation either with Collins bispyridine chromic oxide reagent[6] or the Moffat DMSO–DCC reagent[7] afforded the aldehyde **5**, likewise a diastereomeric mixture. Aldehyde **5** underwent oxidative cleavage upon stirring under an oxygen atmosphere in alkaline *tert*-butyl alcohol[8] to give the ketones **6** and **7** as a nearly 1:1 mixture. These ketones failed to separate on the gas chromatogram under a variety of conditions and the analysis therefore had to be carried out on the alcohols guaiol (**1**) and 7-epiguaiol (**10**) secured *via* treatment with ethereal methyllithium. These two alcohols showed two distinct peaks in the gas chromatogram.[9] Additional base treatment did not alter the composition of the 1:1 mixture of ketones **6** and **7**, a reasonable finding in view of the conditions employed in their formation from aldehyde **5**.[10] Treatment of this mixture with ethereal methyllithium afforded a comparable mixture of guaiol (**1**) and 7-epiguaiol (**10**) from which an appreciable amount of the guaiol epimer could be removed *via* low temperature crystallization from hexane. The epiguaiol-enriched mother liquor was subjected to preparative gas chromatography in order to obtain a pure sample of this substance (Scheme I).

Hypobromite oxidation of the 1:1 mixture of ketones **6** and **7** followed by esterification of the resulting acidic material with ethereal diazomethane afforded a mixture of methyl esters **8** and **9** in 30% yield whose composition was surprisingly found to be 85:15 by gas chromatography. An appreciable residue, presumably products arising from double bond bromination of **7** (possibly *via* a bromolactone intermediate), remained upon distillation of the aforementioned ester. Equilibration in refluxing methanolic sodium methoxide led to a 50:50 mixture of these esters.[10] Each of the pure esters **8** and **9** could be obtained through preparative gas chromatography of the equilibrium mixture thus establishing a possible relay point in our projected guaiol synthesis.

SCHEME I




## Experimental Section[11]

**Hydroboration–Oxidation of α-Guaiene. Alcohol 4.**—A stirred solution of 408 mg of α-guaiene[4] in 15 ml of tetrahydrofuran at 0° was treated dropwise with 7.0 ml of 1 *M* disiamylborane.[5] After 1.5 hr water (3.5 ml), 3 *N* aqueous NaOH (28 ml), and 30% hydrogen peroxide (23.4 ml) were added dropwise and the mixture was stirred at room temperature for 1 hr. The product was isolated with ether and distilled affording 397 mg (88%) of alcohol **4**: bp 130° (bath temperature) (0.1 mm); $\lambda_{max}^{film}$ 3.02, 6.98, and 9.72 μm; $\delta_{TMS}^{CDCl_3}$ 3.58 ($CH_2O$ a pair of doublets, $J$ = 6 Hz), 1.38 (OH), 1.00 ($CH_3$ doublet, $J$ = 7 Hz), 0.96 ($CH_3$ doublet, $J$ = 7 Hz), and 0.90 ppm ($CH_3$ doublet, $J$ = 6 Hz).

*Anal.* Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.05; H, 11.7.

**Oxidation of Alcohol 4. Aldehyde 5. A. Collins Reagent.**[6]—A solution of 873 mg of alcohol **4** comparable to that described above in 200 ml of methylene chloride was treated portionwise with 8.7 g of bispyridine chromium oxide. After 10 min of intermittent swirling the black solution was diluted with 500 ml of ether and washed with ice-cold 5% NaOH until the washes were nearly colorless. The organic phase was washed with 10% HCl, saturated sodium bicarbonate, and saturated brine and dried over anhydrous magnesium sulfate. Distillation afforded 524 mg (61%) of aldehyde **5**: bp 120° (bath temperature) (0.3 mm); $\lambda_{max}^{film}$ 3.72, 5.80, 6.90, 7.20, and 7.34 μm; $\delta_{TMS}^{CCl_4}$ 9.56

(2) *Cf.* H. Minato, *Tetrahedron Lett.*, 280 (1961).

(3) R. Slagel, Ph.D. Thesis, University of Illinois, 1962, p 49.

(4) A sample of this material was generously provided by G. Shaffer, Givaudan Corp.

(5) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 33 (1963).

(6) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(7) K. E. Pitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5670 (1965).

(8) *Cf.* W. Sucrow, *Ber.*, **100**, 259 (1967); V. Van Rheenen, *Tetrahedron Lett.*, 985 (1969).

(9) Ordinary Carbowax columns effected the dehydration of these alcohols, evidently the result of acidic sites since this behavior was not observed with KOH–Carbowax columns.

(10) In the analogous ester mixture prepared in connection with the synthesis of bulnesol, a 71:29 ratio of epimers was secured: J. A. Marshall and J. J. Partridge, *Tetrahedron*, **25**, 2159 (1969).

(11) Reactions were conducted under a nitrogen atmosphere using the apparatus described by W. S. Johnson and W. P. Schneider ("Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 132). Reaction products were isolated by addition of water and extraction with the specified solvent. The combined extracts were washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was removed from the filtered solutions on a rotary evaporator.

(CHO, $J$ = 1 Hz), 1.02 ($CH_3$ doublet, $J$ = 7 Hz), 1.00 ($CH_3$ doublet, $J$ = 7 Hz), and 0.97 ppm ($CH_3$ doublet, $J$ = 6 Hz).

*Anal.* Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.7; H, 11.15.

**B. Moffatt Reagent.**[7]—A solution of 598 mg of alcohol **4**, 285 mg of pyridinium trifluoroacetate, and 1.44 g of dicyclohexylcarbodiimide in 4.6 ml of benzene and 4.6 ml of dimethyl sulfoxide was stirred at room temperature for 12 hr. Ethyl acetate (25 ml) followed by 1 g of oxalic acid in 8 ml of methanol was added and after 0.5 hr of stirring the product was isolated with hexane and distilled affording 608 mg of aldehyde **5** contaminated with a small amount of dicyclohexylurea.

**Oxidation of Aldehyde 5. Ketones 6 and 7.**—A mixture of 465 mg of aldehyde **5** and 200 mg of powdered KOH in 20 ml of *tert*-BuOH was vigorously stirred under an oxygen atmosphere for 0.5 hr.[8] The product was isolated with hexane and distilled affording 213 mg (48%) of a nearly 1:1 mixture of ketones **6** and **7**:[12,13] bp 107° (bath temperature) (0.1 mm); $\lambda_{max}^{film}$ 5.88, 8.61 $\mu$m; $\delta_{TMS}^{CCl_4}$ 2.06 ($CH_3CO$), 2.05 ($CH_3CO$), 1.17–0.84 ppm ($CH_3$ doublets). Replicate C and H analyses on a purified sample of this mixture showed successively decreasing carbon percentages indicative of rapid oxygen uptake.

**Oxidation of Ketones 6 and 7. Esters 8 and 9.**—A solution of NaOBr was prepared from 1.36 g of NaOH in 11.8 ml of water, 1.41 g of bromine, and 7.7 ml of dioxane. This cold (0°) solution was added with stirring to 510 mg of ketone mixture **6** and **7** in 35.5 ml of dioxane and 10.5 ml of water at 0°. After 3 hr a solution of 0.56 g of sodium sulfite in 5.6 ml of water was added. The solution was poured into 15 ml of 10% NaOH and washed with ether. The aqueous phase was acidified with dilute sulfuric acid and the product was isolated with ether affording the crude acid which was directly esterified with ethereal diazomethane to give 157 mg (29%) of an 85:15 mixture[14] of esters **8** and **9**: bp 110° (bath temperature) (0.05 mm); $\lambda_{max}^{film}$ 5.78, 7.00, and 8.60 $\mu$m; $\delta_{TMS}^{CCl_4}$ 3.56 ($CH_3O$), 1.02 ($CH_3$ doublet, $J$ = 7 Hz), and 0.97 ppm ($CH_3$ doublet, $J$ = 7 Hz).

Equilibration in refluxing methanolic sodium methoxide (0.4 $M$) afforded a 50:50 mixture. The equilibrium mixture of these esters was separated *via* preparative gas chromatography[15] ($t_R$ of **8**:**9** = 1.1).

**Ester 8**: $\lambda_{max}^{film}$ 5.78, 6.92, 7.00, 8.59, and 9.75 $\mu$m; $\delta_{TMS}^{CCl_4}$ 3.56 ($OCH_3$), 1.02 ($CH_3$ doublet, $J$ = 7 Hz), and 0.96 ppm ($CH_3$ doublet, $J$ = 7 Hz).

*Anal.* Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.8; H, 10.1.

**Ester 9**: $\lambda_{max}^{film}$ 5.77, 6.92, 7.00, 8.62, and 9.63 $\mu$m; $\delta_{TMS}^{CCl_4}$ 3.56 ($OCH_3$), 1.00 ($CH_3$ doublet, $J$ = 7 Hz), and 0.94 ppm ($CH_3$ doublet, $J$ = 6 Hz).

*Anal.* Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.4; H, 10.1.

**Guaiol (1) and Epiguaiol (10). A. From Ketones 6 and 7.**—To a stirred solution of 1.10 g of ketones **6** and **7** (1:1 mixture) in 50 ml of ether was added 10 ml of 1.6 $M$ ethereal methyllithium. After 1 hr, 2 ml of water was carefully added and the product was isolated with ether. Low temperature crystallization from hexane yielded 342 mg of guaiol (**1**): mp 82–85°; $\lambda_{max}^{KBr}$ 3.00, 7.37, 8.69, 8.70, 10.03, 10.41, 10.80, 10.97, 11.36, and 12.18 $\mu$m; $\delta_{TMS}^{CDCl_3}$ 1.18 ($CH_3$), 0.98 ($CH_3$ doublet, $J$ = 7.5 Hz), and 0.96 ppm ($CH_3$ doublet, $J$ = 7 Hz).

From the mother liquor was obtained an enriched sample (75%) of epiguaiol (**10**) which was purified by preparative gas chromatography[16] ($t_R$ of **1**:**10** = 0.92): $\lambda_{max}^{film}$ 2.95, 6.85, 7.32, 8.82, 10.79, and 11.14 $\mu$m; $\delta_{TMS}^{CDCl_3}$ 1.19 ($CH_3$), 1.04 ($CH_3$ doublet, $J$ = 7 Hz), and 1.03 ppm ($CH_3$ doublet, $J$ = 6 Hz).

*Anal.* Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.9; H, 11.8.

**B. From Esters 8 and 9.**—A purified sample of ester **8** (10 mg) was treated with ethereal methyllithium (1.0 ml of 1.6 $M$) as described above affording 9.6 mg (96%) of guaiol (**1**) identified by spectral comparison.

A sample of ester **9** when similarly treated afforded epiguaiol (**10**) identified by spectral comparison with the aforementioned sample.

**Registry No.**—**1**, 489-86-1; **4** (11*R*), 30166-94-0; **4** (11*S*), 30166-99-5; **5** (11*R*), 30166-95-1; **5** (11*S*), 30167-00-1; **6**, 30246-75-4; **7**, 30246-76-5; **8**, 30166-96-2; **9**, 30166-97-3; **10**, 30166-98-4.

**Acknowledgments.**—We are indebted to the National Institutes of Health for their support of this research through a grant (National Cancer Institute, 5 RO1 CA11089) and a predoctoral fellowship (Institute of General Medical Sciences, 5 FO1 GM41100). A generous gift of $\alpha$-guaiene from G. Shaffer, Givaudan Corp., is also acknowledged.

(12) This ratio was determined by gas chromatographic analysis of the alcohols secured through addition of ethereal methyllithium to this mixture.

(13) A 22 ft × 1/8 in. column of 1% Carbowax 20M on 80–100 mesh CG, AW-DMCS, was used.

(14) A 15 ft × 1/8 in. column of 3% FFAP on Chromosorb G, 70–80 mesh AW-DMCS, was used for this analysis.

(15) A 15 ft × 3/8 in. column of 6% FFAP on 60–80 mesh Chromosorb G-NAW was used.

(16) A 15 ft × 0.25 in. column of 24% 1:4 KOH–Carbowax 20M on 60–80 mesh Chromosorb G was used for the separation.

## Inhibition of the Hydrolysis of Bis-2,4-dinitrophenyl Phosphate by a Nonionic Detergent[1]

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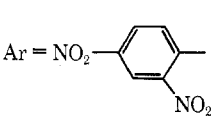
There are many examples of catalysis or inhibition by micellized detergents, and they generally follow the simple electrostatic rules put forward by Hartley to explain equilibrium effects (for reviews, see ref 3–5). In agreement with these rules, nonionic detergents generally have only small effects upon the rates of ionic reactions.[3–5] However, micellar effects depend very markedly upon hydrophobic interactions, and a few reactions between an ionic reagent and an uncharged substrate are inhibited by nonionic micelles,[6,7] probably because the substrate becomes buried in the interior of the micelle.

We unexpectedly observed that the reaction of hydroxide ion with bis-2,4-dinitrophenyl phosphate monoanion is strongly inhibited by Igepal,[8] and we suggested that despite its negative charge the ionic substrate is

$$(ArO)_2PO_2^- + OH^- \xrightarrow{k_1} ArO^- + ArOPO_3^{2-}$$

$$ArOPO_3^{2-} \xrightarrow{k_2} ArO^- + PO_3^- \longrightarrow HPO_4^{2-}$$




(1) Support of this work by the National Institute of Arthritis and Metabolic Diseases and the University of Chile–University of California Cooperative Program supported by the Ford Foundation is gratefully acknowledged.

(2) To whom inquiries should be addressed.

(3) E. H. Cordes and R. B. Dunlap, *Accounts Chem. Res.*, **2**, 329 (1969).

(4) E. J. Fendler and J. H. Fendler, *Advan. Phys. Org. Chem.*, **8**, 271 (1970).

(5) T. C. Bruice in "The Enzymes," Vol. 2, 3rd ed, Academic Press, New York, N. Y., 1970, p 217.

(6) R. A. Anderson and A. M. Slade, *J. Pharm. Pharmacol.*, **18**, 640 (1966).

(7) C. A. Bunton and L. Robinson, *J. Org. Chem.*, **34**, 773 (1969).

(8) G. J. Buist, C. A. Bunton, L. Robinson, L. Sepulveda, and M. Stam, *J. Amer. Chem. Soc.*, **92**, 4072 (1970).