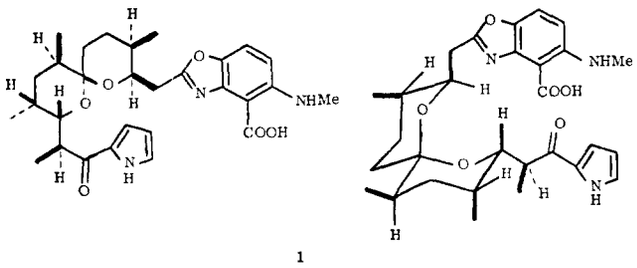
(*E*)-**2a** (R = Et), 74185-33-4; (*Z*)-**2a** (R = Et), 74185-34-5; **2b** (R = H), 74185-35-6; (*E*)-**2b** (R = Et), 74185-36-7; (*Z*)-**2b** (R = Et), 74185-37-8; **3a**, 74185-38-9; **3b**, 74185-39-0; dimethyl diselenide, 7101-31-7; dimethyl ditelluride, 20334-43-4.

Communications

Elaboration of the C(3)–C(12) Carbon Fragment of Calcimycin (A-23187). Formal Total Synthesis of Calcimycin

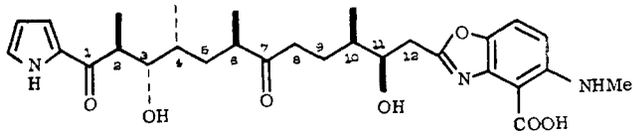
Summary: A formal synthesis of calcimycin is reported which features construction of the C(3)–C(12) carbon fragment **3** from bicyclo[2.2.1]heptenone **4**.

Sir: The structure of the unique divalent cation ionophore calcimycin (**1**; A-23187) produced from cultures of *Streptomyces chartreusensis* was recently established by Chaney and co-workers at the Lilly Research Laboratories.[1] The high Ca^{2+} specificity exhibited by calcimycin coupled with its ability to transport ions across cell membranes is, in part, responsible for the extensive attention this antibiotic has received since its structure was announced in 1974.[2]



1

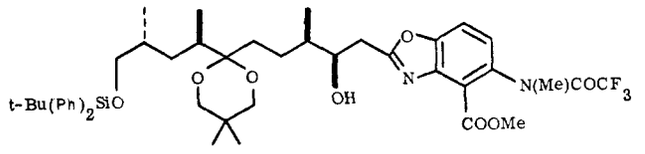
The structure of **1** reveals, in addition to a benzoxazole and an α-ketopyrrole unit, a novel 1,7-dioxaspiro[5.5]undecane ring system. Analysis of **1** suggests that the acyclic keto diol **2** or its equivalent should close to the desired



2

dioxaspirane under thermodynamically controlled acid-catalyzed conditions. This point has recently been demonstrated by Evans and co-workers, whose endeavors have culminated in the first total synthesis of calcimycin.[3] Herein, we describe our efforts in this area. We detail below the synthesis of the racemic C(3)–C(12) segment **3** of calcimycin.

The synthetic route to **3**, which originated with the bicyclo[2.2.1]heptenone **4**[4] (Chart I), was performed in two



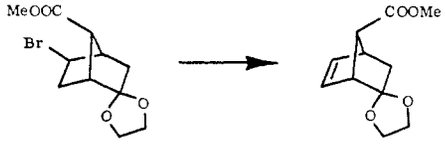
3

stages: (1) synthesis of the C(3)–C(9) fragment **10** (Chart I) and (2) elaboration of **10** into the C(3)–C(12) segment **3**.

Treatment of the Baeyer–Villiger oxidation product of bicyclo[2.2.1]heptenone **4**[6,7] with boron trifluoride etherate promoted facile rearrangement, giving rise to bicyclic lactone **5**.[6,7] Transformation of γ-lactone **5** into δ-lactone **6**[6] was efficiently carried out in five steps in approximately 70% overall yield as outlined in Chart I. Alkylation of lactone **6** with methyl iodide proceeded smoothly, affording

(1) Chaney, M. O.; Demarco, P. V.; Jones, N. D.; Occolowitz, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 1932.
(2) Pfeiffer, D. R.; Taylor, R. W.; Lardy, H. A. *Ann. N.Y. Acad. Sci.* **1978**, *307*, 402.
(3) Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6798.

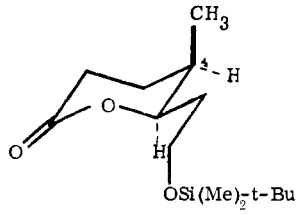
(4) Bicyclo[2.2.1]heptenone **4** was prepared in ~45% overall yield from the known bicyclo[2.2.1]heptane derivative i[5] via a five-step sequence: (1) DBU, DMF, reflux; (2) $LiAlH_4$, Et_2O; (3) TsCl, pyridine; (4) $LiEt_3BH$, THF; (5) HCl, THF. Note, the major product obtained during treatment of i with DBU is the isomerized ketal ester ii.



i ii

(5) Grieco, P. A.; Pogonowski, C. S.; Burke, S. D.; Nishizawa, M.; Miyashita, M.; Masaki, Y.; Wang, C.-L. J.; Majetich, G. *J. Am. Chem. Soc.* **1977**, *99*, 4111.
(6) All new compounds have been fully characterized, including combustion analysis and/or high-resolution mass spectra.
(7) **4**: IR ($CHCl_3$) 1730 cm^{-1}; NMR (250 MHz, CCl_4) δ 1.00 (d, 3 H, J = 6.98 Hz), 1.68 (dd, 1 H, J = 2.25, 16.65 Hz, C(3) endo proton), 1.96 (dd, 1 H, J = 3.15, 16.65 Hz, C(3) exo proton), 2.53 (m, 1 H, C(7) proton), 2.64 (br s, 1 H, C(4) proton), 2.82 (br s, 1 H, C(1) proton), 6.10 (m, 1 H, C(5) proton), 6.54 (dd, 1 H, J = 2.70, 5.60 Hz, C(6) proton). **5**: IR ($CHCl_3$) 1770 cm^{-1}; NMR (90 MHz, CCl_4) δ 1.04 (d, 3 H, J = 6.8 Hz), 2.36 (dd, 1 H, J = 1.5, 7.5 Hz) 2.94 (m, 2 H), 3.17 (dd, 1 H, J = 7.5, 16.0 Hz), 5.35 (br d, 1 H), 5.7–6.1 (m, 2 H, olefinic protons). **7**: IR (CCl_4) 1738 cm^{-1}; NMR (60 MHz, CCl_4) δ 0.0 (s, 6 H), 0.82 (s, 9 H), 1.02 (d, 3 H, J = 7.3 Hz), 1.4–2.6 (m, 6 H), 3.60 (m, 2 H), 4.30 (m, 1 H). **8**: IR (CCl_4) 3450, 1720 cm^{-1}; NMR (90 MHz, CCl_4) δ 1.02 (d, 3 H, J = 6.7 Hz), 1.23 (d, 3 H, J = 6.7 Hz), 1.5–2.2 (m, 5 H), 2.50 (m, 1 H), 3.43 (br s, 1 H, OH), 3.67 (br t, 1 H, CH_2OH), 4.53 (m, 1 H). **9**: IR (CCl_4) 1730 cm^{-1}; NMR (60 MHz, CCl_4) δ 1.03 (d, 3 H, J = 7.0 Hz), 1.33 (d, 3 H, J = 7.0 Hz), 1.5–2.9 (m, 4 H), 4.80 (m, 1 H), 5.1–6.2 (m, 3 H, CH=CH_2). **10**: IR ($CHCl_3$) 3610, 3450 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 0.85 (d, 6 H, J = 6.0 Hz), 1.20 (dd, 2 H, J = 6.3, 7.1 Hz), 1.4–1.9 (m, 2 H), 3.40 (br d, 2 H, J = 6.8 Hz), 4.00 (br t, 1 H, J = 4.8 Hz), 5.0–6.2 (m, 3 H, CH=CH_2). **11**: IR ($CHCl_3$) 1718 cm^{-1}; NMR (90 MHz, CCl_4) δ 0.80 (d, 3 H, J = 7.5 Hz), 0.82 (d, 3 H, J = 7.5 Hz), 1.08 (s, 9 H), 1.10 (t, 3 H, J = 7.0 Hz), 1.20 (m, 2 H), 1.75 (m, 2 H), 2.25 (q, 2 H, J = 7.0 Hz), 3.47 (d, 2 H, CH_2OSi), 5.0–6.0 (m, 4 H, CH=CH_2, CHOCO), 7.3–7.8 (m, 10 H). **13**: IR (CCl_4) 1738, 970 cm^{-1}; NMR (600 MHz, CCl_4) δ 0.89 (d, 3 H, J = 7.0 Hz), 0.93 (d, 3 H, J = 7.0 Hz), 1.05 (s, 9 H), 1.09 (d, 3 H, J = 7.0 Hz), 1.30 (m, 2 H), 1.63 (m 1 H), 2.04 (m, 2 H), 2.25 (m, 1 H), 2.38 (m, 1 H), 3.38 (m, 1 H), 3.49 (m, 1 H), 3.59 (s, 3 H), 5.13 (m, 1 H), 5.28 (m, 1 H), 7.33 (m, 6 H), 7.67 (m, 4 H). **16**: IR (CCl_4) 1735, 1710 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 0.90 (d, 3 H, J = 6.5 Hz), 1.01 (d, 3 H, J = 6.9 Hz), 1.09 (s, 9 H), 1.15 (d, 3 H, J = 6.9 Hz), 1.42 (t, 2 H, J = 6.9 Hz), 1.6–1.9 (m, 3 H) 2.3–2.7 (m, 4 H), 3.46 (q, 2 H, J = 2.9 Hz), 3.66 (s, 3 H), 7.40 (m, 6 H), 7.70 (m, 4 H).

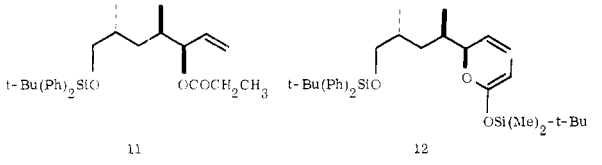
0022-3263/80/1945-3537$01.00/0



6

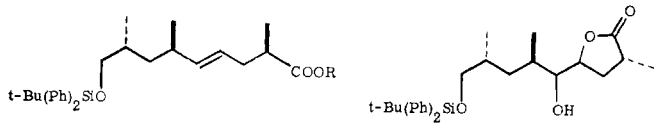
lactone **7**[6,7] as the sole product in 81% yield. The observed stereospecificity is apparently due to the methyl group at C(4) which is axially oriented, thus directing the alkylation from the α face of the molecule.[8] Desilylation of **7** generated primary alcohol **8**[6,7] which, upon exposure to *o*-nitrophenyl selenocyanate[9] in the presence of tri-*n*-butylphosphine and subsequent oxidation[10] with 50% hydrogen peroxide, provided olefinic lactone **9**.[6,7] Reduction of lactone **9** furnished the C(3)–C(9) fragment **10**[6,7] of calcimycin possessing the correct configuration at C(4) and C(6).

Elaboration of the stereochemical center at C(10) was achieved by taking advantage of the configuration of the C(7) hydroxyl-bearing carbon atom present in the acyclic segment **10**. Silylation of **10** (*t*-Bu(Ph)$_2$SiCl, Et$_3$N, DMAP,[11] CH$_2$Cl$_2$) followed by treatment with propionyl chloride gave rise to a 90% yield of ester **11**.[6,7] Ester



11 12

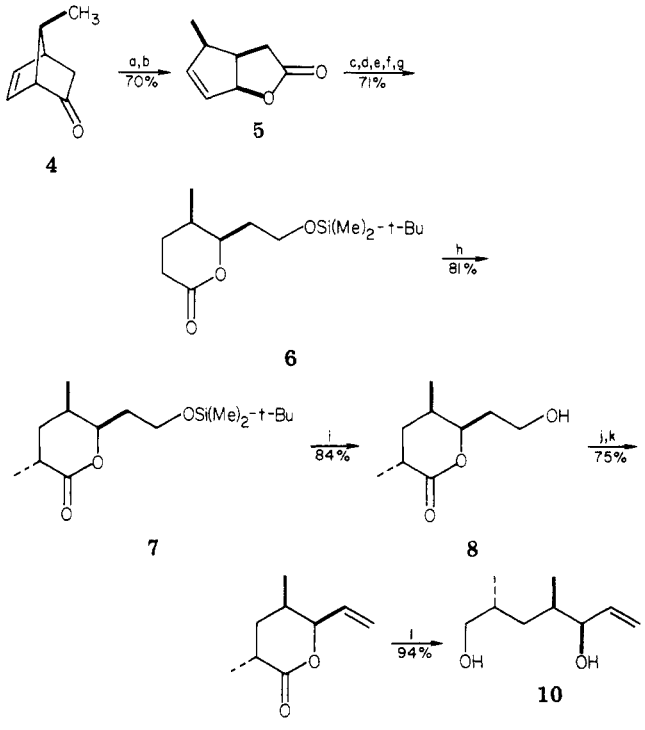
enolate Claisen rearrangement[12] of the (*E*)-*O*-silylketene acetal **12**, prepared by treatment of **11** with LDA and THF and subsequent addition of *tert*-butyldimethylchlorosilane in HMPA, provided the corresponding silyl ester **13** (R = Si(Me)$_2$-*t*-Bu) which was immediately transformed (KOH; CH$_2$N$_2$) into methyl ester **13** (R = Me).[6,7,13] The overall yield for the transformation **11** → **13** was 90%.



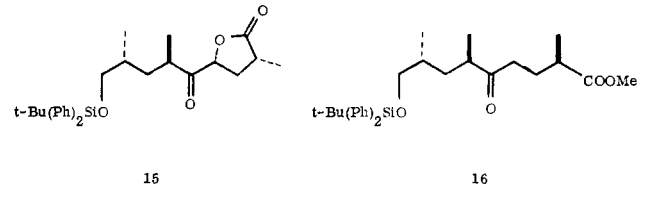
13 14

Reintroduction of a C(7) oxygen function was carried out as outlined below. Glycolation (OsO$_4$, pyridine) of the olefinic linkage in compound **13** followed by workup with sodium bisulfite and brief (5 min) treatment with a catalytic amount of camphorsulfonic acid in benzene generated a diastereomeric mixture of γ-lactones **14**.[6] Oxidation (PCC, NaOAc, CH$_2$Cl$_2$)[14] of **14** gave rise to keto lactone **15**[6] which was reductively cleaved[15] by employing aluminum amalgam in aqueous ethanolic tetrahydrofuran. Esterification of the crude keto acid with ethereal diazomethane provided keto ester **16**[6,7] in 75% overall yield from **14**. Ketalization (2,2-dimethyl-1,3-propanediol, HC(OMe)$_3$, TsOH, CH$_2$Cl$_2$) of **16** and subsequent reduction (LiAlH$_4$) of the ester function gave rise to alcohol **17**[6,16] which was shown to be identical in all respects with a sample of **17** prepared from the corresponding benzyl ether which was kindly supplied by Professor Evans.[17] Condensation (−100

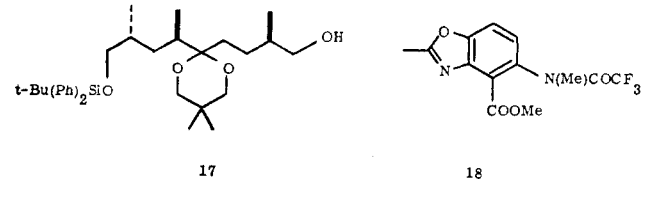
Chart I. Synthesis of the C(3)-C(9) Fragment **10**[a]



[a] a, H_2O_2, OH^-; b, $BF_3 \cdot Et_2O$, CH_2Cl_2; c, $LiAlH_4$, Et_2O; d, H_2, PtO_2, EtOAc; e, *t*-Bu(Me)$_2$SiCl, DMF, imidazole; f, $CrO_3 \cdot 2Py$; g, MCPBA, CH_2Cl_2; h, LDA, MeI, THF; i, 10% HCl and THF (1:1); j, *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF, k, 50% H_2O_2, THF; l, $LiAlH_4$

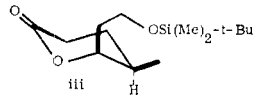


15 16



17 18

(8) It is of interest to note that the chair conformation of lactone **6** in which the [(*tert*-butyldimethylsilyl)oxy]ethyl group is axially oriented (cf. iii) would also be expected to give rise to **7**.



iii

(9) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

(10) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947. Grieco, P. A.; Masaki, Y.; Boxler, D. *J. Am. Chem. Soc.* **1975**, *97*, 1597.

(11) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

(12) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(13) ^{1}H NMR analysis at 600 MHz of the crude methyl ester of **13** derived from the ester enolate Claisen rearrangement of **11** revealed a single substance as evidenced by only three distinct doublet methyls.[7]

(14) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(15) Use of calcium in liquid ammonia at −60 °C or lithium dimethylcuprate in ether gave only low yields of the desired ketone.

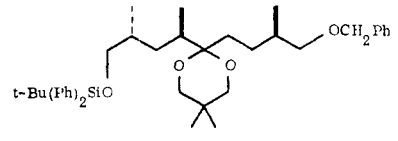
(16) During the ketalization, equilibration at C(6) occurs. This is of no consequence since Evans[3] has shown (see ref 8 in ref 3) that stereochemical control at C(6) need not be addressed.

°C, THF) of the aldehyde obtained upon Collins oxidation of **17** with the lithiated benzoxazole **18**,[18] prepared at −100 °C in the THF by using LDA, provided, as the major product (36%), the C(3)–C(12) fragment **3**.[6] Since **3** has been converted into calcimycin on a previous occasion, the preparation of **3** constitutes a formal total synthesis of the antibiotic.

Acknowledgment. This research was supported by a Public Health Research Grant from the National Institute of Allergy and Infectious Diseases, the National Institutes of Health NMR Facility for Biomedical Studies (Mellon Institute), and, in part, by a grant from G. D. Searle & Co.

Registry No. **3**, 74244-53-4; **4**, 74281-17-7; **5**, 74231-22-4; **6**, 74231-23-5; **7**, 74231-24-6; **8**, 74231-25-7; **9**, 74231-26-8; **10**, 74231-27-9; **11**, 74231-28-0; **12**, 74231-29-1; **13** (R = $Si(Me_2)$-*t*-Bu), 74231-30-4; **13** (R = Me), 74231-31-5; **14**, 74231-32-6; **15**, 74231-33-7; **16**, 74231-34-8; **17**, 74281-80-4; **18**, 72297-84-8; *tert*-butylchlorodiphenylsilane, 58479-61-1; propionyl chloride, 79-03-8; 2,2-dimethyl-1,3-propanediol, 126-30-7; *t*-Bu$(Me)_2$SiCl, 18162-48-6.

(17) We are grateful to Professor Evans for providing us with a generous sample of compound iv and a detailed procedure for cleaving the benzyl ether.



iv

(18) Grieco, P. A.; Kanai, K.; Williams, E. *Heterocycles* **1979**, *12*, 1623.

(19) Author to whom correspondence should be addressed at the Department of Chemistry, Indiana University, Bloomington, Indiana 47405.

Paul A. Grieco,*[19] Eric Williams, Hideo Tanaka Sydney Gilman

Department of Chemistry
University of Pittsburgh
Pittsburgh, Pennsylvania 15260

Received April 9, 1980

Nonlinearity of Hammett $\sigma\rho$ Correlations for Benzylic Systems: Activation Parameters and Their Mechanistic Implications

Summary: Bromide–bromide substitution rates have been measured for a series of *p*-substituted and 1-(3,4-dimethylphenyl)bromoethanes. The activation parameter data support an ion-pair transition state.

Sir: The nonlinearity of Hammett $\sigma\rho$ and related free-energy correlations for benzylic systems has frequently been observed.[1-3] This nonlinearity ranges from curvature to "L"-shaped and even "U"- or "V"-shaped plots. It is in the solvolyses of variously substituted benzyl halides that such behavior has most commonly been observed,[2] but it has been noted for a wide variety of other nucleophilic substitutions with both neutral (Ph_3P, Ph_3As, Et_2S $(NH_2)_2CS$, amines ...) and charged nucleophiles (N_3^-, NCS^-, $S_2O_3^-$, halide ions ...) in a variety of solvents, protic, aprotic, and mixed.[3]

The origins of these frequent failures of the linear free-energy correlations have been extensively discussed over the years with the usual approach being a rationale based upon the relative degree of bond making and breaking at the transition state.[2,3d,4,5] These discussions have varying levels of sophistication, but they all in effect assume an S_N2-type transition state. Given this assumption, it is logical that a system better able to support a positive charge on the carbon attached to the leaving group should have a transition state with a greater degree of bond breaking, one more able to support a negative charge, with a greater degree of bond formation than some "normal" substrate. Consequently the degree and even the sign of the charge developing in the transition state could change with the substituent on the benzylic system. These rather subtle mechanistic changes could account for the changes in slope or even the acceleration of the reaction by both electron-donating and -withdrawing substituents and the resultant V- or U-shaped free-energy correlations.

Unfortunately this facile explanation, which we in fact have ourselves used,[3d] is not consistent with the activation parameters reported here. Bromide–bromide substitutions for a series of *p*-substituted and 1-(3,4-dimethylphenyl)-bromoethanes were kinetically followed through the racemization of optically active substrates. These "symmetrical" reactions, where the leaving group and the nucleophile are the same, were chosen to minimize other effects. Data for the racemizations in acetone using LiBr at 0.002 00 M are given in Table I.[6]

The data in Table I have not been corrected for the degree of dissociation of the lithium bromide or the variation in dissociation constant with temperature, but since the same temperature range, 25–45 °C, was used for the whole series, contributions to the observed rate constant and to $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ from incomplete dissociation should be the same for all compounds. Thus while the absolute values may not be "correct", the relative values will be of significance. It is perhaps worth noting that for the unsubstituted case the activation parameters were independent of the concentration of lithium bromide over the range of 5×10^{-4} to 1×10^{-2} M.

The relative rates of the reactions reflect the free energies of activation reported. The enthalpy and entropy terms though are of much greater interest here. If the rationale discussed earlier is accepted, the amount of bond formation should be increasing with the more electron-withdrawing substituents and the enthalpy of bond formation should at least partially compensate for the enthalpy of bond breaking. Thus $\Delta H^{\ddagger}$ should decrease or at least not increase appreciably with such substituents. The

(1) For access to the earlier literature, see (a) A. Streitwieser, Jr., *Chem. Rev.*, **56**, 571 (1956); (b) O. Exner, "Advances in Linear Free Energy Relationships", N. B. Chapman and J. Shorter, Eds., Plenum Press, London, 1972, Chapter 1.

(2) (a) P. R. Young and W. P. Jencks, *J. Am. Chem. Soc.*, **101**, 3288 (1979), and references therein; (b) J. M. Harris, S. G. Shafer, J. R. Moffatt, and A. R. Becker, *J. Am. Chem. Soc.*, **101**, 3289 (1979), and references therein; (c) H. C. Brown, M. Ravindranathan, E. N. Peters, C. G. Rao, and M. M. Rho, *J. Am. Chem. Soc.*, **99**, 5373 (1977).

(3) (a) T. Thorstenson, R. Eliason, and J. Songsted, *Acta Chem. Scand., Ser. A*, **31**, 276 (1977); (b) T. Thorstenson and J. Songsted, *Acta Chem. Scand., Ser. A*, **30**, 724 (1976); (c) F. P. Ballistreri, E. Maccarone, and A. Mamo, *J. Org. Chem.*, **41**, 3364 (1976); (d) A. R. Stein, *Tetrahedron Lett.*, 4145 (1974); (e) E. C. F. Ko and K. T. Leffek, *Can. J. Chem.*, **50**, 1297 (1972); (f) S. D. Yoh, D. S. Lee, and S. Y. Hong, *Doehan Hwahak Hwogie*, 215 (1969); *Chem. Abstr.*, **72**, 99877 (1970); (g) K. Kalliorinne and E. Tommila, *Acta Chem. Scand*, **23**, 2567 (1969); (h) S. Sugden and J. B. Willis, *J. Chem. Soc.*, 1360 (1961).

(4) (a) K. C. Westaway and S. F. Ali, *Can. J. Chem.*, **57**, 1354 (1979); (b) H. Aronovitch and A. Pross, *J. Chem. Soc., Perkin Trans. 2*, 541 (1978).

(5) The still controversial theoretical basis for free-energy correlations, of which the Hammett equation is but one, and the theoretical implications of their successes and failures are beyond the scope of this communication. Interested readers are referred to reviews such as: (a) ref 1b, pp 4–19; (b) C. D. Johnson, "The Hammett Equation", Cambridge University Press, 1979, pp 133–158; (c) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, 1963.

(6) For a discussion of the experimental procedures employed see A. R. Stein, *J. Org. Chem.*, **41**, 519 (1976); **38**, 4022 (1973).

0022-3263/80/1945-3539$01.00/0