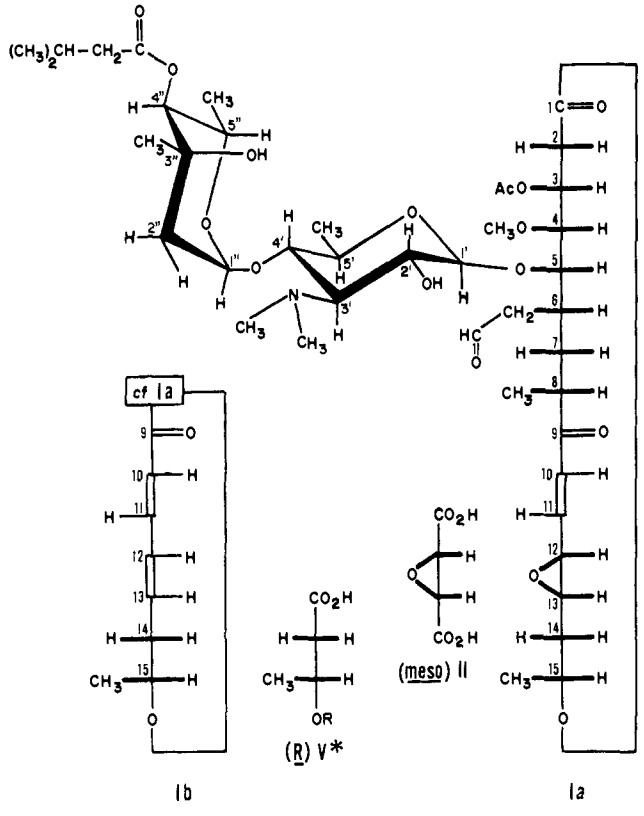
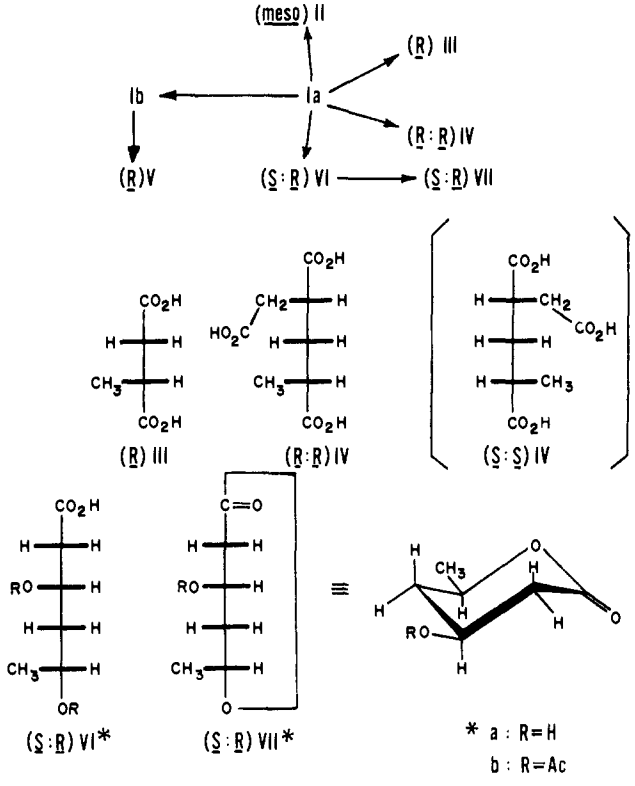
Macrolide Stereochemistry.[1] IV.[2] On the Total Absolute Configuration of Carbomycin (Magnamycin)[3]

Sir:

Representation I for carbomycin[3,4] (Chart I)[5] is in accord with reports on (a) gross structure,[6,7] (b) olefinic geometry,[6] (c) stereochemistry of sugar constituents,[1b,8-10] (d) certain relative configurations,[6,7b] and (e) provisional specifications for all macrocycle asymmetric centers.[11] The latter view, derived from recent workings[11] of a macrolide configurational model[1c,12] (Chart II),[13,14] has served to call attention to previous specifications[7b] $6S:8S$[5b] regarded as tantamount to "biogenetically exceptional" configurations.

Chart I





This report announces new configurational determinations $6R:8R:12R:13S:15R$ which substantiate pertinent correlations outlined in Chart II and necessitate revision of the earlier "exceptional" assignments. Thus, only $3R:4S:5S$ from Chart II remain to be tested. It is noted further that carbomycin could conceivably contain another element of chirality[5b] (space-handedness) imposed by theoretically possible restricted rotation of the sp^2-hybridized

(1) (a) Part I: *J. Am. Chem. Soc.*, **87**, 1797 (1965); (b) part II: *ibid.*, **87**, 1799 (1965); (c) part III: *ibid.*, **87**, 1801 (1965).

(2) (a) For a preliminary account see W. D. Celmer, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, No. P 47; (b) for macrolide reviews, see M. Berry, *Quart. Rev.* (London), **17**, 343 (1963), and also ref 11.

(3) (a) Magnamycin is the registered trademark of Chas. Pfizer & Co., Inc., for the antibiotic carbomycin. Two forms, A (Ia) and B (Ib), are described (*cf.* Chart I and ref 4b,d; chemical conversion of A to B is reported in ref 6 and 7a).

(4) (a) F. W. Tanner, A. R. English, T. M. Lees, and J. B. Routien, *Antibiot. Chemotherapy*, **2**, 441 (1952); (b) R. L. Wagner, F. A. Hochstein, K. Murai, N. Messina, and P. P. Regna, *J. Am. Chem. Soc.*, **75**, 4684 (1953); (c) P. P. Regna, F. A. Hochstein, R. L. Wagner, Jr., and R. B. Woodward, *ibid.*, **75**, 4625 (1953); (d) F. A. Hochstein and K. Murai, *ibid.*, **76**, 5080 (1954); (e) F. A. Hochstein and P. P. Regna, *ibid.*, **77**, 3353 (1955).

(5) (a) The macrocycle and its linear degradation products are portrayed as *Fischer* projections; six-membered cycles are projected as *spatially realistic* conformations; (b) the *R*/*S* specifications in this report follow the system of R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem.*, **78**, 413 (1966); *Angew. Chem. Intern. Ed. Engl.*, **5**, 385 (1966).

(6) R. B. Woodward, *Angew. Chem.*, **69**, 50 (1957); *Festschr. Arthur Stoll*, 524 (1957).

(7) (a) M. Kuehne and B. W. Benson, *J. Am. Chem. Soc.*, **87**, 4660 (1965); (b) R. B. Woodward, L. S. Weiler, and P. C. Dutta, *ibid.*, **87**, 4662 (1965).

(8) (a) A. B. Foster, T. D. Inch, J. Lehmann, M. Stacey, and J. M. Webber, *J. Chem. Soc.*, 2116 (1962); (b) A. C. Richardson, *ibid.*, 2758 (1962); (c) W. Hofheinz and H. Grisebach, *Z. Naturforsch.*, **17b**, 355 (1962).

(9) (a) F. Korte, U. Claussen, and K. Göhring, *Tetrahedron*, **18**, 1257 (1962); (b) W. Hofheinz, H. Grisebach, and H. Friebolin, *ibid.*, **18**, 1265 (1962); (c) D. M. Lemal, P. D. Pacht, and R. B. Woodward, *ibid.*, **18**, 1275 (1962).

(10) W. Hofheinz and H. Grisebach, *Chem. Ber.*, **96**, 2867 (1963).

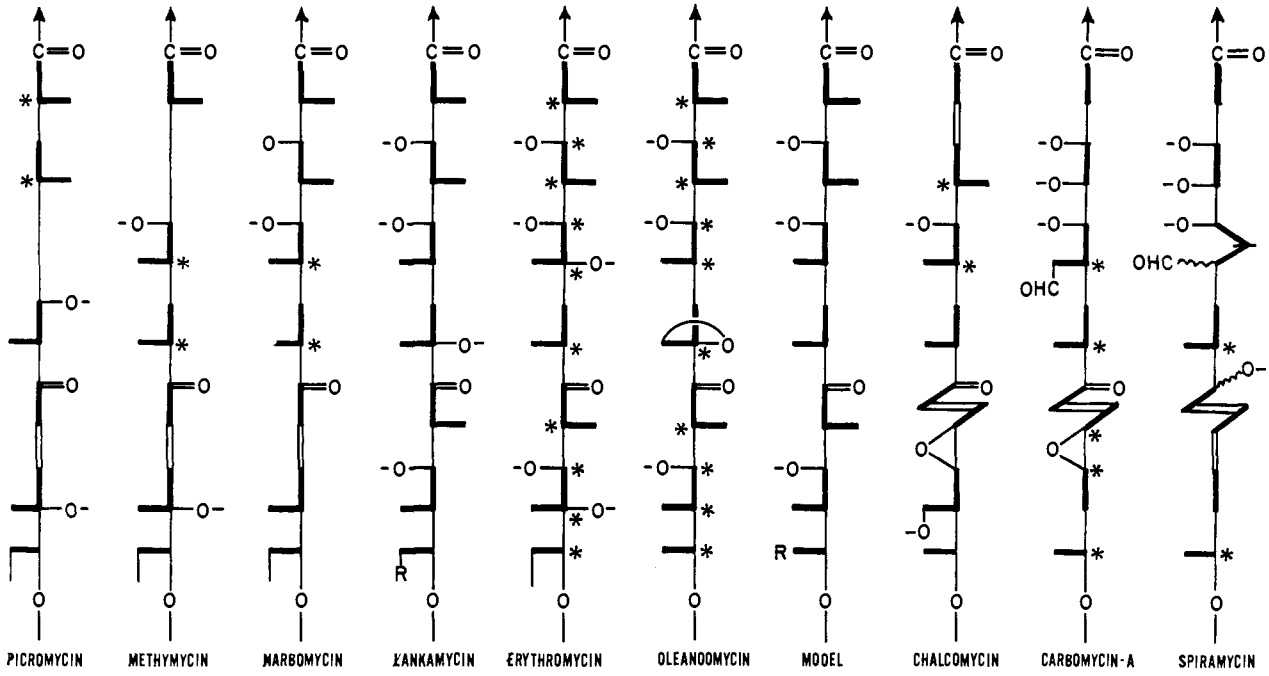
(11) (a) W. D. Celmer in "Antimicrobial Agents and Chemotherapy—1965," G. L. Hobby, Ed., American Society for Microbiology, Ann Arbor, Mich., 1966, p 144; (b) Fifth Interscience Conference on Antimicrobial Agents and Chemotherapy—IVth International Congress of Chemotherapy, Oct 17-21, 1965, Washington, D. C., Abstracts of Papers, p 20.

(12) W. D. Celmer in "Biogenesis of Antibiotic Substances," Z. Vanek and Z. Hostalek, Ed., Publishing House of the Czechoslovak Academy of Sciences, Prague, 1965, pp 99-130.

(13) (a) K. Gerzon, E. H. Flynn, M. V. Sigal, Jr., P. F. Wiley, R. Monahan, and U. C. Quarck, *J. Am. Chem. Soc.*, **78**, 6396 (1956); (b) C. Djerassi and J. A. Zderic, *ibid.*, **78**, 6390 (1956); (c) P. W. K. Woo, H. W. Dion, and Q. R. Bartz, *ibid.*, **86**, 2724 (1964); (d) F. A. Hochstein, H. Els, W. D. Celmer, B. L. Shapiro, and R. B. Woodward, *ibid.*, **82**, 3225 (1960); (e) C. Djerassi, O. Halpern, D. I. Wilkinson, and E. J. Eisenbraun, *Tetrahedron*, **4**, 369 (1958); (f) D. R. Harris, S. G. McGeachin, and H. H. Mills, *Tetrahedron Letters*, **No. 11**, 679 (1965); (g) W. Keller-Schierlein and G. Roncari, *Helv. Chim. Acta*, **47**, 78 (1964); (h) V. Prelog, A. M. Gold, G. Talbot, and A. Zomojski, *ibid.*, **45**, 5 (1962); (i) R. Anliker and K. Gubler, *ibid.*, **40**, 119, 1768 (1957); (j) H. Brockmann and R. Oster, *Ber.*, **90**, 605 (1957); (k) R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. France*, 150 (1960).

(14) For detailed gross structures (reviewed in ref 11) and pertinent determinations of indicated configurations, consult: picromycin,[13i,j] methymycin,[13b,e] narbomycin,[13h] lankamycin,[13g] erythromycin,[1b,13a,e,f] oleandomycin,[1a,13d] model,[1c,11] chalcomycin,[13c] carbomycin-A (*vide infra;* Chart I), spiramycin.[7a,13k]

Chart II



* Substantiated to date.

carbon bonds[12,15] in the highly substituted, *trans*-olefinic, 16-membered cycle.

Earlier Definitions of Asymmetric Centers in Carbomycin. (1′*R*),[1b,10] (2′*R*:3′*R*:4′*S*:5′*R*),[8] (1″*R*),[1b] (3″*R*:4″*R*:5″*S*),[9] (*cis*-C-6:C-8),[7b] (*cis*-C-6:C-8).[6] These specifications follow previous determinations.

Revision (6*R*:8*R*) of Previous Specifications. Earlier localization of C-8 in methylsuccinic acid, allegedly as the (−) (*i.e.*, *S*) enantiomorph,[6] coupled with other information, logically led to previous assignment of (*S*:*S*)IV,[7b] hence 6*S*:8*S* in carbomycin. However, new C-8 experiments have repeatedly afforded optically pure (+)-(*R*)-methylsuccinic acid (III).[16,17] Since the argument[7b] for relative configuration of C-6:C-8 in IV remains unaltered,[17b] it follows that revised specifications 6*R*:8*R* evidently apply to carbomycin, *via* (*R*:*R*)-IV. Treatment of carimbose-A (deisovalerylmycarosyl-carbomycin-A)[4a,6,18] with 50% nitric acid followed by silica gel H chromatography (benzene–HOAc, 9:1) afforded (*R*)-III,[18] $C_5H_8O_4$, mp 108°, $[\alpha]^{25}D$ +9° (*c* 10, water).

Fixing 15*R*. The lactone terminus center of I was fixed as 15*R* *via* localization in (−)-(*R*)-β-hydroxybutyric acid (Va).[19,20] Carimbose-B (deisovalerylmycarosyl-carbomycin-B)[3,6,18] was sequentially treated with lithium aluminum hydride, acetic anhydride in pyridine, and periodate–permanganate and then fractionated on silica gel H (benzene–EtOAc–HOAc, 15:5:1) to afford (−)-(*R*)-β-acetoxybutyric acid (Vb),[18] $C_6H_{10}O_4$, $[\alpha]^{25}D$ −5.9° (*c* 25, EtOH), which was then converted to (*R*)-Va,[18] $C_4H_8O_3$, $[\alpha]^{25}D$ −17.3° (*c* 12, EtOH).

Coupling 12*R*:13*S* with 15*R*. Centers C-13:C-15 of carbomycin-A were localized in conformationally stable (+)-β-acetoxy-δ-methylvalerolactone (VIIb) which clearly disclosed 1,3-diaxial methine protons (nmr).[21] This evident relative configuration together with the fixed (*R*) nature of the lactone terminus center provides *S*:*R* definition in VIIb and hence 13*S* in Ia. Thus, 12*R* is automatically coupled with 13*S* in Ia considering earlier determination of C-12:C-13 relative configuration, *cf. meso*-II.[6] Carimbose-A was subjected to the same reaction sequences described above for carimbose-B; products were fractionated on silica gel H (benzene–EtOAc–HOAc, 10:10:1) to afford (−)-β,δ-diacetoxyhexanoic acid, (*S*:*R*)-VIb,[18] $C_{10}H_{16}O_6$, $[\alpha]^{25}D$ −17° (*c* 15, EtOH). Conversion of VIb to VIa, followed by heating *in vacuo*, furnished liquid (+)-β-hydroxy-δ-methylvalerolactone, (*S*:*R*)-VIIa,[18] $C_6H_{10}O_3$, $[\alpha]^{25}D$ +15° (*c* 2, EtOH), $\lambda_{max}^{CHCl_3}$ 2.90, 5.75 μ (sharp). Acetylation of VIIa afforded liquid (*S*:*R*)-VIIb,[18] $C_8H_{12}O_4$, $[\alpha]^{25}D$ +12° (*c* 10, $CHCl_3$), $\lambda_{max}^{CHCl_3}$

(15) A. C. Cope, C. R. Ganellin, H. W. Johnson, Jr., T. B. Van Auken, and H. J. S. Winkler, *J. Am. Chem. Soc.*, **85**, 3276 (1963).

(16) The *R* nature of (+)-methylsuccinic acid is rigorously established; *cf.* previous comparable encounters in the cases of spiramycin[13k] and erythromycin[13c] and a pertinent X-ray corroboration.[13f]

(17) (a) At our request, Dr. R. B. Woodward and Mr. Larry S. Weiler reexamined a sample of methylsuccinic acid obtained from Magnamycin (carbomycin) by oxidation with nitric acid by Dr. T. Oiwa in 1956, and purported at that time to be L-(−)- (*i.e.*, *S*-) methylsuccinic acid (*cf.* ref 6). This reexamination has revealed that the previous attribution of sign (and therefore of configuration) was in error; the acid is in fact D-(+)- (*i.e.*, *R*-) methylsuccinic acid, in full consonance with the results and conclusions described in this communication. Professor Woodward and Mr. Weiler are thanked for their following measurements on the samples of methylsuccinic acid previously in question: sample 1 (*cf.* ref 6) $[\alpha]^{30}D$ +10.7 ± 3.2° (*c* 0.075, water); sample 2 (*cf.* this report) $[\alpha]^{31}D$ +8.8 ± 0.6° (*c* 1.080, water); both samples exhibited positive plain ORD curves. (b) R. B. Woodward, private communication.

(18) Each indicated compound was shown to be chemically homogeneous (elemental analyses, tlc, and, where applicable, vpc) and exhibited constitutionally diagnostic absorption spectra (nmr, infrared, and, where applicable, ultraviolet).

(19) For correlation with established D-(−)- (*i.e.*, *R*-) lactic acid, see: (a) L. A. Levene and H. L. Haller, *J. Biol. Chem.*, **67**, 329 (1926); **69**, 165 (1926); (b) L. A. Levene and A. Walti, *ibid.*, **68**, 415 (1926); (c) P. Karrer and W. Klarer, *Helv. Chim. Acta*, **8**, 393 (1925).

(20) It is noted that a comparable center of spiramycin was localized in methyl (−)- (*i.e.*, *R*-) β-hydroxybutyrate, *cf.* ref 13k and 19.

(21) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 77–85.

5.75 μ (broad), nmr ($CDCl_3$): α-H_aH_e and γ-H_aH_e τ ~7–9 (4 H), β-H_a at τ 4.72 (1 H; half-band width ~15 cps), δ-H_a at τ 5.53 (1 H; half-band width ~20 cps), β-OAc at τ 7.93 (3 H; sharp), and δ-CH_3 at τ 8.56 (3 H; J = 6.0 cps).

Provisional Specifications from Biogenetic Considerations. 1*R*′:1′′*R*:6*R*:8*R*:12*R*:13*S*:15*R* (substantiated) and 3*R*:4*S*:5*S* (untested). The workings of a macrolide configuration model,[22] in dictating biogenetically expected specifications (Fischer projections) for asymmetric centers in various macrolide[14] macrocycles, are summarized in Chart II. Provisional specifications for Ia were gained as follows (*cf.* Charts I and II). Straightforward matchings with the model leads to 3*R*:5*S*:6*R*:8*R*:13*S* and 15*R*; 4*S* is in accord with an "extra"[6] oxygen proviso;[23] 12*R* follows 13*S* from after-the-fact knowledge of C-12:C-13 relative configuration (which happens to be consistent with the assumption that C-12 of carbomycin-A is comparable with C-10 of the model); 1′*R*:1′′*R* stem from a corollary[1c] applicable to pyranosyloxy constituents of macrolides.

Acknowledgment. Special thanks are extended to Mr. M. Jefferson for technical assistance and to Dr. I. A. Solomons and many research colleagues for their helpful interest.

(22) See ref 1c, 11, and 12 for development and applications of the model in the face of some six confrontations, all of which have been dispatched in favor of the model (*cf.* ref 1b, 13f, and this report).

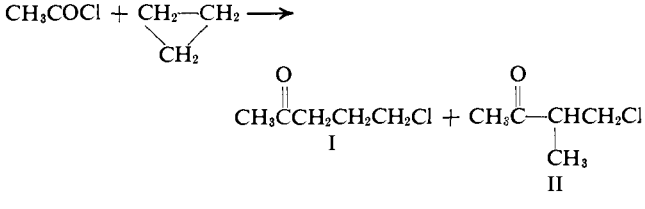
(23) The proviso now states that a branched or unbranched asymmetric center containing an "extra" oxygen, either as a ligand or on the branch, remains configurationally subservient to the model; *cf.* ref 1c, 11, and K. R. Hanson, *J. Am. Chem. Soc.*, **88**, 2731 (1966).

W. D. Celmer
Medical Research Laboratories, Chas. Pfizer & Co., Inc.
Groton, Connecticut 06340
Received August 22, 1966

Bridged Ionic Intermediates in the Acylation of Cyclopropane

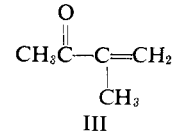
Sir:

Some years ago we observed that addition of cyclopropane to a 1:1 acetyl chloride–aluminum chloride complex in chloroform gave not only the expected 5-chloro-2-pentanone (I) but also, and as the major product, the β-chloro ketone II.[1] The rearrangement was also observed with several substituted cyclopropanes;[2] indeed, with some cyclopropanes, only the "abnormal" product was isolated. These results have been described[3] as "curious...difficult to account for," and have remained in the literature for some years as an enigma. We have recently reinvestigated this reaction with the help of vpc and nmr. The earlier work has been confirmed and extended, with the result that a plausible mechanism can now be suggested.

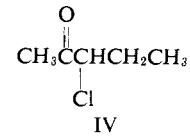


(1) H. Hart and O. E. Curtis, Jr., *J. Am. Chem. Soc.*, **79**, 931 (1957).
(2) H. Hart and G. Levitt, *J. Org. Chem.*, **24**, 2161 (1959).
(3) R. Breslow in "Molecular Rearrangements," P. deMayo, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p 256.

Cyclopropane was acetylated as previously described,[1] and the products separated by vpc (5-ft SE-30 column, 50 cc of He/min, 115°). Four peaks were observed, two of which were due to I (6.6 min, 23 ± 2%) and II (4.8 min, 42 ± 3%); their nmr spectra were consistent with the previously assigned structures. The two additional products were shown to be III (0.7 min, 31 ± 3%) and IV (3.2 min, 4 ± 1%). The nmr spectrum and other properties of III agreed with the previously assigned structure.[4]



III



IV

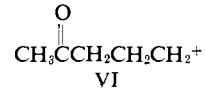
The structure of IV was clear from its infrared spectrum ($\nu_{C=O}$ at 1718 cm^{-1}, ν_{CCl} at 758 cm^{-1}), nmr spectrum (τ 7.75 (singlet, 3H), 5.96 (two doublets, J = 7.4 cps, 1 H), 8.12 (multiplet, 2 H), 8.97 (triplet, J = 7.1 cps, 3 H assigned to the protons on C-1, -3, -4, and -5, respectively)), and mass spectrum,[5] which in addition to the parent peak (*m/e* 120, 122) had prominent peaks at *m/e* 92, 94 ($CH_3C(OH)$=$CHCl^+$) and 43 (CH_3CO^+). IV synthesized from 2-pentanone and sulfuryl chloride[6] was found to be identical (retention time, infrared, nmr) with the acylation product.

All four products were also formed using CH_2Cl_2, CS_2, or nitrobenzene as solvent; the highest yield of IV was 10% (in CS_2).

Direct nmr examination of the homogeneous reaction mixture (in CCl_4) showed that all four products were present before work-up. Integration of the $-CH_2Cl$ peak of I *vs.* the $CH_3CH<$ peak of II gave (after statistical correction) a ratio of II:I of 1.20; the vpc ratio after work-up was 1.17. This not only verifies the reliability of the vpc method, but establishes that III is formed directly, and not by dehydrohalogenation of II during work-up.[7]

The data in Table I show that the chloro ketones are not interconverted during the reaction and that acetylcyclopropane (V) does not suffer ring opening in the acylating medium. Indeed, treatment of V with HCl and $AlCl_3$ in CH_2Cl_2 at 5° for 1 hr led only to recovered starting material. Thus acetylcyclopropane cannot be a reaction intermediate.

Any mechanism which begins with the formation of a classical carbonium ion (*i.e.*, VI, with or without stabilization by the carbonyl oxygen) seems doomed to a series of irrational subsequent steps to account for the observed products. We suggest instead that an



VI

acetyl group displaces a proton from cyclopropane, but that the proton remains associated with the cyclo-

(4) In the previous work[1] the reaction mixture was dehydrohalogenated with Na_2CO_3 before product isolation; III was identified, and the initial formation of II was inferred. With other acyl halides, however, the β-chloro ketones were isolated and identified.
(5) We are indebted to S. Meyerson, American Oil Company, Whiting, Ind., for the mass spectrum.
(6) E. R. Buchman and E. M. Richardson, *J. Am. Chem. Soc.*, **67**, 395 (1945).
(7) Separate experiments showed that II was not dehydrohalogenated under the vpc conditions used.