mixture in an over-all yield of 26% from **1b**. Direct alkylation of tetrahydroeucarvone with ethyl α-bromopropionate afforded in 30% yield a similar epimeric mixture of **1c**, albeit in 90% purity (vpc), and for convenience this slightly impure but more directly accessible material was used in the next stage.

Generation of the requisite bicyclo[4.2.1]nonane intermediate was accomplished by base-catalyzed intramolecular acylation of keto ester **1c** under carefully defined conditions. Treatment of a 1% (w/v) solution of the latter substance in glyme with 3 molar equiv of sodium hydride and one drop of ethanol for 14 hr at 75° under nitrogen and subsequent quenching of the reaction with acetic acid in ether at 0° produced in 65% yield a single diketone [mp 88–89°; $\lambda_{max}^{CHCl_3}$ 5.70 and 5.81 μ (CO); $\delta_{TMS}^{CCl_4}$ (100 Mcps) 1.10 (d, CH_3CHCO–, J = 7.5 cps[13]), 2.10 (d, –COC*H*CO–, J = 1.7 cps[13]), and 2.28 (quartet of doublets, CH_3CHCO–, J = 1.7, 7.5 cps[13])] to which we have assigned structure **2a** with an *endo*-methyl group on the following basis. The penultimate product of cyclization is probably sodium enolate **3** rather than the alternate bridgehead enolate since significant conjugative stabilization in the latter would require a high degree of ring strain and probably lead to a violation of recently redefined limitations of Bredt's rule.[14,15] Furthermore, a molecular model of the bicyclo[4.2.1]nonane ring system reveals that approach to the five-membered ring should be strongly directed to the face opposite the four-carbon bridge due to steric interference by the latter. On this basis stereoisomer **2a** is envisaged to arise *via* stereospecific kinetically controlled *exo* protonation of enolate **3** during work-up. This same argument rationalizes the high stereoselectivity observed in reactions described below which also involve attack on the five-membered ring of a bicyclo[4.2.1]nonane.

Completion of the tricyclic ring system of culmorin was effected by construction and Dieckmann cyclization of keto diester **5b**. Addition of methyllithium in ether to diketone **2a** afforded in 84% yield a single ketol, **2b** [mp 130–131°; $\lambda_{max}^{CHCl_3}$ 2.77, 2.86 (OH), and 5.82 μ (CO)], which on treatment with thionyl chloride in pyridine underwent dehydration to olefinic ketone **2c** [$\lambda_{max}^{CHCl_3}$ 5.80 (CO) and 6.07 μ (C=CH_2); $\delta_{TMS}^{CCl_4}$ 4.90 and 5.08 (broad singlets, C=CH_2)] in 58% yield after separation by preparative vpc. Treatment of the latter with sodium hydride in glyme and alkylation of the resulting sodium enolate with ethyl bromoacetate produced a single olefinic keto ester, **2d** (82%) [$\lambda_{max}^{CHCl_3}$ 5.77 (ester and ketone CO) and 6.06 μ (C=CH_2); $\delta_{TMS}^{CCl_4}$ 2.07 (br s, –CH_2CO_2–), 2.39 (br s, –COC*H*C=CH_2), 3.98 (q, –OCH_2CH_3, J = 7.0 cps), and 5.05 and 5.12 (broad singlets, C=CH_2)]. Structures **2b** and **2d** have been assigned to the ketol and olefinic keto ester, respectively, in line with the steric argument presented above for formation of diketone **2a**.[16] Hydroboration of **2d** with concurrent reduction of carbonyl functionality yielded triol **4** [mp 170–172°; λ_{max}^{KBr} 2.97 μ (v br, OH)], which was oxidized with ruthenium tetroxide–sodium periodate[17] to keto diacid **5a** [mp 237–242°; λ_{max}^{KBr} 5.86 and 5.75 μ (CO); $\delta_{TMS}^{C_5D_5N}$ 12.13 (br s, –CO_2H)]. Esterification of the latter with diazomethane then produced the desired keto diester **5b** [$\lambda_{max}^{CCl_4}$ 5.74 μ (ester and ketone CO)] in an over-all yield of 58% from **2d**. The physical properties of triol **4** and keto diacid **5a** made unambiguous analysis for stereochemical composition difficult. However, the methoxyl proton absorption in the nmr spectrum of keto diester **5b** in the range δ 3.5–3.9 revealed the presence of a minor stereoisomer which was probably carried through from the triol stage.[19]

Finally, Dieckmann cyclization ($NaOC_2H_5$–C_2H_5OH) converted keto diester **5b** to diketo ester **6a** (43%) [mp 120–122.5°, $\lambda_{max}^{CHCl_3}$ 5.69, 5.73, and 5.81 μ (ester and ketone CO); $\delta_{TMS}^{CDCl_3}$ 2.14 (s), 2.83 (br s), 3.23 (d, J = 1 cps) (–COC*H*C*H*COC*H*$CO_2C_2H_5$), and 4.12 (q, –OCH_2–CH_3, J = 7.0 cps)], which on hydrolysis–decarboxylation (aqueous HCl–HOAc) afforded in 73% yield *dl*-culmorin diketone, **6b** [mp 117–118.5°], the solution infrared, nmr, and mass spectra of which were identical in detail with those of material prepared from authentic culmorin.[2] Since the diketone has previously been converted to culmorin,[2] the preparation of racemic **6b** completes the synthesis.

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(13) These coupling constants were obtained by first-order analysis and may be apparent values.

(14) (a) J. A. Marshall and H. Faubl, *J. Am. Chem. Soc.*, **89**, 5965 (1967); (b) J. R. Wiseman, *ibid.*, **89**, 5966 (1967).

(15) There is experimental evidence to support this supposition. Thus, bicyclo[4.2.1]nonan-9-one and the homologous bicyclo[5.2.1]-decan-10-one are nonenolizable and enolizable ketones, respectively: C. D. Gutsche and T. D. Smith, *J. Am. Chem. Soc.*, **82**, 4067 (1960).

(16) *exo* carboethoxymethylation of olefinic ketone **2c** is essential for the synthesis, and ultimate obtention of culmorin diketone (**6b**) confirms the course of alkylation.

(17) This oxidation was effected by a highly efficient modification developed in our laboratory of the catalytic method:[18] S. K. Ladisch and J. P. Greenberg, to be published.

(18) R. Pappo and A. Becker, *Bull. Res. Council Israel*, **5A**, 300 (1956).

(19) Since the one-carbon bridge is an epimerizable center in **5b**, stereochemical integrity at this stage is not vital to completion of the synthesis.

(20) National Science Foundation Summer Fellow, 1965; National Science Foundation Trainee, 1965–1967; National Institutes of Health Predoctoral Fellow, 1967–1968.

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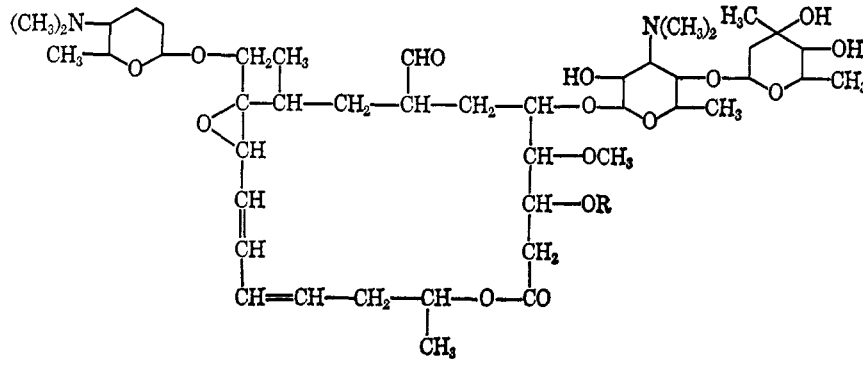
Structure of the Spiramycins (Foromacidines) and Their Relationship with the Leucomycins and Carbomycins (Magnamycins)

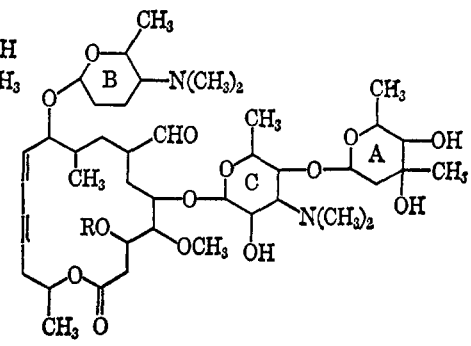
Sir:

Paul and Tchelitcheff, following a series of reports,[1] proposed[1f] structures Ia–c for the spiramycins[1g] I–III,

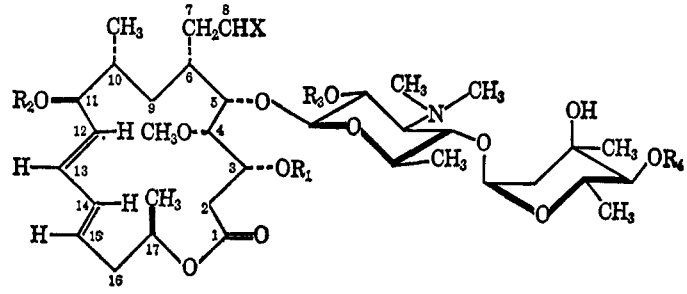
(1) (a) R. Paul and S. Tchelitheff, *Bull. Soc. Chim. France*, 443 (1957); (b) *ibid.*, 724 (1957); (c) *ibid.*, 1059 (1957); (d) *ibid.*, 150 (1960); (e) *ibid.*, 189 (1965); (f) *ibid.*, 650 (1965); (g) S. Pinnert-Sindico, L. Ninet, J. Preud'Homme, and C. Cosar, *Antibiot. Ann.*, 724 (1954); (h) R. Corbaz, L. Ettlinger, E. Gaumann, W. Keller-Schierlein, E. Kyturz, L. Neipp, V. Prelog, A. Wettstein, and H. Zahaer, *Helv. Chim. Acta*, **39**, 304 (1956).



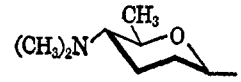
R		
Ia	H	$C_{45}H_{76}O_{15}N_2$
b	$COCH_3$	$C_{47}H_{78}O_{16}N_2$
c	$COCH_2CH_3$	$C_{48}H_{80}O_{16}N_2$



R		
Ia′	H	$C_{43}H_{74}O_{14}N_2$
b′	$COCH_3$	$C_{44}H_{76}O_{15}N_2$
c′	$COCH_2CH_3$	$C_{45}H_{78}O_{15}N_2$



X	R_1	R_2	R_3	R_4
IIa =O	H	Z	H	H
b =O	$COCH_3$	Z	H	H
c =O	$COCH_2CH_3$	Z	H	H
IVa =O	H	H	H	$COCH_2CH(CH_3)_2$
b =O	$COCH_3$	H	H	$COCH_2CH(CH_3)_2$
V =O	$COCH_3$	Z	$COCH_3$	$COCH_3$
VI =O	$COCH_3$	Z	$COCH_3$	H
VII $=NNHC(S)NH_2$	$COCH_3$	Z	$COCH_3$	$COCH_3$



a family of *Streptomyces* elaboration products which correspond to the foromacidines[1h] A–C, respectively.[2] Kuehne and Benson[3] found it necessary to revise the empirical formulas of the spiramycins which, together with other considerations, led to the proposal of alternative structures Ia′–c′. As the result of extensive studies on the leucomycins[4] coupled with comparisons with the spiramycins and the carbomycins (magnamycins),[3,5] we now wish to announce further revision of the structures of the spiramycins as IIa–c and to point out their relationships with the other aforementioned antibiotics. Absolute configurational assignments here are in accord with literature data on the spiramycins,[3,5i,6] the leucomycins (IVa,b),[4b,e,f,5i] and the magnamycins (IIIa,b).[5f,g,h,i]

It is interesting that certain "out-of-step" features noted by Celmer[7] in earlier proposed structures of the leucomycins,[8] the spiramycins,[1f,3] and the magnamycins[5f] now appear to have been "normalized" in terms of conforming to a definite pattern.[5h,9]

(2) Notations spiramycin-A, -B and -C are employed in the text of this communication.

(3) M. E. Kuehne and B. W. Benson, *J. Am. Chem. Soc.*, **87**, 4660 (1965).

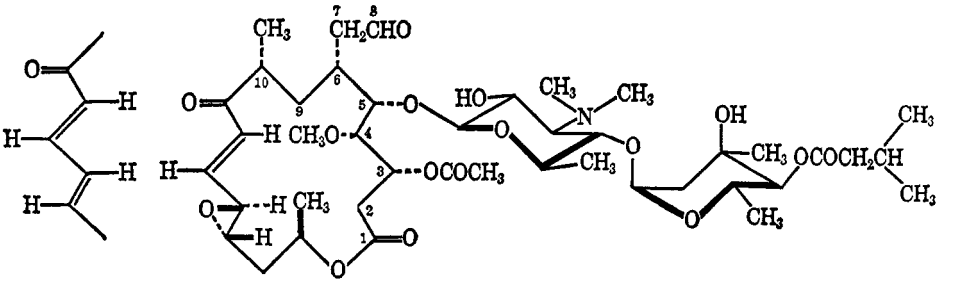
(4) (a) S. Ōmura, M. Katagiri, H. Ogura, and T. Hata, *Chem. Pharm. Bull.* (Tokyo), **15**, 1529 (1967); (b) *ibid.*, **16**, 1167 (1968); (c) S. Ōmura, M. Katagiri, and T. Hata, *ibid.*, **16**, 1181 (1968); (d) S. Ōmura, M. Katagiri, and T. Hata, *J. Antibiot.* **21**, 199 (1968); (e) M. Hiramatsu, A. Furusaki, T. Noda, K. Naya, Y. Tomiie, I. Nitta, T. Watanabe, T. Take, and J. Abe, *Bull. Chem. Soc. Japan*, **40**, 2982 (1967); (f) S. Ōmura, M. Katagiri, T. Hata, M. Hiramatsu, T. Kimura, and K. Naya, *Chem. Pharm. Bull.* (Tokyo), **16**, 1402 (1968).

(5) (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); (f) R. B. Woodward, *Angew. Chem.*, **69**, 50 (1957); *Festschr. Arthur Stoll*, 524 (1957); (g) R. B. Woodward, L. S. Weiler, and P. C. Dutta, *J. Am. Chem. Soc.*, **87**, 4662 (1965); (h) W. D. Celmer, *ibid.*, **88**, 5028 (1966); (i) W. D. Celmer, *ibid.*, **87**, 1799 (1965).

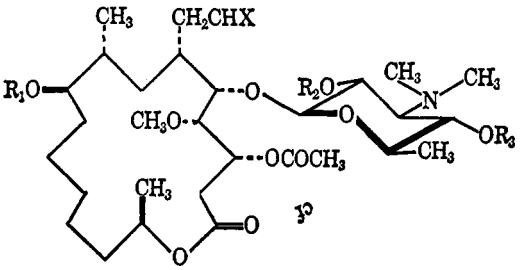
(6) C. L. Stevens, G. E. Gutowski, K. G. Taylor, and C. P. Bryant, *Tetrahedron Letters*, 5717 (1966).

(7) W. D. Celmer in "Antimicrobial Agents and Chemotherapy–1965," G. L. Hobby, Ed., American Society for Microbiology, Ann Arbor, Mich., 1966, 144.

(8) T. Watanabe, T. Fuji, H. Sakarai, and A. J. Satske, *Angew. Chem.*, **76**, 792 (1964).



IIIa, (as shown)
b, (*cf.* offset)



	X	R_1	R_2	R_3
X	=O	Z	H	X
XI	=O	H	H	H
XII	=O	H	H	Y
XIII	=NNHC(S)NH_2	H	H	H
XIV	=O	$COCH_3$	$COCH_3$	$COCH_3$

X = X; Y = Y

Nmr Behavior of the Aldehyde Group. In an earlier discussion of the structures of magnamycin and the spiramycins it was pointed out that the difference in the proton absorption of the aldehyde group in their nmr spectra constituted direct evidence for the difference in the partial structure of C-6 to C-7 in the two antibiotics. In the magnamycin spectrum, this proton absorption appeared as a singlet at 9.6 ppm whereas the absorption was split in the spiramycins, appearing at 9.6 and 9.7 ppm, and it was contended that the latter two absorptions were due to two kinds of stereoisomers formed by the facile isomerization at the C-7 position to the carbonyl. On the other hand, we have found during structural studies on leucomycins[4] that the aldehydic proton in leucomycin A_1 (IVa), in which the 3 position on the lactone is a hydroxyl, appears at 9.78 ppm in the nmr spectrum, while that of leucomycin A_3 (IVb), in which the hydroxyl has been acetylated, appears at 9.65 ppm. Comparison of the nmr spectra of the aldehyde proton in spiramycin-A and -C in $CDCl_3$ showed that it appeared as a singlet in both, at 9.90 ppm in the former and at 9.65 ppm in the latter. This absorption appeared also as a singlet at 9.65 ppm in the nmr spectrum of the triacetyl compound[1e] (V) of spiramycin-A. Thus, it was found that there is a difference in the absorption of the aldehyde proton of the spiramycins when the C-3 position of the lactone is a free hydroxyl or acetylated, as in the case of leucomycins. This fact threw doubt on the interpretation[3] leading to formula I′. Therefore, the nmr spectrum of the thiosemicarbazone VII, $[\alpha]^{25}D$ −15.4° (*c* 0.5, EtOH), of monoacetylspiramycin-B^{10} (VI) was measured in deuterioacetone (as in the case of leucomycins), and absorption originating in the aldehyde proton (C-8) was observed as a triplet at 7.67 ppm.

Chemical Constitutions of the Spiramycins and the Leucomycins. In order to prevent the isomerization[4f] of monoacetylspiramycin-B_{II}[10] (VI) at the time of acid decomposition by the rearrangement of the hydroxyl in the allyl group, VI was catalytically reduced to the tetrahydro compound X and then submitted to acid decomposition (0.3 *N* HCl, 60°, 1 hr) to remove mycaminose (sugar A) and forosamine (sugar B) and to obtain tetrahydroforocidine-B (XI), $[\alpha]^{25}D$ −28.0° (*c* 1, MeOH). On the other hand, tetrahydroleucomycin-A_3[4a] (XII) was decomposed by acid to demycarosyltetrahydroleucomycin-A_3, which was confirmed to be the same product with XI. These two products were then converted to the same thiosemicarbazone (XIII), mp 108–110°, $[\alpha]^{25}D$ −66.3° (*c* 1, EtOH), and a triacetyl compound (XIV), $[\alpha]^{25}D$ −15.0° (*c* 1, MeOH), CD[11] (*c* 0.2, dioxane) $[\phi]_{260}$ 0°, $[\phi]_{280}$ −600°, $[\phi]_{295}$ −1347°, $[\phi]_{310}$ −600°, $[\phi]_{325}$ 0°, which gave the same ir and nmr spectra, and were identical in other properties, including R_f (0.51) on thin-layer chromatogram (Kieselgel G, acetone–benzene 1:1).

Exhaustive hydrogenation[12] was carried out on the spiramycins and a lactonic hydrocarbon was obtained. The mass spectrum of this hydrocarbon was compared with the mass spectra of the skeletal hydrocarbon (VIII) (*cf.* formula I′) and of the skeletal hydrocarbon

(9) W. D. Celmer, *J. Am. Chem. Soc.*, 87, 1801 (1965).

(10) H. Takehira, H. Kato, N. Sugiyama, S. Ihii, T. Haneda, K. Uzu, K. Kumabe, and R. Kojima, *J. Antibiot., Ser. B*, 19, 95 (1966).

(11) CD curves were measured with a Nihon Bunko spectropolarimeter, Model ORD/UV-5.

(12) A. C. Cope, R. K. Bly, E. P. Burrows, U. J. Ceder, E. Ciganek, B. T. Gillis, R. F. Rorter, and H. E. Johnson, *J. Am. Chem. Soc.*, 84, 2170 (1962).

(IX) of magnamycin (or leucomycin) obtained by synthesis.[13]

$CH_3(CH_2)_7CH(CH_3)CH_2CH(CH_3)(CH_2)_5CH_3$
VIII

$CH_3(CH_2)_7CH(CH_3)CH_2CH(C_2H_5)(CH_2)_4CH_3$
IX

In the mass spectra of the hydrocarbon obtained from spiramycin and the hydrocarbon IX, *m/e* (rel intensity) 253 (M − CH_3) (0) and 239 (M − C_2H_5) (14) were characteristically observed, accompanying a weak molecular ion at *m/e* 268 (3), and in that of VIII, *m/e* 253 (M − CH_3) (4) and 239 (M − C_2H_5) (4) were characteristically compared with a strong molecular ion, *m/e* 268 (13). These facts indicate that the α position of the aldehyde is a methylene group in the spiramycins, as in magnamycin and leucomycin, and that the spiramycin skeleton should be corrected to a 16-membered ring.

Stereochemical Considerations. In the nmr spectrum (100 Mcps) of the spiramycin, the absorptions in the olefinic region (5.5–7 ppm), H_{12} (5.60 ppm; $J_{12,13}$ = 15.4 cps), H_{13} (6.55 ppm; $J_{13,14}$ = 15.3 cps), and H_{14} (6.05 ppm; $J_{14,15}$ = 15.2 cps) indicate the *trans, trans* conformation, as in leucomycin.[4c] These facts show that the fundamental structure of the spiramycins is correlated to the absolute structure of leucomycin[4] and that spiramycins have steric structures indicated by IIa,b,c, excluding the nature of the anomeric center linking the forosamine[6] portion.

Acknowledgment. We are indebted to the Kyowa Hakko Kogyo Co., Ltd., for the supply of spiramycins, and thank Dr. Uzu of that company for making the nmr spectral data for spiramycin-A and -C available for the present work.

(13) The skeletal hydrocarbons, VIII and IX, were synthesized as follows. 2-Bromodecane (1) was condensed with diethyl malonate; the product was decarboxylated to 2-methylundecylenic acid (2) which was chlorinated to form its acid chloride (3). The Wurtz reaction, used for the synthesis of tuberculostearic acid,[12] was applied to the reaction of 3 and diamylcadmium in benzene and afforded 8-methylhexadecan-6-one (4) which was treated with ethylmagnesium iodide, followed by dehydration and catalytic reduction over platinum, to obtain 6-ethyl-8-methylhexadecane (IX) (*m/e* 268).

$CH_3(CH_2)_7CHBrCH_3$ (1) ⟶
$CH_3(CH_2)_7CH(CH_3)CH_2COOH$ (2) ⟶
$CH_3(CH_2)_7CH(CH_3)CH_2CHCl$ (3) ⟶
$CH_3(CH_2)_7CH(CH_3)CH_2CO(CH_2)_4CH_3$ (4) ⟶ VIII

7,9-Dimethylheptadecane (VIII) was prepared from 3 and dipentylcadmium under the same conditions as above, followed by Grignard reaction with methylmagnesium iodide, dehydration, and finally catalytic reduction over platinum.

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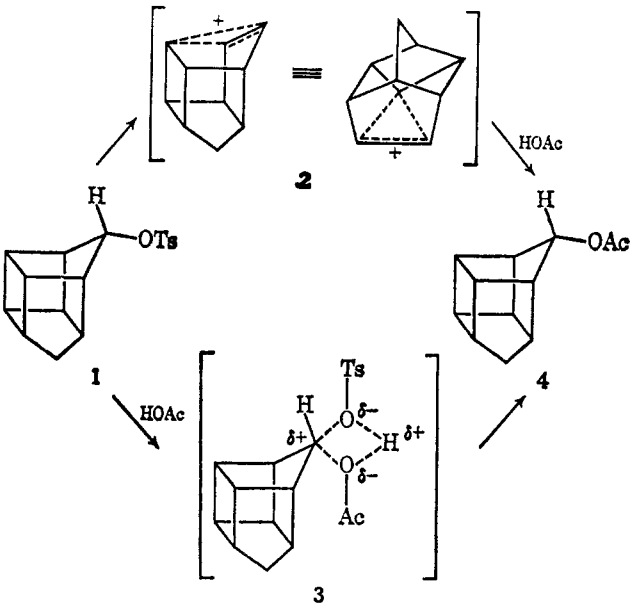
Pentacyclodecane Chemistry. VI. Acetolysis and Formolysis of Pentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]dec-6-*d*-*syn*-6-yl Tosylate. Evidence for a Symmetrical Intermediate[1]

Sir:

We present evidence which establishes the intermediacy of a symmetrical bridged carbonium ion, **2**, or its equivalent of two rapidly equilibrating classical ion pairs, in the solvolysis of the *syn*-1,3-bishomocubyl tosylate **1**.[1] Preliminary rate data for solvolysis and internal return in both acetic and formic acids are also presented.

An alternate explanation to the bridged ion **2** for the almost complete retention of stereochemistry observed in the acetolysis of the *syn*-tosylate **1**[1] is a front-side displacement, perhaps with assistance by the leaving group (see **3**),[2] as has been proposed for several acyclic



systems.[3,4] The latter explanation predicts no skeletal rearrangement of the pentacyclodecane nucleus while the former implies that one-half of the product acetate **4** would be rearranged to the enantiomer of that shown for **4**.[5]

The α-deuterated tosylate **5** and acetate **6** were prepared in manners analogous to those reported previously for the nondeuterated compounds.[1] Lithium aluminum deuteride, or better, aluminum deuteride,[1,6] was substituted for lithium aluminum hydride in the reduction of *endo*-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one. The formate **8** was prepared by the procedure described by Vogel.[7,8] All of the esters were 100% deuterated in the α (6) position as determined by the absence of nmr resonances at −4.51, −4.71, and −4.99 ppm[9] which appear in the spectra of the nondeuterated ana-

(1) Part V: W. L. Dilling, C. E. Reineke, and R. A. Plepys, *J. Org. Chem.*, in press.
(2) Six-membered-ring transition states may also be drawn.
(3) (a) H. L. Goering and S. Chang, *Tetrahedron Letters*, 3607 (1965); (b) H. L. Goering, R. G. Briody, and J. F. Levy, *J. Am. Chem. Soc.*, **85**, 3059 (1963); (c) H. Hart and H. S. Eleuterio, *ibid.*, **76**, 1379 (1954).
(4) 7-Norbornyl tosylate and brosylate have been shown to undergo solvolysis with 80–90% retention of configuration. No skeletal rearrangement occurs in these reactions leading to 7-norbornyl products. See (a) P. G. Gassman and J. M. Hornback, *J. Am. Chem. Soc.*, **89**, 2487 (1967); (b) F. B. Miles, *ibid.*, **89**, 2488 (1967); **90**, 1265 (1968); (c) P. G. Gassman, J. M. Hornback, and J. L. Marshall, *ibid.*, **90**, 6238 (1968).
(5) The racemic mixture of tosylate **1** was used in the previous experiments[1] as well as in this work. Only one enantiomer is shown in this paper.
(6) W. L. Dilling and R. A. Plepys, *Chem. Commun.*, 417 (1969).
(7) A. I. Vogel, *J. Chem. Soc.*, 624 (1948).
(8) All new compounds gave satisfactory elemental analyses or high-resolution mass spectra, as well as satisfactory infrared, nmr, and mass spectra.
(9) All nmr spectra were run as $CDCl_3$ solutions.