ice bath to maintain 75°; later heating was commenced as necessary. The reaction was allowed to proceed for 1 hr and was then worked up as described above.

Effect of Solvent (Table III).—A solution of 0.30 mol of phenyl isocyanate in 100 ml of the appropriate solvent was added dropwise over 1 hr to a slurry of 0.16 mol of KOCN in 200 ml of solvent. The temperature (initially ambient) rose to 35–40° during the addition. The reaction was stirred for 0.5 hr after completing the addition and then worked up in the usual manner. In the reactions using acetone and acetonitrile, part of the reaction product precipitated from solution and was therefore isolated in admixture with KOCN. The organic materials were separated by stirring the mixture with DMF, filtering, and distilling off the DMF.

Effect of Temperature (Table IV).—A solution of 0.30 mol of phenyl isocyanate in 100 ml of DMF was added over 1 hr to a stirred slurry of 0.16 mol of sodium cyanate in 200 ml of DMF at the appropriate reaction temperature. After stirring at temperature for 1 hr additional, the reaction was worked up in the usual manner.

Effect of Cyanate Ion Concentration (Table V).—Phenyl isocyanate (0.3 mol) in 100 ml of DMF was added over 1 hr to a mixture of 0.16 mol of the appropriate metal cyanate and 200 ml of DMF. The temperature rose from ambient to 35–40° during the addition, and the reaction was stirred 1 hr thereafter. The products were isolated as usual.

Effect of Added Electrolytes (Table VI).—The $LiClO_4$ or KI (to give the indicated concentration in the total amount of DMF used) was dissolved in 200 ml of DMF and cooled to ambient. A charge of 0.16 mol of NaOCN was added to the solution, and 0.30 mol of phenyl isocyanate in 100 ml of DMF was added over 1 hr. The reaction was stirred at ambient for 1 hr afterward, and the products were then isolated as previously described.

Registry No.—Phenyl isocyanate, 103-71-9; NaOCN, 917-61-3; KOCN, 590-28-3; LiOCN, 2363-79-3.

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Studies on Reactions of Isoprenoids. IX.[1] The Ritter Reaction of 5,5-Dimethyl-1-vinylbicyclo[2.1.1]hexane

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Treatment of the olefin (**1**) in the title with benzonitrile in H_2SO_4 afforded 2,3,3-trimethyl-1-benzamidobicyclo[2.2.1]heptane (**2**), 2-phenyl-4,4-dimethyl-8-ethyl-3-azabicyclo[3.3.0]octa-2,7-diene (**3**), and 2-phenyl-4,4-dimethyl-8-ethyl-8-benzamido-3-azabicyclo[3.3.0]oct-2-ene (**4**), indicating that this Ritter reaction involved the competing reactions between the cyclobutane ring expansion (C-5 migration) to give a 2,3,3-trimethylbicyclo[2.2.1]heptyl-1 cation and the cyclobutane ring opening at the C-1–C-5 linkage. In the reactions of **1** with a large excess of acetonitrile in H_2SO_4 and with a small excess of acetonitrile in AcOH–H_2SO_4, 2,3,3-trimethyl-1-hydroxybicyclo[2.2.1]heptane (**7**), 2,3,3-trimethyl-1-acetamidobicyclo[2.2.1]heptane (**9**), and, furthermore, 2,3,3-trimethyl-1-acetoxybicyclo[2.2.1]heptane (**8**) only in the latter reaction, together with a small amount of 8-(2,3,3-trimethylbicyclo[2.2.1]heptyl)-γ-sultone (**6**), were obtained, while treatment of **1** in AcOH–H_2SO_4 afforded **7** and **8**. These results suggest that only the cyclobutane ring expansion of **1** occurred in diluted sulfuric acid. The C-2 stereochemistry of **2**, **7**, **8**, and **9** disclosed that the cyclobutane ring enlargement is nonstereospecific. A plausible mechanism for the formation of **2**–**9** was proposed.

Heterocyclic syntheses with nitriles under the Ritter reaction conditions have attracted much attention from the preparative point of view.[2] Most of the examples, however, are limited to intramolecular cyclizations of appropriate 1,*n*-bifunctional systems *via* intermediate nitrilium cations.[3] In a previous paper,[4] we reported the ring-enlargement reaction of 5,5-dimethylbicyclo[2.1.1]hexane-1-epoxyethane to a bicyclo[2.2.1]heptane ring system by acidic hydrolysis, where no cyclobutane ring-fission products were isolated. This paper deals with the results of the Ritter reaction of 5,5-dimethyl-1-vinylbicyclo[2.1.1]hexane (**1**) with benzonitrile and acetonitrile under several reaction conditions.

We expected that the cyclobutane ring fission of **1** might be caused by initial protonation of the vinyl group in such strongly acidic media as H_2SO_4, and subsequent reactions of the resulting carbonium ions with nitriles might afford azabicyclic compounds after rearrangement and cyclization.

Results and Discussion

Structural Elucidation of Products.—Products **2**–**9** were isolated in the Ritter reaction of **1** with benzonitrile and acetonitrile under several conditions as summarized in Table I. Their melting points and analyses are summarized in Table II. Products **2**–**5** were produced only in the presence of benzonitrile, and **9** was formed in the presence of acetonitrile, indicating that these might be derived from **1** and nitriles, but **6**–**8** were produced also in absence of nitriles, indicating that these were derived only from **1** and solvents.

The structural elucidation of **2**–**9** was carried out as follows. Product **2** ($C_{17}H_{23}NO$) contained a benzamido group (ir); the nmr spectrum had a doublet at τ 9.20 assignable to $CHCH_3$ as well as two singlets (τ 8.96 and 9.08) assignable to a *gem*-dimethyl protons, suggesting that **2** is not a normal Ritter reaction product of **1** involving the same ring system, but a cyclobutane ring-expansion product, 2,3,3-trimethyl-1-benzamidobicyclo[2.2.1]heptane or 2,7,7-trimethyl-1-benzamido-

(1) Part VIII: T. Sasaki, S. Eguchi, and T. Ishii, *Bull. Chem. Soc. Jap.*, **43**, 543 (1970).

(2) (a) F. Johnson and R. Madronero, *Advan. Heterocycl. Chem.*, **6**, 95 (1966); (b) L. I. Krimen and D. J. Cota, *Org. React.*, **17**, 213 (1969); (c) A. Hassner, R. A. Arnold, R. Geult, and A. Terada, *Tetrahedron Lett.*, 1241 (1968).

(3) Recently an example of the double intermolecular Ritter reactions of 4-methyl-3-pentenenitrile has been reported: J. W. Ducker and M. J. Gunter, *Aust. J. Chem.*, **21**, 2809 (1968).

(4) Part VII of this series: T. Sasaki, S. Eguchi, and T. Ishii, *J. Org. Chem.*, **35**, 219 (1970).

TABLE I

SUMMARY OF THE PRODUCTS ISOLATED IN THE RITTER REACTION OF 1

Expt no.[a]	Nitrile[b]	Solvent system	Products,[c] (yield, %)[d]			
i	C_6H_5CN	H_2SO_4	**2** (10.5)	**3** (11.5)	**4** (5)	**5** (trace)
ii	C_6H_5CN	H_2SO_4	**6** (5)			
iii	CH_3CN	H_2SO_4	**7** (12)	**9** (trace)		
iv	CH_3CN	AcOH–H_2SO_4	**6** (2.7)	**7** (20.5)	**8** (21.0)	**9** (0.1)
v	CH_3CN	H_2SO_4	**6** (3)	**7** (4)	**9** (18)	
vi	None	AcOH–H_2SO_4	**6** (trace)	**7** (13)	**8** (34)	

[a] Generally a mixture of **1** and nitrile was added to the solvent system, except ii where **1** was added to a mixture of benzonitrile and H_2SO_4. For the detailed procedure, see Experimental Section. [b] In v, a large excess amount of acetonitrile was used compared with small excess amounts of nitrile in i–iv. [c] Products only from nitriles such as benzamide are not included. [d] Yields are based on **1**.

TABLE II

ANALYSES AND MELTING POINTS OF THE RITTER REACTION PRODUCTS OF 1

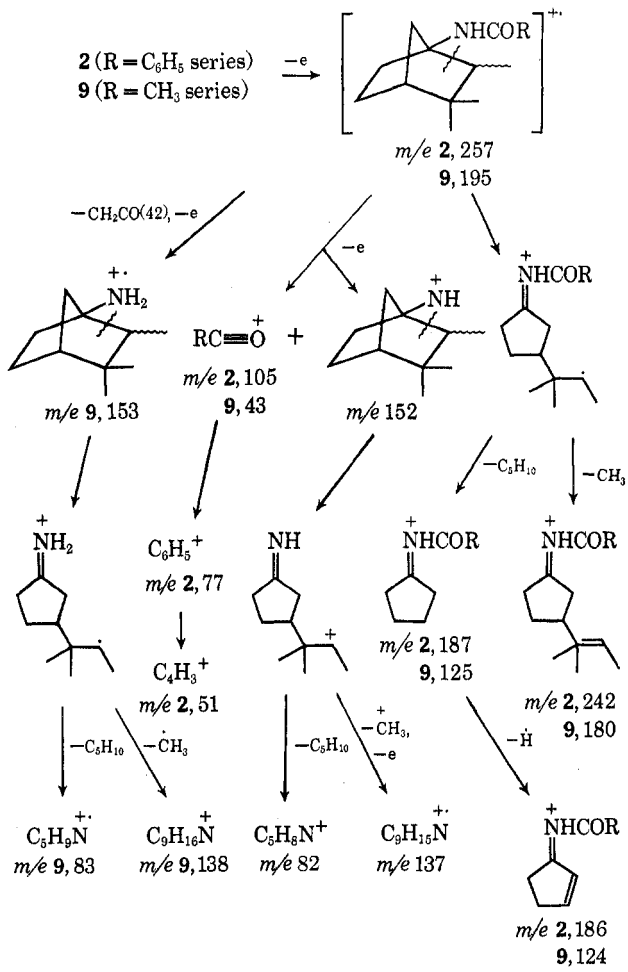
Products	Mp, °C	Formula	Calcd, %			Found, %		
			C	H	N	C	H	N
2	219–221	$C_{17}H_{23}NO$	79.33	9.01	5.44	79.38	8.99	5.42
3	102–103	$C_{17}H_{21}N$	85.30	8.84	5.85	85.33	9.13	6.12
4	177–178	$C_{24}H_{28}N_2O$	79.96	7.83	7.77	79.94	8.04	7.79
5	247–247.5	$C_{24}H_{30}N_2O_2$	76.15	7.99	7.40	76.24	7.87	7.29
6	101–103	$C_{10}H_{16}O_3S$	55.52	7.46		55.65	7.34	
7	98–100	$C_{10}H_{18}O$	77.86	11.76		77.43	12.05	
9	159–163	$C_{12}H_{21}NO$	73.79	10.84	7.17	73.81	11.11	7.40

bicyclo[2.2.1]heptane. The former structure for **2** was established by the fact that treatment of 2-*exo*-methyl-3,3-dimethyl-1-hydroxybicyclo[2.2.1]heptane (**7**) with benzonitrile under similar conditions afforded **2**, which was identified by vpc retention time. Vpc analysis revealed also that **2** was a mixture of 2-*exo*-methyl and 2-*endo*-methyl isomers in approximately 4.5:1 ratio. The mass spectral main fragmentations are explained in Chart I, in which some common fragmentations to the corresponding acetamide derivative **9** due to a 1-acylamido-2,3,3-trimethylbicyclo[2.2.1]-heptane skeleton were observed in addition to those (*m/e* 105 → 77 → 51) due to a benzamido moiety.[5]

Product **3** ($C_{17}H_{21}N$) had no amide absorptions but an absorption at 1635 cm^{-1} (C=C, C=N) in the ir spectrum; the uv spectrum had λ_{max}^{EtOH} 236 nm (ϵ 12,300) which shifted to 265 nm (ϵ 16,700) in a 1% HCl–EtOH solution. This uv spectral behavior is similar to that reported for 2-phenyl-3,3-diphenyl-Δ^1-pyrroline,[6] suggesting the presence of a 2-phenyl-Δ^1-pyrroline moiety in **3**. The nmr spectrum (Figure 1) contained a multiplet at τ 4.68 (1 H) which changed to a partly overlapped double triplet (d, J = 2.1 Hz, and t, J = *ca.* 1.8 Hz) when H_d and H_e were irradiated and to a doublet (J = 2.1 Hz) when H_d, H_e, and $-CH_2CH_3$ were irradiated. This fact suggested the presence of a vinyl proton H_a in a partial structure $-CH_2CH{=}C(Et)CH-$. A triplet at τ 9.08 and an asymmetrical broad multiplet at τ 8.05–8.48 were assignable to an ethyl group. A broad doublet (J = *ca.* 8.5 Hz) at τ 5.58 was assignable to an allylic methine proton (H_b) which coupled with H_c (J = 8.5 Hz), H_a (J = *ca.* 2.1 Hz), H_d, H_{5e}, and $-CH_2CH_3$ from the spin–spin decoupling experiment (Figure 1). A double triplet at τ 7.16 (J = 8.5 and *ca.* 5.0 Hz) was assignable to a methine proton (H_c) which coupled with *vic*-methylene protons (H_d and H_e)

CHART I

MASS SPECTRAL FRAGMENTATION OF 2 AND 9



with J = *ca.* 5.2.[7] A complex multiplet at τ 7.40–7.75 (2 H) was assigned to H_d and H_e. Two sharp

(5) J. L. Cotter, *J. Chem. Soc.*, 5477 (1964); 5742 (1965).

(6) (a) $\lambda_{max}^{i\text{-PrOH}}$ 249 nm (ϵ 12,000) and $\lambda_{max}^{0.01\ N\ HCl\text{-}90\%\ i\text{-PrOH}}$ 271.4 nm (ϵ 10,500): P. J. A. Demoen and P. A. J. Janssen, *J. Amer. Chem. Soc.*, **81**, 6281 (1959). (b) 2-Phenyl-Δ^1-pyrroline, λ_{max}^{MeOH} 244 nm (log ϵ 4.33): F. Korte and H.-J. Steinen, *Chem. Ber.*, **95**, 2444 (1962).

(7) The same magnitude of the coupling constants between the *cis*- and *trans*-*vic* protons in five-membered-ring systems has been often observed; for example, see E. D. Becker and M. Beroza, *Tetrahedron Lett.*, 157 (1962).

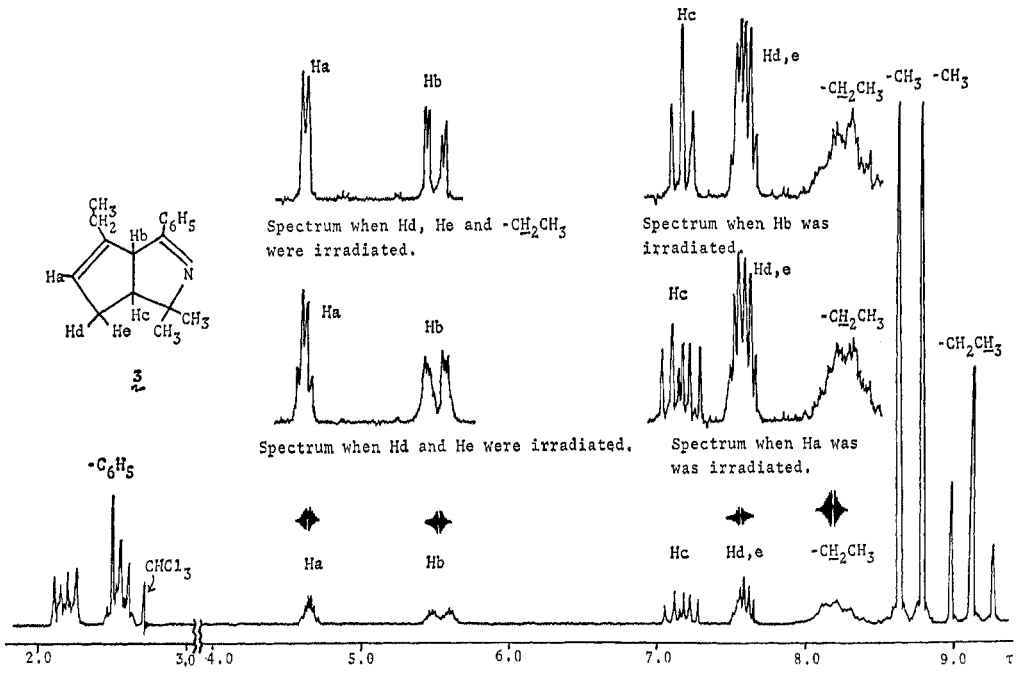


Figure 1.—Nmr spectrum of **3** in $CDCl_3$ at 100 MHz.

singlets at τ 8.62 and 8.79 were assigned to *gem*-dimethyl protons. All these data led us to formulate the structure as 2-phenyl-4,4-dimethyl-8-ethyl-3-azabicyclo[3.3.0]octa-2,7-diene. In the mass spectrum, ion peaks due to loss of CH_3, C_6H_5, and C_6H_5CN[8] from M^+ (*m/e* 239, 67.5) were observed at *m/e* 224 (5.5), 162 (12.5), and 136 (94.1), respectively. The base ion peak appeared at *m/e* 121 (100) which can be derived from the *m/e* 136 ion on loss of CH_3. The skeletal fragmentation between C–1∼C–2 and C–4∼C–5 was observed in ion peaks at *m/e* 145 (52.9) and 94 (28.2) which might be ascribable to 3,3-dimethyl-2-phenylazirine ($C_{10}H_{11}N$) and ethylcyclopentadiene (C_7H_{10}), respectively. These mass spectral data were consistent with the assigned structure.

Product **4** ($C_{24}H_{28}N_2O$, M^+ *m/e* 360) was assigned as 2-phenyl-4,4-dimethyl-8-ethyl-8-benzamido-3-azabicyclo[3.3.0]oct-2-ene, a secondary Ritter reaction product of **3**: the presence of a benzamido group was supported by ir spectrum; the uv spectral behavior (λ_{max}^{EtOH} 232 nm and $\lambda_{max}^{1\%\ HCl\text{-}EtOH}$ 270 nm) was very similar to that of **3**, indicating the presence of the same chromophore as **3**. From the fact that **3** was isolated together with **4** and from the reaction mechanism (Chart IV), we assigned the above structure to **4**, but further study shall be necessary for the definite determination.

The structure of **5** might be a dibenzamide derivative such as 1-benzamido-1-ethyl-3-(2-benzamido-2-propyl)-cyclopentane from the analytical (Table II) and ir data; this product seems plausible as one of the possible products from the cyclobutane ring fission (Chart IV) but the isolated amounts were too small to be further investigated.

The structure of sultone **6** was shown by ir (SO_2, 1342, 1173; no OH, C=O, or C=C) and nmr (Figure 2). The typical ABC pattern (τ 6.57, H_b; 6.96, H_a; 7.64, H_c)

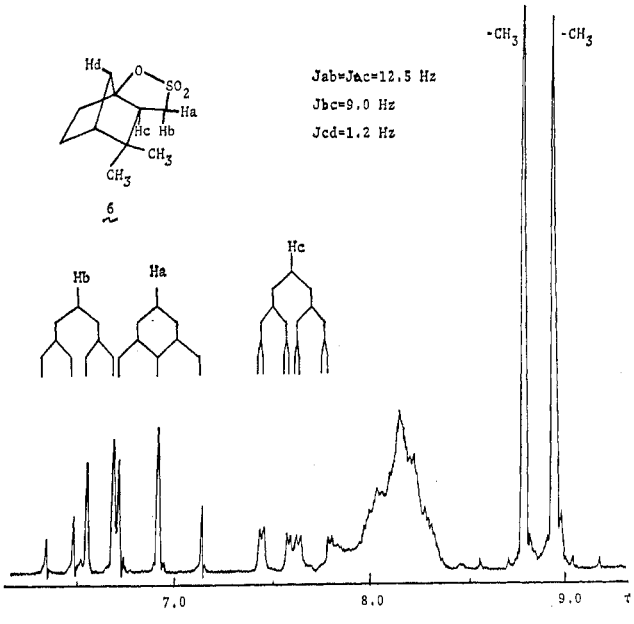


Figure 2.—Nmr spectrum of **6** in $CDCl_3$ at 60 MHz.

suggested the $-CHCH_2SO_2O-$ group. The chemical shift of H_b and H_a were very similar to those reported for $-CH_2SO_2O-$ protons of camphene sultone (τ 6.95) and 10-isobornyl sultone (τ 6.75).[9] The lack of any lower field signal corresponding to the $-CHOSO_2-$ proton which appeared at τ 5.60 in 10-isobornyl sultone[9] led us to formulate such a cyclic sultone between the C–1 and C–8 positions in a 2,3,3-trimethylbicyclo[2.2.1]heptane ring. The presence of a long-range coupling between H_c and H_d (Figure 2) supported the above formulation. In the mass spectrum, the loss of SO_2 from the parent ion (*m/e* 216) was observed by appearance of the ion at *m/e* 152 (Chart II), which can be further cleaved to ions at *m/e* 137, 123, 96, 82, 69,

(8) This fragment appeared at *m/e* 104 (38.4) after hydrogen abstraction (ion–molecule reaction) as often observed in the mass spectra of nitriles: F. W. McLafferty, *Anal. Chem.*, **34**, 26 (1962).

(9) J. Wolinsky, D. R. Dimmel, and T. W. Gibson, *J. Org. Chem.*, **32**, 2087 (1967).

CHART II

MASS SPECTRAL FRAGMENTATION OF 6

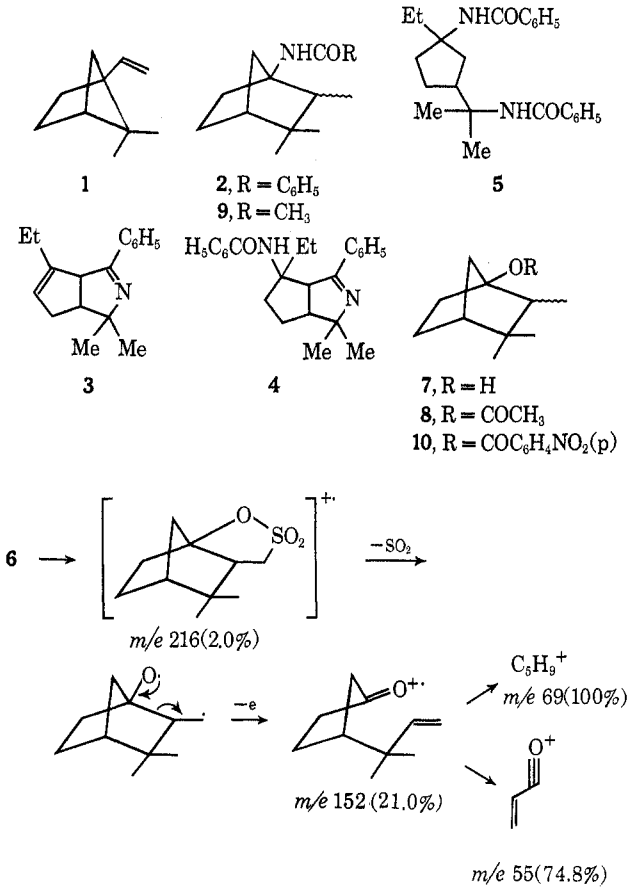
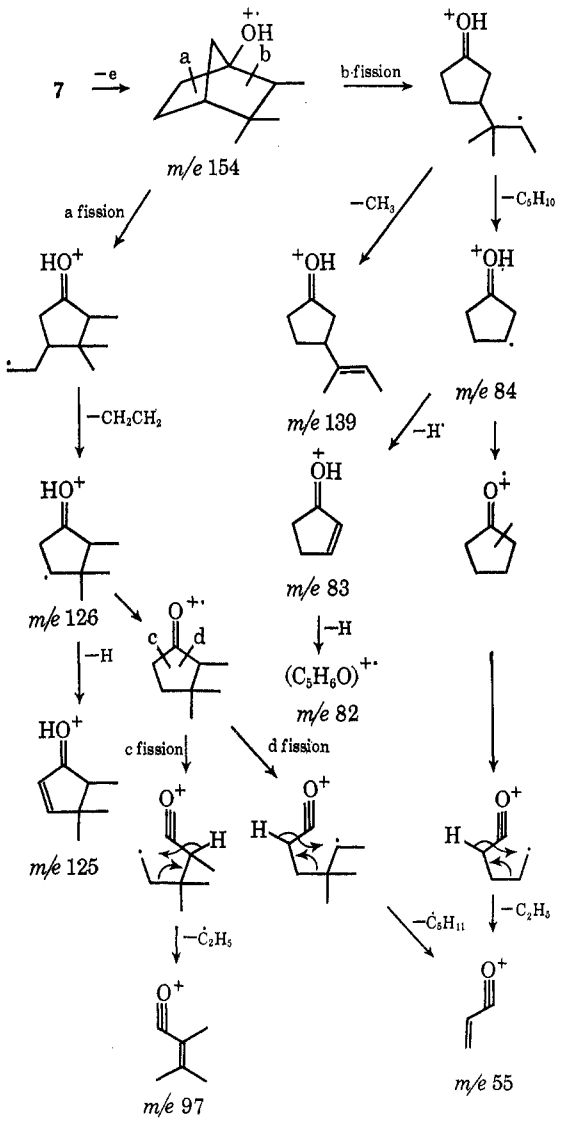


CHART III

MASS SPECTRAL FRAGMENTATION OF 7



and 55, etc, similar to those observed in the known spectrum of 3-(1,1-dimethyl-2-propenyl)cyclopentanone.[4] An ion peak at *m/e* 41 (62.0) appeared in a higher abundance supporting the structure, since this ion is known to be common for all norbornane derivatives, and, furthermore, its relative abundance is known to be enhanced by the presence of a *gem*-dimethyl group.[10]

Product **7** ($C_{10}H_{18}O$) was a saturated alcohol from ir (3300 and 1106 cm^{-1}); the nmr had signals at τ 7.60 (1 H, s, OH), 7.80–8.90 (7 H, m, methylene, and methine protons), 9.01 (*ca.* 4.5 H, s, methyl protons overlapped with a half of a doublet due to $-CHCH_3$), 9.08 (3 H, s, methyl protons), 9.17 (*ca.* 1.5 H, a half of a doublet due to $CHCH_3$), and 9.50 (1 H, m, C-2 *endo* proton),[11] suggesting that **7** is 2-*exo*-methyl-3,3-dimethyl-1-hydroxybicyclo[2.2.1]heptane, a cyclobutane ring-expansion product.[12] The structure and stereochemistry of **7** were justified by the chemical conversion to *exo*-isocamphane (2,2-dimethyl-3-*exo*-methylnorbornane).[13] **7** gave the corresponding acetate and *p*-nitrobenzoate **10**. The main mass spectral fragmentations can be explained by two ring cleavages (a and b fission in Chart III), which are quite different from those of 2-norbornanols.[10] The most interesting feature is the appearance of an ion at *m/e* 83 as the base peak and the relatively lower abundances of the ions at *m/e* 43 and 41. The b fission can yield ions at *m/e* 84, 83, and 82 as well as those at *m/e* 69 ($C_5H_9^+$) and 55, etc. The a fission can afford ions at *m/e* 126, 125, 97, and 55, etc.[14]

An oily product **8** showed the ir spectrum quite similar to that of an acetate derived from **7**, suggesting the **8** might be **7**-acetate. Vpc, however, revealed that **8** is a mixture of *ca.* 1:1 *endo* and *exo* isomers. Hydrolysis of **8** afforded a crystalline product which had a superimposable ir spectrum on that of **7**, and a satisfactory analysis for $C_{10}H_{18}O$. Its nmr spectrum was also similar to that of **7**. The hydrolyzed product was treated with *p*-toluenesulfonyl chloride, followed by lithium aluminum hydride reduction to afford a mixture of *exo*- and *endo*-isocamphane in *ca.* 1:1 ratio (vpc),

(10) D. R. Dimmel and J. Wolinsky, *J. Org. Chem.*, **32**, 2735 (1967).

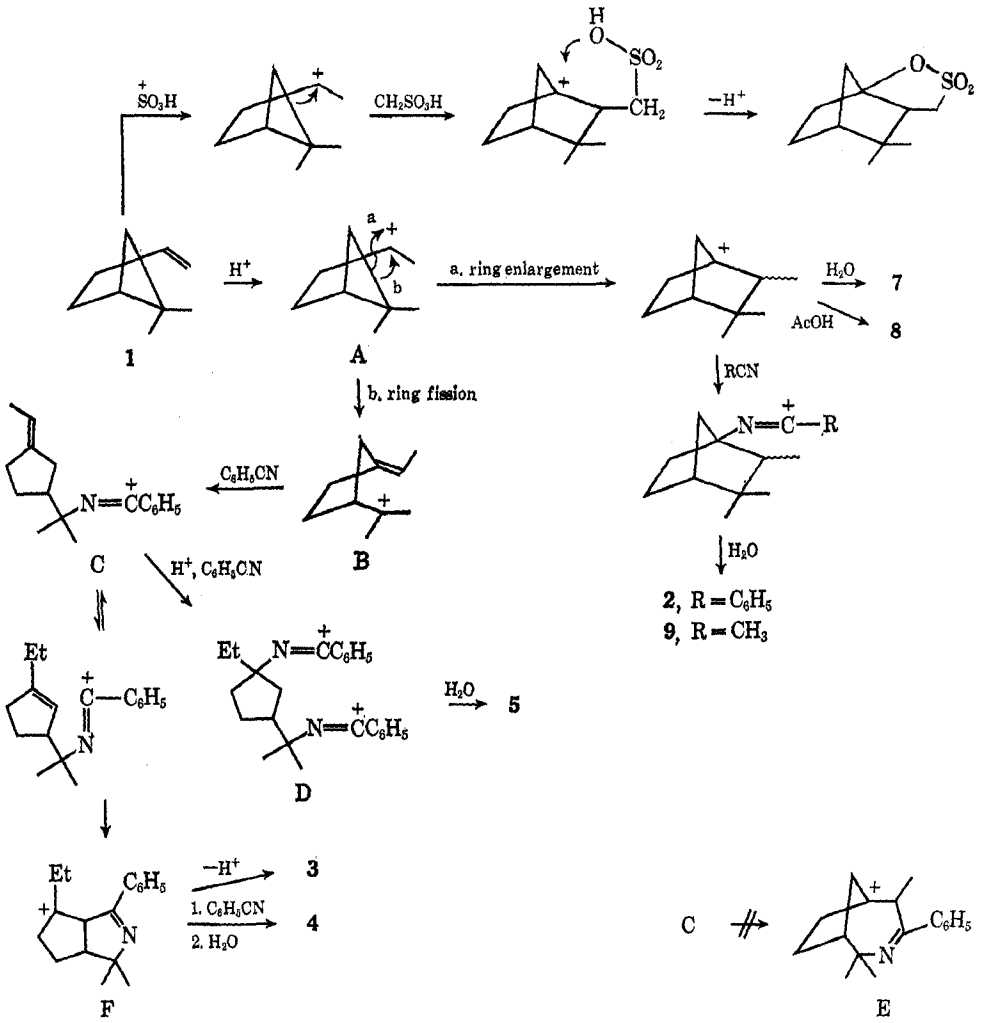
(11) E. Pretsch, H. Immer, C. Pascual, and W. Simon, *Helv. Chim. Acta*, **50**, 105 (1967); R. G. Foster and M. C. McIvon, *Chem. Commun.*, 280 (1967); J. A. Claisse and D. I. Davies, *J. Chem. Soc., B*, 679 (1962).

(12) Vpc analysis of **7** purified by sublimation showed a single peak, though that of crude **7** obtained by chromatography had two peaks in *ca.* 3:1 ratio, indicating that both C-2 *exo* and C-2 *endo* isomers were produced but in favor of the C-2 *exo*-methyl isomer.

(13) (a) S. Beckmann and B. Geiger, *Chem. Ber.*, **94**, 1910 (1961); (b) J. A. Berson, C. J. Olsen, and J. S. Walia *J. Amer. Chem. Soc.* **84**, 3337 (1962).

(14) For mass spectra of alcohols see (a) J. H. Beynon R. A. Saunders, and A. E. Williams, "The Mass Spectra of Organic Molecules," Elsevier Publishing Co., New York, N. Y., 1968, pp 132–153, 190–210; (b) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, pp 94–128.

CHART IV



indicating **8** to be a 1:1 mixture of **7** acetate and its 2-*endo*-methyl isomer.

Product **9** was characterized as 2,3,3-trimethyl-1-acetamidobicyclo[2.2.1]heptane from the analytical (Table II) and spectral data. Vpc revealed a very unsymmetrical peak, suggesting that **9** might be a mixture of C-2 stereoisomers. The ratio was estimated as roughly 2:1. The major peak had the same retention time with a product obtained by treatment of **7** with acetonitrile in H_2SO_4, supporting the above structural assignment. In the mass spectrum, a characteristic fragmentation due to loss of the ketene molecule[15] was observed by an ion at *m/e* 153 which can afford ions at *m/e* 138 and 83, etc., in addition to the common fragmentation patterns to **2** by ions at *m/e* 180, 152, 137, 125, 124, and 82, etc., as depicted in Chart I.

Mechanistic Consideration.—A plausible mechanism for the formation of **2**–**9** is summarized in Chart IV. A cyclobutane ring expansion of **1** to a cyclopentane (path a) *via* a secondary cation (A) affords a 2,3,3-trimethylbicyclo[2.2.1]heptyl-1 cation which can give the corresponding Ritter reaction products **2** and **9** by addition to benzonitrile and acetonitrile, followed by hydrolysis. Before additions to nitrile, the addition to acetic acid can afford **8** and the hydrolysis can give **7**. In the above ring expansion, the selective rearrangement of C-5 can be rationalized by the larger migration aptitude of a tertiary carbon (C-5) than that of a primary carbon (C-6).[16a] The observed stereoselectivity in favor to the C-2 *exo*-methyl isomer suggests the presence of a conformational effect.[16b] A cyclobutane ring cleavage (path b) *via* A affords an olefinic tertiary cation B, which could be the precursor of **3**, **4**, and **5** as illustrated in Chart IV. The preferred fission of the C-1–C-5 bond to C-1–C-6 can be explained by the more stable nature of the tertiary cation B than that of the primary cation from C-1–C-6 fission. The practical isolation of **3** and **4** indicates that a path to F from C is preferable to a direct cyclization of C to E. The formation of **5** in a very small amount could be understood by the unstable dication structure of an intermediate D.[17]

The formation of sultone **6** can be explained similarly to that of camphene sultone.[9] A cyclobutane ring expansion will be caused by the attack of $^+SO_3H$ at the vinyl group to afford a bridgehead cation, followed by cyclization.

Treatment of benzonitrile with sulfuric acid is known to afford benzamide, dibenzamide, and 2,4,6-triphenyl-

(15) Reference 14b, pp 336–366.

(16) (a) C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968, pp 3–60. (b) Further studies are necessary for exploring the stereoselectivity in such conformationally mobile systems; *cf.* C. J. Cheer and C. R. Johnson, *J. Amer. Chem. Soc.*, **90**, 178 (1968), and ref 4.

(17) In order to demonstrate the above possibility, synthesis and the Ritter reaction of 1-vinyl-3-isopropenylcyclopentane are to be studied.

1,3,5-triazine,[18] all of which were also isolated as by-products in i and ii (Table I).

As a conclusion, an expected azabicyclic compound like **3** was obtained when **1** and benzonitrile were added to sulfuric acid but not when **1** and acetonitrile were treated similarly where a heterogeneous reaction afforded mostly intractable by-products; even in the homogeneous reaction of **1** with a large excess acetonitrile, the products were seemingly all derived from a bicyclo[2.2.1]heptyl cation, suggesting the difficulty of A → B conversion in such media as sulfuric acid diluted with acetonitrile, and/or acetic acid. However, the mechanistic consideration suggested a possibility that such azabicyclic compounds like **3** can be produced by the Ritter reaction of appropriately substituted 1,3-bifunctional cyclopentane derivatives.[17]

Experimental Section[19a]

5,5-Dimethyl-1-vinylbicyclo[2.1.1]hexane (1) with Benzonitrile. i.[19b]—A mixture of 3.0 g (0.022 mol) of **1**[20] and 3.4 g (0.033 mol) of benzonitrile was slowly added to 8.0 g of ice-cooled sulfuric acid (sp gr 1.84) with stirring during 15 min, and the stirring was continued for 7 hr at room temperature. The mixture was poured onto ice–water (200 ml) and extracted with chloroform (200 + 100 + 100 ml). The combined chloroform extracts were washed with aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride successively, and dried (Na_2SO_4). Removal of the solvent under reduced pressure left a brownish oil (5.02 g) which was purified by chromatography on a silica gel column (Mallinckrodt, 100 mesh) eluting with dichloromethane and then with dichloromethane–methanol solvent system. The first fraction gave a paraffin-like oil (0.5 g) which was not identified. The second fraction gave recovered benzonitrile (0.5 g). The third fraction afforded **2** (0.6 g) as colorless needles: mp 219–221° (*n*-hexane–CH_2Cl_2); ir (KBr) 3450, 1647, 1550, 1315 (NHCO), 1610, 1585, 1503, and 639 (phenyl) cm^{-1}; nmr ($CDCl_3$) τ 2.10–2.75 (5, m, C_6H_5), 3.80 (1, broad s, NH), 7.60–8.80 (8, m, methylene and methine), 8.96 and 9.08 (6, s, $C(CH_3)_2$), and 9.20 (3, d, J = 7.0 Hz, $CHCH_3$); mass spectrum *m/e* 257 (35.7), 242 (15.0), 187 (15.0), 186 (76.4), 168 (10.4), 152 (8.0), 149 (15.7), 137 (8.0), 136 (12.1), 124 (22.5), 121 (11.5), 105 (100), 83 (12.0), 82 (16.5), 81 (8.5), 77 (35.0), 71 (7.0), 70 (8.0), 69 (11.0), 57 (11.5), 55 (9.5), 51 (10.0), 43 (10.0), and 41 (14.0).

The fourth fraction gave **5** as colorless crystals (0.007 g): mp 247–247.5° (EtOH); ir (KBr), 3340, 3086, 2930, 1648, 1605, 1580, 1546, 1315, and 700 cm^{-1}.

The fifth fraction gave **3** (0.6 g): mp 102–103° (*n*-hexane); ir (KBr) 1635, 1608, 782, and 639 cm^{-1}; mass spectrum *m/e* 239 (67.5), 224 (5.5), 162 (12.5), 145 (52.9), 136 (94.1), 121 (100), 107 (54.9), 104 (38.4), 94 (28.2), and 77 (13.7).

The sixth fraction gave benzamide (1.0 g) and the seventh, a brownish oil (1.0 g) which was further purified on alumina (neutral, Merck, activity grade I) column eluting with benzene to give **4** (0.3 g): mp 177–178° (*n*-hexane–CH_2Cl_2); ir (KBr) 3375, 1635, 1580, 1524, 1303, 767, 713, and 690 cm^{-1}; mass spectrum *m/e* 360 (34.2), 345 (3.1), 239 (18.2), 198 (14.4), 186 (19.9), 185 (100), 184 (32.4), 170 (41.8), 149 (15.9), 105 (67.1), 104 (22.0), 77 (36.7), 71 (14.2), 69 (14.3), 57 (29.4), 56 (16.8), 55 (16.5), 44 (29.8), 43 (31.2), and 41 (29.0).

The residual portion eluted with methanol gave 0.6 g of noncrystalline mass which was not further identified.

The water layer after extraction with chloroform was neutralized with 10% aqueous potassium hydroxide and extracted with chloroform to give benzamide (0.26 g).

ii.—**1** (5 g, 0.037 mol) was stirred to an ice-cooled mixture of benzonitrile (5 g, 0.048 mol) and sulfuric acid (10 g). After 5 hr of stirring at room temperature, the mixture was treated as above, and the chloroform extracts (4.5 g) were purified on a silica gel column to give 0.8 g of recovered **1** and 0.6 g of 2,4,6-triphenyl-1,3,5-triazine, mp 239–240° (lit.[21] mp 239°), from the first fraction eluted with dichloromethane. The second fraction gave the sultone **6** (0.4 g) as colorless crystals which showed a positive sulfur test:[22] mp 118–119° (*n*-hexane); ir (KBr) 2964, 1342, 1173, 1059, 838, and 807 cm^{-1}; mass spectrum *m/e* 216 (2.0), 201 (7.3), 187 (5.0), 152 (21.0), 137 (12.0), 123 (10.5), 109 (18.5), 96 (42.5), 83 (69.0), 82 (36.5), 69 (100), 55 (75.0), and 41 (62.0).

From the third and fourth fractions eluted with methanol–dichloromethane, 0.4 g of dibenzamide, mp 148–149° (lit.[23] mp 148°), and 2.0 g of benzamide were obtained.

1 with Acetonitrile. iv.—A mixture of **1** (3 g, 0.022 mol) and acetonitrile (1.5 g, 0.036 mol) in acetic acid (6 ml) was stirred into an ice-cooled mixture of acetic acid (4 ml) and sulfuric acid (7 ml) during 0.5 hr. After 3 hr of stirring at room temperature, the chloroform extracts (3.5 g) were purified on a silica gel column eluting with chloroform. The first fraction gave 0.66 g of a paraffin-like oil which had no C=O bands in the ir and was discarded. The second fraction gave 0.90 g of the acetate **8** as an oil: ir (neat) 2965, 1735, 1373, 1250, and 1090 cm^{-1}; vpc (silicone SE-30 at 140°) showed two peaks with area ratio of *ca.* 1:1, one of which had the same retention time as the **7** acetate.

The third fraction afforded 0.13 g of **6**. The fourth fraction gave 0.71 g of the alcohol **7** as needles after several sublimations at 40–45° (20 mm):[12] mp 98–100° (sealed tube); ir (KBr) 3300, 2955, 1308, and 1106 cm^{-1}; mass spectrum *m/e* 154 (2.7), 139 (50.2), 125 (11.4), 111 (8.1), 97 (8.4), 84 (23.3), 83 (100), 82 (17.5), 71 (8.9), 69 (12.0), 67 (8.8), 55 (33.2), 53 (9.5), 43 (27.3), 41 (23.9), and 39 (12.3).

The fifth fraction gave 0.005 g of the acetamide **9**: mp 159–163° (*n*-hexane); ir (KBr), 3350, 2950, 1646, 1550, 1370, and 1312 cm^{-1}; nmr ($CDCl_3$) τ 4.10 (1, broad, s, NH), 8.09 (3, s, $COCH_3$), 7.00–8.80 (8, m, methylene and methine protons), 9.02, 9.16, and 9.15 [9, s, s, and d, J = 7.8 Hz, $C(CH_3)_2$ and $CHCH_3$]; mass spectrum *m/e* 195 (36.8), 180 (68.6), 168 (13.5), 166 (14.0), 153 (9.0), 152 (14.4), 149 (11.0), 139 (13.5), 138 (65.3), 137 (7.0), 136 (17.5), 125 (40.8), 124 (100), 121 (28.0), 93 (23.1), 83 (53.4), 82 (94.2), 81 (17.5), 71 (19.0), 70 (20.5), 69 (26.5), 67 (25.0), 55 (65.7), 44 (20.0), 43 (95.3), 42 (45.0), and 41 (97.8).

The last fraction eluted with methanol afforded 0.4 g of brownish oil which might be amide derivatives (ir 1653 and 1550 cm^{-1}), but further identification was unsuccessful.

iii.[19b]—A mixture of **1** (3 g, 0.022 mol) and acetonitrile (1.35 g, 0.022 mol) was stirred into ice-cooled sulfuric acid (7 g). The resulting heterogeneous mixture underwent an exothermic reaction and afforded after chromatography 0.4 g of **7**, trace amount of **9**, and 0.2 g of paraffinlike oil.

v.[19b]—A mixture of **1** (1.19 g, 0.0087 mol) and acetonitrile (4.03 g, 0.098 mol) was added during 40 min into ice-cooled sulfuric acid, and the mixture was stirred for 18 hr at room temperature. Work-up as above afforded **6** (0.05 g), **7** (0.05 g), and **9** (0.31 g).

Hydrolysis of 8.—A mixture of 0.6 g of **8** and 10 ml of 5% aqueous potassium hydroxide in 25 ml of methanol was stirred for 1 week at room temperature. Extraction with chloroform after dilution with water (*ca.* 300 ml) and work-up gave 0.4 g of crystalline solids which were sublimed at 40–45° (20 mm) to give 0.35 g of needles: mp 65–69° (sealed tube); ir (KBr) 3335, 2944, 1310, and 1110 cm^{-1}; nmr ($CDCl_3$) 7.69 (1, s, OH), 7.80–9.80 (*ca.* 7, m, methylene and methine protons), 8.90–9.30 (9, m, $C(CH_3)_2$ and $CHCH_3$), and 9.40–9.80 (*ca.* 0.5, broad m, C-2 *endo* proton); vpc (Silicone SE-30, at 100°) had two peaks in *ca.* 1:1 ratio, one of which had the same retention time as **7**.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.43; H, 12.19.

Acetylation of 7.—Treatment of **7** (0.055 g) with acetic anhydride (2.5 ml) and *p*-toluenesulfonic acid (0.07 g) at room temperature for 24 hr gave 0.06 g (87%) of **7** acetate as an oil: ir (neat) 2960, 1736, 1480, 1327, 1253, and 1087 cm^{-1}; nmr

(18) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. 1, W. A. Benjamin, Inc., New York, N. Y., 1965, pp 209–231.

(19) (a) Uv spectra were determined with a JASCO Model ORD/UV-5 spectrometer and mass spectra with a JEOL Model JMS-01SG mass spectrometer at 70 eV. Vpc analyses were performed on a Hitachi K-23 gas chromatograph or a Yanagimoto gas chromatograph, Model GCG-220, using a 2-m column packed with silicone SE-30, DOP, or Apiezon L; see also ref 4, footnote 9. (b) Corresponds to experiment number in Table I.

(20) R. H. Liu and G. S. Hammond, *J. Amer. Chem. Soc.*, **89**, 4936 (1967).

(21) B. W. Frizmmon, C. Hewlett, and R. A. Shaw, *J. Chem. Soc.*, 4779 (1965).

(22) R. I. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1956, pp 57–62.

(23) E. Fischer and H. Troschke, *Ber.*, **13**, 708 (1880).

($CDCl_3$) τ 7.95 (3, s, $COCH_3$), 7.40–8.70 (*ca.* 8, m, methylene and methine protons), 8.97, 9.08, and 9.16 [9, s, $C(CH_3)_2$ and $CHCH_3$]; mass spectral mol wt 196.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.28; H, 10.42.

p-Nitrobenzoylation of 7.—Treatment of **7** (0.15 g) with *p*-nitrobenzoyl chloride (0.25 g) in dry pyridine (2 ml) at room temperature for 40 hr and work-up gave 0.2 g (68%) of the *p*-nitrobenzoate of **7** (**10**): mp 125° (EtOH); ir (KBr) 3120, 2964, 1720, 1605, 1526, 1350, 1295, 1122, 1110, and 715 cm^{-1}; nmr ($CDCl_3$) τ 1.79 (4, s, phenyl protons), 7.50–8.80 (8, methylene and methine protons), 8.91 and 9.02 [6, s, $C(CH_3)_2$], and 9.17 (3, d, J = 8.0 Hz, $CHCH_3$).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.29; H, 7.01; N, 4.63.

Formation of 2 from 7.—A mixture of **7** (0.15 g) and benzonitrile (0.20 g) was treated with sulfuric acid (2.0 g) for 1 day at room temperature. Work-up gave 0.14 g of crude product which exhibited a peak having the same retention time (7.5 min) with that of the main peak of **2** (the minor peak, 6.5 min) on vpc (silicone SE-30, at 250°).

Formation of 9 from 7.—A mixture of **7** (0.19 g) and acetonitrile (1.0 g) was treated with sulfuric acid (1.5 g) similarly. Vpc analysis (200°) of the products showed a peak having the same retention time with **9** (4.7 min).

Conversion of 7 to *exo*-Isocamphane.—Treatment of **7** (0.15 g) with *p*-toluenesulfonyl chloride (0.20 g) in pyridine (2 ml) gave **7**-tosylate (0.15 g) as an oil: ir (neat) 2960, 1603, 1365, 1195, 1180, 1043, 1030, 880, and 675 cm^{-1}. The tosylate was reduced with lithium aluminum hydride (0.5 g) in tetrahydrofuran (5 ml) under refluxing for 1 week. The product was taken in ether and was analyzed on vpc to reveal two main peaks. The major peak was recovered tosylate and the minor (*ca.* 5% peak area of the main peak) had the same retention time (6 min) with that of *exo*-isocamphane, which was prepared as a mixture of *exo* (85%) and *endo* (15%) isomers by catalytic reduction of camphene with Pd-C (10%) in ethanol,[13b] and had bp 160–165° and mp 54–60°.[24] Similar treatment of the alcohol from **8** revealed also isocamphane peaks in a low yield (*ca.* 3%).

Reaction of 1 with a Mixture of Sulfuric Acid and Acetic Acid. vi.—**1** (1.0 g, 0.008 mol) was stirred into an ice-cooled mixture of sulfuric acid (2.5 g) and acetic acid (4 ml), and the mixture was stirred for 20 hr at room temperature. Work-up as above afforded 0.45 g of paraffin-like oil, 0.16 g (13%) of the acetate **8**, and 0.38 g (34%) of the alcohol **7** in addition to a trace amount of **6**.

Registry No.—**1**, 16626-39-4; **2** (*exo*), 24454-04-4; **3**, 24454-00-0; **4**, 24454-01-1; **5**, 24454-02-2; **6**, 24454-03-3; **7**, 24454-05-5; **7** acetate, 24454-07-7; **9**, 24454-08-8; **10**, 24454-06-6; **8** (*endo*), 24454-35-1; **2** (*endo*), 24454-36-2.

(24) The isomer ratio was estimated from the relative peak area on vpc and nmr signal at τ 9.51; *cf.* ref 11.

Steroid Rearrangements. Reactions of a 16,17α-Epoxypregnan-20-one with Hydrogen Fluoride and Thermal Dehydrofluorinations

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Treatment of 16,17α-epoxypregnan-3α-ol-11,20-dione acetate (**1**) with anhydrous hydrogen fluoride afforded a mixture from which three fluorine-containing steroids and three rearranged olefins were separated and their structures established. Two of the products were the unrearranged 16β-fluoro- and 17α-fluoropregnanes **11** and **12**, respectively. The remaining four products had formed as a result of migration of the 18-methyl to C-17, and were identified as the three isomeric C-ring olefins **2**, **3**, and **6**, and the 14-fluoro steroid **8**. Stereospecific thermal elimination of hydrogen fluoride from the tertiary fluoro steroids was employed to interrelate certain of the reaction products and as an aid to elucidation of their stereochemistry.

The reaction of steroid epoxides with hydrogen fluoride is a frequently used method for introduction of fluorine into various selected ring positions. Utility of this reaction for synthesis of 16-fluoro steroids, however, has been hampered by the well-documented[1,2] tendency for 16,17α-epoxy-20-keto steroids to undergo Wagner–Meerwein rearrangements involving shift of the angular methyl group from C-13 to C-17. Shapiro and coworkers,[3] for example, found that 16,17α-epoxyprogesterone was transformed into a rearranged Δ^{13} steroid upon treatment with hydrogen fluoride in chloroform containing ethanol.

Beyler and Hoffman[4] reported lack of success in preparing 16-fluoropregnanes by the action of hydrogen fluoride on the epoxy steroid **1** under a variety of conditions. An early patent report[5] claims synthesis of a 9,16-difluoro steroid by means of simultaneous opening of both oxirane rings in a 9,11β:16,17α-bisepoxy steroid with HF, but the properties of the 16-fluoro steroid were not described.

The original objective of this investigation, *i.e.*, synthesis of 16-fluorinated cortical steroids,[6] was broadened as the complexity of the HF-catalyzed reactions of **1** became apparent. Structures of the several reaction products were determined in order to provide a more detailed understanding of the multiple transformations involved.

Results

When **1** was allowed to react in a 1:1 HF–THF mixture for 5 hr at room temperature, about 70% of the epoxide was consumed, giving rise to a complex mixture of products. Examination of the mixture using tlc revealed six well-defined spots, and combinations of

(1) N. L. Wendler in "Molecular Rearrangements," Vol. II, P. DeMayo, Ed., Interscience Publishers, New York, N. Y., 1964, Chapter 16.

(2) W. F. Johns, *J. Org. Chem.*, **26**, 4583 (1961), and references cited therein.

(3) E. L. Shapiro, M. Steinberg, D. Gould, M. J. Gentles, H. L. Herzog, M. Gilmore, W. Charney, E. B. Hershberg, and L. Mandel, *J. Amer. Chem. Soc.*, **81**, 6483 (1959).

(4) R. E. Beyler and F. Hoffman, *J. Org. Chem.*, **21**, 572 (1956).

(5) C. G. Bergstrom, U. S. Patent 2,703,799 (March 8, 1955); *Chem. Abstr.*, **50**, 1935 (1956).

(6) Fluorohydrin E (**11**) served as an intermediate for synthesis of 16β-fluoroprednisone, mp 243–246°, $[\alpha]^{25}D$ +108° ($CHCl_3$), using standard procedures (D. R. Hoff, J. K. Bennett, and G. E. Arth, unpublished). Entirely different syntheses of the closely related 16β-fluorohydrocortisone acetate and 16β-fluoroprednisolone acetate were subsequently disclosed by other workers.[7]

(7) (a) D. E. Ayer and M. P. Schneider, *J. Amer. Chem. Soc.*, **82**, 1249 (1960); (b) Fred Kagan, B. J. Magerlein, and R. D. Birkenmeyer, *J. Org. Chem.*, **28**, 3477 (1963).