BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 1820—1824 (1970)

Synthesis of Adamantane Derivatives. IX.[1] The Ritter Reaction of 1-Hydroxymethyladamantane with Acetonitrile

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(Received November 27, 1969)

The Ritter reactions of 1-hydroxymethyladamantane (**1**) and 3-homoadamantanol (**14**) with acetonitrile in concd. sulfuric acid were investigated. Two products, *N*-3-homoadamantyl acetamide (**2**) and *N*-1-adamantylmethyl acetamide (**3**) were isolated. Their total- and relative yields were determined in various reaction conditions by GLC analysis, indicating the facile conversion of *N*-3-homoadamantyl acetonitrilium cation (**12**) into *N*-1-adamantylmethyl acetonitrilium cation (**13**).

In contrast with numerous examples of the Ritter reactions of tertiary, secondary alcohols and their corresponding derivatives, there seem to be no reports concerning a similar reaction of aliphatic primary alcohols.[2] We wish to describe the results of the Ritter reaction of 1-hydroxymethyladamantane (**1**), regarded as one of the primary alcohols, and 3-homoadamantanol (**14**) in various conditions.

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[1] Preceding paper of this series: T. Sasaki, S. Eguchi and T. Toru, *J. Amer. Chem. Soc.*, **91**, 3390 (1969).

[2] a) L. I. Krimen and D. J. Cota, "The Ritter Reaction," in "Organic Reactions," Vol. 17, John Wiley & Sons, Inc., New York (1969), pp. 213—325; b) F. Johnson, "Heterocyclic Syntheses Involving Nitrilium Salts and Nitriles under Acidic Conditions," in "Advances in Heterocyclic Chemistry," Vol. 6, ed. by A. R. Katritzky and A. J. Boulton, Academic Press Inc., New York, N. Y. (1966), pp. 95—146; c) H. Stetter, J. Mayer, M. Schwarz and K. Wulff, *Chem. Ber.*, **93**, 226 (1960); T. Sasaki, S. Eguchi and T. Toru, This Bulletin, **41**, 236 (1968).

Stetter and his coworkers[3,4] have reported that both the Koch-Haaf carboxylation of **1** and the Demjanov reaction of 1-aminomethyladamantane afford the ring-expanded homoadamantyl derivatives at the sacrifice of the strain-free ring structure. On the contrary, the ring-contraction of homoadamantane to the strain-free adamantane ring system has also been described in the reaction of 3-homoadamantanol with hydrogen halide in acetic acid at 150°C to 1-hydroxymethyladamantane, though the simple bridgehead substitutions have been accomplished under the milder reaction conditions or with some other reagents, in the maintenance of the skeletal integrity of homoadamantane ring.[4] This delicate change in the reaction products might be effected by the presence of equilibrium between the primary adamantylcarbinyl cation and the tertiary homoadamantyl cation under the given reaction conditions. These problems in the solvolytic conditions have been extensively studied by Nordlander and Schleyer.[5] The Ritter reaction of **1** might provide a new synthetic method for *N*-3-homoadamantyl amide derivatives if the corresponding nitrilium cations are stable in the reaction conditions.

Results and Discussion

The Ritter reaction of **1** with acetonitrile in concd. sulfuric acid proceeded smoothly. However, the ring-expanded *N*-3-homoadamantyl acetamide **2** was produced only in low yields and the major product was *N*-1-adamantylmethyl acetamide **3**. The total yields and relative yields of the two prodcuts were dependent on reaction temperature and time (see Table 1).

$$\mathbf{1} \longrightarrow \mathbf{2} + \mathbf{3}$$

Product Analysis. The crude amide product obtained by the reaction of **1** with acetonitrile in sulfuric acid, followed by hydrolysis was purified on a silica-gel column to afford two kinds of crystalline amides, mp 138—139°C and 126—127°C to which the structures **2** and **3** were assigned respectively based on the following data. Both compounds gave satisfactory analytical results as that of $C_{13}H_{21}ON$. The IR absorption bands at 3330 (NH), 1640 (amide-I) and 1570 (amide-II) cm^{-1} for **2**, and 3300 (NH), 1640 (amide-I) and 1570 (amide-II) cm^{-1} for **3** indicate both compounds to be secondary amides. In the NMR spectrum of **2**, a signal assignable to methyl protons of acetamide moiety appeared at τ 8.05 superimposed to those of homoadamantane ring protons. However, in the NMR spectrum of **3**, a signal assignable to N–CH$_2$– protons appeared at τ 6.97 (2H) in a doublet with J=6.75 Hz and also the typical signals at τ 7.95, 8.22, and 8.41 due to 1-adamantyl ring protons besides that of –NHCOCH$_3$ protons at τ 7.93. The structures of **2** and **3** were further verified by comparison with specimens prepared by the following reaction sequences, **2** *via* 3-homoadamantylamine **7**[6] and **3** *via* 1-adamantylmethylamine **9**:[4]

Table 1. Reaction of **1** with acetonitrile in sulfuric acid*

Reaction temp.	Reaction time hr	Total yields of amides** %	Relative yields of **2** and **3**	
			2, %	**3**, %
room temp.	1	20	66	34
(*ca.* 15°C)	5	20	35	65
	12	50	15	85
	24	42	10	90
	48	51	16	84
50°C	1	40	2.9	97.1
	5	95	1.3	98.7
	12	92	1.9	98.1
	24	92	0.2	99.8

* A mixture of **1**(1.2 mmol) and acetonitrile (76.5 mmole) was added to stirred sulfuric acid (1.5 m*l*).

** Most of the other products were recovered **1**.

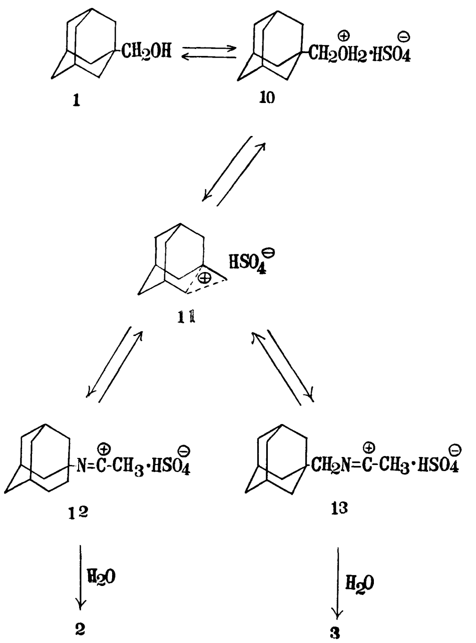

Chart I.

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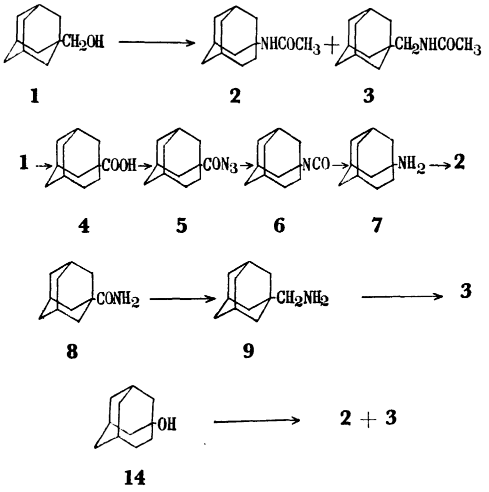
3) H. Stetter, M. Schwarz and A. Hirshhorn, *Chem. Ber.*, **92**, 1629 (1959).

4) H. Stetter and P. Goebel, *ibid.*, **96**, 550 (1963).

5) a) J. E. Nordlander, S. P. Jindal, P. von R. Schleyer, R. C. Fort, Jr., J. J. Harper and R. D. Nicholas, *J. Amer. Chem. Soc.*, **88**, 4475 (1966); b) S. H. Liggere, R. Sustmann, P. von R. Schleyer, *ibid.*, **91**, 4571 (1969).

6) J. R. Geigh A.-G., Belg. 661640 (1955); *Chem. Abstr.*, **65**, 10515d (1966).

1 → 4 → 5 → 6 → 7 → 2, 8 → 9 → 3.



Equilibrium Problem. As summarized in Table 1, the total and relative yields of **2** and **3** were much influenced by the reaction time and temperature even in the presence of excess acetonitriles. From these data, it can be concluded that with the prolonged reaction time, the total yields of amides increase but the relative amounts of **2** to **3** decrease rapidly. This tendency was also observed at 50°C and the total and relative yields at both temperatures reached approximately constant values after 12 and 5 hr respectively.

Formation of **2** and **3** could be visualized as shown in Chart I: the practical isolation of **2** and **3** indicates the formation of nitrilium cations **12** and **13**. However, there are two possibilities that **12** and **13** can be produced by the addition of acetonitrile to the corresponding carbonium ions, 1-adamantylcarbinyl- and 3-homoadamantyl cations respectively, which are derivable from **1** *via* **10**, and/or **12** and **13** by addition of acetonitrile to a bridged- or nonclassical cation. This was recently demonstrated to be an intermediate in solvolytic rearrangements of 1-adamantylcarbinyl tosylate and 3-homoadamantyl bromide.[5b)] Nonclassical form (**11**) is tentatively depicted in Chart 1. Our results indicate that the *N*-3-homoadamantyl acetonitrilium cation **12** is a kinetically controlled product and is converted gradually to the more stable *N*-1-admantylmethyl acetonitrilium cation **13**. The relative stability between 1-adamantylcarbinyl- and 3-homoadamantyl derivatives seems to be very much dependent on the substituents.[7)] In the Ritter reaction, the ring strain of **12** could not be compensated by the stabilizing effect of the tertiary carbon.

Another aspect of this Ritter reaction is manifested by the lower yields of the amides compared to higher yields of those for the typical tertiary adamantyl bromide in similar reaction conditions.[2c)] The reaction of 3-homoadamantanol **14** as the tertiary alcohol with excess acetonitrile in sulfuric acid was examined, the results of which are summarized in Table 2. Obviously, under the same conditions, **14**→**2**+**3**, higher total yields than those in the reaction of **1** were obtained, indicating the formation of the carbonium ion from **14** was more facile than from **1**.

TABLE 2. REACTION OF **14** WITH ACETONITRILE IN SULFURIC ACID*

Reaction temp.	Reaction time hr	Total yields of amides %	Relative yields of **2** and **3**	
			2, %	**3**, %
room temp. (*ca.* 15°C)	24	93	16.5	83.5
50°C	24	98	10	90

* A mixture of **14** (1.2 mmol) and acetonitrile (76.5 mmol) was added to stirred sulfuric acid (1.5 m*l*).

Effects of Addition of Other Lewis Acids. The results of the Ritter reactions of **1** and **14** in the presence of aluminum trichloride and/or boron trifluoride etherate in concd. sulfuric acid are summarized in Tables 3, 4 and 5. In the reaction of **1** using sulfuric acid-aluminum trichloride system, the relative yield of **2** to **3** was much higher than those in sulfuric acid after 24 hr.

It required about 4 days to obtain an approximately constant yield. The total and relative yields of amides were almost similar to those in sulfuric acid (Table 1). These results could be explained by weaker reactivity of the catalyst-system in which an acidic calcide like aluminum sulfate might be produced.[8)] Such supression of

TABLE 3. REACTION OF **1** WITH ACETONITRILE IN ALUMINUM TRICHLORIDE - SULFURIC ACID*

React. temp.	React. time hr	Total yields of amides %	Relative yields of **2** and **3**	
			2, %	**3**, %
room temp.	24	23	92	8
(*ca.* 15°C)	52	25	45	55
	96	42	17	83
50°C	12	52	13.5	86.5
	24	32	12	88
	48	45	9	91

* A mixture of **1** (1.2 mmol) and acetonitrile (76.5 mmol) was added to a stirred mixture of aluminum trichloride (0.6 g) and sulfuric acid (1.5 m*l*).

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7) R. C. Fort, Jr., and P. von R. Schleyer, *Chem. Rev.*, **64**, 277 (1964).

8) G. A. Olah, "Catalysts and Solvents," in "Friedel-Crafts and Related Reactions," Vol. I, ed. by G. A. Olah, Interscience Publishers, Inc., New York, N. Y. (1963), pp. 201—366.

Table 4. Reaction of **1** with acetonitrile in boron trifluoride etherate - sulfuric acid*

React. temp.	React. time hr	Total yields of amides %	Relative yields of **2** and **3**	
			2,%	**3**,%
room temp. (*ca.* 15°C)	24	24	12	88
	48	44	8.5	91.5

* A mixture of **1** (1.2 mmol) and acetonitrile (76.5 mmole) was added to a stirred mixture of boron trifluoride etherate (1.5 ml) and sulfuric acid (1.5 ml).

Table 5. Reaction of **14** with acetoniitrile in aluminum trichloride - sulfuric acid and boron trifluoride etherate - sulfuric acid at room temperature (*ca.* 15°C)

Catalyst system	React. time hr	Total yields of amides %	Relative yields of **2** and **3**	
			2,%	**3**,%
$AlCl_3$(0.6 g)-H_2SO_4(1.5 ml)	24	72	31	69
BF_3 etherate (1.5 ml)-H_2SO_4 (1.5 ml)	24	76	3	97

* A mixture of **14** (1.2 mmol) and acetonitrile (76.5 mmol) was added to the respective catalyst-system with stirring.

the rearrangement of **12** to **13** is interesting from the view point of preparation. The effects of addition of boron trifluoride etherate were different from those of the above system. The total yields were similarly as low as 24% after 24 hr at room temperature, but an extreme inclination of the products to **3** was observed. A mixture of boron trifluoride-sulfuric acid known as an effective mixed catalyst system for the Friedel-Crafts alkylation seems to have an ionized form.[8)] Therefore, the observed rapid establishment of the equilibrium could be ascribed to the increased dielectric property of the reaction system. Similar effects of addition of aluminum trichloride and boron trifluoride etherate were observed in the reactions of **14** (Table 5).

The reaction of **1** with acetonitrile in sulfuric acid-acetic acid afforded 1-adamantylcarbinyl acetate (52%), **2** (9%) and **3** (trace), but no trace of 3-homoadamantyl acetate could be detected by GLC analysis.

Other fuctionalized 1-adamantylmethyl systems like tosylate and bromide were stable in acetonitrile - sulfuric acid at room temperature, indicating the lower reactivity of adamantylcarbinyl system than that of 1-adamantyl system[2c)] in the Ritter reactions.

It should be mentioned that the Ritter reactions of **1** and **14** with acetonitrile afford both *N*-3-homoadamantyl acetamide (**2**) and *N*-1-adamantylmethyl acetamide (**3**) in contrast with the Koch-Haaf carboxylation of **1**, in which the exclusive formation of 3-homoadamantanecarboxylic acid is known,[3)] even though both reactions are performed in sulfuric acid. Interesting effects of aluminum trichloride for the Ritter reaction were observed, in which the kinetically controlled product **2** was obtained in 21—23% yields compared to *ca.* 10% yields in the reactions without aluminum trichloride.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus (hot-stage type) and are uncorrected. NMR spectra were determined on a JEOLCO MINMAR spectrometer at 60 MHz using TMS as an internal standard and infrared spectra, on a JASCO Model IR-S infrared spectrophotometer. GLC analysis was carried out on a Yanagimoto Gas Chromatograph Model GCG-220 and a Hitachi Gas Chromatograph Model K-23 using 2 m column packed with Apiezon-L and/or Silicone SE-30. Percentage composition of the products was estimated by relative peak area (uncorrected). For microanalyses a Yanagimoto Automatic C.H.N. Corder Model MT-1 was used.

General Procedure for the Ritter Reactions. A mixture of 1-adamantylmethyl alcohol **1**[3)] (0.2 g, 1.2 mmol) and/or 3-homoadamantanol **14**[5a)] (0.2 g, 1.2 mmol) and acetonitrile (4 ml, 76.5 mmol) was added slowly to stirred concd. sulfuric acid (sp. gr., *ca.* 1.84, 1.5 ml). After stirring was continued for an appropriate time, the reaction mixture was poured onto ice-water (*ca.* 300 g) and the resulting mixture was neutralized with 10% aqueous sodium hydroxide, extracted with ether (100 ml×4) and the ether extracts were washed with water (100 ml×2) and dried (Na_2SO_4). Removal of the solvent afforded crude amides as a mixture of **2** and **3**. The crude products were analyzed by GLC. The results are summarized in Tables 1—4.

Isolation of 3-Homoadamantyl Acetamide (2) and *N*-1-Adamantylmethyl Acetamide (3). Crude amides obtained from the reactions of **1** (0.5 g, 3.0 mmol) with acetonitrile (10 ml, 191 mmol) in concd. sulfuric acid (3.5 g) at room temperature (*ca.* 15°C) for 40 hr, were purified on a silica-gel (Mallinckrodt, 100 mesh) column eluting with chloroform. From the first fractions, 45 mg (7.7%) of **2** was obtained as colorless crystals, mp 138—139°C (*n*-hexane - acetone).

Found: C, 75.38; H, 9.95; N, 6.65%. Calcd for $C_{12}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76%.

From the second fractions, 215 mg (36.7%) of **3** was obtained as colorless crystals, mp 126—127°C (*n*-hexane - acetone).

Found: C, 75.61; H, 10.51; N, 6.78%. Calcd for $C_{12}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76%.

Both **2** and **3** were identified by mixed-melting points determination and by the complete superposition of their IR spectra on those of authentic samples.

Preparation of 3-Homoadamantylamine (7). Preparation of this amine has been described in a Patent[6)] *via* 3-homoadamantyl isocyanate (**6**) by using the Hofmann reaction of 3-homoadamantylcarboxamide. We prepared the amine similarly *via* **6**, though **6** was prepared by the Curtius reaction of 3-homoadamantylcarbonyl azide **5**, since the Hofmann reaction caused considerable side reactions lowering the yield of **7** in our experiments. A solution of sodium azide (5.5 g, 0.085 mol) in 14 m*l* of water was added to a stirred ice-cooled solution of 3-homoadamantylcarbonyl chloride[9] prepared from 1.7 g (8.75 mmol) of 3-homoadamantylcarboxylic acid **4** and thionyl chloride. After stirring was continued overnight at room temperature, the mixture was diluted with water and extracted with ether (100 m*l* × 3). The combined ether extracts were washed with water (30 m*l* × 2) and dried (Na_2SO_4), which gave crude azide **5** (1.7 g) as an oil after removal of the solvent under reduced pressure. **5** had strong IR absorption bands at 2150 ($-N_3$) and 1705 (C=O) cm^{-1}, and it was directly decomposed by heating under reflux in 50 m*l* of dry benzene for 2 hr. Removal of the solvent afforded 1.4 g (95%) of **6** as colorless crystals, mp 150—152°C (lit,[6] 144—146°C), which had strong IR absorption at 2280 (-N=C=O) cm^{-1}.

A mixture of 1.15 g (6.0 mmol) of **6**, 10 m*l* of dioxane and 20 m*l* of 2N hydrochloric acid was heated under reflux overnight. The cooled reaction mixture was made alkaline with 10% aqueous sodium hydroxide and extracted with ether. The work-up gave colorless crystals of **7** (0.9 g, 91%), mp 193—194°C (lit,[6] 191—193°C).

Acetylation of *N*-3-Homoadamantylamine (7). A mixture of **7** (0.2 g, 1.21 mmol), dry pyridine (2 m*l*) and acetic anhydride (0.2 g, 1.96 mmol) was stirred at room temperature overnight. Addition of water resulted in the precipitation of crystals of **2**, which were filtered and recrystallized from *n*-hexane to give 0.2 g (80%) of pure **2**, mp 138—139°C.

Preparation of *N*-1-Adamantylmethyl Acetamide (3). This was prepared similarly as above by acetylation of 1-adamantylmethylamine[4] with acetic anhydride in pyridine as colorless crystals, mp 126—127°C (*n*-hexane) in 70% yield.

The Ritter Reaction of 1 with Acetonitrile in Sulfuric Acid - Acetic Acid. A mixture of **1** (0.2 g, 1.2 mmol) and acetonitrile (4 m*l*, 76.5 mmol) was added to a stirred mixture of acetic acid (1.5 m*l*) and sulfuric acid (1.5 m*l*). The mixture was stirred for 48 hr at room temperature (*ca.* 15°C) and the work-up product was analyzed on GLC. For the analysis authentic specimens of 1-adamantylcarbinyl acetate and 3-homoadamantyl acetate[5a] were used.