# Synthesis of Adamantane Derivatives. II.[1] Preparation of Some Derivatives from Adamantylacetic Acid

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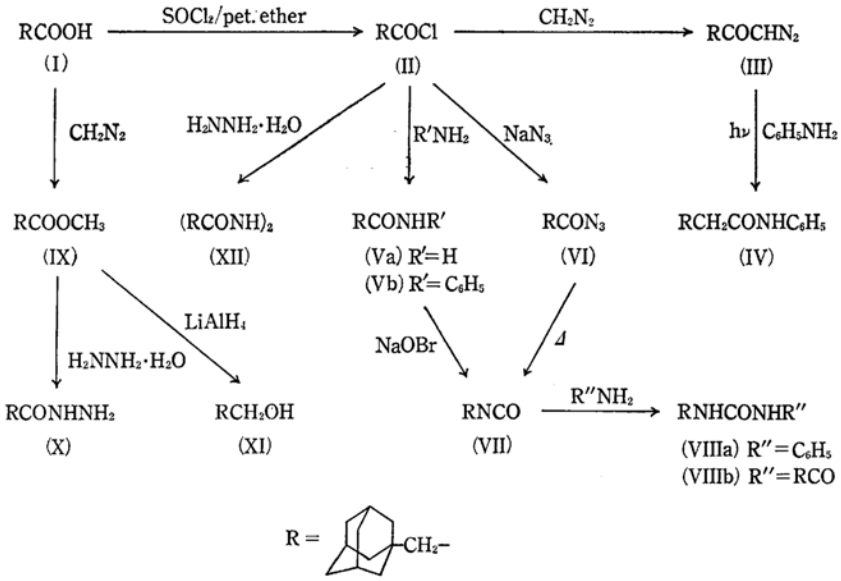
Adamantylacetic acid (I) was prepared in 1959 for the first time by Stetter and his co-workers[2] through the Arndt-Eistert rearrangement of the corresponding diazoketone; recently Bott and Hellmann[3] have prepared it in good yields directly from vinylidene chloride and 1-bromoadamantane, which is now commercially available.*1 The present paper will deal with the syntheses of some derivatives starting from adamantylacetic acid (I). Acid chloride II was obtained by stirring a mixture of I and thionyl chloride diluted with petroleum ether at room temperature for two days, since heating I with thionyl chloride without a solvent lowered the yield of II and some decomposition products were observed. II was an oily material exhibiting an infrared band at 1810 $cm^{-1}$ ($\nu_{CO}$) and was used for the following reactions directly, without any further purification.

The treatment of this crude II with an excess amount of ethereal diazomethane gave adamantyl acetyl diazomethane III as an oil ($\nu_{N_2}$ at 2160 $cm^{-1}$ and $\nu_{CO}$ at 1630 $cm^{-1}$), which was identified by the formation of adamantylpropionyl anilide IV, mp 154—155°C, after irradiation in the presence of aniline. The reaction of II with such amines as ammonia and aniline gave the corresponding amides, in those cases Va and Vb respectively, in good yields.

The Hofmann reaction of Va with bromine and alkali afforded crystalline solids with mps of

1) Part I: T. Sasaki, S. Eguchi and T. Toru, This Bulletin, **41**, 236 (1968).
2) H. Stetter, M. Schwarz and A. Hirschhorn, *Chem. Ber.*, **92**, 1629 (1959).
3) K. Bott and H. Hellmann, *Angew. Chem.*, **78**, 932 (1966).
*1 Aldrich Cat. No. 967 (1967).




Scheme 1. Reactions of adamantylacetic acid.

254—255°C (dec.) in 76.5% yield based on I. The structure of this compound was identified as VIIIb on the basis of the results of the microanalysis and the infrared spectrum. The formation of the isocyanate (VII) as an intermediate was confirmed by the appearance in the course of the reaction of a band at 2280 $cm^{-1}$ ($\nu_{NCO}$) in the infrared spectrum of the reaction mixture, but it could not be isolated.

On the contrary, this isocyanate (VII) could be separated as an oil ($\nu_{NCO}$ at 2280 $cm^{-1}$) in a good yield by the Curtius rearrangement of acid azide VI, which was easily obtainable as an oil ($\nu_{N_3}$ at 2150 $cm^{-1}$ and $\nu_{CO}$ at 1715 $cm^{-1}$) from II and sodium azide. The isocyanate structure of VII was confirmed by its conversion to the corresponding urea derivative, VIIIa, with aniline.

Acid chloride II and hydrazine hydrate afforded the corresponding bishydrazide XII, while methyl adamantylacetate IX and hydrazine hydrate gave monohydrazide X. The lithium aluminum hydride reduction of IX gave adamantylethanol XI with a mp of 73.5—75.0°C.

All of these results are summarized in Scheme 1.

## Experimental

Microanalyses were performed on a Yanagimoto C. H. N. Corder Model MT-1, while the IR spectra were obtained on a JASCO Model IR-S infrared spectrophotometer. All the melting points were measured on a Yanagimoto micromelting-point apparatus and have not been corrected.

**Adamantyl-1-acetamide (Va).** Concentrated aqueous ammonia (11.0 m*l*) was, over a period of 30 min, stirred, drop by drop, into a stirred solution of II, prepared from 1.0 g of I, in 4.0 m*l* of dry tetrahydrofuran under cooling with ice-water. The stirring was continued for 6 hr, and then crystalline precipitates were filtered out. The addition of water to the filtrate gave the second crop. The combined precipitates were washed with water and dried to give 740 mg (74%*2) of Va. Repeated recrystallizations from aqueous methanol gave an analytical sample with a mp of 180°C.

$\nu_{max}^{KBr}$ 3360 (NH), 3200 (NH), 1660 (amide-I) and 1628 (amide-II) $cm^{-1}$.

Found: C, 72.00; H, 9.82; N, 6.85%. Calcd for $C_{12}H_{19}ON \cdot \frac{1}{2}H_2O$: C, 71.24; H, 9.97; N, 6.92%.

**Hofmann Reaction of Va.** Into an ice-cooled bromine-alkali reagent, freshly prepared from 1.0 g of bromine, 1.0 g of sodium hydroxide, and 10 m*l* of water, 0.5 g of Va was stirred. The temperature was then slowly raised to 80°C over a 3.5-hr period and kept there for 10 min. After cooling, the separated solids were filtered and washed with water. Recrystallization from chloroform-petroleum ether (bp 38—65°C) gave pure VIIIb, 380 mg (76.5%*2), mp 254—255°C.

$\nu_{max}^{KBr}$ 3300 (NH), 3240 (NH), 3120 (NH), 1685 (amide-I) and 1565 (amide-II) $cm^{-1}$.

Found: C, 74.82; H, 9.56; N, 7.34%. Calcd for $C_{24}H_{36}O_2N_2$: C, 74.96; H, 9.44; N, 7.29%.

**Adamantyl-1-acetanilide (Vb).** A mixture of II, prepared from 0.5 g of I, 0.5 g of aniline, and 20 m*l* of dry benzene, was refluxed for 15 min. The cooled reaction mixture was washed with 5% hydrochloric acid and then with water, and dried over anhydrous sodium sulfate. After the removal of the solvent, the residue was recrystallized from methanol to give 0.4 g (71%*2) of Vb, mp 195—196°C.

$\nu_{max}^{KBr}$ 3280 (NH), 3050 (phenyl CH), 1660 (amide-I), 1605 (phenyl C=C) and 1548 (amide-II) $cm^{-1}$.

Found; C, 79.90; H, 8.22; N, 4.98%. Calcd for $C_{18}H_{23}ON$: C, 80.25; H, 8.61; N, 5.20%.

*2 All yields are based on I.

***N, N'* - Bisadamantyl - 1 - acetohydrazide (XII).** Into an ice-cooled solution of 1.6 g of 80% hydrazine hydrate in 1.0 m*l* of tetrahydrofuran was stirred and stirring was continued for 7 hr at room temperature, and then the mixture was allowed to stand in a refrigerator overnight. The deposited solids were then filtered and recrystallized from methanol to give pure XII, 380 mg (71%*2), mp 268—269°C.

$\nu_{max}^{KBr}$ 3200 (NH), 1680 (shoulder, CO), 1640 (shoulder, CO), 1610 (CO) and 1520 (NH) $cm^{-1}$.

Found: C, 74.51; H, 9.36; N, 7.20%. Calcd for $C_{24}H_{36}O_2N_2$: C, 74.96; H, 9.44; N, 7.29%.

**Acid Azide VI and Its Curtius Rearrangement.** Into a solution of II, prepared from 0.5 g of I, in 2 m*l* of acetone, a solution of 2.0 g of sodium azide in 5 m*l* of water was stirred. Stirring was continued for 2 hr at room temperature. The reaction mixture was then diluted with 15 m*l* of water and extracted with ether (30 m*l*×2). The combined ether extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to give an oil which had an infrared band at 2290 $cm^{-1}$ (weak, $\nu_{NCO}$) as well as one at 2160 $cm^{-1}$ (strong, $\nu_{N_3}$); the appearance of the former band shows that the rearrangement had already occurred during the procedure. To complete the rearrangement, this crude azide was heated in dry benzene for 1 hr. The infrared spectrum of the oil after the removal of the solvent had a very strong band at 2290 $cm^{-1}$ ($\nu_{NCO}$), while the band at 2160 $cm^{-1}$ ($\nu_{N_3}$) had almost completely disappeared.

A half amount of this oil was treated with 0.15 m*l* of aniline in *n*-hexane at room temperature for 13 hr. The precipitates were then filtered to give 200 mg (55%*2) of crude VIIIa. Recrystallization from methanol gave an analytical sample, mp 172—173°C.

$\nu_{max}^{KBr}$ 3340 (NH), 3050 (phenyl CH), 1645 (amide-I) and 1570 (amide-II) $cm^{-1}$.

Found: C, 75.91; H, 8.78; N, 10.01%. Calcd for $C_{18}H_{24}ON_2$: C, 76.02; H, 8.51; N, 9.85%.

**Adamantyl-1-propionanilide (IV).** A solution of II, prepared from 0.5 g of I, in 10 m*l* of ether was added to a solution of diazomethane in 100 m*l* of ether under ice-water cooling, after which the reaction mixture was allowed to stand for two days at room temperature. The solvent was stripped off *in vacuo*, and the residual oil, III, was characterized as having a diazoketone structure on the basis of the infrared absorptions at 2100 ($\nu_{N_2}$) and 1625 ($\nu_{CO}$) $cm^{-1}$. III and 0.7 g of aniline were dissolved in 100 m*l* of anhydrous benzene, and the mixture was irradiated with a 100-W high-pressure mercury lamp (Ushio, UM-102) through a quartz cooler in a nitrogen stream at room temperature. After 9 hrs' irradiation, the solution was washed successively with 10% hydrochloric acid, 5% sodium hydroxide, and then water. The solution was dried over anhydrous sodium sulfate, and the benzene was distilled off *in vacuo*. The residual brown oil was triturated with 10 m*l* of *n*-hexane to give white crystals. The isolated solids were dissolved in 50 m*l* of ethanol, and the solution was treated with active charcoal. The solvent was distilled off *in vacuo*, and the residue was recrystallized from methanol to afford colorless needles, 100 mg (14%*2), mp 154—155°C.

$\nu_{max}^{KBr}$ 3240 (NH), 3029 (phenyl CH), 1655 (amide-I), 1600 (phenyl C–C) and 1555 (amide-II) $cm^{-1}$.

Found: C, 80.32; H, 8.74; N, 5.06%. Calcd for $C_{19}H_{25}ON$: C, 80.52; H, 8.89; N, 4.94%.

**Adamantyl-1-ethanol (XI) from I *via* IX.** To an ethereal solution of diazomethane, a solution of 0.5 g of I in 20 m*l* of ether was gradually added. The solution was allowed to stand overnight at room temperature, and then the ether was removed *in vacuo* to give a colorless oil, which was characterized as IX on the basis of the infrared band at 1730 ($\nu_{CO}$) $cm^{-1}$. All of this oil was dissolved in 50 m*l* of dry ether, and then 1.1 g of lithium aluminum hydride was added to the solution. The reaction mixture was then stirred overnight at room temperature and diluted with 50 m*l* of water. The aqueous solution was acidified with concentrated hydrochloric acid and extracted with ether. The ether extract was washed with water and dried over anhydrous sodium sulfate. The ether was removed to give colorless crystals, 340 mg (73.2%*2). Recrystallization from *n*-hexane gave an analytical sample, mp 73.5—75.0°C.

$\nu_{max}^{KBr}$ 3300 (OH), and 1047 (CO) $cm^{-1}$.

Found: C, 79.91; H, 11.11%. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18%.

**Adamantyl-1-acetohydrazide (X).** A mixture of the crude methyl ester, prepared from 0.5 g of I, 0.2 m*l* of 80% hydrazine hydrate and 0.2 m*l* of water, was heated at 95—100°C for 9 hr and then at 110—120°C for 1 day in a sealed tube. After cooling, a 50 m*l* portion of water was added to the reaction mixture and the separared crystals were filtered and recrystallized from methanol to give white granular crystals of X, 390 mg (73%*2), mp 113—118°C.

$\nu_{max}^{KBr}$ 3280 (NH), 1640 (amide-I) and 1520 (amide-II) $cm^{-1}$.

Found: C, 68.85; H, 10.11; N, 13.04%. Calcd for $C_{12}H_{20}ON_2$: C, 69.19; H, 9.68; N, 13.45%.