

## The Adamantyl Group in Medicinal Agents.

### I. Hypoglycemic N-Arylsulfonyl-N'-adamantylureas

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In order to evaluate the pharmacodynamic potential of the symmetrical, lipophilic adamantyl group, a limited number of N-arylsulfonyl-N'-adamantylureas were prepared for evaluation as hypoglycemic agents. N-p-Tolylsulfonyl-N'-1-adamantylurea—the adamantyl analog of tolbutamide—was found to be one of the most potent oral agents synthesized thus far.

The pronounced lipophilic nature associated with the compact, highly symmetrical architecture of the adamantane molecule<sup>1</sup> invites a study of its influence on characteristics and biological potential of compounds which contain this unique hydrocarbon moiety.

Such a study has now become possible as a result of Schleyer's startling discovery of a direct synthesis<sup>2</sup> of adamantane and of Stetter's extensive exploration<sup>3</sup> of its functional derivatives.

As a first situation in which to assess the possible pharmacodynamic effects of the adamantyl group we selected the complex structure-activity relationships existing within the class of orally active hypoglycemic sulfonylureas.<sup>4</sup> In the series of N-arylsulfonyl-N'-alkylureas, according to previous experience in our laboratories, the alkyl group may be varied widely with maintenance of activity and the inclusion of cyclohexyl and cycloheptyl radicals frequently has produced agents of maximum efficacy.<sup>5</sup> If the influence of the adamantyl group were indeed to be a beneficial one, the synthesis and pharmacological evaluation of N-p-tolylsulfonyl-N'-1-adamantylurea and closely related analogs would provide an initial test of this possibility.



The analogs studied were primarily designed to assess the effect of (a) substituents on the phenyl ring, (b) substituents on the adamantyl radical, and (c) the position, on a secondary or tertiary carbon, of the ureido group on the adamantane skeleton.

The synthesis of these analogs (see Table I) involved the previously described condensation<sup>6</sup> of the appropriately substituted ethyl N-arylsulfonylcarbamates<sup>6</sup> with the desired aminoadamantanes. Adamantyl-1-amine<sup>7</sup> and *dl*-adamantyl-2-amine<sup>8</sup> have been reported.<sup>9</sup> Reduction of adamantane-1-carboxamide<sup>7</sup>

(1) S. Landa, V. Machacek, and J. Mzourek, *Chem. Listy*, **27**, 415, 443 (1933).

(2) F. von R. Schleyer and M. M. Donaldson, *J. Am. Chem. Soc.*, **82**, 4645 (1960).

(3) H. Stetter, *Angew. Chem.*, **74**, 301 (1962).

(4) L. J. P. Duncan and J. D. Baird, *Pharmacol. Rev.*, **12**, 91 (1960).

(5) F. J. Marshall, M. V. Sigal, Jr., H. R. Sullivan, C. Cosnik, and M. A. Root, *J. Med. Chem.*, **6**, 60 (1963).

(6) F. J. Marshall and M. V. Sigal, Jr., *J. Org. Chem.*, **23**, 927 (1958).

(7) H. Stetter, J. Mayer, M. Schwarz, and K. Wulff, *Chem. Ber.*, **93**, 226 (1960).

(8) G. W. Smith and H. D. Williams, *J. Org. Chem.*, **25**, 2207 (1961).

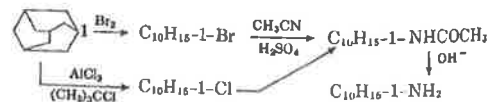
(9) The starting material required for the preparation of adamantyl-2-amine, namely adamantanone [F. von R. Schleyer and R. D. Nicholas, *J. Am. Chem. Soc.*, **83**, 182 (1961)] was kindly prepared for us by Dr. Donald L. Heywood, Union Carbide Chemicals Co., South Charleston, West Virginia.

with lithium aluminum hydride gave 1-aminomethyladamantane which was used for the preparation of the compounds XIX and XX with a methylene bridge between the N'-atom and the adamantyl function.

3-Methyladamantyl-1-amine (for XVII) and 3,5-dimethyladamantyl-1-amine (for XVIII) were prepared from 1-methyl- and 1,3-dimethyladamantane,<sup>10</sup> respectively, according to Stetter's procedure<sup>3,11</sup> for adamantyl-1-amine. This procedure involves as a first step the conversion of the hydrocarbon to the tertiary bromide with excess bromine. In the latter case the tertiary nature of the bromide and the absence of skeletal rearrangements in this and subsequent conversions to the amine has been well established.

By analogy, a similar bromination of 1-methyl- and 1,3-dimethyladamantane may be expected to give the tertiary derivatives also, and the nuclear magnetic resonance spectra of the respective bromides were found to support this structural assignment. The hydrogens of the methyl groups all appear as single peaks with the expected frequency ( $\tau = 9.17$ , relative to tetramethylsilane). The remaining protons were accounted for in multiplets at about  $\tau 8$  and the absence of peaks at  $\tau 5.8$ , typical for a proton in the function -CHBr- (cyclohexyl bromide), is further evidence for the tertiary nature of the bromides.

For the preparation of adamantyl-1-amine on a larger scale the use of bromine as a solvent in the foregoing procedure proved impractical. Instead, a mixture of adamantane and *t*-butyl chloride was treated with catalytic amounts of aluminum chloride (see Experimental) to give a high yield of adamantyl-1-chloride which, without further purification, was converted to the amine through the acetamido intermediate.



The various arylsulfonylalkylureas were produced without difficulty by carrying out the condensation of carbamates and amines in hot toluene. Occasionally, however, as observed previously,<sup>5</sup> the product obtained lacked stability in hot ethanol, used for recrystalliza-

(10) P. von R. Schleyer and R. D. Nicholas, *Tetrahedron Letters*, No. 4, 305 (1961).

(11) (a) H. Stetter, M. Schwarz, and A. Hirschhorn, *Angew. Chem.*, **71**, 429 (1959); (b) H. Stetter, M. Schwarz, and A. Hirschhorn, *Chem. Ber.*, **94**, 1620 (1961).

TABLE I  
 SUBSTITUTED N-ARYLSULFONYLUREAS, ArSO<sub>2</sub>NHCONHR

No.	Aryl subst. phenyl	R	Relative potency	M.p., °C.	Formula	% Calcd.			% Found		
						C	H	N	C	H	N
I	4-CH <sub>3</sub> -	<i>n</i> -Butyl <sup>a</sup>	1								
II	4-CH <sub>3</sub> -	Adamantyl-1	15.5	172-174	C <sub>18</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub> S	62.04	6.94	8.04	61.96	6.72	7.84
III	4-CH <sub>3</sub> -	Cyclohexyl <sup>b</sup>	12.8								
IV	4-C <sub>2</sub> H <sub>5</sub> -	Adamantyl-1	14.8	153-155	C <sub>19</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub> S	62.95	7.23	7.73	63.13	7.39	7.81
V	4-C <sub>2</sub> H <sub>5</sub> -	Cyclohexyl <sup>c</sup>	9.3								
VI	4-CH <sub>2</sub> S-	Adamantyl-1	8.7	155-158	C <sub>18</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub> S <sub>2</sub>	56.81	6.36	7.36	56.78	5.87	7.28
VII	4-CH <sub>2</sub> S-	Cyclohexyl <sup>d</sup>	4.1								
VIII	4-Cl-	<i>n</i> -Propyl <sup>d</sup>	2.1								
IX	4-Cl-	Adamantyl-1	5.1	150-151	C <sub>17</sub> H <sub>21</sub> ClN <sub>2</sub> O <sub>2</sub> S	55.35	5.74	7.54	55.89	6.04	7.37
X	4-Cl-	Cyclohexyl <sup>e</sup>	5.6								
XI	4- <i>i</i> -C <sub>3</sub> H <sub>7</sub> -	Adamantyl-1	2.9	190-192	C <sub>20</sub> H <sub>28</sub> N <sub>2</sub> O <sub>2</sub> S	63.80	7.50		63.61	7.62	
XII	4-CH <sub>2</sub> CO-	Adamantyl-1	1.6	163-165	C <sub>19</sub> H <sub>24</sub> N <sub>2</sub> O <sub>4</sub> S			7.44			7.71
XIII	4-CH <sub>2</sub> CO-	Cyclohexyl <sup>c</sup>	4.0								
XIV	4-CH <sub>3</sub> , 3-NH <sub>2</sub> -	Adamantyl-1	0	175 dec.	C <sub>18</sub> H <sub>23</sub> N <sub>2</sub> O <sub>2</sub> S	59.48	6.93		59.84	7.02	
XV	4-CH <sub>3</sub> , 3-NH <sub>2</sub> -	Cyclohexyl <sup>f</sup>	5.0								
II	4-CH <sub>3</sub> -	Adamantyl-1 <sup>g</sup>	15.4								
XVI	4-CH <sub>3</sub> -	Adamantyl-2	4.0	206-208	C <sub>18</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub> S	62.04	6.94	8.04	62.19	7.04	7.71
XVII	4-CH <sub>3</sub> -	3-Methyladaman- tyl-1	2.8	184-186	C <sub>19</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub> S	62.95	7.23	7.73	62.86	7.17	7.81
XVIII	4-CH <sub>3</sub> -	3,5-Dimethylada- mantyl-1	0	166-168	C <sub>20</sub> H <sub>28</sub> N <sub>2</sub> O <sub>2</sub> S			7.44			7.30
IV	4-C <sub>2</sub> H <sub>5</sub> -	Adamantyl-1 <sup>g</sup>	14.8								
XIX	4-C <sub>2</sub> H <sub>5</sub> -	Adamantyl-1-CH <sub>2</sub> -	0.2	203-205	C <sub>20</sub> H <sub>28</sub> N <sub>2</sub> O <sub>2</sub> S	63.80	7.50	7.44	63.87	7.50	7.56
XII	4-CH <sub>2</sub> CO-	Adamantyl-1 <sup>g</sup>	1.6								
XX	4-CH <sub>2</sub> CO-	Adamantyl-1-CH <sub>2</sub> -	0	204-206	C <sub>20</sub> H <sub>28</sub> N <sub>2</sub> O <sub>4</sub> S			7.17			6.97

<sup>a</sup> Tolbutamide (ref. 14). <sup>b</sup> Toleyclamide: J. J. Paullada and J. L. del Villar, *Metabolism*, 10, 221 (1961). <sup>c</sup> See ref. 5; XIII is acetohexamide. <sup>d</sup> See ref. 6; VII is thiohexamide, VIII is chlorpropamide. <sup>e</sup> British Patent 808,073; *Chem. Abstr.* 53, 12241a (1959). <sup>f</sup> Metahexamide, C. F. Boehringer and Soehne, Mannheim, Waldhof, Germany. <sup>g</sup> II, IV, and XII are repeated for ease of comparison with the N'-analogs. <sup>h</sup> II, IV, XVI, XVII, XVIII, and XIX were recrystallized from chloroform-Skelly B (petroleum ether, b.p. 60-71°); VI, IX, XI, XII, XIV, and XX from methanol.

tion. The reformed amine, resulting from a partial breakdown, combined with the remaining sulfonylurea to form an insoluble salt.

This problem required special attention in the case of preparations of N-*p*-tolylsulfonyl-N'-1-adamantylurea (II) on a larger scale. In an effort to find a suitable solvent for the recrystallization of II, toluene proved impractical because of extensive solvation which required prolonged heating at 120° to remove last traces of solvent. Recrystallization from chloroform-petroleum ether (b.p. 60-71°) was carried out successfully only after it was discovered that traces of alcohol present in chloroform must be removed by shaking with alumina.

**Pharmacological Evaluation.**—The hypoglycemic activities of the new sulfonylureas are listed in terms of relative potency in Table I together with some reference compounds reported previously.<sup>5</sup>

All compounds were tested in normal male rats of a strain derived from Wistar stock. The rats were fasted 18 hr. and the compounds were administered by stomach tube as a suspension in a 5% solution of acacia. Each rat was used only once. Blood glucose concentrations were determined in the autoanalyzer<sup>12</sup> on samples of blood obtained from the tail veins before and at 1, 2, 3, 5, and 7 hr. after drug administration. Each compound was tested at 3 or 4 doses between 5 and 100 mg./kg. and each dose was administered to from 6 to 18 rats. The relative hypoglycemic potency of the compounds was calculated by the method previously described.<sup>13</sup> This method for calculating relative hypo-

glycemic potency includes the degree as well as the duration of the activity produced. Therefore, increased potency as expressed here may be due to a greater fall in blood glucose, to a more prolonged fall, or to a combination of both parameters. The value for relative potency given has been expressed in relation to the hypoglycemic activity of tolbutamide<sup>14</sup> (I) which has been assigned the potency of 1.0.

An examination of the relative potencies listed in Table I reveals that N-*p*-tolylsulfonyl-N'-1-adamantylurea (II) and the *p*-ethylphenyl analog IV are approximately 15 times as active as tolbutamide (I, N-*p*-tolylsulfonyl-N'-*n*-butylurea) on a weight basis. Both compounds are also somewhat more potent, 1.2 and 1.6 times, respectively, than their N'-cyclohexyl analogs<sup>5</sup> III and V which, thus far, are among the most active hypoglycemic agents of this type.

It is of interest to note the time course (Fig. 1) of glucose levels for the pair II and III. During the first 3 hr. after drug administration the decrease in blood glucose level attained with N-*p*-tolylsulfonyl-N'-cyclohexylurea (III) is actually greater than that attained by the N'-adamantyl compound II, but the prolonged hypoglycemic activity of II reverses this relation during the final 3 hr. of the observation period.

A striking feature is the constancy of glucose levels attained with a single dose of the adamantyl compound II. These levels vary less than 10 mg./100 over a 6-hr. period while the cyclohexyl compound III varies over a range of 35 mg./100.

It is further noted that changes in the structure of II, be it in the nature of the phenyl substitution or in

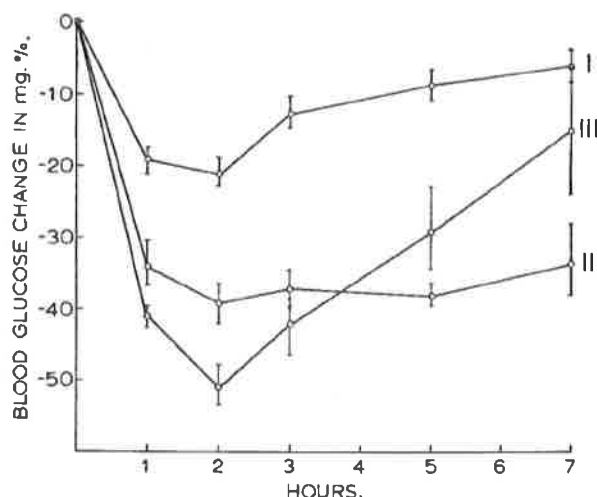


Fig. 1.—Hypoglycemic activity at a dose orally of 25 mg./kg. for tolbutamide (I), *N-p*-tolylsulfonyl-*N'*-adamantylurea (II), and *N-p*-tolylsulfonyl-*N'*-cyclohexylurea (III). The individual points show the mean glucose levels at the time indicated, while the bars represent the standard errors of these mean values.

the adamantyl group, invariably result in lowered potency. Thus, replacement of the *p*-methyl substituent of II by  $\text{CH}_2\text{S}$ - (VI), Cl- (IX), *i*- $\text{C}_6\text{H}_7$ - (XI), and  $\text{CH}_2\text{CO}$ - (XII) leads to compounds of progressively lower activity, while the 4-methyl-3-aminophenyl analog XIV is without noticeable activity at the highest dose level tested (100 mg./kg.).

Also, what would appear to be minor changes in the adamantyl moiety do cause a sharp reduction in potency. For example, the introduction of a single methyl substituent, as in XVII, reduces the potency drastically. Two methyl substituents (in XVIII) virtually abolish activity. A great reduction in potency results from the insertion of a methylene bridge between the *N'*-atom and the adamantane fragment as in XIX and in XX.

As adamantyl-2-amine (in XVI) differs from the 1-isomer merely in the orientation of the C-N bond relative to the "spherical" carbon skeleton, the strongly reduced activity of XVI—about 25% of II—is surprising indeed.

It is obvious that the activity profile in the rat observed for the adamantane-containing compounds is a composite of (a) their absorption characteristics, (b) their metabolic disposition, and (c) the precision with which they fit at the receptor site. Which of these factors is primarily responsible for the favorable activity of the *N'*-1-adamantyl compound II can only be decided on the basis of future experimentation. It seems of interest to study the pharmacodynamic influence of the 1-adamantyl group in other selected cases. Work now in progress in our laboratories to verify this assumption will be the subject of subsequent publications.

**Toxicological and Clinical Observations.**—In view of the favorable hypoglycemic activity observed in rats with *N-p*-tolylsulfonyl-*N'*-1-adamantylurea (II) toxicological studies<sup>15</sup> were undertaken in anticipation of clinical investigation<sup>16</sup> of this agent.

(15) We are indebted to Dr. R. C. Anderson and H. M. Worth, Division of Toxicology of The Lilly Research Laboratories, for the report on acute and chronic toxicity.

A single oral dose of 2.0 g./kg. given to 35 normal mice of both sexes did not kill any of the animals either immediately or during the 7 days following drug administration. At no time did these animals show any toxic effects from the drug. Larger doses were not administered.

Groups of six normal male and six normal female rats fed for one month on a standard diet containing this drug at a concentration such that the daily intake of drug averaged 1 g./kg. gained weight slightly less rapidly than did the rats in control groups not receiving the drug. At the end of the month of treatment all animals were killed and the organs and tissues were examined for pathological changes. No changes were noted except for a slight degranulation of the  $\beta$  cells of the pancreatic islets. All of the hypoglycemic sulfonylurea compounds which have been studied extensively produce  $\beta$  cell degranulation.

Dogs were treated for 232 days by the oral route with daily doses as high as 100 mg./kg. Aside from a slight elevation of the serum alkaline phosphatase levels in the dogs given the highest dose, no unusual changes were observed throughout the experiment. At necropsy there were no abnormalities in the organs or tissues that could be attributed to the administered drug.

At the time of the preparation of this manuscript, information on preliminary clinical studies of II was available. In one phase of these studies<sup>16</sup> thirty adult diabetics were managed with the drug and observed for periods varying from 8 to 12 weeks. The patients were grouped according to their prior therapy, if any, in order that a comparison with existing hypoglycemic agents could be made.

The data obtained thus far indicate II to be a most satisfactory, potent oral hypoglycemic agent with an effective average dose, single or divided, of 400 mg./day. Equal to chlorpropamide<sup>5</sup> on a weight basis, the drug II possesses about five times the potency of tolbutamide.<sup>14</sup> The activity of II is rapid in onset with a tentative duration of 4–6 hr., indicating that the drug is rapidly absorbed and utilized by the body.

## Experimental

Because of the tendency of most adamantane derivatives to sublime, melting points were commonly taken in sealed, submerged capillary tubes. Generally speaking, melting point determinations were less conclusive than the comparison of X-ray diffraction patterns and vapor-phase chromatographic behavior.

**Adamantyl Amines.** 1-Aminomethyladamantane.<sup>17</sup>—A solution of 9 g. (0.05 mole) of adamantane-1-carboxamide<sup>7</sup> in 200 ml. of dry ether was added dropwise to a well stirred suspension of 10 g. (0.26 mole) of lithium aluminum hydride in 500 ml. of dry ether. The reaction was carried out in a three-necked, round-bottom flask equipped with a mechanical stirrer in a close-fitting socket and an efficient water-cooled condenser. After the addition had been completed, the reaction mixture was heated under reflux for 4 hr. The well agitated mixture was then cooled to  $-5^\circ$ , and 10 ml. of water was added dropwise, followed by 30 ml. of a 10% sodium hydroxide solution, and, finally, 10 ml. of water.

The precipitated solids were removed by filtration and washed with 500 ml. of ether. The combined ether layers were dried with anhydrous magnesium sulfate and concentrated to dryness.

(16) The clinical studies were performed in two parts: (a) At The Lilly Research Laboratories under the direction of William R. Kirtley, M.D., assistant director for Clinical Research, and (b) under the direction of Robert S. Radding, M.D., at the Metabolic Research Foundation, 6615 Travis Street, Houston, Texas.

(17) After our work was concluded the preparation of this amine was re-

under reduced pressure. The residue was taken up in 50 ml. of dry ether, filtered from a small amount of insoluble material, and treated with dry hydrogen chloride gas. The precipitated hydrochloride salt was recrystallized from ethanol to give 7 g. (70%) of white product, m.p. 320°.

*Anal.* Calcd. for  $C_{11}H_{20}ClN$ : C, 65.49; H, 9.99; N, 6.94. Found: C, 65.35; H, 10.01; N, 6.83.

**3-Methyladamantyl-1-amine. 3-Methyladamantyl 1-Bromide.**—The bromination of 1-methyladamantane<sup>10</sup> was carried out by the procedure reported for adamantyl 1-bromide<sup>11</sup> and gave the product as a distillable oil, b.p. 65–67° (0.05 mm.), in a yield of 93%.

*Anal.* Calcd. for  $C_{11}H_{17}Br$ : C, 57.65; H, 7.48; Br, 34.87. Found: C, 57.85; H, 7.61; Br, 35.27.

**1-Acetamido-3-methyladamantane.**—The crude amide, prepared from the bromide by the  $CH_3CN-H_2SO_4$  procedure,<sup>7</sup> was purified by sublimation at 90–100° (0.05 mm.). The amide melted at 108–109°.

*Anal.* Calcd. for  $C_{13}H_{21}NO$ : N, 6.76. Found: N, 6.88.

**3-Methyladamantyl-1-amine Hydrochloride.**—Deacetylation by potassium hydroxide in diethylene glycol<sup>7</sup> and ether extraction gave a solution of the amine which by infrared spectral analysis was found to contain approximately 5% of unchanged starting amide. The hydrochloride, prepared in ether solution with dry hydrogen chloride gas, was obtained in 87% yield and melted at 295–300°. The over-all yield from 1-methyladamantane was 81%.

*Anal.* Calcd. for  $C_{11}H_{20}ClN$ : Cl, 17.62; N, 6.94. Found: Cl, 17.77; N, 6.78.

**3,5-Dimethyladamantyl-1-amine. 3,5-Dimethyladamantyl 1-bromide** was prepared, as previously described, from 1,3-dimethyladamantane<sup>10</sup> in 77.5% yield as a light yellow oil,  $n_D^{20}$  1.5178, b.p. 67–69° (0.03 mm.).

*Anal.* Calcd. for  $C_{13}H_{19}Br$ : C, 59.26; H, 7.80; N, 6.33. Found: C, 59.89; H, 8.10; N, 32.38.

**1-Acetamido-3,5-dimethyladamantane** was prepared, as previously described, from the bromide in 96% yield of crude product. Purification of a sample by sublimation gave the amide, melting at 80–82°.

*Anal.* Calcd. for  $C_{15}H_{23}NO$ : C, 57.97; H, 10.47; N, 6.33. Found: C, 75.54; H, 10.49; N, 6.41.

**3,5-Dimethyladamantyl-1-amine** was obtained by alkaline hydrolysis from the crude amide and was isolated as the hydrochloride salt, m.p. 290–295°, in a yield of 87%. The over-all yield based on 1,3-dimethyladamantane amounted to 63%.

*Anal.* Calcd. for  $C_{13}H_{20}ClN$ : N, 6.46. Found: N, 6.51.

**Adamantyl-1-amine via Adamantyl 1-Chloride.**—A solution of 100 g. (0.74 mole) of adamantane<sup>2</sup> and 100 ml. (85 g., 0.92 mole) of *t*-butyl chloride in 400 ml. of anhydrous cyclohexane was prepared in a 1-l., three-necked, round-bottom flask fitted with a thermometer, mechanical stirrer with close-fitting socket, and gas exhaust tube leading to a bubbler submerged in water. The catalyst, aluminum chloride (total 4.6 g., 0.06 mole), was added in batches of 0.5 g. at regular intervals over a period of 8 hr. Progress of the reaction was followed conveniently by the rate of escaping isobutane gas. Upon completion of the reaction, 100 ml. of *N* hydrochloric acid solution was added with vigorous stirring, followed by 500 ml. of ether. The organic layer was separated, first extracted with 50 ml. of cold water, then with 50 ml. of a 5% sodium bicarbonate solution, and finally dried with the aid of anhydrous calcium chloride. After removal of the solvents under reduced pressure there remained 115 g. (93%) of crude product

melting at 152–156° (lit.<sup>7</sup> m.p. 165°). Vapor chromatographic analysis of this material revealed a composition of 90–95% of adamantyl 1-chloride and 5–10% of adamantane. Recrystallization of a sample of this material from ethanol at –50° gave pure adamantyl 1-chloride which was found to be identical with an authentic sample<sup>7</sup> by mixture melting point determination and by X-ray diffraction patterns.

*Anal.* Calcd. for  $C_{10}H_{15}Cl$ : C, 70.37; H, 8.86; Cl, 20.76. Found: C, 76.22; H, 8.96; Cl, 20.69.

The crude product was converted, without further purification, by the acetonitrile-sulfuric acid procedure to 1-acetamidoadamantane,<sup>7</sup> melting at 144–146° (lit. m.p. 149°). Recrystallization from ethanol gave the pure amide, m.p. 147–149°, identical with an authentic sample by mixture melting point and X-ray diffraction pattern. The crude amide (108 g., 83%), again without prior purification, was saponified<sup>7</sup> and pure adamantylamine (m.p. 160–200°, reported 160–190°) was isolated in an over-all yield of 60% (51 g.) based on adamantane.

**N-Aryl-N'-adamantylsulfonureas.**—The preparation of the new ureas reported followed the published procedure<sup>8</sup> and will be exemplified in detail for compound II.

**N- $\gamma$ -Tolylsulfonyl-N'-1-adamantylurea (II).**—A solution of 302.5 g. (2 moles) of 1-aminoadamantane and 535 g. (2.2 moles) of ethyl N-(4-methylphenylsulfonyl) carbamate<sup>8</sup> in 6 l. of dry toluene was heated under reflux for 5 hr. The reaction mixture was allowed to cool to room temperature, and the crystalline product was collected by filtration and then dissolved without the application of heat in about 2 l. of chloroform which had previously been shaken with 50 g. of alumina to remove traces (0.54%) of ethanol. The chloroform solution was washed with a total of 1600 ml. of cold 5% hydrochloric acid solution, then with water until neutral, and dried with the aid of anhydrous magnesium sulfate. The chloroform solution was concentrated under reduced pressure to about one-half its volume, warmed to about 50°, and hot Skelly B (petroleum-ether, b.p. 60–71°) was added to start crystallization. After chilling the mixture overnight the crystals were isolated by filtration to give 400 g. of product melting at 175–179°. Two further recrystallizations from purified chloroform-Skelly B gave 356 g. (51%) of final product II, melting at 178–179°.

*Anal.* Calcd. for  $C_{18}H_{26}N_2O_2S$ : C, 62.04; H, 6.94; N, 8.04; mol. wt., 348.5. Found: C, 61.96; H, 6.72; N, 7.84; mol. wt. (electrometric titration in 66% dimethylformamide,  $pK_a$  7.98), 350.

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