The Adamantyl Group in Medicinal Agents. IV. Sedative Action of 3,5,7-Trimethyladamantane-1-carboxamide[1] and Related Agents

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3,5,7-Trimethyladamantane-1-carboxylic acid (III) was prepared in 90–95% yield by fusion of the corresponding bromide (I) with acetamide and treatment of the resulting acetamido-3,5,7-trimethyladamantane (IIa) in H_2SO_4 with HCOOH. The sedative activity in mice of 3,5,7-trimethyladamantane-1-carboxamide (IVa) and of additional adamantane and mono-, di-, and trimethylated adamantane derivatives is reported. The pattern of structure–activity relationships observed for these compounds is contrasted with that noted among previously described adamantane-containing agents.

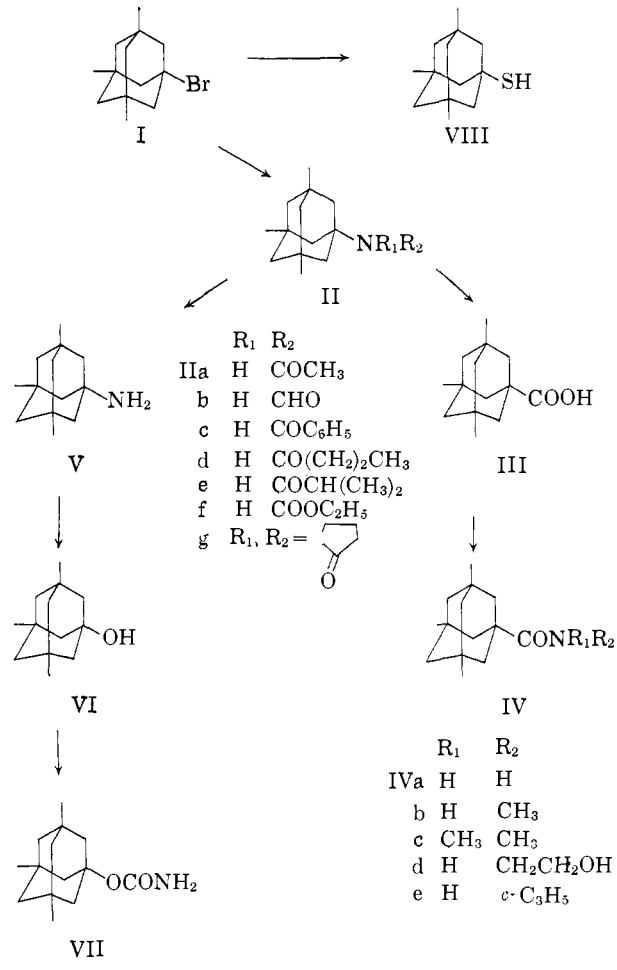
It has been reported in preceding papers in this series[2-4] that the biological activity of adamantane-containing agents is, in general, quite reduced as the result of seemingly minor structural changes in the adamantane moiety. For instance, the hypoglycemic activity of N-*p*-tolylsulfonyl-N′-1-adamantylurea[2] is reduced by about 70% by a single 3′-methyl substituent and is eliminated in the 3′,5′-dimethyl compound; the anabolic activity of nortestosterone 17β-adamantoate[3] is reduced by 80–90% in the 3′-methyladamantoate, while the 3′,5′-dimethyl and 3′,5′,7′-trimethyl analogs[5] possess even less activity; finally, the ability of 5′-adamantoyladenosine[4] to reverse ADP-induced platelet aggregation *in vitro*, while retained in the monomethyl adamantoate, is much reduced in the dimethyl and in the trimethyl analogs.

In the course of this work, the lipid solubility of 1,3,5-trimethyladamantane compounds has been noted in our laboratory. Thus, while adamantanol[6] is only moderately soluble in ethyl ether, 3,5,7-trimethyladamantan-1-ol is quite soluble in petroleum ether. Adamantylamine hydrochloride[7] is freely soluble in H_2O, but 3,5,7-trimethyladamantyl-1-amine hydrochloride is quite insoluble.

It has been stated[8] that "the characteristics of a high degree of lipoid solubility, low extent of ionization, and lack of plasma-protein binding virtually ensure that a compound will enter brain and cerebrospinal fluid freely and attain equilibrium rapidly." Possibly, suitable trimethyladamantane derivatives might fulfill these criteria and thus penetrate to the tissues and fluids of the central nervous system.

The preparations of a number of trimethyladamantane derivatives including 3,5,7-trimethyladamantane-1-carboxamide and 3,5,7-trimethyladamantan-1-ol are reported in this paper together with an evaluation of the effects of these derivatives on mouse behavior. Where appropriate, a comparison with the effects of the corresponding 3,5-dimethyl-, 3-methyl-, and nonmethylated adamantyl analogs is made.

SCHEME I



Chemistry.—For the preparation of the necessary quantities of 1,3,5-trimethyladamantane, the $AlBr_3$-catalyzed rearrangement of perhydrofluorene,[9] when carried out at temperatures between 120–130°, was found to be much superior to the multistep synthesis of Koch and Franken,[10] starting from mono- or dimethyladamantane.

Fusion of 1-bromo-3,5,7-trimethyladamantane[10] (I) with a variety of amides, including acetamide, formi-

(1) The correct designation 3,5,7-trimethyladamantane-1-carboxylic acid has been used in this paper instead of the trivial name adamantoic acid used in papers II[3] and III[4] of this series.

(2) K. Gerzon, E. V. Krumkalns, R. L. Brindle, F. J. Marshall, and M. Root, *J. Med. Chem.*, **6**, 760 (1963).

(3) R. T. Rapala, R. J. Kraay, and K. Gerzon, *ibid.*, **8**, 580 (1965).

(4) K. Gerzon and D. Kau, *ibid.*, **10**, 189 (1967).

(5) The trimethyl analog was evaluated by Drs. Rapala and Kraay, The Lilly Research Laboratories, after publication of the paper in ref 3.

(6) S. Landa, S. Kriebel, and E. Knobloch, *Chem. Listy*, **48**, 61 (1954).

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

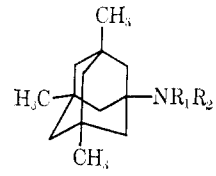
(8) D. P. Rall and C. G. Zubrod, *Am. Rev. Pharmacol.*, **2**, 115 (1962).

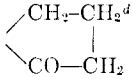
(9) A. Schneider, R. W. Warren, and E. J. Janoski, *J. Org. Chem.*, **31**, 1617 (1966), and references cited therein.

(10) H. Koch and J. Franken, *Chem. Ber.*, **96**, 213 (1963).

TABLE I

N-ACYL-1-AMINO-3,5,7-TRIMETHYLADAMANTANES[a]

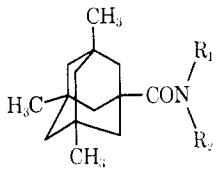


Compd	R_1	R_2	Reaction temp, °C (time, hr)	Mp, °C	Crystn solvent[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
IIa	H	$COCH_3$	125–130 (4)	194–196	...	$C_{15}H_{25}NO$	76.54	10.70	5.95	76.58	10.89	6.10
IIb	H	CHO	120 (16)	84–87	...	$C_{14}H_{23}NO$	75.97	10.47	6.33	76.15	10.61	6.05
IIc	H	COC_6H_5	135 (16)	160–161	E–W	$C_{20}H_{27}NO$	80.76	9.15	4.71	81.19	9.61	4.36
IId	H	$CO(CH_2)_2CH_3$	135–140 (8)	121–123	H–C	$C_{17}H_{29}NO$	77.51	11.08	5.33	77.80	11.16	5.27
IIe	H	$COCH(CH_3)_2$	135–140 (9)	181–182	H–C	$C_{17}H_{29}NO$	77.51	11.08	5.33	77.42	11.37	6.05
IIf	H	$COOC_2H_5$[c]	130 (16)	81–83	H–C	$C_{16}H_{27}NO_2$	72.41	10.26	5.28	72.13	10.19	5.26
IIg			135 (24)	104–105	E–W	$C_{17}H_{27}NO$	78.11	10.41	5.36	78.10	10.63	5.62

[a] Prepared by the fusion of 1-bromo-3,5,7-trimethyladamantane and the appropriate amide (see Experimental Section). [b] E = EtOH, W = H_2O, H = hexane, C = $CHCl_3$. [c] Starting material, ethylurethan. [d] Starting material, pyrrolidone.

TABLE II

3,5,7-TRIMETHYLADAMANTANE-1-CARBOXAMIDE DERIVATIVES[a]



Compd	R_1	R_2	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	MAD,[c] mg/kg
IVa	H	H	145–146[d]	75.97	10.47	6.33	75.69	10.56	6.21	16
IVb	H	CH_3	160[d]	76.54	10.71	5.95	76.44	10.89	5.99	100
IVc	CH_3	CH_3	99–100[d]	77.06	10.91	5.62	77.25	11.38	5.64	200
IVd	H	CH_2CH_2OH	109–110[d]	72.41	10.26	5.28	72.14	10.39	5.09	200
IVe	H	c-C_3H_5	169–170	78.11	10.41	5.36	77.99	10.51	5.11	50

[a] Prepared from 3,5,7-trimethyladamantane-1-carbonyl chloride[4] and the appropriate amine by the general method described in the Experimental Section. [b] Minimum ataxic dose; see Experimental Section, Pharmacology, for definition. [c] See ref 10. [d] Recrystallized from hexane.

amide, and benzamide, gave the corresponding N-acylamines II (see Table I and Scheme I). Preparation of 3,5,7-trimethyladamantane-1-carboxylic acid (III) from 1-bromo-3,5,7-trimethylamantane[10] (I), using the H_2SO_4–HCOOH method,[10,11] proceeds unsatisfactorily to give only 30% of the theoretical yield.[12]

Utilizing the reversibility of the Ritter reaction[13] and the solubility of 1-acetamido-3,5,7-trimethyladamantane (IIa) in H_2SO_4, the acid III was obtained from this amide (IIa) by the H_2SO_4–HCOOH method[10,11] in an over-all yield of 85–90%, based on 1-bromo-3,5,7-trimethyladamantane (I).[14]

Following standard procedures, the acid III was converted to 3,5,7-trimethyladamantane-1-carboxamide[10] (IVa) and other N-substituted amides (IVb–e) (see Table II).

Hydrolysis of IIa with NaOH in ethylene glycol solution[8] furnished 1-amino-3,5,7-trimethyladamantane (V), which was converted to the corresponding adamantanol VI by diazotization in CH_3COOH.[15] 3,5,7-Trimethyladamantan-1-yl carbamate (VII) was prepared from the alcohol VI *via* the chloroformate, using the procedure developed for the preparation of 1-adamantyl chloroformate.[16]

3,5,7-Trimethyladamantane-1-thiol (VIII) was prepared from the bromide I and thiourea following the procedure used in the preparation of adamantane-1-thiol.[17]

3-Methyl- or 3,5-dimethyladamantyl derivatives needed for pharmacological comparison and not previously reported in the literature were prepared by the methods described above for the corresponding 3,5,7-trimethyladamantyl compounds.

(11) H. Koch and W. Haaf, *Angew. Chem.*, **72**, 628 (1960).

(12) Vapor phase chromatography of the neutral products of the reaction indicated that 1,3,5-trimethyladamantane was formed as a by-product in approximately 30–40% yield.

(13) W. Haaf, *Chem. Ber.*, **96**, 3359 (1963).

(14) Using this two-step procedure, the 3-methyl and 3,5-dimethyl acids[6c] were also prepared in 80–90% yield.

(15) W. H. W. Lunn, The Lilly Research Laboratories, has observed that this alcohol (VI) can be obtained conveniently from the bromide by alkaline hydrolysis in 2-propanol solution.

(16) W. L. Haas, E. V. Krumkalns, and K. Gerzon, *J. Am. Chem. Soc.*, **88**, 1988 (1966).

(17) Belgian Patent 629,370 (1964).

TABLE III

MINIMUM ATAXIC DOSE AND TOXIC DOSE[a] OF SUBSTITUTED ADAMANTANE-1-CARBOXAMIDES, ADAMANTAN-1-OLS, AND N-ADAMANTYL-1-FORMAMIDES

	RCONH$_2$			ROH			RNHCHO		
R	Ref	MAD	TD	Ref	MAD	TD	Ref	MAD	TD
Adamantyl-1-	*b*	100	1600	*d*	140	800	*f*	..[g]	200
3-Monomethyl-	*c*	35	400	*e*	50	400	*h*	50	400
3,5-Dimethyl-	*c*	25	400	*e*	25	800	*i*	35	400
3,5,7-Trimethyl-	IVa	16	400	VI	35	1600	IIb	50	400

[a] Minimum ataxic dose (MAD, see Experimental Section, Pharmacology, for definition) and toxic dose (TD) in mice by single oral dose in milligrams per kilogram. [b] Reference 7. [c] IVa, ref 10. [d] Reference 6. [e] R. C. Fort, Jr., and P. Schleyer, *Chem. Rev.*, **64**, 277 (1964). [f] W. Haaf, *Angew. Chem.*, **73**, 144 (1961). [g] No depressant action observed (see Results). [h] Prepared by the general method described for II; mp 56–59°. *Anal.* Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.51; H, 10.15; N, 7.22. [i] Prepared by the general method described for II; mp 65–67°. *Anal.* Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.43; H, 10.48; N, 6.82.

Experimental Section[18]

N-Acyl-1-amino-3,5,7-trimethyladamantanes (II). General Method.—A mixture of 1-bromo-3,5,7-trimethyladamantane[10] (30 g) and acetamide (70 g) was heated with stirring in an oil bath at 125–130° for 4 hr. The hot solution was poured into 800 ml of H_2O, and the precipitated solids were filtered, washed with water, and dried with air to yield 26.5 g of product, mp 194–196°. Additional acylaminoadamantanes (II) were similarly prepared from the appropriate amide and are listed in Table I.

3,5,7-Trimethyladamantane-1-carboxylic Acid (III).—To a vigorously stirred solution of 2.5 ml of 98% formic acid in concentrated H_2SO_4 (1250 ml), cooled to 10°, was added 50 g of 1-acetamido-3,5,7-trimethyladamantane (IIa). To the resulting solution 75 ml of 98% formic acid was slowly added over a period of 7.5 hr while maintaining the temperature at 13–16°. The reaction mixture was poured into 8 l. of an ice–water mixture. The precipitate that formed was isolated by filtration and washed with water. The crude product III was dissolved in ethanol and the solvent was removed under reduced pressure. This procedure was repeated twice. The remaining solids were recrystallized from a 2-propanol–hexane mixture to yield 43.1 g (91%) of III, mp 140–141° (lit.[10] mp 140.5–141°).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.41; H, 10.03.

3,5,7-Trimethyladamantane-1-carboxamides (IV). General Method.—To 200 ml of ether, saturated with NH_3 (or containing an excess of the appropriate amine; see Table II) at 0° was added slowly 8.5 g of crude 3,5,7-trimethyladamantane-1-carbonyl chloride[4] in 50 ml of ether. The reaction mixture was poured into 250 ml of H_2O, and the ether layer was separated. The water layer was extracted with three 100-ml portions of ether, and the combined ether layers were extracted first with 100 ml of 5% KOH then with two 100-ml portions of H_2O, and dried (Na_2SO_4). The ethereal solution was filtered; the ether was removed *in vacuo* to leave a residue which was recrystallized from hexane to give 7 g of product, mp 145–146° (lit.[10] 105–106°).

1-Amino-3,5,7-trimethyladamantane Hydrochloride (V).—To a solution of NaOH (35 g) in diethylene glycol[8] (300 ml) was added 18 g of 1-acetamido-3,5,7-trimethyladamantane (IIa). The reaction mixture was refluxed for 6 hr, cooled, poured onto ice, and extracted three times with 250 ml of ether. The combined ether layers were washed twice with 200 ml of H_2O and dried (Na_2SO_4). The ethereal solution was filtered; the ether was removed *in vacuo*, and the residue was dissolved in dry ether. The ethereal solution was saturated with HCl; a precipitate formed and was filtered, washed with ether, and dried in a desiccator to yield 11.3 g of product subliming above 300°.

Anal. Calcd for $C_{13}H_{23}N \cdot HCl$: C, 67.94; H, 10.53; N, 6.10. Found: C, 67.97; H, 10.65; N, 5.89.

3,5,7-Trimethyladamantan-1-ol (VI).—To a solution of 1-amino-3,5,7-trimethyladamantane hydrochloride (V, 40 g) in acetic acid (250 ml) was added 270 ml of H_2O. To the resulting mixture was added 2 *N* NaOH (270 ml) and then, dropwise, $NaNO_2$ (24 g) dissolved in 66 ml of H_2O. After addition of the $NaNO_2$ solution, the reaction mixture was heated under reflux for 2 hr and allowed to cool to room temperature. The solution was extracted with 500 ml of H_2O, four times with 250 ml of saturated $NaHCO_3$ solution, and twice again with 250 ml of H_2O, then dried (Na_2SO_4). The ethereal solution was filtered and cooled in an acetone–Dry Ice bath, and the solids that formed were filtered to yield 10 g of product, mp 120–122°. Recrystallization from ether at −50° afforded a product with mp 124–125°.

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.05; H, 11.44.

3,5,7-Trimethyladamantan-1-yl Carbamate (VII).—To a solution of liquid phosgene (15 g) in anhydrous benzene (100 ml), a solution of 3,5,7-trimethyladamantan-1-ol (4.9 g) and pyridine (10 ml) in dry ether (50 ml) was added dropwise with stirring over a 45-min period while maintaining the reaction temperature at 4°. The reaction mixture was allowed to stir for 1 hr; then the solution was filtered, and the filtrate was extracted twice with 100-ml portions of iced water and dried (Na_2SO_4). This solution was filtered and concentrated *in vacuo* to approximately 50 ml and then slowly added to benzene (300 ml), saturated with NH_3 at 0°. The reaction mixture was stirred overnight and filtered, and the filtrate was washed twice with 100-ml portions of iced water and dried (Na_2SO_4). The benzene solution was filtered; the solvent was removed *in vacuo* to leave a residue which was recrystallized from hexane to yield 3.6 g of product, mp 179–181°.

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.72; H, 9.77; N, 5.64.

3,5,7-Trimethyladamantane-1-thiol (VIII).—1-Bromo-3,5,7-trimethyladamantane (26 g) was added to a solution of 48% HBr (25 ml) and 8 g of thiourea in glacial acetic acid (50 ml). The mixture was heated under reflux for 2 hr and then poured into 500 ml of an ice–water mixture. The precipitate that formed was filtered and added to a solution of 5 g of NaOH in 150 ml of 20% ethanol–water. The resulting mixture was stirred overnight, then acidified, and the precipitate that formed was filtered, washed with water, and recrystallized from methanol to yield 14.2 g of product, mp 91–92°.

Anal. Calcd for $C_{13}H_{22}S$: C, 74.21; H, 10.54; S, 15.24. Found: C, 74.46; H, 10.72; S, 14.97.

Pharmacology.—The effects of adamantane derivatives on animal behavior were evaluated with the aid of procedures that have been employed in these laboratories for a number of years.[19] For the study of behavioral effects in mice, suspensions of the compounds (Tables II and III) were administered intraperitoneally to male white mice (Cox) weighing 16–20 g. Three mice were given each standard dose and observed for changes in behavior, appearance, and response to certain stimuli. The standard doses used were 10, 25, 50, 100, 200, 400, 800, and 1600 mg/kg. Potency and toxicity determined the range of doses that was necessary to study each compound. Most observed effects were scored for each mouse as "1, 2, or 3" with a score of 1 indicating a minimum effect and a score of 3 indicating a near maximum or maximum effect. The minimum ataxic dose (MAD) was used as a measure of sedative potency and, as used here, is the dose at which the sum of the three scores for ataxia equals 2, 3, or 4. In some instances it was necessary to report inter-

(18) All melting points were taken on a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were obtained in $CHCl_3$. All compounds exhibited the typical nmr spectrum reported for 1-substituted 3,5,7-trimethyladamantanes [R. C. Fort, Jr., and P. R. Schleyer, *J. Org. Chem.*, **30**, 789 (1966)] when taken on a Varian Associates Model HR-60 spectrometer, in $CDCl_3$ or DMSO-d_6 with Me_4Si as an internal standard.

(19) (a) R. C. Rathbun, J. K. Henderson, R. W. Kattau, and C. E. Keller, *J. Pharmacol. Exptl. Therap.*, **122**, 64A (1958); (b) R. C. Rathbun and I. H. Slater, *Psychopharmacologia*, **4**, 114 (1963); (c) E. Van Heyningen, C. N. Brown, F. Jose, J. K. Henderson, and P. Stark, *J. Med. Chem.*, **9**, 675 (1966).

polated values. Doses tabulated for toxicity are doses at which at least one mouse died.

In cats the behavioral effects of trimethyladamantane-1-carboxamide (IVa) and of trimethyladamantan-1-ol (VI) were evaluated by the oral route (capsules); the amide IVa was administered to dogs orally in capsules and by gavage as a suspension or as a solution in propylene glycol.

Results

In mice, low doses of the amides and alcohols studied (Tables II and III) produced a variable increase of motor activity, slight ataxia, and an increased pinna response. Larger doses produced loss of the righting reflex, depression of respiratory rate, and depression of the pinna reflex. A notable exception to this general sedative pattern of these compounds was the stimulatory effect produced by N-adamantylformamide (Table III). Mice receiving this compound showed a consistent increased irritability; larger doses caused tremors and convulsions. No ataxia, no depression of the pinna reflex, or righting loss was observed with this amide.

Though the differences are not great, the adamantane 1-carboxamides show a more potent sedative action than the alcohols or the formamides (Table III). This is best exemplified in the 3,5,7-trimethyladamantane group (IVa is more active than VI or IIb). In the series of 3,5,7-trimethyladamantane-1-carboxamides (IV), N-alkylation or N,N-dialkylation invariably reduced potency (Table II). Trimethyladamantane-1-thiol (VIII) showed no appreciable sedative action.

In the group of four adamantane-1-carboxamides (Table III, column 1) the successive introduction of methyl substituents results in a progressive increase of sedative activity: 3,5,7-trimethyladamantane-1-carboxamide (IVa) is about six times as active as the nonmethylated carboxamide. The same trend, albeit less precise, of increased activity following methyl substitution is noted for the four adamantan-1-ols; 3,5,7-trimethyladamantan-1-ol (VI) possesses about four times the activity of adamantan-1-ol.

3,5,7-Trimethyladamantane-1-carboxamide (IVa) was given orally to five cats. Between 15 and 30 min after a dose of 20 mg/kg, the animals became ataxic and after about 1 hr, one cat vomited. Doses of 10 mg/kg were given to four of these animals and caused a lesser degree of ataxia. One cat treated with 5 mg/kg showed minimal ataxia which lasted less than 1 hr. The effects of the larger doses lasted less than 2 hr.

Two cats treated with 10 mg/kg of 3,5,7-trimethyladamantan-1-ol (VI) remained unchanged. One cat given 20 mg/kg showed a moderate degree of ataxia which lasted about 2 hr.

The EEG changes were consistent with the observed behavioral state of the cat. The sleepy, ataxic cats showed an increase in high-voltage, low-frequency activity in most deep and surface leads.

Two male dogs were given 20 mg/kg of 3,5,7-trimethyladamantane-1-carboxamide (IVa) in capsules. After 30 min both dogs showed salivation, increased respiratory rate, and tremors, which were most evident in the forepaws. These effects were of short duration. A dose of 20 mg/kg given by gavage as an acacia suspension to one male dog caused a slight ataxia with an increase in activity. After approximately 1 hr the animal tended to sleep. A female that received the same treatment tended to sleep only if undisturbed.

Because the amide IVa is so poorly soluble and its absorption was in doubt,[20] it was administered to dogs as a solution in propylene glycol. A dose of 40 mg/kg (orally) produced slight ataxia after about 30 min. One of the two dogs was restless and the other tended to sleep, but after 4–5 hr the dogs returned to normal. By the intraperitoneal route, 40 mg/kg caused a pronounced motor impairment within 15 min. Ataxia was followed by weakness and prostration. One dog vomited, showed miosis, and had two brief episodes of clonic convulsions. Three hours after treatment, the dogs appeared normal. The corresponding volume of propylene glycol in another two dogs caused no detectable change.

In review, in the mouse the amide IVa and the alcohol VI are sedative agents of appreciable potency; when given orally to cats, these compounds produce a moderate degree of sedation of relatively short duration. In dogs the amide IVa produces a mixed pattern of mild sedation and stimulation. The stimulatory properties of the amide IVa, exemplified by the occurrence of convulsions in one dog given this agent by the intraperitoneal route, when coupled with the low efficacy of this compound given by the oral route to dogs, preclude further study of this agent in man.

Discussion

The structure–activity relationship pattern previously reported for three groups of adamantane containing agents[2–4] stands in surprising contrast to that displayed by the sedative adamantane-1-carboxamides and adamantan-1-ols (Table III). While in the former groups of compounds, the successive introduction of methyl substituents led to a progressive *decrease* of the respective biological activities, in the present series of amides and alcohols such substitution effects a definite, if somewhat smaller, *increase* of sedative activity. For the former type of active agents, a mode of action was postulated[3] involving a precise and specific binding of the adamantane moiety to a receptor-site protein molecule. Extensive methylation presumably interferes with such binding and is detrimental to the activities of this type of agent. On the other hand, lack of binding of the sedative trimethyladamantane-1-carboxamide (IVa) and trimethyladamantan-1-ol (VI) to plasma protein may enable these sedative agents to penetrate readily to the tissues and fluids of the central nervous system and to exert the pharmacodynamic action described.

The further evaluation of the methylated adamantane group as a potentially useful moiety is at present under investigation in our laboratories.

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(20) Metabolism studies with labeled 3,5,7-trimethyladamantane-1-carboxamide (IVa) have been performed by H. A. Sullivan, R. Billings and A. E. McMahon, The Lilly Research Laboratories. These studies will be submitted in a separate communication to this journal.