Synthesis and Antiviral Activities of Adamantane Spiro Compounds. 1. Adamantane and Analogous Spiro-3′-pyrrolidines

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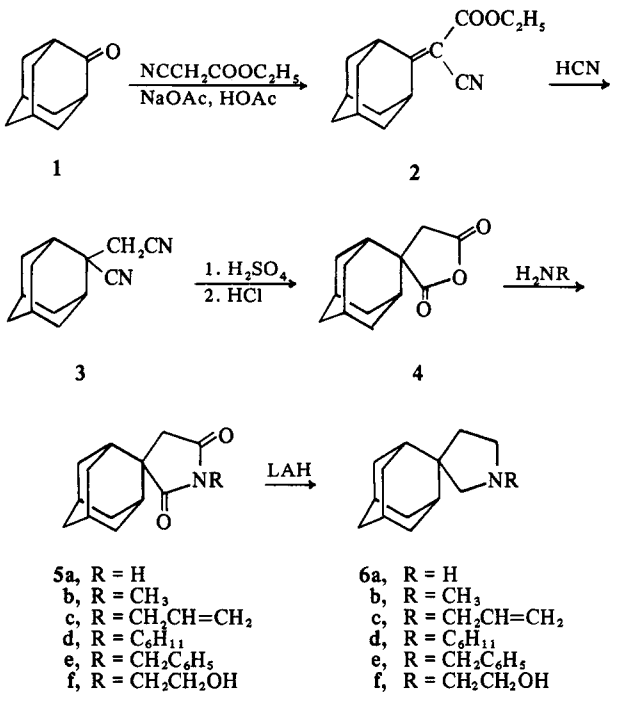
Adamantanespiro-3′-pyrrolidine and several N-substituted derivatives were synthesized. In particular smaller alkyl-substituted derivatives displayed interesting antiviral action against influenza A, parainfluenza Sendai, coxsackie A21, and rhinovirus. This activity was compared with that of spiropyrrolidines derived from other alicyclic compounds. The *N*-methyl adamantanespiro-3′-pyrrolidine is superior to 1-adamantanamine in level and spectrum of activity.

In view of the interesting antiviral properties of 1-adamantanamine[1] it was deemed worthwhile to study the influence of structural modifications on antiviral activity. The discovery of a suitable method for the synthesis of 2-adamantanone[2] furthered the possibilities of substitution at a bridge atom of the adamantane nucleus and made the synthesis of secondarily substituted adamantanes, including spiro compounds, feasible. This paper deals with the synthesis and antiviral activity of a number of adamantanespiro-3′-pyrrolidines. The importance of the adamantane nucleus for antiviral activity was investigated by comparison with spiropyrrolidines derived from bornane, bicyclo[3.3.1]nonane, perhydro-4,7-methanoindane, and cyclohexane. The synthesis and antiviral properties of related adamantane spiro heterocyclic compounds will be the subject of a further paper.[3]

Synthesis. 2-Adamantanone (**1**) was condensed with cyanoacetic ester using Cope conditions[4] to give **2** (Scheme I). Addition of HCN to **2** in strongly alkaline medium proceeded smoothly and gave, with subsequent saponification and decarboxylation, 2-cyano-2-cyanomethyladamantane (**3**). Hydrolysis of **3** afforded the adamantanespiro-2′-succinic anhydride (**4**) which was converted by treatment with NH_3 into adamantanespiro-3′-pyrrolidine-2,5-dione (**5a**). Compd **5a** could also be synthesized by treatment of the dinitrile **3** with HBr and hydrolysis of the reaction product[5] (Scheme II). Reaction of **4** with primary amines gave the corresponding substituted pyrrolidines diones **5b–5f** (Table I). The adamantanespiro-3′-pyrrolidines **6a–6f** (Table II) were synthesized by reduction of the corresponding diones with LAH. Catalytic reduction of **3** followed by pyrolysis of the diamine dihydrochloride[6] **7** led to an alternate synthesis of **6a** (Scheme III). Compd **6h** was formed by acetylation of **6a** and subsequent reduction; **6i** was formed by alkylation of **6a** with acetone and subsequent reduction. Compd **6g** was obtained by treatment of **6f** with $SOCl_2$. The synthesis of the spiropyrrolidine derivatives of bornane, bicyclo[3.3.1]nonane, perhydro-4,7-methanoindane, and cyclohexane has been achieved by the same methods (Table III).

Biological Results. The *in vivo* antiviral activities against Influenza A_2 Japan are presented in Tables II and III. *In vitro* data (Table IV) were obtained by the plaque inhibition method.[7] The compounds were added just before virus inoculation. *In vivo* experiments were carried out using mice (Swiss SPF) weighing 19–21 g each. The substances were administered orally twice a day for 5 days. The dose was 5.10^{-4} mole/kg per day or 1.10^{-4} mole/kg per day in comparative experiments with 1-adamantanamine.[9] Virus challenge (by aerosolation) took place between the two administrations of the compounds on the first day of the experiment.

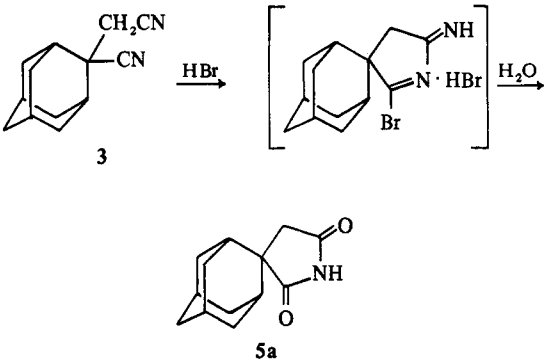
Scheme I



5a, R = H
b, R = CH_3
c, R = $CH_2CH{=}CH_2$
d, R = C_6H_{11}
e, R = $CH_2C_6H_5$
f, R = CH_2CH_2OH

6a, R = H
b, R = CH_3
c, R = $CH_2CH{=}CH_2$
d, R = C_6H_{11}
e, R = $CH_2C_6H_5$
f, R = CH_2CH_2OH

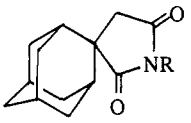
Scheme II



Discussion

The antiviral activity of the *N*-methyl derivative **6b** has been the subject of a previous communication.[9] Compared with 1-adamantanamine this compound is about 3 times more active *in vivo* against Influenza A_2 Japan and A_2 Hong Kong. *In vitro* it shows a broader antiviral spectrum: **6b** was demonstrated to be active against Coxsackie A21 and Rhino 2 (HGP) in qualitative (Table IV) and quantitative experiments,[9] whereas 1-adamantanamine was inactive. The adamantanespiro-3′-pyrrolidines which have smaller alkyl sub-

Table I. Adamantanespiro-3′-pyrrolidine-2′,5′-diones[a]

No.	R	Formula	Analyses	Mp, °C	Yield, %
					
5a	H	$C_{13}H_{17}NO_2$	C, H, N, O	187-189	91
b	CH_3	$C_{14}H_{19}NO_2$	C, H, N, O	214-216	85
c	$CH_2CH{=}CH_2$	$C_{16}H_{21}NO_2$	C, H, N	84.5-87.5	81
d	C_6H_{11}	$C_{19}H_{27}NO_2$	C, H, N, O	142.5-144	70
e	$CH_2C_6H_5$	$C_{20}H_{23}NO_2$	H, N, O; C[b]	138-138.5	90
f	CH_2CH_2OH	$C_{15}H_{21}NO_3$	C, H, N, O	144-145	63

[a]Prepd by procedure A described in the Experimental Section. The synthesis of **5a** has been described separately. [b]C: calcd, 77.63; found, 77.13.

Scheme III

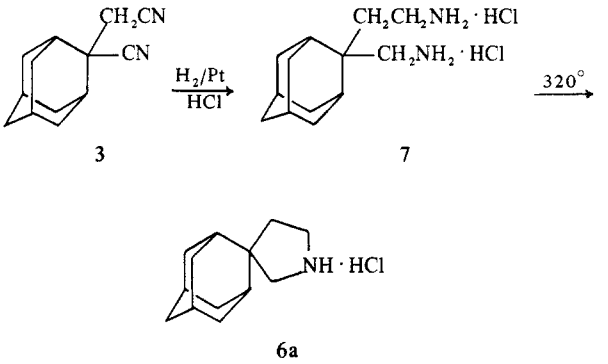
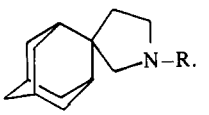
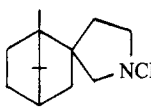
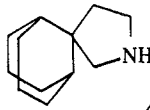
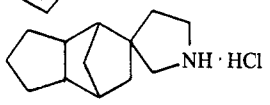
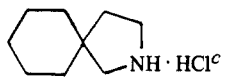


Table II. Adamantanespiro-3′-pyrrolidines[a]

No.	R	Formula	Analyses	Mp, °C	Yield, %	Antiviral act. *in vivo*[b]
						
6a	H	$C_{13}H_{21}N \cdot HCl$	C, H, N, Cl	253-254	77	++
b	CH_3	$C_{14}H_{23}N$ hydromaleate	C, H, N, O	144-145[d]	92	++
h	C_2H_5[c]	$C_{15}H_{25}N \cdot HCl$	C, H, N	266-268	87	++
i	$i\text{-}C_3H_7$[c]	$C_{16}H_{27}N \cdot HCl$	C, H, N, Cl	273-276	60	+
c	$CH_2CH{=}CH_2$	$C_{16}H_{25}N \cdot HCl$	C, H, N, Cl	256-260 dec	83	+
d	C_6H_{11}	$C_{19}H_{31}N \cdot HCl$	C, H, N	262-264	47	–
e	$CH_2C_6H_5$	$C_{20}H_{27}N \cdot HCl$	[e]	302-306	85	+
f	CH_2CH_2OH	$C_{15}H_{25}NO \cdot HCl$	C, H, N, O, Cl	236-237.5	80	+
g	CH_2CH_2Cl[c]	$C_{15}H_{24}ClN \cdot HCl$	H, N; C[f]	254 dec	94	+

[a]Prepd by procedure B described in the Experimental Section unless otherwise stated. [b]++ = activity comparable to that of 1-adamantamine or better; + = significant activity but less than that of 1-adamantanamine; – = inactive. [c]Procedure given separately in the Experimental Section. [d]Mp of hydrochloride, 266-267.5°. [e]Analysis for picrate (mp 171-171.5°): C, H, N, O. [f]C: calcd, 62.06; found, 61.63.

Table III. Analogous Spiro-3′-pyrrolidines

No.	Structure	Formula	Analyses	Mp, °C	Yield, %	Antiviral act. *in vivo*[a]
8		$C_{14}H_{25}N \cdot HCl$	C, H; N[b]	246-247	90	+
9		$C_{12}H_{21}N \cdot HCl$	C, H, N	219-221	81.5	++
10		$C_{13}H_{21}N \cdot HCl$	C, H, N	186-188	70.5	+
11		$C_9H_{17}N \cdot HCl$		83-85[d]		

[a]See footnote *b*, Table II. [b]N: calcd, 5.74; found, 6.18. [c]See reference 8. [d]Picrate mp 148-149°, lit.[c] mp 151°.

stituents generally are comparable to **6b** in level and spectrum of activity (Tables II and IV). Increasing size of the substituents at the N-atom tends to diminish *in vivo* activity against Influenza A_2 Japan. A similar trend has been observed in a series of bicyclo[2.2.2]octan- and -oct-2-enamines.[10] In general cytotoxicity is found with **6d-6g**, making an estimation of antiviral activity *in vitro* impossible in the procedure used.

Of the analogous spiro-3′-pyrrolidines activity is highest for **9** structurally most closely related to adamantane. Nevertheless **9** is less active than **6b**, but comparable to 1-adamantanamine. The cyclohexane derivative **11** does not in fact possess any activity at all. This stresses the importance of the adamantane nucleus for antiviral activity in this series.** In general no activity was found against B strains of Influenza neither *in vitro* nor *in vivo*.

Note Added in Proof. After completion of this manuscript, the diamantanespiro-3′-pyrrolidine and its *N*-methyl derivative were prepared. Both compounds were less active *in vivo* against Influenza A_2 Japan than **6b.

Table IV. *In Vitro* Antiviral Properties of the Spiro-3′-pyrrolidines Hydrochlorides[a]

No.	Influenza A_2 Japan[b]	Parainfluenza Sendai[c]	Coxsackie A_{21}[d]	Rhino 2(HGP)[d]
6a	+	T	–	++
6b	++	+	+	++
6h	+	+	±	++[e]
6i	+[e]	±	±	T
6c	++[e]	–	+[e]	T
8	±	+	±	++[e]
9	+[e]	T	±	–
10	+	–	T	T
11	–	–	±	±
1-AA	++	±	–	–

[a] ++ = >70% inhibition; + = 40–70% inhibition; ± = 20–40% inhibition; – = <20% inhibition; T = cytotoxic. Concn of compounds 10^{-4} *M*. [b] In chick embryo fibroblasts. [c] In calf kidney cells. [d] In M. HeLa cells. [e] Slightly toxic. [f] 1-AA = 1-adamantanamine.

Experimental Section†

Ethyl adamant-2-ylidenecyanoacetate (2) was prepd from 2-adamantanone according to Cope, *et al.*:[4] yield, 90%; crystd from EtOH; mp 81–82°. *Anal.* ($C_{15}H_{19}NO_2$) C, H, N, O.

2-Cyano-2-cyanomethyladamantane (3). 2 (100 g, 0.41 mole) was dissolved in EtOH (800 ml); a soln of KCN (64 g, 0.98 mole) in H_2O (140 ml) was added. The mixt was stirred and kept at 65° for 16 hr. After cooling, the ppt was filtered with suction. By concn of the filtrate some further crops were obtained. The crystals were stirred in a 0.2 *N* KOH soln (500 ml), filtered, washed with H_2O, and dried: yield, 77.5 g (96%); mp 126–127°. *Anal.* ($C_{13}H_{16}N_2$) C, H, N.

Adamantanespiro-2′-succinic Anhydride (4). 3 (76 g, 0.38 mole) was dissolved at 90° in concd H_2SO_4 (750 ml). The temp rose to approx 110°. The soln was shaken for 5 min and poured on ice (approx 10 l.). The mixt was neutralized with 50% NaOH, and the ppt was filtered with suction and washed with H_2O. The moist substance was heated, with stirring, in concd HCl (2.1 l.) for 2 hr at 80°. After cooling, the solid was filtered off, washed, and crystd from C_6H_6: yield, 5.6 g (76%); mp 226–229°. *Anal.* ($C_{13}H_{16}O_3$) C, H, O.

Adamantanespiro-3′-pyrrolidine-2′,5′-dione (5a). 4 (52.1 g, 0.24 mole) was melted and heated at 230° for 3.5–4 hr, NH_3 being passed in continuously (4 l./hr). After cooling, the residue was crystd from EtOH (0.5 l.) to give **5a** (see Table I).

General Procedure A. Adamantanespiro-3′-pyrrolidine-2′,5′-diones (5). 4 (33 g, 0.15 mole) was dissolved in hot C_6H_6 (50 ml) and with vigorous stirring RNH_2 (0.15 mole) in C_6H_6 (30 ml) was added at 60–65°. After standing for 0.5 hr at 60–65°, the mixt was cooled, and the ppt was filtered and washed (C_6H_6). A further crop was obtained by concn of the mother liquor. The solid carboxamidecarboxyadamantane was heated under N_2 for 15–30 min at 220–225°. After cooling, the residue was crystd from EtOH. A further crop was obtained by addn of H_2O. Yields and properties are given in Table I.

General Procedure B. Adamantanespiro-3′-pyrrolidines (6). 5 was reduced with LAH in refluxing THF according to known methods.[11] The bases were converted into the hydrochlorides and crystd from EtOH. Yields and properties are given in Table II.

Adamantanespiro-3′-pyrrolidine-2′,5′-dione (5a). Procedure of Scheme II.‡ 3 was converted into **5a** according to ref 5: yield, 93%.

Adamantanespiro-3′-pyrrolidine Hydrochloride (6a). Procedure of Scheme III. 3 (10 g, 0.05 mole) in EtOH (250 ml) and concd HCl (10 ml) was hydrogenated with PtO_2 (1 g) at 50°. After 6–8 hr the uptake of H_2 ceased. The catalyst was filtered off and a colorless soln resulted in which **6a** and the diamine **7** were present according to tlc.§ The solvent was evapd and the resulting residue was heated under N_2 at 320° for 5–10 min. After cooling the reaction product was converted into the free base by treatment with 2 *N* NaOH and was extd with CH_2Cl_2. The solvent was evapd, the residue dissolved in MeOH (30 ml) and the soln acidified with concd HCl (5 ml). **6a** crystd after addn of Et_2O: yield, 7.2 g (63%).

***N*-Ethyladamantanespiro-3′-pyrrolidine Hydrochloride (6h).** The free base of **6a** was acylated with Ac_2O in a usual way. The acetamide was reduced with LAH in refluxing THF in 16 hr: yield, 87%; see Table III.

***N*-Isopropyladamantanespiro-3′-pyrrolidine Hydrochloride (6i).** The free base of **6a** (2.8 g, 0.015 mole) was dissolved in EtOH (10 ml). Me_2CO (4 ml, 0.05 mole) and PtO_2 (3.4 g) were added, and the mixt was hydrogenated overnight at 4.2 kg/cm². After removal of the catalyst the soln was acidified with 1.4 *N* dry HCl in EtOH (12 ml) and evapd. Crystn (EtOH–Et_2O) gave 2.45 g of **6i**; see Table II.

***N*-β-Chloroethyladamantanespiro-3′-pyrrolidine Hydrochloride (6g).** 8 (7 g, 0.026 mole) was dissolved in $SOCl_2$ (14 ml) and refluxed for 30 min. The $SOCl_2$ was then evapd and C_6H_6 (3 × 20 ml) was added and evapd to 7.02 g of **6g**; see Table II.

2-Cyano-2-cyanomethylbornane. Ethyl born-2-ylidenecyanoacetate[12] was converted into 2-cyano-2-cyanomethylbornane according to the procedure described for **3**: yield, 67%; mp 152–153°. *Anal.* ($C_{13}H_{18}N_2$) C, H, N.

2-Carboxy-2-carboxymethylbornane. Following the procedure used for the prepn of **4**, 2-cyano-2-cyanomethylbornane (10.5 g, 0.052 mole) was converted into 5.4 g (61%) of 2-carboxy-2-carboxymethylbornane: mp 138–140°. *Anal.* ($C_{13}H_{20}O_4$) C, H; O: calcd, 26.63; found, 26.03.

Bornane-2-spiro-2′-succinic Anhydride. 2-Carboxy-2-carboxymethylbornane (11 g, 0.045 mole) was heated at 180° for 20 min under N_2. After the evoln of gas had ceased the product was distd *in vacuo* to yield 7.65 g of the anhydride as a waxy substance.

***N*-Methylbornane-2-spiro-3′-pyrrolidine-2′,5′-dione.** Prepd according to method A: yield, 51%; mp 86.5–87°. *Anal.* ($C_{14}H_{21}NO_2$) C, H, N; O: calcd, 13.60; found, 14.01.

***N*-Methylbornane-2-spiro-3′-pyrrolidine hydrochloride (8)** was prepd according to procedure B (see Table III).

Ethyl Bicyclo[3.3.1]non-9-ylidenecyanoacetate. Bicyclo[3.3.1]nonan-9-one[13] (13.2 g, 0.096 mole) was condensed with ethyl cyanoacetate by the method used for the prepn of **2**. The resulting oil was purified by dry column chromatog[14] (Merck silica gel 0.05–0.2 mm; column 5 × 150 cm) with C_6H_6 yielding 10.3 g (46%) of cryst product: mp 50–51°. *Anal.* ($C_{14}H_{19}NO_2$) H; C: calcd, 72.07; found, 72.57.

9-Cyano-9-cyanomethylbicyclo[3.3.1]nonane. According to the procedure used for the prepn of **3**, ethyl bicyclo[3.3.1]non-9-ylidenecyanoacetate was converted into the corresponding dinitrile: yield, 96%; mp 135.5–136°. *Anal.* ($C_{12}H_{16}N_2$) H; C: calcd, 76.55; found, 75.68; N: calcd, 14.88; found, 14.34.

Bicyclo[3.3.1]nonane-9-spiro-3′-pyrrolidine Hydrochloride (9). Following the procedure of scheme III for the prepn of **6a**, **9** was obtained from 9-cyano-9-cyanomethyl bicyclo[3.3.1]nonane (see Table III).

Ethyl Perhydro-4,7-methanoind-5-ylidenecyanoacetate. Perhydro-4,7-methanoindan-5-one# (30 g, 0.2 mole) was condensed with ethyl cyanoacetate as in the prepn of **2**. The resulting red oil was purified by dry column chromatog[14] (Merck silica gel 0.05–0.2 mm, column 5 × 150 cm) with C_6H_6 yielding 18.8 g (38%) of a colorless oil.

5-Cyano-5-cyanomethyl perhydro-4,7-methanoindane was obtd by the method used for the prepn of **3**: yield, 64%; mp 99–99.5°. *Anal.* ($C_{13}H_{16}N_2$) C, H, N.

Perhydro-4-7-methanoindane-5-spiro-3′-pyrrolidine Hydrochloride (10). By the method of Scheme III for the prepn of **6a**, **10** was obtd from 5-cyano-5-cyanomethyl perhydro-4,7-methanoindane (see Table III).

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†Melting points were measured in closed capillary tubes in an electrically heated aluminum block. Temperature was indicated by a chromel-alumel couple on a Philips G. M. 6020 tube voltmeter. Ir, nmr, and mass spectroscopic data are fully in accord with the structures proposed. Microanalyses were performed by A. Bernhardt, Mikroanalytisches Lab., Elbach über Engelskirchen, W. Germany, and F. Pascher, Mikroanalytisches Lab. Bonn, W. Germany. Where analyses are indicated only by symbols of the elements, analytical results of those elements were within ±0.4% of the theoretical values.

‡This synthesis was performed by Mr. J. S. Bontekoe.

§Merck, tlc-plates silica gel F 254, solvent CH_2Cl_2–EtOH–25% NH_4OH (3:3:1 v/v).

#Obtained from Aldrich Chemical Co.

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Synthesis and Antiviral Activities of Adamantane Spiro Compounds. 2[1]

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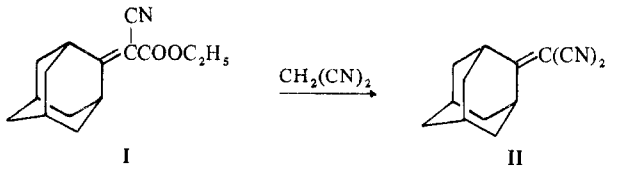
The synthesis of adamantanespiro-3′-piperidine (XV) and adamantanespiro-4′-perhydroazepine (XVIII) is reported. These compounds can be prepared from the key intermediate 2-bromomethyl-2-(β-bromoethyl)adamantane (XII). With the latter several other reactions have been carried out, leading to heterocyclic spiro compounds. The antiviral activity of these compounds is discussed.

The synthesis and antiviral properties of adamantanespiro-3′-pyrrolidine and derivatives have been described in a previous paper.[1] Because of the strong antiviral activities found in the pyrrolidine series, we continued our investigations in this field by preparing 6- and 7-membered ring analogs.

Synthesis. We first tried to obtain the 6-membered analog by an analogous route as for the adamantanespiro-3′-pyrrolidine.[1] For that we had to prepare 2,2-bis(cyanomethyl)-adamantane. Treatment of I with malononitrile did not give a Michael reaction but instead led to the formation of adamantylidenemalononitrile in high yield (Scheme I). We carried out the reaction under various conditions, also with cyanoacetic ester as reagent, but failed to obtain the desired condensation product. A possible explanation may be steric hindrance. Following Scheme II it was possible to prepare the 6-membered ring analog.

Scheme I



I II

Treatment of adamantanespiro-2′-succinic anhydride[1] with MeOH gave the half-ester III. Reduction with LAH in Et_2O yielded the hydroxycarboxylic acid IV, which could be converted into the lactone V with TsOH. Treatment of V with KCN in DMSO resulted in the formation of VI, which could be converted into the diacid by hydrolysis. Refluxing the diacid with Ac_2O gave the anhydride VII in high yield. The cyclic imide VIII was obtained by treatment of the anhydride with $MeNH_2$ in C_6H_6. Finally reduction with LAH gave the spiro compound IX. Starting with adamantanespiro-2′-succinic anhydride[1] we were able to prepare adamantanespiro-4′-perhydroazepine XVIII and adamantanespiro-3′-piperidine XV *via* another route (Scheme III). Reduction of the anhydride with LAH in THF gave the diol X as well as 12% of the hydroxy acid IV. Treatment of the diol X with 48% HBr or with PBr_3 did not produce the de-

Scheme II