

Synthesis and Antiviral Activities of Adamantane Spiro Compounds. 1.

Adamantane and Analogous Spiro-3'-pyrrolidines

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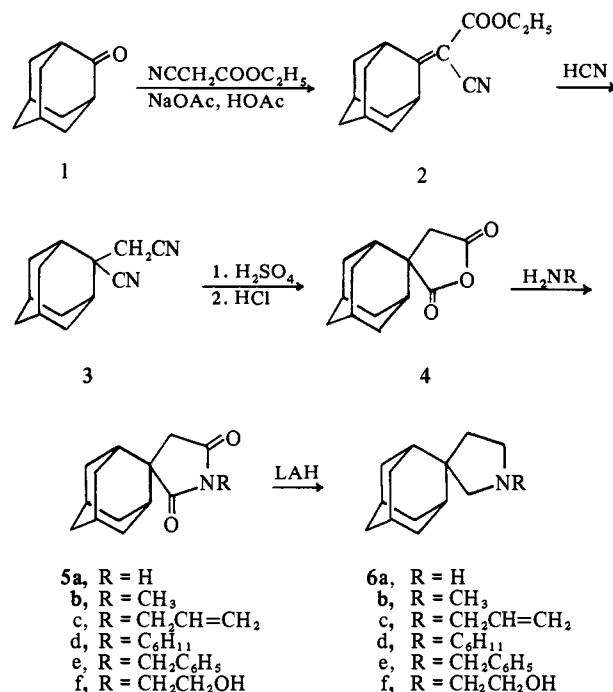
Adamantanespiro-3'-pyrrolidine and several N-substituted derivatives were synthesized. In particular smaller alkyl-substituted derivatives displayed interesting antiviral action against influenza A, parainfluenza Sendai, coxsackie A21, and rhinovirus. This activity was compared with that of spiro-pyrrolidines 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-adamantanamine¹ 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-adamantanone² 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 spiro-pyrrolidines 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

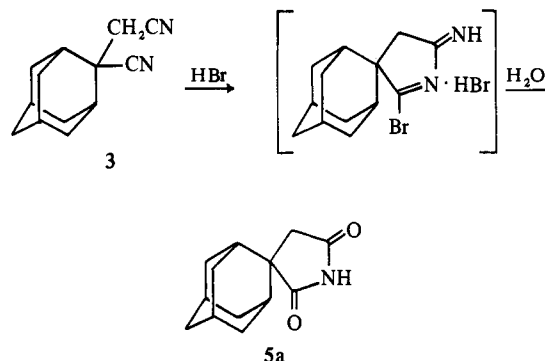
Synthesis. 2-Adamantanone (1) was condensed with cyanoacetic ester using Cope conditions⁴ to give 2 (Scheme I). Addition of HCN to 2 in strongly alkaline medium proceeded smoothly and gave, with subsequent saponification and decarboxylation, 2-cyano-2-cyanomethyladamantane (3). Hydrolysis of 3 afforded the adamantanespiro-2'-succinic anhydride (4) which was converted by treatment with NH₃ 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 product⁵ (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 dihydrochloride⁶ 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 SOCl₂. The synthesis of the spiro-pyrrolidine 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 A₂ 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



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 A₂ Japan and A₂ 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 ₂ CH=CH ₂	C ₁₆ H ₂₁ NO ₂	C, H, N	84.5-87.5	81
d	C ₆ H ₁₁	C ₁₉ H ₂₇ NO ₂	C, H, N, O	142.5-144	70
e	CH ₂ C ₆ H ₅	C ₂₀ H ₂₃ NO ₂	H, N, O; C ^b	138-138.5	90
f	CH ₂ CH ₂ OH	C ₁₅ H ₂₁ NO ₃	C, H, N, O	144-145	63

^aPrepd by procedure A described in the Experimental Section. The synthesis of 5a has been described separately. ^bC: calcd, 77.63; found, 77.13.

Table II. Adamantanespiro-3'-pyrrolidines^a

No.	R	Formula	Analyses	Mp, °C	Yield, %	Antiviral act. <i>in vivo</i> ^b
6a	H	C ₁₃ H ₂₁ N · 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 ₂ H ₅ ^c	C ₁₅ H ₂₅ N · HCl	C, H, N	266-268	87	++
i	<i>i</i> -C ₃ H ₇ ^c	C ₁₆ H ₂₇ N · HCl	C, H, N, Cl	273-276	60	+
c	CH ₂ CH=CH ₂	C ₁₆ H ₂₅ N · HCl	C, H, N, Cl	256-260 dec	83	+
d	C ₆ H ₁₁	C ₁₉ H ₃₁ N · HCl	C, H, N	262-264	47	-
e	CH ₂ C ₆ H ₅	C ₂₀ H ₂₉ N · HCl	^e	302-306	85	+
f	CH ₂ CH ₂ OH	C ₁₅ H ₂₅ NO · HCl	C, H, N, O, Cl	236-237.5	80	+
g	CH ₂ CH ₂ Cl ^c	C ₁₅ H ₂₄ ClN · HCl	H, N; C ^f	254 dec	94	+

^aPrepd by procedure B described in the Experimental Section unless otherwise stated. ^b++ = activity comparable to that of 1-adamantanamine or better; + = significant activity but less than that of 1-adamantanamine; - = inactive. ^cProcedure given separately in the Experimental Section. ^dMp of hydrochloride, 266-267.5°. ^eAnalysis for picrate (mp 171-171.5°): C, H, N, O. ^fC: calcd, 62.06; found, 61.63.

Table III. Analogous Spiro-3'-pyrrolidines

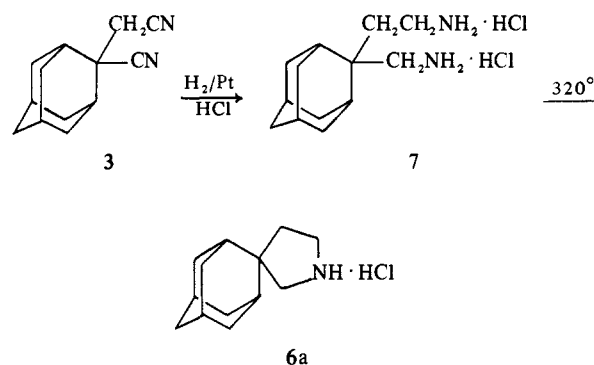
No.	Structure	Formula	Analyses	Mp, °C	Yield, %	Antiviral act. <i>in vivo</i> ^a
8		C ₁₄ H ₂₅ N · HCl	C, H; N ^b	246-247	90	+
9		C ₁₂ H ₂₁ N · HCl	C, H, N	219-221	81.5	++
10		C ₁₃ H ₂₁ N · HCl	C, H, N	186-188	70.5	+
11		C ₉ H ₁₇ N · HCl ^c		83-85 ^d		

^aSee footnote b, Table II. ^bN: calcd, 5.74; found, 6.18. ^cSee reference 8. ^dPicrate mp 148-149°, lit.^e 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 A₂ 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.

Scheme III



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 adamantanespiro-3'-pyrrolidine and its *N*-methyl derivative were prepared. Both compounds were less active *in vivo* against Influenza A₂ 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. Conc'n of compounds 10⁻⁴M. ^bIn chick embryo fibroblasts. ^cIn calf kidney cells. ^dIn M. HeLa cells. ^eSlightly toxic. ^f1-AA = 1-adamantanamine.

Experimental Section†

Ethyl adamant-2-ylidenecyanoacetate (2) was prep'd from 2-adamantanone according to Cope, *et al.*:⁴ yield, 90%; crystd from EtOH; mp 81–82°. *Anal.* (C₁₅H₁₉NO₂) 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 H₂O (140 ml) was added. The mixt was stirred and kept at 65° for 16 hr. After cooling, the ppt was filtered with suction. By conc'n of the filtrate some further crops were obtained. The crystals were stirred in a 0.2 N KOH soln (500 ml), filtered, washed with H₂O, and dried; yield, 77.5 g (96%); mp 126–127°. *Anal.* (C₁₃H₁₆N₂) C, H, N.

Adamantanespiro-2'-succinic Anhydride (4). 3 (76 g, 0.38 mole) was dissolved at 90° in conc'd H₂SO₄ (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 H₂O. The moist substance was heated, with stirring, in conc'd HCl (2.1 l.) for 2 hr at 80°. After cooling, the solid was filtered off, washed, and crystd from C₆H₆; yield, 5.6 g (76%); mp 226–229°. *Anal.* (C₁₃H₁₆O₃) 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, NH₃ 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 C₆H₆ (50 ml) and with vigorous stirring RNH₂ (0.15 mole) in C₆H₆ (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 (C₆H₆). A further crop was obtained by conc'n of the mother liquor. The solid carboxamidecarboxadamantane was heated under N₂ for 15–30 min at 220–225°. After cooling, the residue was crystd from EtOH. A further crop was obtained by addn of H₂O. 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 conc'd HCl (10 ml) was hydrogenated with PtO₂ (1 g) at 50°. After 6–8 hr the uptake of H₂ ceased. The catalyst was filtered off and a colorless soln resulted in which 6a and the diamine 7 were present ac-

ording to tlc. § The solvent was evap'd and the resulting residue was heated under N₂ 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 ext'd with CH₂Cl₂. The solvent was evap'd, the residue dissolved in MeOH (30 ml) and the soln acidified with conc'd HCl (5 ml). 6a crystd after addn of Et₂O; yield, 7.2 g (63%).

N-Ethyladamantanespiro-3'-pyrrolidine Hydrochloride (6h). The free base of 6a was acylated with Ac₂O 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). Me₂CO (4 ml, 0.05 mole) and PtO₂ (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 evap'd. Crystn (EtOH-Et₂O) 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 SOCl₂ (14 ml) and refluxed for 30 min. The SOCl₂ was then evap'd and C₆H₆ (3 × 20 ml) was added and evap'd to 7.02 g of 6g; see Table II.

2-Cyano-2-cyanomethylbornane. Ethyl born-2-ylidenecyanoacetate¹² was converted into 2-cyano-2-cyanomethylbornane according to the procedure described for 3; yield, 67%; mp 152–153°. *Anal.* (C₁₃H₁₈N₂) C, H, N.

2-Carboxy-2-carboxymethylbornane. Following the procedure used for the prep'n 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.* (C₁₃H₂₀O₄) 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 N₂. After the evoln of gas had ceased the product was dist'd *in vacuo* to yield 7.65 g of the anhydride as a waxy substance.

N-Methylbornane-2-spiro-3'-pyrrolidine-2',5'-dione. Prep'd according to method A; yield, 51%; mp 86.5–87°. *Anal.* (C₁₄H₂₁NO₂) C, H, N; O; calcd, 13.60; found, 14.01.

N-Methylbornane-2-spiro-3'-pyrrolidine hydrochloride (8) was prep'd according to procedure B (see Table III).

Ethyl Bicyclo[3.3.1]non-9-ylidenecyanoacetate. Bicyclo[3.3.1]nonan-9-one¹³ (13.2 g, 0.096 mole) was condensed with ethyl cyanoacetate by the method used for the prep'n of 2. The resulting oil was purified by dry column chromatog¹⁴ (Merck silica gel 0.05–0.2 mm; column 5 × 150 cm) with C₆H₆ yielding 10.3 g (46%) of cryst product; mp 50–51°. *Anal.* (C₁₄H₁₉NO₂) H; C; calcd, 72.07; found, 72.57.

9-Cyano-9-cyanomethylbicyclo[3.3.1]nonane. According to the procedure used for the prep'n of 3, ethyl bicyclo[3.3.1]non-9-ylidenecyanoacetate was converted into the corresponding dinitrile; yield, 96%; mp 135.5–136°. *Anal.* (C₁₂H₁₆N₂) 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 prep'n 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-one¹⁵ (30 g, 0.2 mole) was condensed with ethyl cyanoacetate as in the prep'n of 2. The resulting red oil was purified by dry column chromatog¹⁴ (Merck silica gel 0.05–0.2 mm, column 5 × 150 cm) with C₆H₆ yielding 18.8 g (38%) of a colorless oil.

5-Cyano-5-cyanomethyl perhydro-4,7-methanoindane was obt'd by the method used for the prep'n of 3; yield, 64%; mp 99–99.5°. *Anal.* (C₁₃H₁₆N₂) C, H, N.

Perhydro-4,7-methanoindane-5-spiro-3'-pyrrolidine Hydrochloride (10). By the method of Scheme III for the prep'n of 6a, 10 was obt'd from 5-cyano-5-cyanomethyl perhydro-4,7-methanoindane (see Table III).

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§ Merck, tlc-plates silica gel F 254, solvent CH₂Cl₂-EtOH-25% NH₄OH (3:3:1 v/v).

Obtained from Aldrich Chemical Co.

† 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.

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Synthesis and Antiviral Activities of Adamantane Spiro Compounds. 2¹

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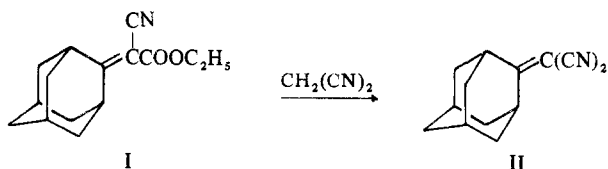
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The synthesis of adamantanespiro-3'-piperidine (XV) and adamantanespiro-4'-perhydroazepine (XVIII) is reported. These compounds can be prepared from the key intermediate 2-bromomethyl-2-(β-bromoethyl)adamantane (XII). With the latter several other 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 car-

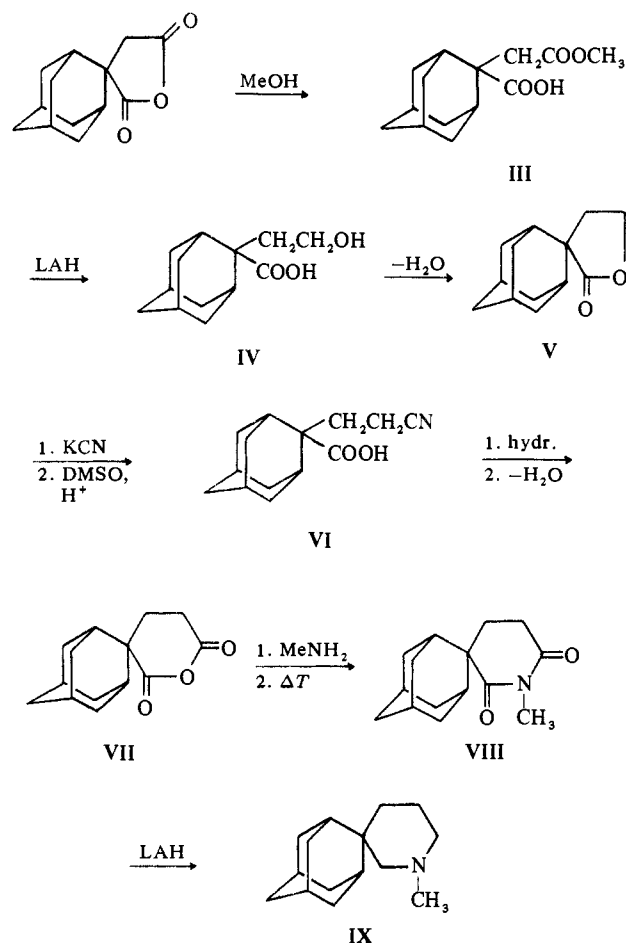
Scheme I



ried 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.

Treatment of adamantanespiro-2'-succinic anhydride¹ with MeOH gave the half-ester III. Reduction with LAH in Et₂O 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 Ac₂O gave the anhydride VII in high yield. The cyclic imide VIII was obtained by treatment of the anhydride with MeNH₂ in C₆H₆. Finally reduction with LAH gave the spiro compound IX. Starting with adamantanespiro-2'-succinic anhydride¹ we were able to prepare adamantanespiro-4'-perhydroazepine XVIII and adamantanespiro-3'-piperidine XV *via* another route (Scheme III). Re-

Scheme II



duction 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 PBr₃ did not produce the de-