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

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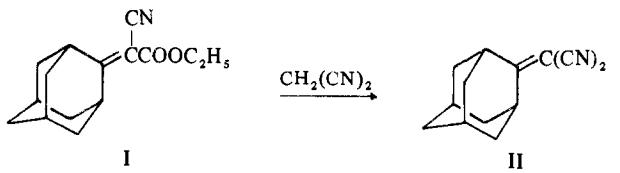
Received May 4, 1971

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.

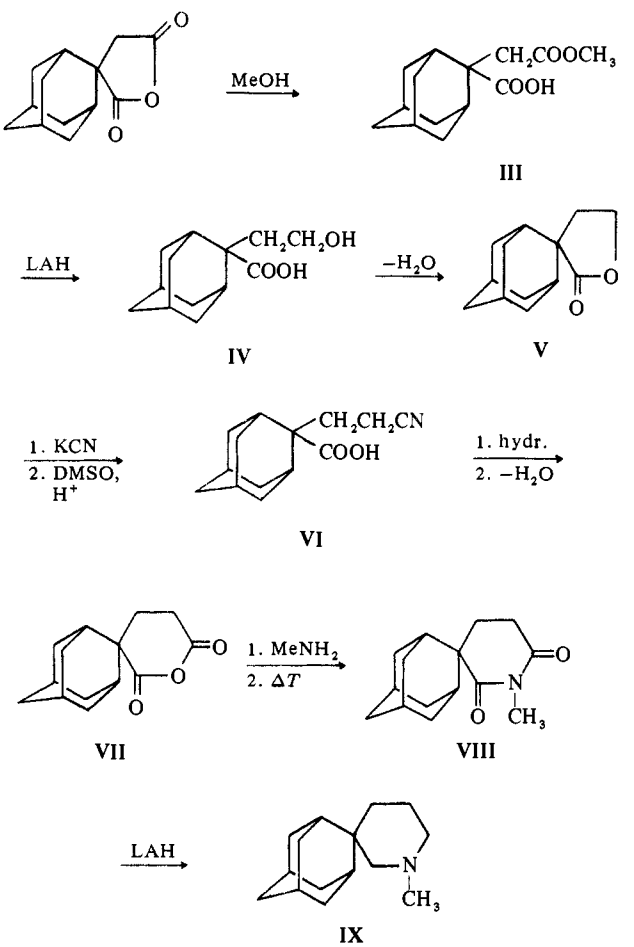
Scheme I



I II

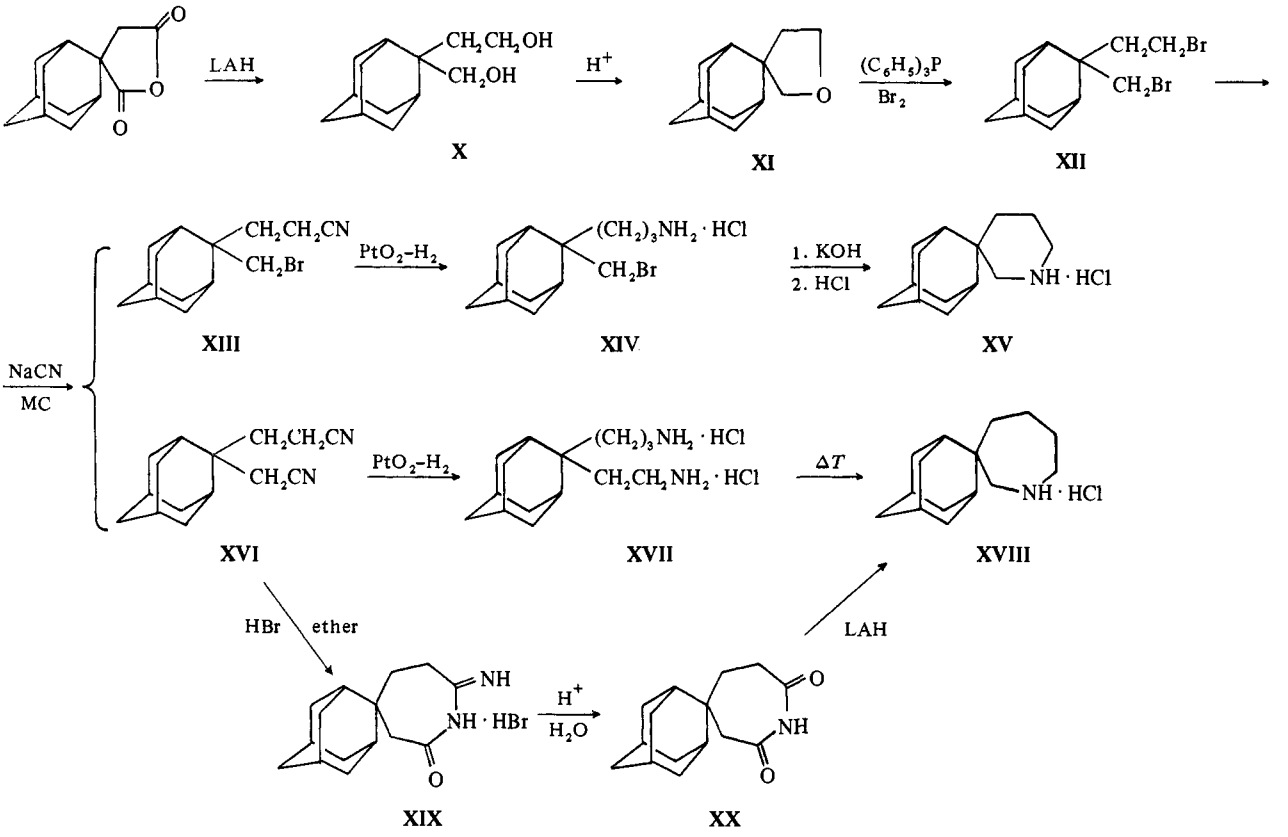
Treatment of adamantanespiro-2′-succinic anhydride[1] with MeOH gave the half-ester III. Reduction with LAH in Et_2O yielded the hydroxycarboxylic acid IV, which could be converted into the lactone V with TsOH. Treatment of V with KCN in DMSO resulted in the formation of VI, which could be converted 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



III IV V VI VII VIII IX

Scheme III



sired dibromide XII but the ether XI. The latter could be converted into the dibromide XII with Ph_3P and Br_2 in benzonitrile.[2] The reaction of the dibromide with NaCN (technical grade) in methyl Cellosolve yielded a mixture of two products, the bromocyano compound XIII in about 30% yield and the dicyano compound XVI in 50% yield, because of the slight reactivity of one of the Br atoms (neopentyl structure) of the dibromide. The 2 compounds could be separated by chromatography. Refluxing of the dibromide with dried NaCN then led to the spiro compound XXI by a Thorpe-Ziegler ring closure of the intermediate dicyanide XVI (see also "Reactions with the Dibromide XII"). The bromocyano compound XIII could be reduced with PtO_2-H_2 in EtOH-HCl to XIV, which cyclized to XV upon treatment with KOH in *n*-BuOH.

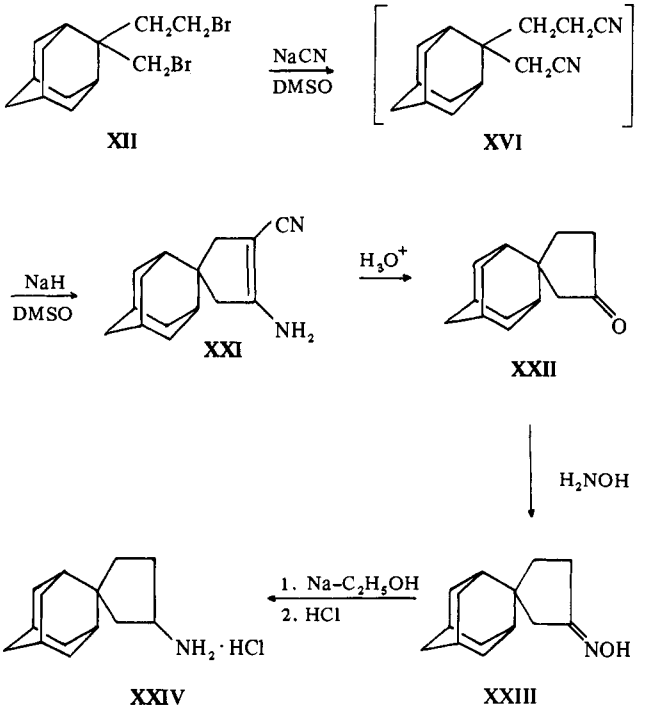
The 7-membered ring analog XVIII could be obtained from XVI by two different methods. Reduction of XVI with PtO_2-H_2 in EtOH-HCl resulted in the formation of XVII. Heating of the latter at about 290° caused ring closure; XVIII was obtained in low yield (16%). In the other method[3] the dicyanide was treated with HBr-Et_2O, followed by hydrolysis, to give the imide XX. Reduction with LAH afforded the desired compound XVIII.

Reactions with the Dibromide XII. As mentioned above, the dibromide could be cyclized to XXI by treatment with NaCN in methyl Cellosolve in a low yield. If the reaction is performed in DMSO[4] with NaH, the results are much better (Scheme IV).

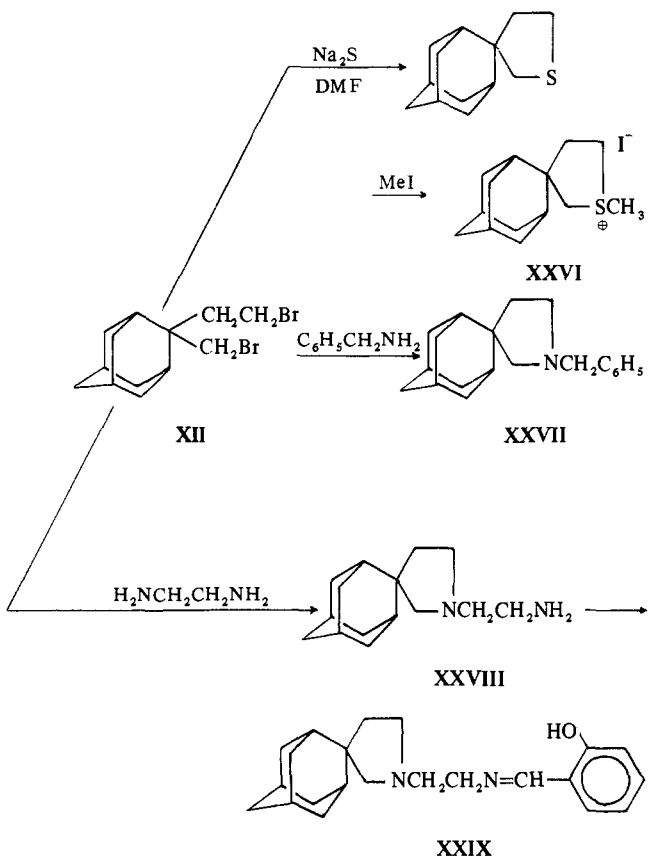
Treatment of a solution of the dibromide XII in DMSO with NaCN, followed by NaH, gave the cyclic product XXI in a yield of 75%. The yield of dinitrile, isolated in the absence of the NaH step, was about 90%. XXI on hydrolysis[5] was converted in high yield to the ketone XXII. Reaction of XXII with H_2NOH resulted in the formation of XXIII. By reduction of XXIII with Na in EtOH the amine XXIV was obtained.

The dibromide could be cyclized with Na_2S in DMF to XXV, which with MeI could be converted to the sulfonium iodide XXVI in good yield. Treatment of the dibromide with primary amines resulted in the formation of spiropyrrolidine compounds (XXVII, XXVIII). The latter com-

Scheme IV



Scheme V



idine derivative XV is about the same as that of 1-adamantanamine. Substitution at the N atom by Me (IX) reduces the activity. The perhydroazepine compound XVIII is about twice as active as 1-adamantanamine, but it still is less active than corresponding pyrrolidine compound. The cyclopentane derivative XXIV has an activity of the same order as that of the *N*-methyladamantanespiro-3′-pyrrolidine.[1] Change of the basic function to a sulfonium or hydrazino group (XXVI, XXX) destroyed, or reduced, respectively, the *in vivo* activity.

Experimental Section

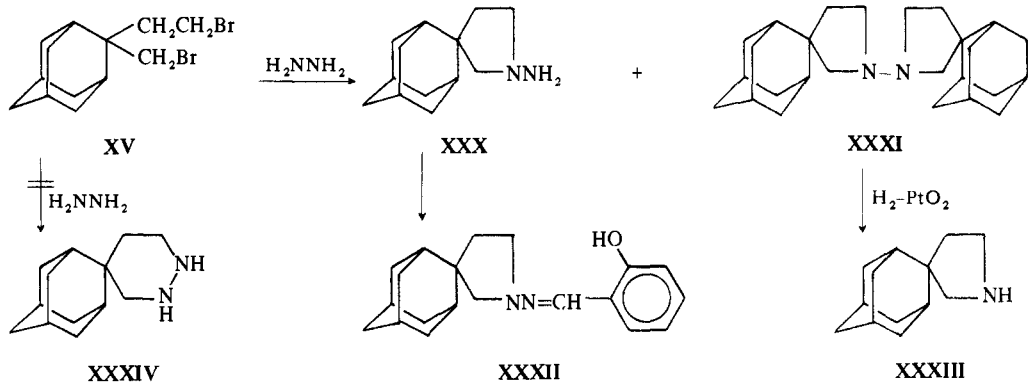
(In collaboration with Mr. H. Heym)

Melting points were determined in open capillary tubes in a Büchi apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Analyses were carried out in the laboratory of A. Bernhard, Elbach über Engelskirchen, West Germany, and in the laboratory of Dornis und Kolbe, Mülheim a.d. Ruhr, West Germany. Ir and mass spectra were recorded, respectively, on a PE 337 and a MS 9 AE 1 spectrometer. Nmr spectra were measured on a Varian HA-100 instrument (Me_4Si). The recording and interpretation of the spectra were carried out under the supervision of Mr. F. W. van Deursen.

Adamantylidenemalononitrile (II). A mixt of 2 g of I and 2.41 g of malononitrile in 10 ml of pyridine was stirred at room temp for 23 hr. The reaction mixt was poured into 250 ml of 2 *N* HCl. The ppt was filtered and crystd from EtOH: yield 1.5 g (94%); mp 180–182°. The compd was identical with an authentic sample.

2-Carboxy-2-methoxycarbonylmethyladamantane (III). A mixt of 15.62 g of adamantanespiro-2′-succinic anhydride,[1] 250 ml of MeOH, and 15 ml of pyridine was boiled for 3 hr, after which the solvent was evapd *in vacuo* and the residue dissolved in 2 *N* KOH. The alkaline soln was washed with Et_2O and then acidified with 2 *N* HCl. The acid soln was extd with Et_2O: yield 16 g (90%) after

Scheme VI



pound was converted to the salicylideneimide XXIX (Scheme V).

The reaction of the dibromide XII with $H_2NNH_2 \cdot H_2O$ gave 2 crystalline products, XXX and XXXI (Scheme VI). The ir spectrum of XXX in CCl_4 displayed bands at 3380, 3200, and 3135 cm^{-1}, characteristic[6] of an $>NNH_2$ group, and excluded the other possible isomer XXXIV. This also followed from the reaction of XXX with salicylaldehyde to a Schiff base. The structure of XXXI was proved by catalytic hydrogenolysis which led to the formation of adamantanespiro-3′-pyrrolidine.

Antiviral Properties. The *in vivo* antiviral activities against influenza A_2 Japan are present in Table I. In *in vitro* experiments these compounds generally appeared to be cytotoxic except the two piperidine derivatives IX and XV. Estimation of *in vitro* antiviral activities was therefore not possible by the used method. The *in vivo* activity of the piper-

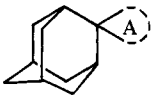
crystn from Et_2O; mp 101–104°; equiv wt, found 247.5; calcd 252.

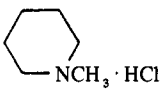
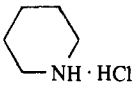
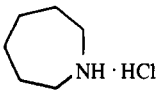
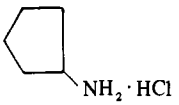
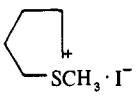
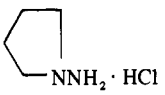
2-Carboxy-2-(β-hydroxyethyl)adamantane (IV). A mixt of 1.81 g of III, 900 mg of LAH, and 90 ml of Et_2O was refluxed 10 min, cooled, decompd with 2 *N* H_2SO_4, and extd with Et_2O. The Et_2O soln was extd with 2 *N* KOH, and then the alkaline soln was acidified. The ppt was filtered and crystd from Me_2CO–hexane: yield 1.28 g (80%); mp 188–191°; equiv wt, found 223; calcd 224. After evapn of the Et_2O soln and crystn of the residue from hexane, 2-hydroxymethyl-2-(β-hydroxyethyl)adamantane (X) was isolated as a by-product: yield 0.19 g (13%); mp 108–110°.

2′-Oxoadamantanespiro-3′-tetrahydrofuran (V). A suspension of IV (9 g) and 50 mg of TsOH in 150 ml of C_6H_6 was refluxed and the H_2O formed was removed by distn. After cooling, the C_6H_6 soln was dried (K_2CO_3) and evapd. Crystn from Me_2CO–hexane afforded pure product: yield 7.8 g (94%); mp 174–177°; mass spectrum, M^+ 206; nmr spectrum ($CDCl_3$), 2 triplets centered at δ 2.34 and 4.17, respectively (CH_2CH_2O); ir spectrum (KBr); 1760 cm^{-1} (γ-lactone).

2-Carboxy-2-(β-cyanoethyl)adamantane (VI). A mixt of 5.5 g of KCN and 5.54 g of V in 110 ml of dry DMSO was refluxed 4 hr, cooled, and poured into 500 ml of H_2O. After acidification with

Table I. Adamantane Spiro Compounds



No.	A	Formula	Analyses	Antiviral act. *in vivo*[a]
IX		$C_{15}H_{26}ClN$	C, H, Cl, N	+
XV		$C_{14}H_{24}ClN$	C, H, Cl, N	++
XVIII		$C_{15}H_{26}ClN$	C[b], H, N	++
XXIV		$C_{14}H_{24}ClN \cdot 0.25H_2O$	C, H, Cl, N	++
XXVI		$C_{14}H_{23}IS$	C, H, I, S	–
XXX		$C_{13}H_{23}ClN_2$	C, H, Cl, N	+

[a] ++ = activity comparable to that of 1-adamantanamine or better; + = significant activity but less than that of 1-adamantanamine; – = inactive. For test conditions see previous paper. [b] C: calcd, 70.4; found, 69.7.

2 *N* HCl the ppt was filtered and crystd from C_6H_6: yield 6 g (96%); mp 150–152°; equiv wt, found 232; calcd 233.

2-Carboxy-2-(β-carboxyethyl)adamantane. VI (6 g), dissolved in 250 ml of 2 *N* NaOH, was refluxed 18 hr. After cooling, the soln was acidified with 2 *N* HCl, and the ppt was filtered: yield 6 g (93%); mp 270–277° after crystn from EtOH; equiv wt, found 128; calcd 126.

2',6'-Dioxoadamantanespiro-3'-tetrahydropyran (VII). A mixt of 1.52 g of 2-carboxy-2-(β-carboxyethyl)adamantane and 30 ml of Ac_2O was refluxed for 2 hr. Then the Ac_2O was evapd *in vacuo*: yield 1.32 g (93%); mp 126–128° after crystn from Me_2CO–hexane; ir spectrum (KBr), 1770 (C=O) and 1805 cm^{-1} (C=O).

2-(*N*-Methyl-β-carboxamidoethyl)-2-carboxyadamantane. A soln of 0.5 g of VII in 60 ml of dry C_6H_6 was refluxed and $MeNH_2$ was introduced simultaneously up to satn. The $MeNH_2$ salt was filtered, dissolved in H_2O, and acidified with 2 *N* HCl. The ppt was filtered and crystd from EtOH–C_6H_6: yield 0.55 g (98%); mp 236–239°; ir spectrum (KBr), 3390 (NH), 2500 (broad, COOH), 1690 (COOH), 1615 cm^{-1} (NC=O).

2',6'-Dioxo-*N*-methyladamantanespiro-3'-piperidine (VIII). 2-(*N*-Methyl-β-carboxamidoethyl)-2-carboxyadamantane (0.5 g) was heated in a sublimation apparatus under N_2 at 250–300°. Sublimate and residue were suspended in CH_2Cl_2 and filtered. The undissolved product was sublimed again. The CH_2Cl_2 soln was evapd and the residue sublimed at 200–300° (15 mm). Crystn from EtOH–H_2O afforded pure VIII: yield 360 mg (78%); mp 119–121°; nmr spectrum (CCl_4), singlet at δ3.01 (NCH_3) and 2 triplets centered at δ2.00 and 2.54 (CH_2CH_2C=O).

***N*-Methyladamantanespiro-3'-piperidine Hydrochloride (IX).** A mixt of VIII (0.5 g) and LAH (0.25 g) in 100 ml of dry Et_2O was refluxed for 5 hr, then the reaction complex was decompd with H_2O and extd with Et_2O. EtOH–HCl was added to the dried Et_2O soln. The ppt was filtered and sublimed at 250–300° (15 mm): yield 687 mg (41.6%); mp 301–306° after recrystn from EtOH–C_6H_6. *Anal.* ($C_{15}H_{26}ClN$): C, H, Cl, N.

2-Hydroxymethyl-2-(β-hydroxyethyl)adamantane (X). Adamantanespiro-2'-succinic anhydride (73 g) was added to 1300 ml of dry THF, followed by slow addn of 21.3 g of LAH. The mixt was boiled for 16 hr, then cooled. Thereupon a mixt of 50 ml of H_2O and 200 ml of THF was added slowly, followed by 500 ml of 2 *N* H_2SO_4. The solids were filtered with suction and washed with THF. The THF soln was washed with a satd NaCl soln and dried ($MgSO_4$); the THF was evapd, and the residue (69.4 g) was added to a mixt of 3800 ml of CH_2Cl_2 and 2700 ml of 1 *N* NaOH. After sepn, the H_2O layer was extd once with 250 ml of CH_2Cl_2. After being dried ($MgSO_4$), the CH_2Cl_2 was evapd, yielding 59.7 g (85.6%) of pure X: mp 109–111°; nmr spectrum ($CDCl_3$), singlet at δ3.82 (CH_2O) and 2 triplets centered at, respectively, δ1.94 and 3.78 (CH_2CH_2O). The H_2O layer was acidified with concd HCl and the ppt filtered: yield 8.95 g (12%) of IV.

Adamantanespiro-3'-tetrahydrofuran (XI). A mixt of 114 ml of 48% HBr, 59.7 g of X, and 11.4 ml of 96% H_2SO_4 was stirred and heated for 3 hr at 110–115°. After cooling, 50 ml of H_2O was added and the mixt was extd with four 100-ml portions of CH_2Cl_2. The combined exts were washed with a 10% $NaHCO_3$ soln and dried ($MgSO_4$). The product was a brown oil: yield 50.7 g (92.9%); nmr spectrum ($CDCl_3$), singlet at δ3.70 (CH_2O) and 2 triplets centered at, respectively, δ1.84 and 3.79 (CH_2CH_2O).

2-Bromomethyl-2-(β-bromoethyl)adamantane (XII). A stirred soln of 62.3 g of Ph_3P in 245 ml of PhCN was treated slowly at 0° with 12.3 ml of Br_2. On completion of the addn, the reaction mixt was heated to 125°, and then 42.2 g of XI was added in 0.5 hr, after which the temp was maintained at 125° for a further 3 hr. After cooling, the reaction mixt was chromatogd over a silica gel column, with petr ether (bp 40–60°) as eluant: yield 63.5 g (86%) after crystn from hexane; mp 80–81°. *Anal.* ($C_{13}H_{20}Br_2$): C, H, Br.

2-Bromomethyl-2-(β-cyanoethyl)adamantane (XIII) and 2-Cyanomethyl-2-(β-cyanoethyl)adamantane (XVI). A mixt of 16.8 g of XII and 5.1 g of NaCN (tech grade) in 50 ml of methyl Cellosolve was stirred and refluxed for 5 hr. Then the solvent was evapd *in vacuo*, and the residue was chromatogd over a silica gel column, with CH_2Cl_2 as eluant. Fraction I, 4.07 g (28.8%) of XIII, had mp 75.5–77° after crystn from hexane. *Anal.* ($C_{14}H_{20}NBr$): H, N, Br. C: calcd, 59.57: found, 60.51. Fraction II, 5.61 g (49%) of XVI, had mp 116–118° after crystn from C_6H_6–hexane. *Anal.* ($C_{15}H_{20}N_2$): C, H, N.

3'-Cyano-4'-aminoadamantanespiro-3'-cyclopentene (XXI). A mixt of 7.05 g of XII and 2.93 g of NaCN (dried *in vacuo* at 110°) in 50 ml of methyl Cellosolve was refluxed for 96 hr. After evapn of the solvent under reduced pressure the residue was suspended in 100 ml of H_2O and extd with four 100-ml portions of CH_2Cl_2. After evapn of the CH_2Cl_2, 6.9 g of solid was obtained. Crystn from C_6H_6

afforded 1.5 g of XXI (31%): mp 239–241°; mass spectrum; exact mass found 228.1624; calcd 228.1626. A better method for prepg XXI is the following. A mixt of 6.05 g of XII, 2.7 g of dry NaCN, and 75 ml of dry DMSO was stirred at room temp for 0.5 hr, followed by stirring at 50° for 105 min, at 80° for 75 min, and 2 hr at 110°. After the mixture had cooled, 0.88 g of NaH (50% dispersion in oil) was added. The suspension was heated to 95° in 15 min and, after being stirred for another 1.5 hr, the reaction mixt was cooled and poured into 500 ml of cold H_2O. The ppt was filtered, washed with H_2O, and dried: yield 3.1 g (75%); mp 238–240°.

Adamantanespiro-3′-cyclopentanone (XXII). A soln of 325 mg of XXI in 10 ml of AcOH and 0.6 ml of H_2O was refluxed for 15 min; then 4 ml of 85% H_3PO_4 was added and the mixt was refluxed under N_2 for 21 hr. After cooling, the reaction mixt was poured into ice-H_2O and the ppt was filtered with suction: yield 250 mg (85%); mp 50.5–51.5° after crystn from EtOH-H_2O. *Anal.* $C_{14}H_{20}O$: C, H, O.

Adamantanespirocyclo-3′-pentanone Oxime (XXIII). A mixt of 0.7 g of KOH, 1.25 g of $H_2NOH \cdot HCl$, and 50 ml of EtOH was stirred for 15 min, filtered, and added to a soln of 1.1 g of XXII in 15 ml of EtOH. After refluxing for 1 hr, the solvent was evapd *in vacuo* and the residue was crystd from hexane: yield 1.1 g (90%); mp 127–129.5°.

Adamantanespiro-3′-aminocyclopentane Hydrochloride (XXIV). A refluxing soln of 0.9 g of oxime XXIII in 60 ml of dry EtOH was treated with 8 g of small pieces of Na in about 2 hr under N_2. To the cooled soln, H_2O and ice (about 300 ml) were added and the reaction mixt was extd with three 100-ml portions of CH_2Cl_2. After drying and evapn of the CH_2Cl_2, a yellow oil was obtained, which was treated with Et_2O and EtOH-HCl: yield 0.9 g (91%); mp 281–283°. *Anal.* ($C_{14}H_{24}ClN \cdot 0.25H_2O$): C, H, Cl, N.

2-(γ-Aminopropyl)-2-bromomethyladamantane Hydrochloride (XIV). A mixt of 2.4 g of XIII, 0.7 g of PtO_2, 100 ml of EtOH, and 4.25 ml of 4.5 *N* EtOH-HCl was reduced in a Parr apparatus in 17 hr. The reaction mixt was filtered and most of the EtOH evapd. After addn of Et_2O, the ppt was filtered and dried: yield 2.28 g (83%); mp 214–215°. *Anal.* ($C_{14}H_{25}BrClN$): C, H, Br, Cl.

2-(γ-Aminopropyl)-2-(β-aminoethyl)adamantane Dihydrochloride (XVII). A mixt of 2.8 g of XVI, 1.2 g of PtO_2, 160 ml of EtOH, and 10 ml of 4.1 *N* EtOH-HCl was reduced in a Parr apparatus in 17 hr. After filtration, most of the EtOH was evapd. Then THF was added, and the ppt was filtered with suction: yield 3.58 g (94%); mp 290–292°. *Anal.* ($C_{15}H_{30}Cl_2N_2$): C, H, Cl, N.

Adamantanespiro-3′-piperidine Hydrochloride (XV). A soln of 3.23 g of XIV in 300 ml of *n*-BuOH was added slowly to a stirred and refluxing soln of 1.68 g of KOH in 200 ml of *n*-BuOH. After being refluxed for 12 hr the reaction mixt was cooled, filtered, and evapd to dryness *in vacuo*. The residue was suspended in 100 ml of H_2O and extd with six 40-ml portions of CH_2Cl_2. After drying of the org layer ($MgSO_4$), EtOH-HCl was added, and then the reaction mixt was evapd to dryness: yield 1.63 g (68%) after crystn from EtOH-THF; mp 252–255°. *Anal.* ($C_{14}H_{24}ClN$): C, H, Cl, N.

Adamantanespiro-4′-perhydroazepine Hydrochloride (XVIII). Compd XVII (190 mg) was heated in a sublimation apparatus at 290° until sublimation ceased. The sublimed product was dissolved in 25 ml of H_2O and washed with Et_2O. Then the H_2O layer was made alkaline and extd with three 10-ml portions of Et_2O. After drying ($MgSO_4$) and the addn of EtOH-HCl, the soln was evapd. The residue was shaken with THF and filtered: yield 26 mg (16.5%); mp 255–262°. *Anal.* ($C_{15}H_{26}ClN$): H, N. C: calcd, 70.42; found, 69.79.

2′,7′-Dioxoadamantanespiro-4′-perhydroazepine (XX). HBr was introduced into a mixt of 5 g of XVI and 200 ml of Et_2O at 0°, until the solid material had dissolved. After standing for 17 hr, the Et_2O was evapd *in vacuo*, and the residue was stirred for 1 hr at 100° in 17 ml of H_2O acidified with a few drops of 48% HBr. After evapn of the solvent *in vacuo* the residue was boiled with 65 ml of C_6H_6 and filtered. After concn of the C_6H_6 soln to 25 ml it was cooled. The ppt was filtered, yielding 560 mg (10.4%) of XX: mp 234–236°; mass spectrum, M^+ 247; ir spectrum (KBr), 3175, 3070 (NH), 1715 (C=O), 1680 cm^{-1} (C=O).

Adamantanespiro-4′-perhydroazepine Hydrochloride (XVIII). A mixt of 560 mg of XX and 0.4 g of LAH in 12 ml of THF was refluxed for 4 hr under N_2, then cooled. Thereupon 1.6 ml of H_2O and 0.4 ml of 15% NaOH were added slowly. The ppt was filtered and washed with THF. After addn of EtOH-HCl the THF was evapd *in vacuo*. The residue was dissolved in 50 ml of H_2O, washed with Et_2O, made alkaline, and extd with three 20-ml portions of Et_2O. After drying of the combined exts, EtOH-HCl was added. The ppt was filtered and crystd from EtOH-Et_2O: yield 0.48 g (83%); mp 259–263°. This product was identical with that obtd by heating of XVII.

Adamantanespiro-3′-tetrahydrothiophene (XXV). A soln of 8.4 g of $Na_2S \cdot 9H_2O$ in 9 ml of H_2O was treated with 3.9 g of XII and 45 ml of DMF. This mixt was maintained at room temp for 15 min and then refluxed for 1 hr. After cooling, the reaction mixt was poured into 300 ml of H_2O and extd with three 100-ml portions of Et_2O. The combined Et_2O exts were washed with H_2O, dried ($MgSO_4$), and evapd: yield 2.3 g (95%) of a yellow-orange oil; nmr spectrum ($CDCl_3$), singlet at δ2.83 (CH_2S), triplet centered at 2.81 (CCH_2S), and triplet centered at 2.01 (CH_2CS).

***S*-Methyladamantanespiro-3′-tetrahydrothiophonium Iodide (XXVI).** A mixt of 1.54 g of XXV and 30 ml of MeI was stirred for 24 hr at room temp. The cryst solid was filtered and washed with Et_2O: yield 2.41 g (93%); mp 181–183° (from EtOH). *Anal.* ($C_{14}H_{23}IS$): C, H, I, S.

***N*-Benzyladamantanespiro-3′-pyrrolidine (XXVII).** A mixt of 320 mg of $C_6H_5CH_2NH_2$, 300 mg of XII, 8 ml of xylene, and a few mg of NaI was refluxed for 48 hr. After the reaction mixt had cooled, 100 ml of Et_2O was added, and the mixt extd with four 30-ml portions of 0.2 *N* HCl. The H_2O soln was made alkaline and extd with four 30-ml portions of Et_2O. After drying and evapn of the Et_2O, an oil was obtained which was chromatogd over a silica gel column, with Et_2O as eluant. The oil obtained was treated with Et_2O and EtOH-HCl. The ppt was filtered, yielding 50 mg of XXVII: mp 285–290°. This compd was identical with an authentic sample.[3]

***N*-(β-Aminoethyl)-adamantanespiro-3′-pyrrolidine (XXVIII).** A soln of 3.5 g of XII and 50 ml of $H_2NCH_2CH_2NH_2$ in 300 ml of EtOH was refluxed for 68 hr. The solvent was evapd and the residue treated with 150 ml of H_2O and 20 ml of concd HCl and then extd with three 50-ml portions of CH_2Cl_2. The H_2O soln was made alkaline and extd with four 50-ml portions of CH_2Cl_2. The CH_2Cl_2 was evapd, yielding 2.3 g (94%) of a yellow oil. Treatment of the oil with EtOH-HCl in THF resulted in the formation of the di-HCl salt: mp 255–258°.

***N*-[*N*′-Salicylidene-(β-aminoethyl)]adamantanespiro-3′pyrrolidine (XXIX).** A mixt of 230 mg of XXVIII, 160 mg of salicylaldehyde, and 1 ml of EtOH was refluxed for 1 hr. After cooling, the cryst ppt was filtered: yield 235 mg (71%); mp 93.5–94.5°. *Anal.* ($C_{22}H_{30}N_2O$): C, H, N, O.

***N*,*N*′-Bis(adamantanespiro-3′-pyrrolidine) (XXXI) and *N*-Aminoadamantanespiro-3′-pyrrolidine (XXX).** A mixt of 2.0 g of XII and 45 ml of $H_2NNH_2 \cdot H_2O$ was stirred and heated for 24 hr at 120°. After evapn of most of the $H_2NNH_2 \cdot H_2O$ *in vacuo*, the residue was suspended in 50 ml of H_2O and then extd with four 100-ml portions of Et_2O. The combined Et_2O solns were washed with a satd NaCl soln and dried ($MgSO_4$), and then the Et_2O was evapd. The residue was chromatogd over a silica gel column, with Et_2O and an increasing amount of EtOH being used as eluant. Fraction I, 200 mg (17%) of compd XXXI, had mp 117–119° after crystn from hexane; mass spectrum, M^+ 380; XXXI · HCl, mp 213–215°. *Anal.* ($C_{26}H_{41}ClN_2$): C, H, Cl, N. The structure was proved by redn of XXXI. A mixt of 85 mg of XXXI, 40 ml of EtOH, 10 ml of H_2O, 1 ml of concd HCl, and 60 mg of PtO_2 was treated in a Parr apparatus with H_2 for 4 hr. After filtration and evapn of the solvent, Et_2O was added, and the ppt was filtered: yield 82 mg (80%). This compd was identical with the compd described in part 1[1] and prepd *via* a different route.

Fraction II was obtained as 500 mg (40%) of compd XXX (oil). With EtOH-HCl in THF the HCl salt was obtained: mp 193.5–195.5° after crystn from THF-MeOH. *Anal.* ($C_{13}H_{23}ClN_2$): C, H, Cl, N.

***N*-Salicylideneamino)adamantanespiro-3′-pyrrolidine (XXXII)** was prepd in the same way as XXIX: yellow needles, mp 108–108.5°. *Anal.* ($C_{20}H_{26}N_2O$): C, H, N, O.

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