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# SYNTHESIS OF SOME 4-MONO- AND 4,5-DISUBSTITUTED HOMOADAMANTANES (TRICYCLO [4·3·1·$1^{3,8}$]UNDECANES)

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**Abstract**—The synthesis of homoadamantanone, homoadamantanedione and some derivatives thereof is described. X-ray analysis of the dione (VII) showed the dihedral angle between the carbonyl groups to be small. Reduction of the homoadamantanone oxime (IV) afforded a very stable aziridine (X) in surprisingly high yield.

The homoadamantane derivatives hitherto described in the literature have been obtained in two ways:

1. by rearrangement of the adamantyl-1-methyl cation, in which way 3- or 3,4-substituted homoadamantanes have been obtained[1,2,3];
2. by ring closure reactions of dimethylbicyclo[3.3.1]nonane-2,6-dione 3,7-dicarboxylate, leading to 2,3,6,7-tetrasubstituted homoadamantanes[4].

In this paper we describe another route to the homoadamantane system which provided us with the unknown* homoadamantan-4-one (tricyclo[4.3.1.$1^{3,8}$]undecan-4-one). This compound enabled us to synthesize 4-mono- and 4,5-disubstituted homoadamantanes. The key reaction in this route was the Demjanov-Tiffeneau ring enlargement[5] of 2-aminomethyl-2-hydroxyadamantane (II) to homoadamantan-4-one (III; fig. 1). 2-Aminomethyl-2-hydroxyadamantane was prepared by known methods from adamantanone in good yields. In this way homoadamantan-4-one was obtained from adamantanone in 48% yield.

Starting from III we have prepared several derivatives. Oximation[6] of III gave homoadamantan-4-one oxime (IV) in 63% yield. According to the NMR spectrum only one isomer was isolated. Its structure could only be established after the other isomer had also been prepared. This was achieved by an oximation of homoadamantan-4-one under strongly alkaline conditions, which led to a mixture of both possible isomers. By comparison of the NMR spectra of this mixture and the pure compound IV the structure of IV was shown to be that with the hydroxyl group anti to the bridgehead carbon atom $\alpha$ to the oximino group.

Bromination of III gave 5-bromohomoadamantan-4-one (VI) in 26% yield. Oxidation of III with $SeO_2$ in dioxan afforded homoadamantane-4,5-dione (VII) in 61% yield.

* After the manuscript had been completed, two communications were published on the synthesis of homoadamantan-4-one: J. E. Nordlander, F.Y–H. Wu and S. P. Jindal, *J. Am. Chem. Soc.* **91**, 3962 (1969); P. von R. Schleyer, E. Funke and S. H. Liggero, *Ibid.* **91**, 3965 (1969). Their results point to the same conclusion about the stereochemistry of the homoadamantane system.

From the homoadamantan-4-one oxime (IV) the corresponding 4-homoadamantanamine (VIII) was prepared by reduction with Raney nickel alloy in aqueous alkali as described by Staskun and v. Es[7]. This amine was of interest to us with respect to its potential antiviral properties compared with those of 1- and 2-adamantanamine.[8,9]* From the bromoketone VI no other derivatives were obtained. Reactions with amines have failed so far.

The homoadamantane-4,5-dione afforded a quinoxaline (IX) by a reaction with *o*-phenylenediamine. To our knowledge IX is the first example of a homoadamantane molecule fused with an aromatic ring.

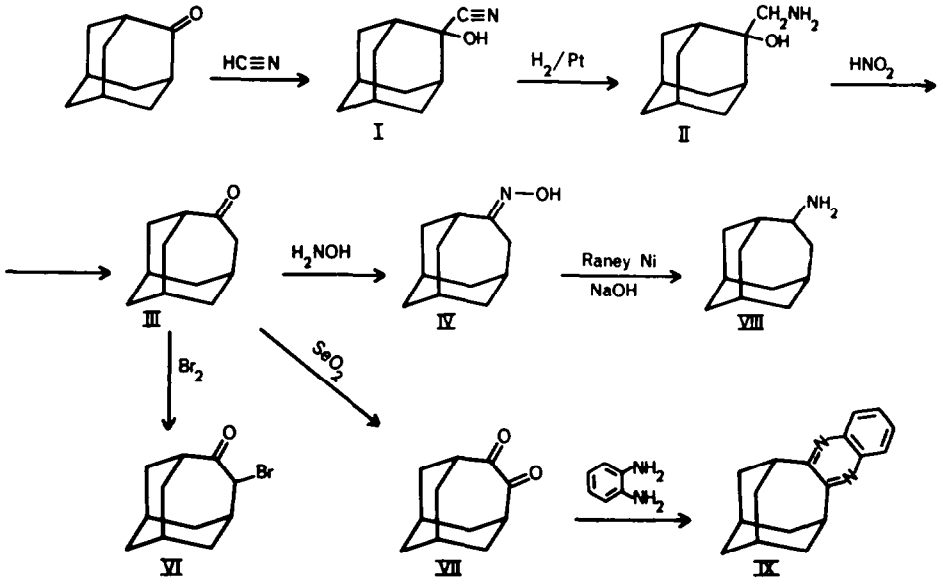


FIG. 1

The UV spectrum of homoadamantane-4,5-dione (VII) took our special interest. Leonard and Mader[10] studied the relation between $\lambda_{max}$ of non-enolizable α-diketones in the UV and the angle between the planes of the carbonyl groups as deduced from molecular models. According to this relationship a $\lambda_{max}$= 418 nm ($\varepsilon$ = 27, ethanol) found for homoadamantane-4,5-dione pointed to an angle ($\ll 60°$) between the CO groups that is rather small compared with the angle of 90–110° found for a non-bridged 7-ring diketone.

An X-ray analysis† of VII confirmed this indication and proved the correctness of the relation established by Leonard and Mader, at any rate in this case. This analysis showed the dihedral angle of the C=O bonds to be as small as 11·9° (Fig. 2). Clearly

* A preliminary investigation has shown that the antiviral properties of this compound are comparable with those of 1-aminoadamantane. Personal communication, A. Peters; N. V. Philips-Duphar Research Laboratories.

† Detailed results of this analysis will be published in a separate paper: P. B. Braun, J. Hornstra and J. I. Leenhouts, Res. Lab. N. V. Philips Gloeilampenfabrieken Eindhoven, The Netherlands, to be published.

a 7-membered ring nearly flat from $C_3$ to $C_6$ is favoured in the dione notwithstanding the strong dipole–dipole interaction of the CO groups. A similarly shaped 7-membered ring might be presumed to be present in other homoadamantane derivatives, in which such dipole–dipole interactions are not found.

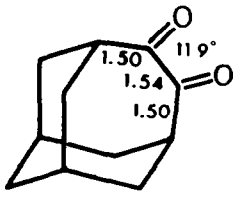


FIG. 2 C—C distances (in Å) and dihedral angle between the carbonyl groups in homoadamantane-4,5-dione.

A striking reaction occurred on reducing homoadamantanone oxime (IV) with LAH in THF. Surprisingly this reduction afforded the *cis*-aziridine (X) in 85% yield (Fig. 3), isolated as a stable hydrochloride. Its structure was established by NMR.

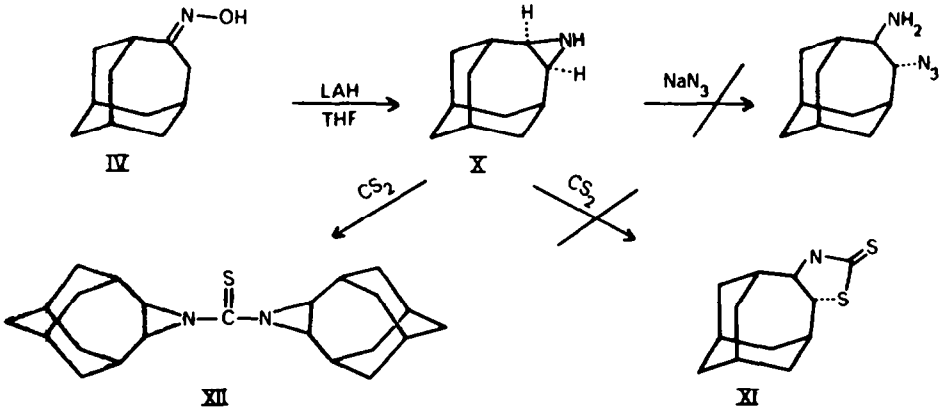


FIG. 3

The synthesis of aziridines by reduction of oximes has been described in the literature[11], but the yields reported for (bridged) alicyclic systems were very poor. Our other results were in agreement with those reported, i.e. the formation of the aziridines depended on the stereochemistry of the oxime used*, only *cis*-aziridines were formed and ring-closure to a tertiary C atom did not occur. The aziridine (X) showed a remarkable stability: a ring-opening with $NaN_3$, as reported for the analogous cyclohexyl derivative[12], was impossible under the same conditions (Fig. 3). Moreover, after a reaction with $CS_2$ the thiocarbonyl compound (XII) was isolated instead of the expected thiazolidine–thione (XI).[13] The ease of formation of this aziridine and its stability might be connected with the almost coplanar position of $C_3$, $C_4$, $C_5$ and $C_6$ in

* The influence of the stereochemistry on the reduction was illustrated by a reduction of an isomer mixture (IV + V in the ratio 1 : 2), yielding a mixture of the aziridine (X) and the amine (VIII) in the ratio 1 : 2.

the homoadamantane skeleton. This coplanarity requires almost eclipsed bonds at $C_4$ and $C_5$ and is therefore favourable for the formation and the stability of a *cis*-aziridine.

## EXPERIMENTAL

*General.* Mps. were measured in closed capillary tubes in an electrically heated aluminium block. Temp was indicated by a chromel–alumel couple on a Philips G.M. 6020 tube voltmeter. IR spectra were recorded on a Perkin Elmer Model 337. NMR spectra were measured on a Varian HA 100 spectrometer. Chemical shifts were expressed in ppm, TMS was used as an internal standard. UV spectra were determined using a Beckmann DK 2 spectrophotometer. Mass spectra were obtained with an AEI–MS 9 mass spectrometer. Micro-analyses were performed by A. Bernhardt, Mikroanalytisches Laboratorium, Elbach über Engelskirchen, W. Germany, or by Dornis und Kolbe, Mikroanalytisches Laboratorium, Mülheim a.d. Ruhr, W. Germany.

*2-Cyano-2-hydroxyadamantane* (I).

Liquid HCN (350 ml) was added to a soln of adamantanone[14] (350 g 2·3 moles) in dry pyridine (700 ml). The reaction mixture was kept overnight at room temp and the excess of HCN together with the pyridine was distilled *in vacuo*. The residue was crystallized from light petroleum (60–80°; 1800 ml), yield 341 g (82%), m.p. 232–233·5°. (Found: C,74·62; H, 8·41; N, 8·05. Calc. for $C_{11}H_{15}NO$: C,74·56; H, 8·53; N, 7·90%); IR (KBr) 3400 (OH), 2240 (C≡N) $cm^{-1}$; MS mass of the molecular ion: Found 177·1153; Calc. for $C_{11}H_{15}NO$ 177·1154.

*2-Aminomethyl-2-hydroxyadamantane hydrochloride* (II)

To a soln of I, (12·4 g, 0·07 mole) in EtOH (175 ml) ethanolic HCl (23 ml 3·2 N) and $PtO_2$ (1·2 g) were added. The mixture was hydrogenated in a Parr apparatus at 4 atm $H_2$ press. After the calculated amount of $H_2$ had been consumed (24 hr), EtOH (40 ml) was added and the mixture was heated to dissolve the ppt. The catalyst was filtered off and the warm filtrate was concentrated to about 60 ml. After cooling the crystals were filtered off and washed with EtOH and $Et_2O$ and dried, yield 10·3 g (65%), m.p. 288–290°C (dec). (Found: C, 60·85; H, 9·15; N, 6·79. Calc, for $C_{11}H_{20}ClNO$: C, 60·64; H, 9·26; N, 6·44%).

*Tricyclo[4.3.1.1$^{3,8}$]undecan-4-one* (III)

The amine II (148·5 g, 0·68 mole) was dissolved in a mixture of anhyd NaOAc (57·5 g, 0·7 mole), AcOH (78·5 ml) and $H_2O$ (600 ml). To this soln was added dropwise while stirring a soln of $NaNO_2$ (47·2 g, 0·68 mole) in $H_2O$ (170 ml) within 35 min. The temp rose to 31°. While stirring, icewater was added to bring the temp down to 20°, and this temp was maintained for 1 hr. The ppt formed was filtered off with suction, washed with $H_2O$ and dried, yield 101·3 g (90%). After recrystallization from light petroleum (40–60°) the m.p. was 258–260°. (Found: C, 80·32; H, 9·65. Calc. for $C_{11}H_{16}O$: C, 80·45; H, 9·82%); IR (KBr) 1700 (C=O)$cm^{-1}$; NMR ($CDCl_3$)$\delta$ 2·72 (m, 1H, C<u>H</u>—C=O), 2·58 (m, 2H, C<u>H</u>$_2$—C=O), 2·36–1·35 (m, 13H, rest of the homoadamantyl protons); MS molecular ion *m/e* 164.

*Tricyclo[4.3.1.1$^{3,8}$]undecan-4-one oxime* (IV)

A soln of III (6·4 g, 0·04 mole) in EtOH (115 ml) was added to a soln of $NH_2OH.HCl$ (16.6 g, 0·24 mole) in $H_2O$ (100 ml) and 2N NaOH (66 ml). The mixture was heated on a steam bath for 20 min and subsequently treated with activated carbon. On cooling the oxime crystallized and was filtered off, yield 4·5 g (63%), m.p. 147–149°. Adding some more $H_2O$ to the mother liquor yielded a second crop from which, after recrystallization from EtOH/$H_2O$, 0·5 g, m.p. 147–149°, was obtained, total yield: 70%. (Found: C, 73·73; H, 9·55; N, 7·88. Calc. for $C_{11}H_{17}NO$: C, 73·68; H, 9·55; N, 7·82%), IR (KBr) 3200 (broad absorption, OH), 1640 (C=N) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2·80 (m, 1H, C<u>H</u>—C=N), 2·66 (d = 4·0 Hz, 2H, C<u>H</u>$_2$—C=N), 2·30–1·30 (m, 13H, rest of the homoadamantyl protons); MS molecular ion *m/e* 179.

*Tricyclo[4.3.1.1$^{3,8}$]undecan-4-one oxime* (isomer mixture IV + V)

To a soln of $NH_2OH$·HCl (4·7 g, 0·07 mole) in $H_2O$ (28 ml) were added 50% NaOH (17 ml) and a soln of III, (3·2 g 0·02 mole) in EtOH (34 ml). The mixture was heated on a steam bath for 1 hr and then

poured into $H_2O$ (270 ml). The ppt formed was filtered off with suction, washed with $H_2O$ and dried, yield 1·4 g (42%), m.p. 128–136°. According to the NMR spectrum the substance consisted of a mixture of IV and V in the ratio 1:2. Acidification of the mother liquor yielded a second crop, consisting of IV and V in a ratio of 1:1, yield 1·3 g (39%), m.p. 138–142°; NMR ($CDCl_3$) $\delta$ 3·72 (m, HC—C=N, V), 2·80 (m, HC—C=N, IV), 2·66 (d, $J$ = 4·0 Hz, $H_2$C—C=N, IV), 2·53 (d, $J$ = 4·0 Hz, $H_2$C—C=N, V), 2·30–1·30 (m, rest of the homoadamantyl protons).

5-*Bromotricyclo*[4.3.1.1$^{3,8}$]*undecan*-4-*one* (VI).

$Br_2$ (1·5 ml) was added while stirring to a soln of homoadamantan-4-one (5g, 0·03 mole) in $CH_2Cl_2$ (60 ml). After 7 min the soln was discoloured. Stirring was continued for 15 min. The mixture was evaporated to dryness *in vacuo*. The residue was dissolved in $CH_2Cl_2$ (8 ml) and purified by dry column chromatography[15] (140 g Kiesel gel 0·05–0·2 mm nr 7754 Merck). Subsequent crystallization from $CH_2Cl_2$/MeOH (1:1) at −25° gave VI, 1·96 g (26%) m.p. 146–147°. (Found: C, 54·28; H, 6·32; Br, 32·90; O, 6·50. Calc. for $C_{11}H_{15}BrO$: C, 54·34; H, 6·22; Br, 32·87; O, 6·58%);IR (KBr) 1700 (C=O) cm$^{-1}$; NMR ($CDCl_3$) $\delta$ 4·69 (d, $J$ = 4·0 Hz, 1H, CHBr), 2·92 (m, 1H, CH—C=O), 2·54–1·52 (m, 13H, rest of the homoadamantyl protons); MS molecular ion *m/e* 242.

*Tricyclo*[4.3.1.1$^{3,8}$]*undecan*-4,5-*dione* (VII)

A mixture of III, (43·7 g, 0·266 mole) and $SeO_2$(30·5 g, 0·274 mole) in dioxan (135 ml) and $H_2O$ (5·7 ml) was refluxed for 3 hr. After filtration the filtrate was evaporated to dryness *in vacuo*.The residue was crystallized twice from light petroleum (60–80°), yield 31·5 g (61%), m.p. 287° (dec). (Found: C, 74·27; H, 7·89; O, 17·98. Calc. for $C_{11}H_{14}O_2$: C, 74·16; H, 7·92; O, 17·96%); IR (KBr) 1725, 1710 (C=O) cm$^{-1}$; NMR ($CDCl_3$) $\delta$ 2·88 (m, 2H, HC—C=O), 2·55–1·70 (m, 12H, rest of the homoadamantyl protons); UV $\lambda_{max}^{EtOH}$ 418 ($\varepsilon$ = 27) nm; MS mass of the molecular ion: Found 178·0993; Calc. for $C_{11}H_{14}O_2$ 178·0994.

4-*Aminotricyclo*[4.3.1.1$^{3,8}$]*undecane hydrochloride* (VIII)

To a soln of IV (10·75 g, 0·060 mole) in a mixture of 2N NaOH (200 ml) and EtOH (200 ml) Raney–Ni alloy (15 g) was added in portions while stirring and cooling in ice water. The mixture was stirred for 90 min and then filtered over hyflo.* The filtrate was concentrated *in vacuo* and extracted with $CH_2Cl_2$ (3 × 70 ml). The combined extracts were washed with $H_2O$ (2 × 50 ml) and dried. After evaporation of the solvent the residue was dissolved in EtOH (15 ml). The soln was acidified with ethanolic HCl (20 ml 3·5 N), and diluted with $Et_2O$ (200 ml). After leaving the soln to stand for one night 9·11 g (75%) of VIII was obtained. Recrystallization from EtOH/$Et_2O$ yielded an analytically pure sample, m.p. 375–376°. (Found: C, 65·44; H, 9·87; N, 7·09. Calc. for $C_{11}H_{20}ClN$: C, 65·50; H, 9·99; N, 6·94%); NMR (TFA) $\delta$ 3·86 (m, 1H, HC—$NH_2$), 2·66–1·50 (m, 16H, rest of the homoadamantyl protons); MS (base) molecular ion *m/e* 165.

7,8,9,10,11,12-*Hexahydro*-6,10;8,12-*dimethano*-6H-*cyclonona*[b]*quinoxaline* (IX)

A mixture of VII, (0·36 g, 0·002 mole) and *o*-phenylenediamine (0·22 g, 0·002 mole) in EtOH (10 ml) was refluxed for 1 hr and then concentrated to 5 ml. After leaving the mixture to stand at 0° for several hr the precipitated quinoxaline was filtered off with suction, washed with ether and dried, yield 0·3 g (60%) m.p. 177–178°. (Found: C, 81·43; H, 7·11; N, 11·15. Calc. for $C_{17}H_{18}N_2$; C, 81·54; H, 7·25; N, 11·19%; UV $\lambda_{max}^{EtOH}$ 239 ($\varepsilon$ = 39·700), 316 ($\varepsilon$ = 9·400) nm; MS mass of the molecular ion: Found 250·1470; Calc. for $C_{17}H_{18}N_2$ 250·1469.

5-*Azatetracyclo*[5.3.1.1$^{3,9}$.0$^{4,6}$]*dodecane hydrochloride* (X)

A soln of IV (1·79 g, 0·01 mole) in dry THF (20 ml) was added dropwise, while stirring, to a soln of LAH (1·24 g, 0·033 mole) in dry THF (150 ml). The mixture was refluxed for 17 hr. While cooling in an icebath a mixture of water (4 ml) and THF (11 ml) was added dropwise. The ppt was filtered off and washed with hot THF. The combined filtrate and washings were evaporated to dryness and the amine was transformed into the hydrochloride as described for VIII. yield 1·7 g (85%), m.p. 221–223° (dec). (Found: C, 66·09; H, 8·97; N, 6·82. Calc. for $C_{11}H_{18}ClN$: C, 66·16; H, 9·08; N, 7·01%); IR (KBr) 2700 ($NH_2^+$) cm$^{-1}$; NMR (TFA) $\delta$ 6·50, 5·45 (m, NH), 3·59 (m, 2H, HC—N), 2·84 (m, 2H, HC—C—N), 2·45–1·50 (m, 12H, rest of the homoadamantyl protons); the presence of two NH-signals points to a cisaziridine; MS (base) molecular ion *m/e* 163.

* Hyflo supercel

*Reaction of* X *with* $NaN_3$

This reaction was performed and worked up by Swift and Swern's[12] method with 7-azabicyclo[4.1.0]heptane. However the starting material was recovered quantitatively.

*Di(5-azatetracyclo[5.3.1.1$^{3,9}$.0$^{4,6}$]dodec-5-yl)-thiocarbonyl* (XII)

The aziridine X (0·22 g, 0·0013 mole) was dissolved in a mixture of $CS_2$ (5 ml) and dry $Et_2O$ (5 ml). The soln was kept for 10 days at room temp. After evaporation of the solvent a yellow solid residue (0·295 g) was obtained. The substance was warmed in an oil bath at 100–110° for 70 min and after cooling extracted with $Et_2O$ (25 ml). The extract was evaporated to dryness. The residue was extracted with EtOH, filtered and the filtrate was evaporated to dryness again. The remaining solid after the extraction with $Et_2O$ was dissolved in benzene (10 ml), treated with charcoal, filtered and evaporated. The residual solids from the benzene and the EtOH-extracts were combined and crystallized from acetone (15 ml), yield 0·09 g (37%), m.p. 208·5–210·5° (dec). (Found: C, 74·97; H, 8·66; N, 7·54. Calc. for $C_{23}H_{32}N_2S$: C, 74·94; H, 8·76; N, 7·60%; NMR ($CDCl_3$) $\delta$ 2·91 (AA'XX' like pattern, $J_{AA'}$ = 7 Hz, $J_{AX}$ = 6·5 Hz, others small, 4H, HC—N), 2·49 (m, 4H, HC—C—N), 2·04–1·40 (m, 24H, rest of the homoadamantyl protons); MS molecular ion *m/e* 368.

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