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SYNTHESIS OF 4^a-, 4^e-PHENYLADAMANTANONES AND 2,4-o-BENZENOADAMANTANE BY π-ROUTE

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Abstract - The acid catalysed reaction of 4-oxa-homoadamantan-5-one (1) with benzene yielded a mixture of 4^a-phenyladamantan-2-one (7), the equatorial isomer (8) and 2-phenyl-2,4-o- benzenoadamantane (9). A plausible reaction pathway for the occurrence of 9 is put forward. The structure of 9 was deduced from spectroscopic data and reaction of the proposed intermediate 2,4^a-diphenyladamantan-2-ol (11) with acid. 2,4-o-Benzenoadamantane (16) is prepared likewise.

INTRODUCTION

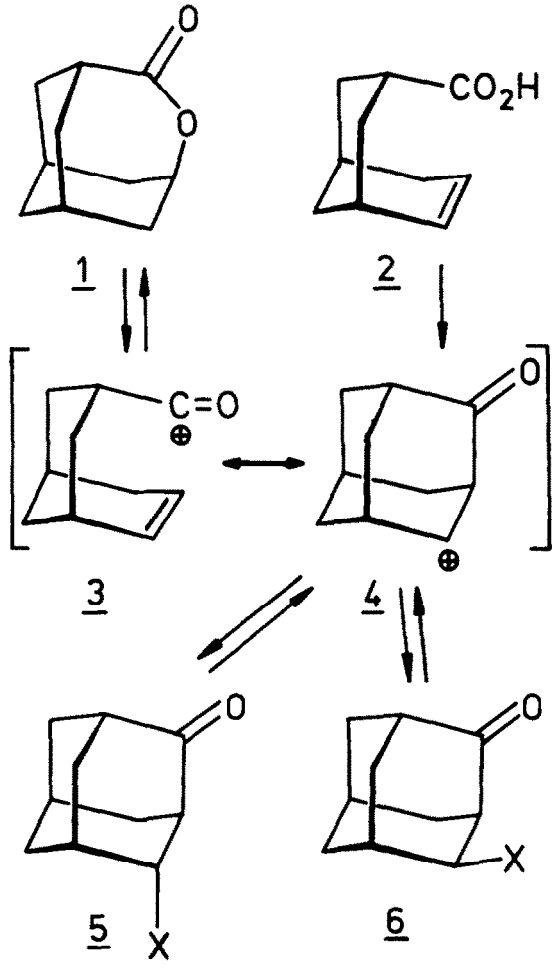
A cyclisation process, involving the formation of a new bond by nucleophilic addition of a carbon-carbon double bond onto an ionising centre, is called the "π-route" to a reaction intermediate or product by Winstein and Carter[1].

McKervey et al.[2,3] used this route to synthesize substituted adamantanones. Reacting 4-oxahomoadamantan-5-one (1) with half-concentrated sulfuric acid, they obtained a mixture of three compounds in the ratio 1:1:5, the educt 1, the equatorial 4-hydroxyadamantan-2-one (5, X=OH) and its axial isomer 6 (X=OH), the latter being the main product. They also found that the same mixture was regenerated from each of the hydroxyadamantanones under identical conditions. These results were explained by a mechanism depicted in scheme 1. Protonation or dehydration of either 1 or 2 leads to a cation represented best by the interconverting structures 3 and 4, which in turn can be trapped by a nucleophile to yield 5 and 6.

RESULTS AND DISCUSSION

Stetter and Koch[4] described the reaction of 1 with hydrobromic acid to give only one 4-bromoadamantan-2-one, without indicating the stereochemistry of the product. In our hands the same procedure yielded the bromides 5 and 6 (X=Br) in yields of 15 and 64 %, resp., along with minor amounts of 1 and the hydroxy products (5 and 6, X=OH).

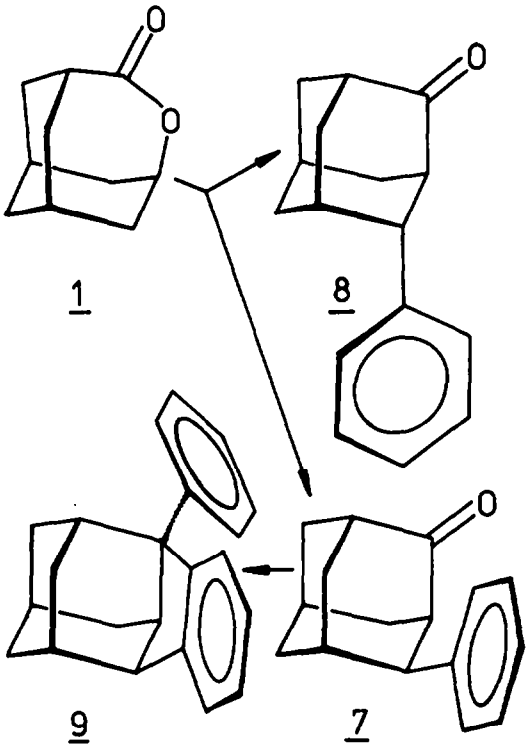
If the cation 4 can be trapped by nucleophiles, it should also be possible to submit it to Friedel-Crafts reactions with aromatic substrates. Indeed, when 1 was



Scheme 1

refluxed in benzene in presence of sulfuric acid, the phenyladamantanones 7 and 8 could be isolated. The reaction was monitored by GLC. After some time a third product was detected, which accumulated on the expense of 7. If the reaction was continued overnight, starting lactone (1) and 7 were completely consumed.

The IR spectrum of the unexpected product showed no indication of an oxygen functionality. From NMR and MS data and the fact that it was generated from 7, structure 9 was deduced.

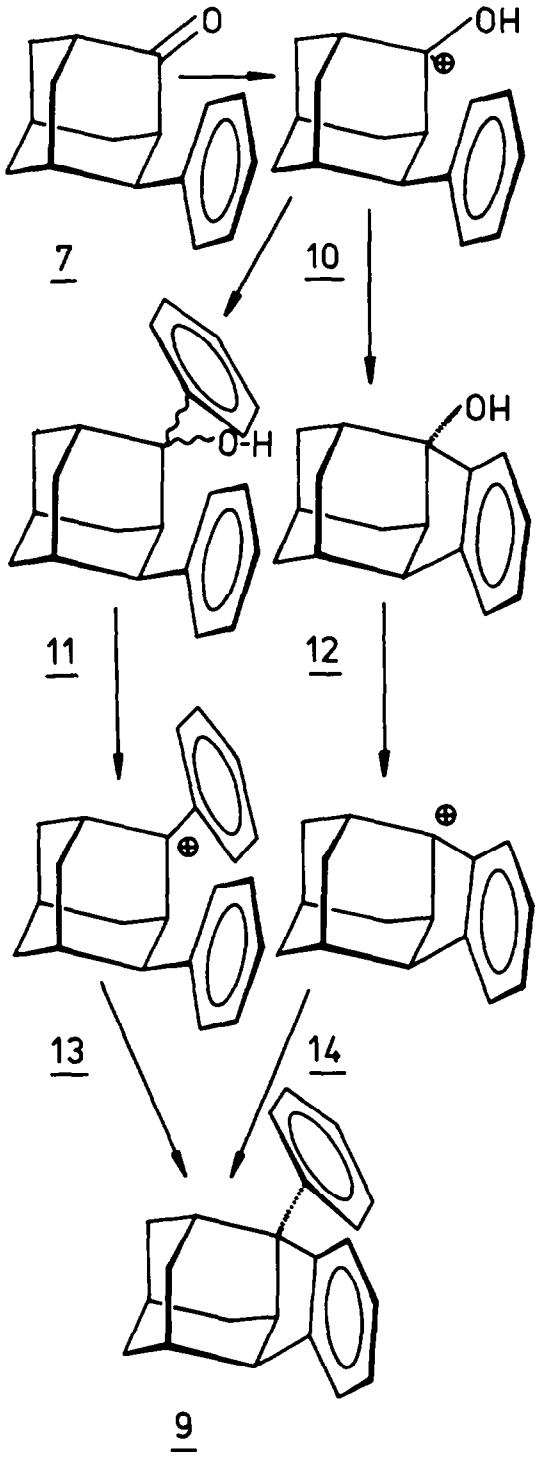


Scheme 2

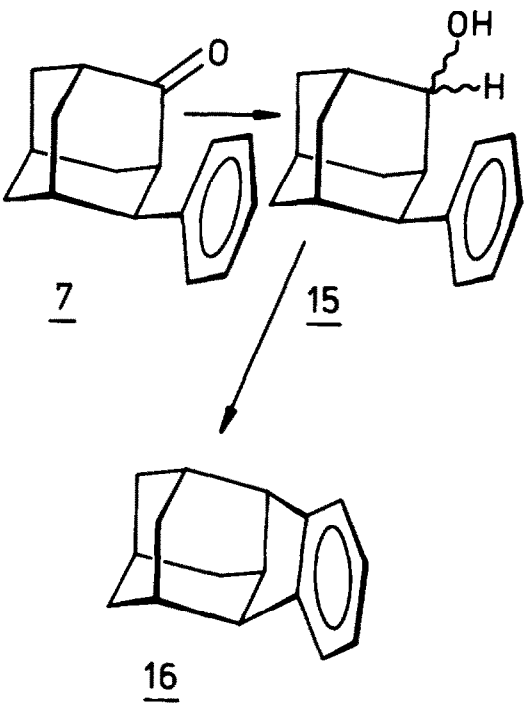
To account for the production of 9 we propose a mechanism depicted in scheme 3. Whether first the benzene moiety of 7 is attacked intramolecularly to yield alcohol 12 followed by an intermolecular reaction or the reversed sequence via 11 takes place, cannot be decided.

In order to prove the structure of 9 and to show that alcohol 11 really is a possible intermediate in the reaction path, 11 was synthesized by addition of phenyllithium to ketone 7. The corresponding Grignard reaction failed. Cyclisation of 11 in cyclohexane with sulfuric acid afforded 9 in 41% yield.

To synthesize the parent hydrocarbon 16, the ketone 7 was reduced to alcohol 15 with $LiAlH_4$ in ether and cyclized as mentioned above. The transformation of 15 to 16 had to be performed in highly diluted solution, because, when reacted in 1% solution with sulfuric acid, the alcohol yielded a product, which showed two times the molecular weight of 16 in the mass spectrum. Only when reacted in about 0.01% solution, the expected product could be isolated in 37% yield.



Scheme 3



Scheme 4

EXPERIMENTAL

TLC was performed on "Kieselgel 60 Fertigplatten, Merck, fluorescent at 254 nm. Products were purified using silica gel 60 - 100 μm. IR spectra were measured with a Shimadzu IR 400, ^{1}H NMR spectra were obtained with a Varian A-60 or T-60, while the ^{13}C NMR spectra were recorded at 22,63 MHz (proton broad band decoupled) on a Bruker WH-90 spectrometer. The multiplicity of signals was determined using off resonance conditions. All NMR values are given in ppm, using the δ-scale and tetramethylsilane as internal reference. The following abreviations are used: s = singulet, d = doublet, t = triplet, m = multiplet, an s in front of this data means sharp, br means broad. Mass spectra are recorded with a Varian MAT CH-5 or CH-7.

4-Oxahomoadamantan-5-one 1 was synthesized according to Mehta and Pandey[5].

4-Bromoadamantan-2-ones (5 and 6, X=Br): 5,0 g 4-oxahomoadamantan-5-one (1) and 150 ml hydrobromic acid (48%) are heated under reflux overnight. After cooling water is added and the mixture extracted three times with CH_2Cl_2. The combined organic phases are washed with water, dried over $MgSO_4$ and the solvent evaporated in vacuum. Chromatography with a light petroleum - acetone mixture (20:1) yielded 1.1 g (14.9%) of 5 (X=Br) and 4.4 g (62.8%) of 6 (X=Br).

4ᵉ-Bromoadamantan-2-one (5, X=Br): mp. 150-152°C; IR(CCl_4): 2935, 2865, 1730, 1710 cm^{-1}; ^{1}H NMR($CDCl_3$): 4.45 (br s, 1 H, H-4), 2.75 (br s, 1 H, H-3), 2.55 (br s, 1 H), 2.35, and 2.2 - 1.6 (9 H); ^{13}C NMR($CDCl_3$): 210.4 (s, C-2), 56.2 (d, C-4), 54.4 (d, C-3), 45.0 (d, C-1), 39.2 (t, C-8), 35.5 (t, C-9 or C-10), 34.7 (d, C-5), 33.9 (t, C-10 or C-9), 30.2 (t, C-6), 26.7 (d, C-7) ppm; MS: 79 (71%), 121 (76%, M$^+$-Br-CO), 149 (100%, M$^+$-Br), 228 (10%, M$^+$), 230 (11%, M$^+$). Found: C, 51.7; H, 5.7%. $C_{10}H_{13}BrO$ requires: C, 52.42; H, 5.72%.

4ª-Bromoadamantan-2-one (6, X=Br): mp. 170-172°C; IR(CCl_4): 2930, 2860, 1735, 1730 cm^{-1}; ^{1}H NMR($CDCl_3$): 4.7 (q, 1 H, H-4), 2.85, 2.7 (2 H), 2.5, 2.25, 2.05, 1.9 (10 H) ppm; ^{13}C NMR($CDCl_3$): 210.8 (s, C-2), 60.1 (d, C-4), 54.8 (d, C-3), 45.8 (d, C-1), 40.6 (t, C-10), 39.2 (t, C-8), 36.9 (t, C-6), 35.1 (d, C-5), 33.6 (t, C-9), 26.1 (d, C-7) ppm; MS: 79 (76%), 121 (92%, M$^+$-Br-CO), 149 (100%, M$^+$-Br), 228 (9%, M$^+$), 230 (8%, M$^+$). Found: C, 52.4; H, 5.6%. $C_{10}H_{13}BrO$ requires: C, 52.42; H, 5.72%.

Preparation of phenyl compounds:

The reaction of 4-oxahomoadamantan-5-one (1) was first performed on a small scale and followed by GLC. The optimum reaction time for the synthesis of the two phenyladamantanones was thus found to be about two hours, wheras a maximum amount of 2-phenyl-2,4-o-benzeno-adamantane (9) is obtained after 16 hours.

Method 1: 21.0 g (0.126 mmol) 4-oxahomoadamantan-5-one (1) are dissolved in 1.5 l of absolute benzene and 17 ml of 98% sulfuric acid are added. The mixture is stirred vigorously and heated under reflux for two hours. The water of reaction is removed by calcium hydride in a Soxhlet thimble. After cooling the reaction mixture, water is added, the phases are separated and the water phase is extracted twice with 200 ml CH_2Cl_2, the combined organic extracts are washed with hydrogen carbonate solution and brine, dried over $MgSO_4$ and the solvents distilled off. Chromatography of the remaining oil (12.2 g) on 1700 g of silica gel with light petroleum containing 5% of acetone yields: 4.0 g of 7 (14%), 4.3 g of 8 (15.1%).

Method 2: 5.0 g of 1 are dissolved in 600 ml of absolute benzene and reacted with 5 ml of H_2SO_4 as described for method 1. The reaction time is raised to 16 hours. After working up as usual, chromatography yields: 1.236 g of 8 (18.3%), 0.112 g of 7 (1.7%), 0.753 g of 9 (8.7%).

4ª-Phenyladamantan-2-one (7): mp. 82-83°C (after distillation), bp. 119-120°C($2\cdot10^{-6}$ bar), IR($CHCl_3$): 3020, 2940, 2870, 1730, 1710, 1610 cm^{-1}; ^{1}H NMR($CDCl_3$): 7.2 (s s, 5H, phenyl protons), 3.45 (br s, H-3), 3.0 (br s, 1 H, H-4), 2.45 (br s, 1 H, H-1), 2.1 (br d, 8 H, methylene protons), 1.8 (br s, 2 H, H-5 and H-8) ppm; ^{13}C NMR($CDCl_3$): 218.7 (s, carbonyl C), 143.8 (s), 128.4 (d), 127.2 (d), 126.2 (d, phenyl group,) 53.2, 50.1, 47.0 34.5 (d, R_3C-H), 41.6, 40.6, 38.3, 32.6 (t, R_2CH_2) ppm; MS: 77 (14%, $C_6H_5^+$), 79 (27%, $C_6H_7^+$), 91 (54%, tropylium$^+$), 198 (4%, M$^+$-CO), 226 (100%, M$^+$). Found: C, 84.7; H, 7.9%. $C_{16}H_{18}O$ requires: C, 84.92; H, 8.02.

4ᵉ-Phenyladamantan-2-one (8): bp. 190°C (4 mbar); IR(film): 3090, 3060, 3040, 2930, 2870, 1720, 1600 cm^{-1}; IR($CHCl_3$): 3020, 2940, 2870, 1710, 1600 cm^{-1}; ^{1}H NMR($CDCl_3$): 7.3 (s s, 5 H, phenyl protons), 3.15 (br s, H 4), 3.10 (br s, H-3), both signals are not clearly separated, 2.6 (br s, 2 H, H-1 and H-5), 2.25-1.9 (8 H, methylene protons), 1.8 (br s, H-8); the assignments of the single proton signals were made by approximate calculations according to Silverstein et al.[6] and assisted by Eu(dpm)$_3$ induced shift measurements on the ketones; MS: 77 (16%, $C_6H_5^+$), 79 (29%, $C_6H_7^+$), 91 (60%, tropylium$^+$), 198 (5%, M$^+$-CO), 226 (100%, M$^+$). Found: C, 84.6; H, 8.2%. $C_{16}H_{18}O$ requires: C, 84.92; H, 8.02%.

2-Phenyl-2,4-o-benzenoadamantane (9): mp. 102-103°C, IR($CHCl_3$): 3020, 2920, 2870, 1610 cm^{-1}; ^{1}H NMR($CDCl_3$): 7.2-6.7 (overlapping m's, 8 H, aromatic protons), 6.6-6.35 (m, 1 H, shielded proton of the o-benzeno ring), 3.1 (br t, 1 H, H-4), 2.75 (br s, 1 H, H-3), 2.3 (br s, 1 H, H-1), 2.1-1.5 (br s, 10 H), 1.1 (br s, 1 H, axial H-9); ^{13}C NMR($CDCl_3$): 152.6 (s), 147.5 (s), 143.4 (s), 128.2 (d, 2 C), 127.4 (d, 2 C), 126.2 (d, 2 C), 126.0 (d), 122.5 (d, 2 C), aromatic carbons, 54.9 (s, C-4) 48.7 (d, C-2), 48.1 (d, C-3), 36.2, 34.5, 33.2, 31.1 (t's, R_2CH_2), 33.0, 29.8, 26.0 (d's, R_3CH) ppm in $CDCl_3$; MS: 91 (17%, tropylium$^+$), 192 (51%), 205 (95%, M$^+$-$C_6H_7^+$), 286 (100%, M$^+$). Found: C, 92.8; H, 7.5%. $C_{22}H_{22}$ requires: C, 92.26; H, 7.74%.

2,4^a-Diphenyladamantan-2-ol (11): 917.3 mg (4.05 mmol) 4^a-phenyladamantan-2-one (7) in 20 ml of absolute ether are added dropwise under nitrogen to a solution of phenyllithium, prepared in the usual manner from 203.7 mg lithium (29.4 mgA) and 1.3 ml (12.4 mmol) phenyl bromide in 50 ml ether. The mixture is heated under reflux for 5 hours, poured onto crushed ice, the water phase extracted three times with ether, the combined etheral extracts are dried over $MgSO_4$, and the solvents distilled off. The remainder is crystallized from light petroleum to yield 1.008 g of colourless crystals (82.6%) with mp. 112-113°C; IR($CHCl_3$): 3600, 3400, 2940, 2890, 1610 cm^{-1}; ^1H NMR($CDCl_3$): 7.6-7.05 (s m, 10 H, phenyl protons), 3.3 (s, 2 H), 2.7-2.4 (br s, 3 H), 1.9 (s, 6 H), 1.75 (s, 2 H), 1.35 (s s, 1 H, exchangeable with D_2O) ppm; MS: 77 (23%, $C_6H_5^+$), 79 (13%, $C_6H_7^+$), 91 (36%, tropylium$^+$), 105 (100%, $PhCO^+$), 210 (46%, M^+-OH•-C_6H_5•), 286 (8%, M^+-H_2O), 287 (M^+-OH•), 304 (51%, M^+). Found: C, 87.0; H, 8.0%. $C_{22}H_{24}O$ requires: C, 86.80; H, 7.95%.

2,4-o-Benzeno-2-phenyladamantane (9) from 11: 611.9 mg (2,0 mmol) 2,4^a-diphenyladamantan-2-ol (11) are dissolved in 50 ml of cyclohexane, 0.5 ml 98% H_2SO_4 are added and the mixture is stirred for two hours at ambient temperature. 50 ml of water are added, the phases are separated, the water phase is extracted three times with 100 ml ether each and the combined organic extracts are washed with hydrogen carbonate solution and water. After drying over $MgSO_4$, the solution is filtered through 1 cm of silica gel, the solvents are evaporated and the resulting, slowly solidifying oil is crystallized from ethanol. Yield: 234.8 mg (41%). The substance is identical with 9 as prepared above.

4^a-Phenyladamantan-2-ol (15): 0.504 g (2.10 mmol) 4^a-phenyladamantan-2-one (7) are dissolved in 10 ml of absolute ether. The solution is added dropwise to a suspension of 144 mg (3.8 mmol) $LiAlH_4$ in 10 ml of ether, then heated under reflux for two hours. The mixture is worked up by careful addition of a saturated solution of magnesium sulfate and the hydroxides are filtered off. After evaporation of the solvents, a crystalline substance is obtained. Yield: 468 mg (96.2%); mp. 78-79°C (from light petroleum); IR($CHCl_3$): 3610, 3450, 3010, 2920, 2860, 1605 cm^{-1}; ^1H NMR($CDCl_3$): 7.6-7.1 (s m, 5 H, phenyl protons), 3.85 (d, J=7 Hz, 1 H, H-2), 3.05 (s, 1 H), 2.1-1.4 (br s, 9 H), 1.05 (s d, J=7 Hz, 1 H, exchangeable with D_2O) ppm; MS: 77 (22%, $C_6H_5^+$), 79 (37%, $C_6H_7^+$), 91 (86%, tropylium$^+$), 210 (91%, M^+-H_2O), 228 (M^+). Found: C, 84.2; H, 8.8%. $C_{16}H_{20}O$ requires: C, 84.17; H, 8.83%.

2,4-o-Benzenoadamantane (16): 195 mg (0.85 mmol) 4^a-phenyladamantan-2-ol (15) are dissolved in 250 ml cyclohexane and added dropwise to a stirred mixture of 1300 ml cyclohexane p. A. and 5 ml 98% H_2SO_4 during 6 hours. Stirring is continued for half an hour, then 100 ml of water are added and it is proceeded as described for hydrocarbon 9 from 11. Distillation at 21 mbar yields 67 mg (37.3%) of a colourless oil; IR(film): 3030, 2920, 2860, 750 cm^{-1}. ^1H NMR($CDCl_3$): 7.0 (s s, 4 H, aromatic protons), 2.9 (s t, J=3.5 Hz, 2 H, H-4 and H-2), 2.2 (br s, 1 H, H-3), 2.05-1.5 (br s, 10 H), 1.05 (br s, 1 H, axial H-9) ppm; ^{13}C NMR($CDCl_3$): 149.2 (s, C-11 and C-16), 126.0 (d, C-12 and C-15), 122.2 (d, C-13 and C-14), 48.0 (d, C-2 and C-4), 44.8 (d, C-3), 35.9 (t, C-6 and C-8), 34.4 and 33.3 (2 t, C-9 and C-10), 30.6 (d, C-1 and C-5), 25.8 (d, C-7) ppm; MS: 129 (63%), 210 (100%, M^+). Found: C, 91.5; H, 8.8%. $C_{16}H_{18}$ requires: C, 1.37; H, 8.63%.

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This work was taken in part from reference 7.

At present we are working at an independent synthesis of o-benzenoadamantane 16 via 4,9-o-benzenoadamantan-2-one.

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