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1-SUBSTITUTED 2-HETEROADAMANTANES

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We report the preparation of the 1-substituted 2-heteroadamantanes ⑦, ⑧, and ⑭, R = H, in four steps from readily accessible 1,3-dibromoadamantane (①)$^{(1)}$. Heating 1 mole of ① * in 3 l of dioxane and 3 l of 1N sodium hydroxide at 180° for 18 hours in a steel autoclave gave the methylene ketone ③$^{(2)}$ in 85 % yield; mp 160-164°; $\nu_{C=0}$ 1720 cm^{-1}; δ 1.94 ppm, 2H-singlet; ca. 2.38, 10 H-multiplet; 4.77, 2H-s. The process undoubtedly involves fragmentation of the intermediate hydroxy-bromide ②, a reaction mode recently also reported for N-(3-bromoadamantyl-1)-methylurethane (④, X = $NHCOOCH_3$)$^{(2)}$ and 1-bromo-3-bromomethyladamantane (④, X = CH_2Br)$^{(3)}$.

Ozonization of ③ as described by Stetter et al.$^{(2)}$ led to the diketone ⑤, mp 254-256°; δ 2.2-2.7, 10 H-m; 2.84, 2H-m. A 1:1 mixture of the cis- and trans-dioximes ⑥ was obtained in 96 % yield after heating ⑤ with four equivalents of hydroxylamine in water and ethanol for 24 hours; mp 240-243° dec; δ 1.85, 4H-m; 2.33, 6H-m; 3.22, 1H-d, J=15Hz; 3.32, 1H-d, J=15Hz; 10.5 broad, exchangeable 2H-s.

Hydrogenation of ⑥ in ethanol and hydrochloric acid over platinum oxide afforded 90 % 1-amino-2-azaadamantane dihydrochloride, characterized as the free base ⑦, mp 185-187°; δ 1.72, 10 H-s; 1.81, ex 3H-s; 2.20, br 2H-s; 3.30 br 1H-s. Nitrous acid transformed ⑦ to 1-hydroxy-2-azaadamantane (⑧)$^{(4)}$.

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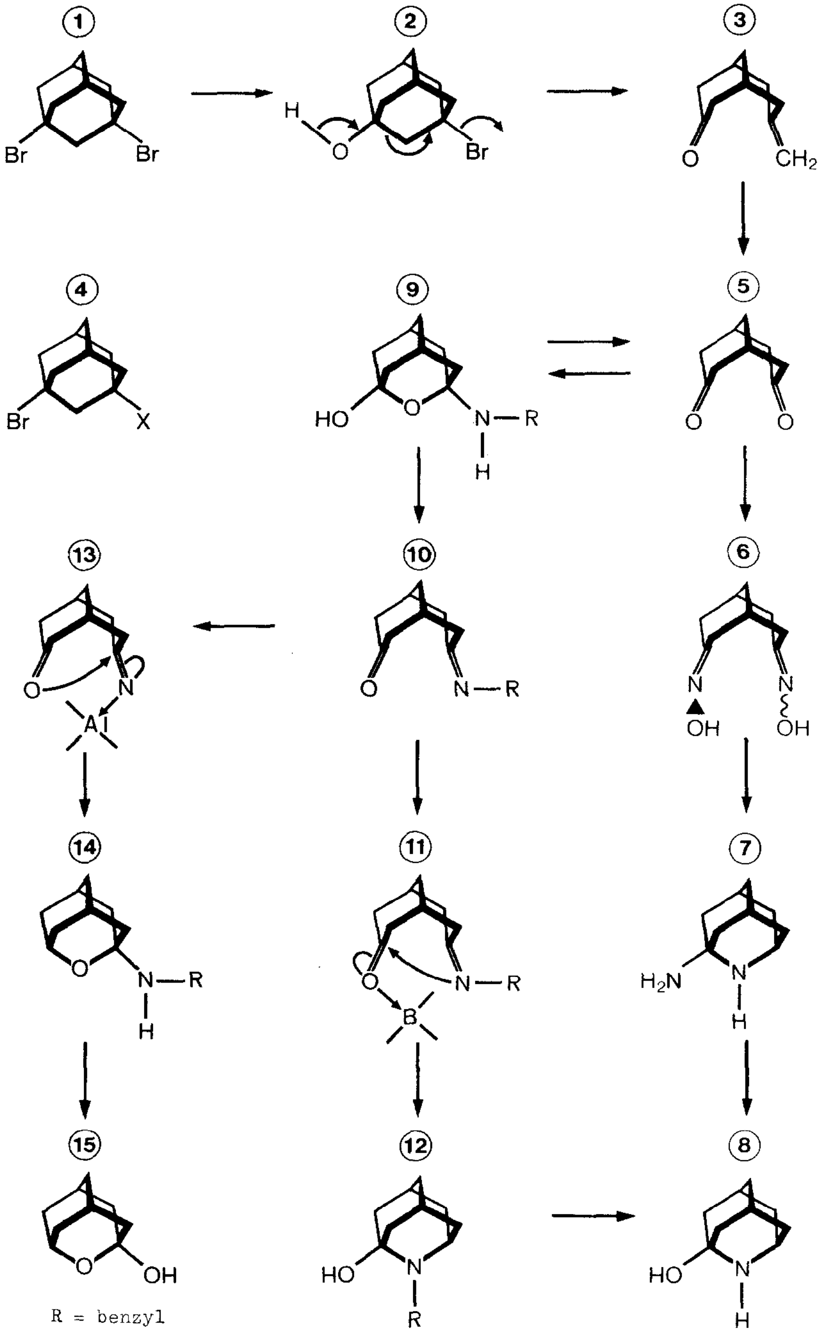
* Satisfactory elemental analyses were obtained for all compounds. Ir-spectra were run in methylene chloride or tetrahydrofuran, nmr-spectra in deuterochloroform at 60 or 100 MHz with tetramethylsilane as an internal standard.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R = benzyl

The aminoalcohol ⑧ was also prepared in the following manner: equivalent amounts of ⑤ and benzylamine were refluxed in ethanol for 2 hours and subsequently stirred with 2 equivalents of sodium borohydride at 20° for 3 hours to yield 80 % 1-hydroxy-2-benzyl-2-azaadamantane (⑫), mp 92-95°; δ 1.20-2.30, 13H-m with main peaks at 1.47, 1.72 and 2.17; 2.96, br 1H-s; 3.92, 2H-s; 7.27, 5H-m. The hydrochloride, mp 252-254°, underwent quantitative hydrogenolytic debenzylation to ⑧ at 120° in ethanol with Raney-nickel as a catalyst.

When 0.2 moles each of ⑤ and benzylamine in 300 ml of absolute dioxane were added to 0.3 moles of lithium aluminium hydride in refluxing diethylether, 1-benzylamino-2-oxaadamantane (⑭) was formed in 70 % yield; mp 48-50°; δ 1.30-2.30, 13H-m; 3.92, 2H-s; 41.7, br 1H-s; 7.27, 5H-m; hydrochloride mp 253-255°. Hydrogenation of the latter in ethanol at 90° and 50 atm over palladium-charcoal resulted in 90 % 1-amino-2-oxaadamantane (⑭ , R=H), mp 154-156°; δ 1.30-2.30, 14H-m, main peaks at 1.72, 1.84 ex, and 2.20; 4.15, br 1H-s. Nitrous acid converted the amine to 1-hydroxy-2-oxaadamantane ⑮ (4) which was also prepared by reduction of ⑤.

The specificity of the hydride reductions follows from the absence of ⑭ (less than 3 %) in the sodium borohydride product, on the one hand, and the isomeric purity of the lithium aluminium hydride reduction product (containing less than 3 % of ⑫), on the other. The solutions used in these reactions were investigated by nmr with the following results: when either equimolar amounts of ⑤ and benzylamine, or the crystalline addition product ⑨ * were added to absolute perdeuteroethanol, an equilibrium mixture A containing 55 % ⑨ as well as 45 % ⑤ and benzylamine was instantaneously formed. Sodium borohydride reduction of this solution at 20° for 3 hours afforded 90 % ⑮ , indicating inertness of ⑨ toward the reagent. Refluxing mixture A for 2 hours changed it to B, consisting of 10 % ⑨, 85 % ⑩ , and small amounts of ⑤ and benzylamine. Since solution B yields 80 % ⑫ upon reduction, we conclude that boron coordinates with the oxygen of the Schiffbase ⑩ , as indicated by ⑪ , before hydride attack occurrs at the iminocarbon.

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* ⑨ was isolated in 85 % yield after adding pentane to an equimolar solution of ⑤ and benzylamine in tetrahydrofuran: mp 95-97°; δ 1.70, br 10H-m; 1.92, br ex 2H-m; 2.32, br 2H-m; 3.95, 2H-s; 7.31, 5H-m. In CF_3COOH, ⑨ was transformed to protonated ⑩ , $\delta_{(CF_3COOH)}$ 2.40, br 2H-s; 2.76, br 4H-m; 3.10, 6H-m; 4.93, 2H-d, J=5.5Hz, 7.40, 5H-m.

Another equilibrium mixture was obtained when either ⑨ or its components were dissolved in perdeuterodioxane at 40°; 75 % ⑨ along with 25 % ⑤ and benzylamine. Refluxing this solution did not change its composition. The formation of ⑭ by direct reduction of the aminoalcohol ⑨ seems unlikely because analogues of the latter, e.g. ⑭ , R=H, and ⑮ failed to react with lithium aluminium hydride in refluxing dioxane. The reagent presumably dehydrates ⑨ to ⑩ , which now binds its nitrogen to the metal as in ⑬, before hydride attacks the carbonylcarbon. The rates of these reactions significantly surpass that of the diketone reduction, since ⑮ could not be detected among the products.

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