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Versatile Intermediates for Heteroatom-Substituted Adamantane Derivatives

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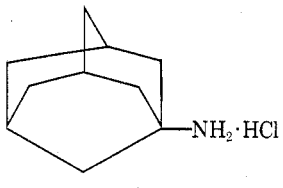
9-Acetoxybicyclo[3.3.1]nona-2,6(7)-diene (**18**), a versatile intermediate for the synthesis of heteroatom substituted adamantanes, was prepared in eight steps from the commercially available 1,4-cyclohexanediol. This intermediate may be used in the synthesis of substituted oxa-, aza-, and thiaadamantanes. Utility of this intermediate was shown by synthesis of 2-oxa-6-adamantanol (**19**), 2-oxa-6-adamantanone (**22**), 2-oxa-6-adamantanamine hydrochloride (**23**), and 2-oxa-6-adamantanecarboxylic acid (**26**).

There has been much interest in compounds containing the adamantane moiety since they exhibit many interesting medicinal properties. Adamantane derivatives have shown effectiveness against several types of viruses,[1-4] and in treatment of leukemia.[5] They were also found to be active in vitro against angeosarcoma, pancreatic sarcoma,[6] and antineoplastic activity.[7-9] Davies et al.[10] discovered the inhibitory effects of 1-adamantanamine hydrochloride (**1**) against in-



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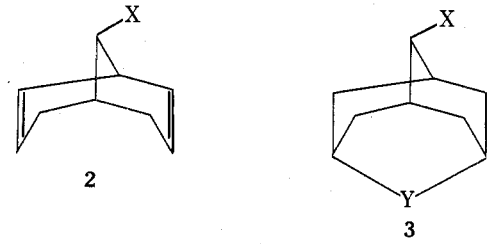
fluenza group A. 1-Adamantanamine was also found, quite by accident, to be active against Parkinson's disease.[11]

In view of the ability of adamantane to modify the biological activity of various compounds and the importance of heteroatoms in medicinal chemistry, we launched a program to synthesize adamantane derivatives with a heteroatom (oxygen, nitrogen, or sulfur) incorporated in the adamantane ring system.[12] We report here the synthesis of versatile intermediates for heteroatom-substituted adamantanes, and the synthesis of 2-oxaadamantan-6-amine and 2-oxaadamantane-6-carboxylic acid.

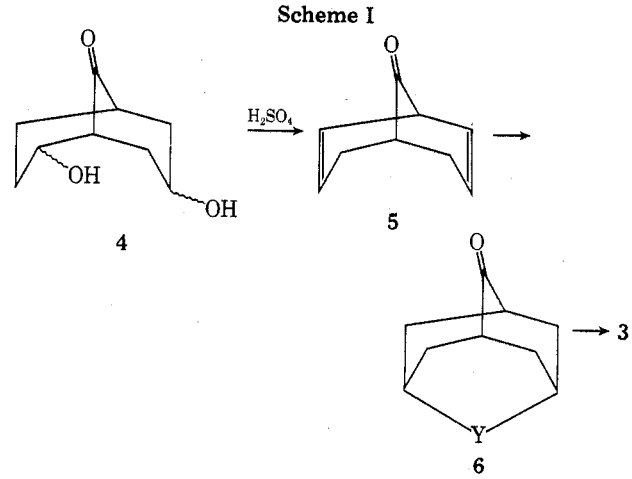
The immediate goal was to synthesize 9-substituted derivatives of bicyclo[3.3.1]nonadiene (**2**). Our long-range goal was to synthesize 2-substituted heterocyclic compounds **3** of the adamantane series through the intermediacy of compound **2**. The envisioned synthesis that was proposed for the aforementioned goals is depicted in Scheme I.



2 **3**

X = OH, OTs, NH_2, COOH
Y = O, N, S

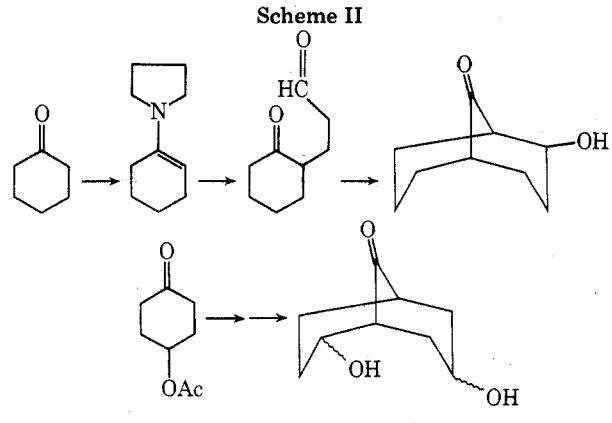
Scheme I



4 **5** **6**

Our plans for accomplishing the synthesis of the diol **4** involved modification of a procedure originally worked out by Cope[13] and Woodward.[14] If these procedures were now applied to 4-acetoxycyclohexanone, compound **4** should result (Scheme II).

Scheme II



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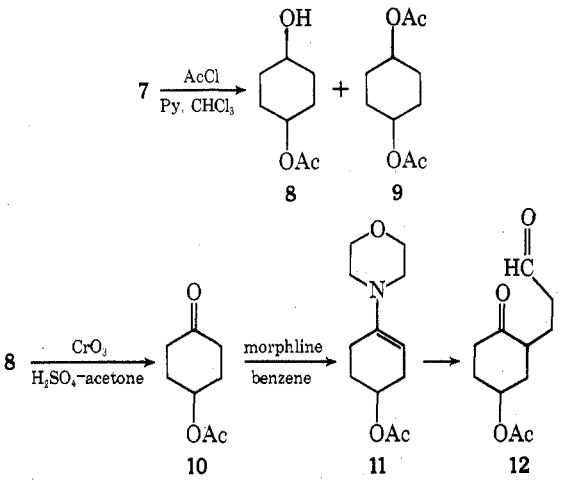
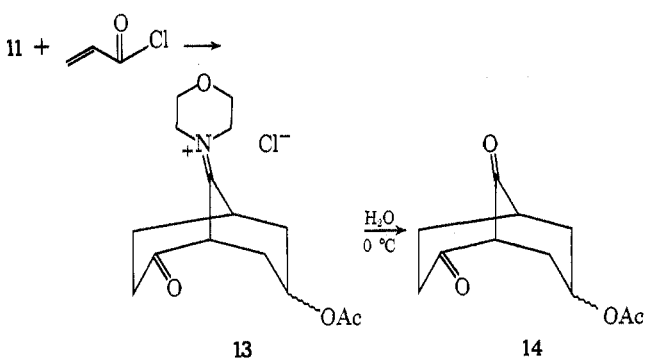
We found that the acetate 8 could be produced in excellent yield by the direct acetylation of quinitol (7) with acetyl chloride and pyridine. Reactions with acetic anhydride gave inferior results. Although the ratio of 8 to 9 (Scheme III) was

Scheme III



65:35 when 1 mol of quinitol was used per mole of acetyl chloride, this ratio increased to 87:13 when a 2.4 molar excess of quinitol was used. Use of excess reagent causes no isolational problems since quinitol is soluble in water and practically insoluble in chloroform. It was not necessary to remove the diacetate 9 from 8 since the presence of 9 did not interfere with the subsequent reaction in which 8 and 9 had to be utilized. Furthermore, 9 could be removed from the acetoxy enamine 11 by fractional distillation. Oxidation of the mixture of 8 and 9 with Jones reagent gave 10 in good yield in addition to the unchanged diacetate 9.

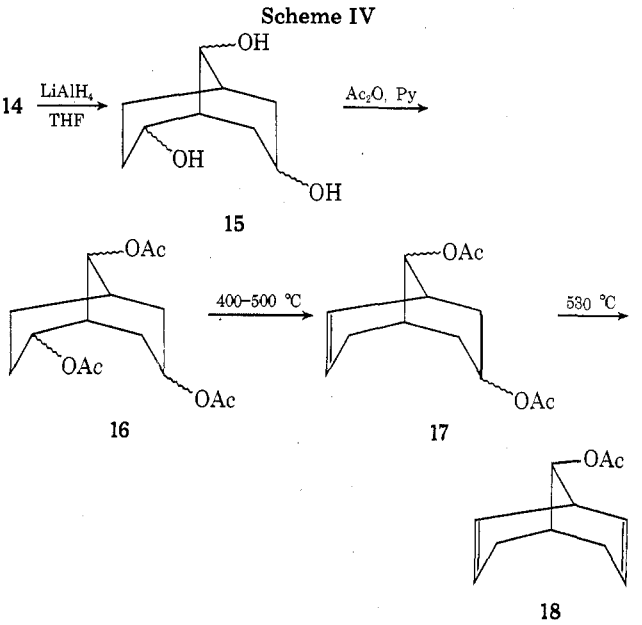
Hickmott[15] has worked out a procedure in which morpholinocyclohexene, when treated with acryloyl chloride, produces bicyclo[3.3.1]nonane-2,9-dione directly. A bicyclic dione can be produced even if the 3 and 4 positions of the enamine are fused to another ring system.[16] By applying the Hickmott procedure to the enamine 11, we were able to synthesize in good yield the bicyclic acetoxy dione 14 depicted below.

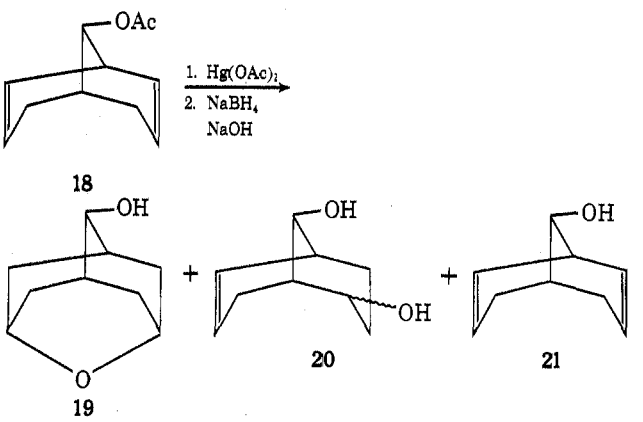


The procedure adopted for synthesis of the bicyclic diene 18 is depicted in Scheme IV. The dione 14 was reduced to the corresponding triol 15, which was converted to the triacetate 16. Pyrolysis of the triacetate 16 was best accomplished as a two-step sequence. In the first step the neat syrup was heated at 400–500 °C in a Pyrex test tube and the product, which consisted mainly of the monoolefin 17, was collected as a distillate. Pyrolysis of 17 in the vapor phase over glass beads led to the dienyl acetate 18 which could be isolated in relatively pure form by distillation. The overall yield of 18 from the diol 7 was 2.3%.

Cyclization. Our first step after the synthesis of the diene was cyclization to the oxaadamantane structure. Four methods were tried with this diene. Treatment of the bicyclic diene with mercuric acetate in a THF/water solvent system[17] gave the oxaadamantanol 19 in about 25% yield. Attempts to reduce the amounts of side products by longer reaction time did not increase the yield of oxaadamantanol. Separation was accomplished using an alumina column. Preparative gas chromatography was also used to separate these compounds.

Scheme IV





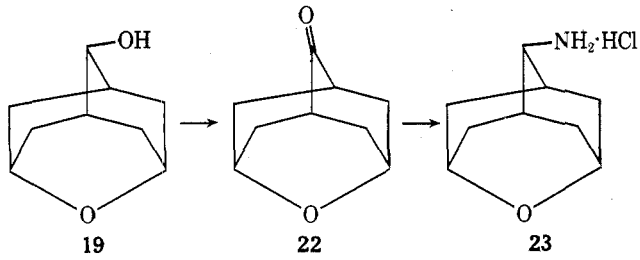
A method which showed great promise because of the lack of side products was treatment of the bicyclic diene 18 with mercuric acetate in water.[18] Gas chromatography showed that 19 was 90% of the product, but was isolated only in 10% yield.

Another method given much consideration in the early stages of the research was the addition of bromine in 10% KBr in water,[19] followed by a two-step reduction. The bromines were removed by treatment with Raney nickel and the acetoxy group was reduced with lithium aluminum hydride. This method was successful on a small scale, 100–200 mg of the diene 18. However, attempts to duplicate on a larger scale, 1-g quantity, proved unsuccessful.

The refluxing of the bicyclic diene with formic acid provided another possible route.[20] The number of side products, somewhat more plentiful than expected, made this an unacceptable procedure.

2-Oxa-6-adamantanamine Hydrochloride. The oxidation of oxaadamantanol 19 by Jones reagent provided a very efficient method[21] for obtaining the ketone 22 in yields of 90–97%. From the ketone 22, we considered two possible routes to the amine hydrochloride 23: reductive amination and the formation of the oxime followed by reduction of the amine.

Catalytic hydrogenation of adamantanone with Raney



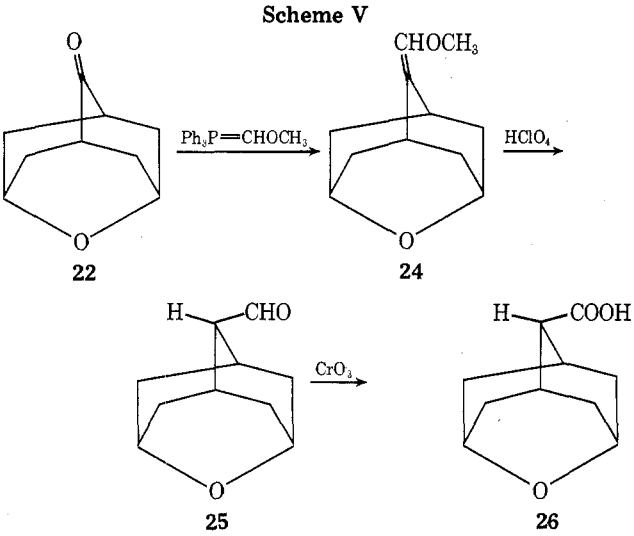
19 22 23

nickel, under 50 psi hydrogen pressure in ethanol saturated with ammonia, gave the amine in 15% yield. Excess ammonia was used to prevent the formation of secondary amines. The low yield of the amine was due to the formation of adamantanol as a side product. A less active catalyst was sought. Ten percent palladium on carbon was found to work well, producing yields of about 65%. When the same procedure was applied to oxaadamantanone **22**, a yellow oil was obtained, which was not crystallized, but converted directly to the amine hydrochloride, purified by sublimation in a 60% yield.

Our effort to reduce adamantanone oxime to the amine, either with lithium aluminum hydride or diborane in diglyme, was unsuccessful.

Carboxylic Acid. Alberts, Wynberg, and Strating reported[22] supposedly the best method of converting 2-adamantanone to 2-adamantanecarboxylic acid. Their method, modified for our system, is shown in Scheme V. The aldehyde

Scheme V



25 was oxidized by Jones reagent to the oxaadamantanecarboxylic acid **26**. The yield of acid from ketone **22** was 20%.

Experimental Section[23]

Acetylation of 1,4-Cyclohexanediol. The diol **7** (400 g, 3.4 mol) in 1.1 l. of chloroform and 1.0 l. of dry pyridine was chilled to 0 °C and to it was added, with rigorous mechanical stirring over a period of 9.5 h, a solution of 110 ml (121 g, 1.5 mol) of acetyl chloride in 0.6 l. of chloroform. Stirring overnight resulted in a clear golden yellow solution which was neutralized at 0 °C by the addition of 1.9 l. of 6 N HCl with vigorous stirring. The chloroform layer was separated and washed with saturated $NaHCO_3$ and aqueous NaBr, and then dried over $MgSO_4$. Removal of solvent on a steam bath and then on a rotary evaporator at 93 °C (20 Torr) left 171 g of a clear orange residual liquid. Gas chromatography of the neat liquid at 143 °C showed that only **8** and **9** were present in a ratio of 87:13. The hydroxy acetate eluted first from the column and the CCl_4 solution spectrum of the eluent showed OH (3620, 3440 cm^{-1}) and acetate (1735, 1248 cm^{-1}). The eluent derived from the second peak showed acetate and carbonyl (1735 and 1240 cm^{-1}) but no OH absorption.

4-Acetoxycyclohexanone (10). The residual liquid derived from the above acetylation procedure (94.8 g, 0.60 mol, **8**) was dissolved in 2.4 l. of reagent grade acetone and chilled in an ice bath. Jones reagent was made by dissolving 60 g of CrO_3 in 49 ml of concentrated sulfuric acid and then diluting with 120 ml of water, giving a total volume of 184 ml. Approximately 122 ml of this reagent was placed in a vented dropping funnel and 112 ml of this volume was added to the acetone solution with vigorous mechanical stirring maintaining a reaction temperature of 10–15 °C. At this point the reaction mixture had a definite orange color and enough 2-propanol was added to turn the reaction color green again. To this mixture was added 200 g of solid $NaHCO_3$ and 30 g of Na_2CO_3 and stirring was continued for an additional 0.5 h at 15 °C. The mixture was filtered and the residue was washed thoroughly with four portions of acetone. The combined acetone filtrates were stirred over solid Na_2CO_3 and filtered. The solution was concentrated on a steam bath and then on a rotary evaporator at 30 °C until two liquid phases were clearly visible. This mixture was extracted with methylene chloride (3 × 300 ml) and the CH_2Cl_2 extracts were dried over $MgSO_4$. Removal of the solvent on a steam bath and then on a rotary evaporator at 90° (20 Torr) left 98.0 g of a clear, light yellow liquid. Gas chromatography of the neat liquid on a 4-ft silicone rubber column at 138 °C showed the presence of only two peaks which corresponded to the keto acetate **10** and the diacetate **9** in order of their retention times, respectively. The ratio of the two peaks was 87:13 and the peak corresponding to **10** was collected. The infrared spectrum showed bands at 1730 (carbonyl) and 1740 and 1240 cm^{-1} (acetoxyl); NMR τ 4.86 (distorted quartet, 1 H), 7.40–8.20 (multiplet, 11 H), 7.98 (sharp singlet, acetoxyl 3 H). A 2,4-DNP derivative was prepared from the ketone, mp 184–186 °C (lit.[16] 183 °C).

Preparation of Enamine 11. To the residual liquid from the above oxidation (85 g, 0.54 mol, of actual **10**) in 2 l. of reagent grade benzene was added 81 g (0.93 mol) of morpholine and the solution was refluxed with continuous separation of water through a Dean-Stark trap for 40 h. The solvent was removed on a rotary evaporator and the residual orange oil was distilled at 0.03 Torr. With steam being sent through the condenser the diacetate **9** was distilled at 75–97 °C. A total of 95 g of distillate was collected at 97–110 °C and 0.02 Torr. Gas chromatography showed that the diacetate was completely removed during this distillation. The ir spectrum of **11** (neat) showed bands at 3070 (C=CH), 2960, 2860, 2815, 1735, 1650, 1375, and 1250 cm^{-1}; NMR τ 5.15 (m, 1 H), 5.59 (m, 1 H), 6.38 and 7.20 (both centers of an A^2B^2 pattern, 4 H), 7.5–8.5 (m, 7 H).

Preparation of 2-Keto-7-acetoxybicyclo[3.3.1]nonan-9-one (14). To a refluxing solution of 95 ml of the above enamine **11** in 870 ml of dry benzene was added, over a period of 2 h with stirring, a solution of 42 ml of acryloyl chloride in 435 ml of benzene. Refluxing was continued for 18 h with sporadic magnetic stirring due to the fact that the brittle salt intermediate adhered to the bottom of the flask quite tenaciously. After cooling, the supernatant liquid was decanted, the residue was thoroughly washed four times with reagent grade dry benzene, and the solvent was removed under reduced pressure (20 Torr and then 0.2 Torr). Hydrolysis of the residue was accomplished by the addition of 1.1 l. of ice water and stirring was continued for 3.5 h at 0–2 °C. Solid sodium bromide (100 g) was then added to the mixture and it was extracted with methylene chloride (6 × 500 ml). After drying ($MgSO_4$) the solvent was removed on a steam bath and then on a rotary evaporator at 80 °C, leaving 87 g of a dark brown, viscous residual liquid. Distillation gave 52 g of **14**, bp 110–120 °C (0.5 Torr). The ir spectrum of **14** showed both ketone and acetoxyl absorptions at 1748, 1718, and 1240 cm^{-1}; NMR τ 4.5–5.1 (m, 1 H), 6.8–8.2 (m, 13 H).

2,7,9-Triacetoxybicyclo[3.3.1]nonane (16). The dione acetate **14** (30.2 g, 0.144 mol) in 600 ml of THF was added, with stirring under a nitrogen atmosphere at room temperature, to a suspension of 8.9 g (0.24 mol) of $LiAlH_4$ in 500 ml of THF. The temperature rose to 45 °C during addition and the color of the deep gray solid lightened considerably as the addition was continued. The solution was then refluxed with stirring under nitrogen for 18 h and after cooling 25 ml of ethyl acetate dissolved in 25 ml of THF was added to the mixture. Refluxing was then continued for 1 h. After cooling to 40 °C, 40 ml of water was added and the mixture was stirred for 35 min. This was followed by the addition of 30 ml of 15% NaOH solution with 50 min of stirring. An additional 20 ml of water was added and stirring was continued for 15 min. The resulting off-white granular precipitate was removed by filtration and washed with hot THF. Removal of solvent on a steam bath and then on the rotary evaporator at 100 °C (20 Torr) afforded 26.8 g of a light tan, waxy solid. The solid was further dried at 1 Torr and 100 °C with only insignificant weight loss. This solid was then dissolved in 122 ml of pyridine and 142 ml of acetic anhydride and the resulting solution was stirred at 63–65 °C for 18 h. After cooling, 500 ml of methylene chloride was added and the solution was acidified by the addition of 680 ml of 6 N HCl with stirring at ice bath temperatures. The aqueous layer was extracted with 200 ml of methylene chloride and the combined extracts were washed three times with 5% NaOH and once with brine. The solution was dried

($MgSO_4$) and concentrated on a steam bath and then on a rotary evaporator at 100° (20 Torr), giving 37.3 g (87%) of a honey-colored syrup (**16**). The ir spectrum of **16** (neat) showed acetate absorptions at 1735 and 1250 cm^{-1}; NMR τ 5.02 (m, 3 H), 7.5–8.5 (m, 19 H) (sharp singlet at 8.01). Gas chromatography of an acetone solution of the syrup revealed only trace quantities of lower molecular weight impurities.

Liquid Phase Pyrolysis of Triacetate 16. The above triacetate **16** (15.2 g, 0.051 mol) was placed in a 19/22 Pyrex test tube. Into this was set a 19/22 Pyrex air condenser which in turn supported a conventional distillation take-off apparatus. The test tube and approximately ⅔ the length of the air condenser was set into a furnace and the entire system was purged with nitrogen before heating. Distillation of a liquid was observed as the temperature of the furnace was increased from 354 to 400 °C during a 6-min period. As the temperature was increased from 400 to 470 °C during a 20-min period foaming and distillation occurred simultaneously. During a 33-min. period as the temperature was increased from 470 to 512 °C smooth distillation gave rise to a yellowish distillate which comprised the main bulk of the distillate. The distillate was dissolved in ether and the upper portions of the distillation apparatus were rinsed down with ether. The combined ethereal solution was washed with brine and 5% NaOH. Drying ($MgSO_4$) and removal of the solvent on the steam bath and then on the rotary evaporator gave rise to 10.1 g (84%) of **17**, a pale yellow residual liquid which showed bands for olefinic and acetoxyl functions at 3040 (m), 1740 (br), 1650 (w), and 1250 cm^{-1} (br). Analysis of the liquid by gas chromatography at 168 °C followed by programming at 5 °C/ min up to 235 °C showed the product ratio to be 76% the diacetoxy olefin **17**, 16% the acetoxydiene **18** and 6% the unchanged triacetate **16**. An NMR spectrum of **17** was obtained after collection from the column: τ 3.9–5.4 (2 multiplets, 2 olefinic H and 2 *O*-acetoxyl H), 7.2–8.6 (series of multiplets with a sharp singlet at 8.02, 14 H).

Pyrolysis of 17. Preparation of 9-Acetoxybicyclo[3.3.1]nona-2,6- (and 2,7-) diene (18). The neat diacetate **17** (9.8 g, 0.042 mol) was added, under a stream of nitrogen at a rate of 12 drops/min, to a 13-in. column of glass beads contained in a 24-in. 24/40 Pyrex tube. The tube was preheated at 530 °C by means of a furnace and its bottom was set into a trap which was almost entirely submerged in an ice bath. A brownish-black liquid collected in the trap, and after addition was complete, the hot column was washed down dropwise with benzene. After cooling, the column was thoroughly washed down with ether. The resulting ethereal benzene solution was washed with brine and 5% NaOH, dried ($MgSO_4$), and concentrated on the steam bath and then on a rotary evaporator at 80 °C, yielding 5.1 g of a brown liquid. The liquid was distilled giving dienyl acetate **18**, 3.2 g (68%), bp 80–110 °C (12 Torr). The bulk of the fraction was contaminated by only trace quantities of other compounds. Collection of the product from the column gave a sample which displayed an ir spectrum that showed characteristic absorptions for olefinic and acetoxyl moieties at 3040 (m), 1730 (s), 1370 (m), 1250 (s, br), and 1040 cm^{-1} (s, out of plane olefinic C–H mode); NMR τ 4.45 (m, 4 H), 5.18 (m, 1 H), 7.0–8.5 (m, 9 H) (sharp singlet at 8.05).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.83; H, 7.89.

Oxymercuration–Demercuration of Dienyl Acetate 18. A mixture of 1.0 g of 9-acetoxybicyclo[3.3.1]nona-2,6(7)-diene (**18**) and 3 g of mercuric acetate in 12 ml of tetrahydrofuran and 12 ml of water was stirred for 24 h at room temperature. To this was added 24 ml of tetrahydrofuran and 24 ml of 0.5 M sodium borohydride solution in 15% sodium hydroxide. Stirring was continued for 3 h followed by addition of 12 g of sodium chloride. The solution was allowed to stand overnight. The solution was filtered through glass wool and the residue washed with ether. The aqueous layer was separated and extracted with five 20-ml portions of ether. The organic layers were combined, dried over magnesium sulfate, and concentrated. Gas chromatographic analysis showed three products: **21** (15%), **19** (40%), and **20** (45%). The 2-oxaadamantan-6-ol (**19**) was isolated by column chromatography on an alumina column, 0.24 g (24%), mp 254.0–257.0 °C. Yields of other runs varied between 16 and 30%.

Anal. Calcd for $C_9H_{14}O_2$ (**19**): C, 70.10; H, 9.15. Found: C, 70.18; H, 9.14.

2-Oxaadamantan-6-one (22). Jones reagent, prepared from 18 g of chromium trioxide, 25 ml of water, and 10 ml of concentrated sulfuric acid, was added dropwise to 0.42 g of the above oxaadamantanol **19** in 25 ml of acetone at 0 °C until a light orange color appeared through the green precipitate. This was stirred for 15 min to ensure that the orange color remained. After 1.5 g of sodium bicarbonate and 0.3 g of sodium carbonate were added, the stirring was continued for 0.5 h. The solids were removed by filtration and the solvent removed on the rotary evaporator. The product was dissolved in ether and dried over magnesium sulfate. Removal of the solvent yielded 0.4 g (95%) of the oxaadamantanone **22**. Analysis by gas chromatography on silicon oil 710 and Carbowax 20M columns at 200 °C showed this to be about 98% pure. Infrared spectrum showed a triplet between 1700 and 1730 cm^{-1} indicating C=O stretching.

Anal. Calcd for $C_9H_{12}O_2$ (**22**): C, 71.03; H, 7.95. Found: C, 70.75; H, 7.89.

2-Oxa-6-adamantanamine Hydrochloride (23). 2-Oxa-6-adamantanone (**22**, 0.4 g) was dissolved in 30 ml of 95% ethanol saturated with ammonia. This was hydrogenated in a Parr hydrogenation apparatus with 0.3 g of 10% palladium on carbon and 45 psi hydrogen at 50–55 °C for 24 h. The solution was cooled and filtered to remove the catalyst. The solvent was removed, leaving an oil. The oil was dissolved in ether with a minimum amount of absolute ethanol. Dry HCl gas was bubbled through the solution which was cooled overnight and filtered. Crystals were vacuum sublimed at 175 °C, then recrystallized from ethanol–ether, giving 0.28 g (70%) of **23**, mp 375–380 °C.

Mass spectrum of **23** had peaks at *m/e* 153 (M − HCl), 152, 136 (M − NH_4Cl), 92, 70, and 56 (base peak).

Anal. Calcd for $C_9H_{16}ONCl$: C, 56.87; H, 8.57. Found: C, 56.93; H, 8.57.

2-Oxa-6-adamantanecarboxylic Acid (26). Methylmethoxytriphenylphosphonium bromide (2.5 g)[24] was added slowly to a 100-ml three-neck flask containing 5.6 ml of 1.26 M *n*-butyllithium and 30 ml of anhydrous ether at −10 to −15 °C under a nitrogen atmosphere while stirring. Stirring was continued at −10 to −15 °C for 1 h. While stirring the suspension looked orange to brown. When the suspended material was allowed to settle, the solution above it was scarlet red. To this, 0.15 g of the oxaadamantanone **22** in 10 ml of ether was added dropwise with stirring under nitrogen atmosphere at −10 to −15 °C. Stirring was continued overnight at room temperature. Anhydrous zinc chloride was added until the red color disappeared. This enol ether **24** was stirred for 1 h followed by acidification with perchloric acid (60.5%). After removal of the solvent, the residue containing the aldehyde **25** was dissolved in reagent acetone and oxidized with Jones reagent. The solvent was removed and 75 ml of water was added. This was extracted with five 20-ml portions of ether. The organic layer was extracted with five 20-ml portions of 5% sodium hydroxide solution. The alkaline phase was acidified with 37% hydrochloric acid, cooled, and extracted with five 20-ml portions of ether. The ethereal phase containing the acid **26**, was dried over magnesium sulfate and concentrated. The crystals, formed upon cooling in a refrigerator, were washed with pentane and sublimed at 125 °C at 2 Torr, yielding 0.037 g (20%) of **26**. Infrared spectrum in chloroform of the enol ether **24** showed an absorbance at 1690 cm^{-1} characteristic of an enol ether. The aldehyde **25** showed the characteristic peaks at 2860, 2720, and 1720 cm^{-1}. The acid **26** displayed absorption at 3515, 3300–2500, and 1700 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.90; H, 7.84.

Acknowledgments. We wish to thank Dr. Kenneth Rinehart for the mass spectrum.

Registry No.—**7**, 556-48-9; **8**, 58512-50-8; **9**, 19843-75-5; **10**, 41043-88-3; **11**, 57438-52-5; **14**, 58512-51-9; **16**, 58512-52-0; **17**, 58512-53-1; **18** (2,7-diene), 58512-54-2; **18** (2,6-diene), 58526-81-1; **19**, 58512-55-3; **22**, 58512-56-4; **23**, 58512-57-5; **24**, 58512-58-6; **25**, 58512-59-7; **26**, 58512-60-0; acetyl chloride, 75-36-5; morpholine, 110-91-8; acryloyl chloride, 814-68-6; ethyl acetate, 141-78-6; mercuric acetate, 1600-27-7; methylmethoxytriphenylphosphonium bromide, 33670-32-5.

References and Notes

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Reactions of Dicarbonyl Compounds with Dimethyl β-Ketoglutarate. 2. Simple Synthesis of Compounds of the [10.3.3]- and [6.3.3]Propellane Series[1]

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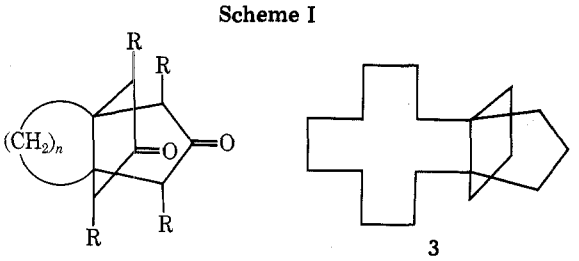
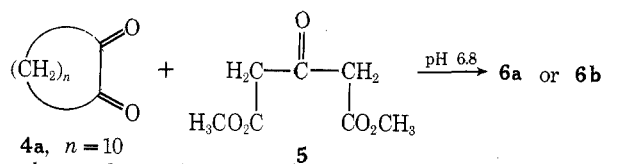
Reaction of cyclododecane-1,2-dione (**4a**) or cyclooctane-1,2-dione (**4b**) with dimethyl β-ketoglutarate (**5**) at room temperature in aqueous buffer (pH 6.8) provided good yields of tetramethyl[10.3.3]propellane-14,17-dione 13,15,16,18-tetracarboxylate (**6a**) and tetramethyl[6.3.3]propellane-10,13-dione 9,11,12,14-tetracarboxylate (**6b**), respectively. Hydrolysis and decarboxylation of **6a** and **6b** furnished the propellanediones **7a** and **7b.** The dione **7a** was converted to [10.3.3]propellane by Wolff–Kishner reduction while Clemmensen reduction of the propellanediones yielded the cyclic substituted bisnoradamantyl alcohols **11** and **12.**

Chemistry of propellanes has been given much attention in recent years.[2] In particular, a large effort has been spent upon the synthesis of propellanes containing small rings and upon the study of the bonding character of their central bond.[3] On the other hand, no propellanes with medium or large rings ($n > 6$) seem to have been prepared, presumably because of difficulties in synthesizing such compounds. However, the approach used by Weiss and Edwards[4] for the synthesis of diketo derivatives of [4.3.3]- (**1**) and [3.3.3]propellane (**2**) through reaction of cyclohexane-1,2-dione and cyclopentane-1,2-dione, respectively, with dimethyl β-ketoglutarate seemed to be capable of extension to medium-ring 1,2-diketones. This proved indeed to be the case. We wish to report here on the synthesis and properties of several compounds of the [10.3.3]- and [6.3.3]propellane series, including the parent hydrocarbon (**3**) of the former.[5]

Scheme I



1, $n = 4$; R = H
2, $n = 3$; R = H
6a, $n = 10$; R = CO_2CH_3
6b, $n = 6$; R = CO_2CH_3
7a, $n = 10$; R = H
7b, $n = 6$; R = H

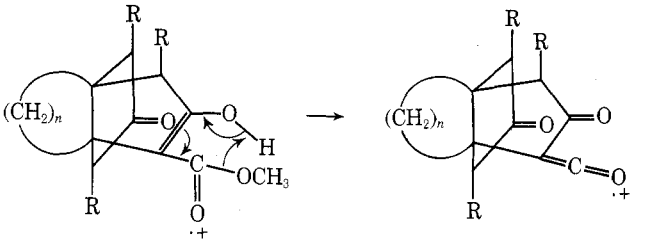


4a, $n = 10$
b, $n = 6$

5

Reaction of 1 mol of cyclododecane-1,2-dione (**4a**)[6] with 2 mol of dimethyl β-ketoglutarate (**5**) in a mixture of methanol and citrate–phosphate buffer (pH 6.8) for 24 h at room temperature gave a precipitate (94%) of tetramethyl[10.3.3]propellane-14,17-dione 13,15,16,18-tetracarboxylate (**6a**), mp 156.5–158 °C (from methanol); high-resolution mass spectrum, calcd for $C_{26}H_{36}O_{10}$, 508.2308; found, 508.2300. This product of 1:2 stoichiometry was homogenous on TLC with several solvent systems; only one of the several possible stereoisomers seems to have been obtained. Structure **6a** is consistent with ir, NMR, and mass spectral data. Three successive losses of 32 units (CH_3OH) were observed from the parent ion in the mass spectrum of **6a.** This can be formulated to occur as illustrated in Scheme II to generate ketene intermediates. Similar fragmentations have been reported by

Scheme II



6a