Behavior of *endo*-7-Aminomethylbicyclo[3.3.1]nonan-3-one under Reducing Conditions[1]

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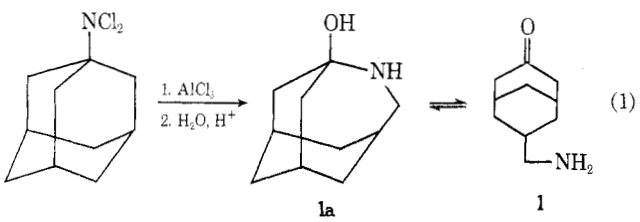
The behavior of *endo*-7-aminomethylbicyclo[3.3.1]nonan-3-one (1) toward various reducing agents was investigated. Sodium borohydride gave a mixture of endo and exo alcohols (mainly endo) whose ratio varied depending upon the nature of the alcohol used as the medium. Sodium–alcohol reduction provided the exo alcohol as essentially the only product. With hydrogenation in ethanol in the presence of Raney nickel, carbonyl reduction, N-alkylation, and reductive cyclization occurred. Either mono- or dialkylation on nitrogen took place depending upon the temperature. The cyclization reaction produced *N*-ethyl-4-azahomoadamantane. Conversion to the diamine, *exo*-3-amino-*endo*-7-aminomethylbicyclo[3.3.1]nonane, was effected by sodium–ethanol reduction of the oxime of **1**. Mechanistic and conformational aspects are also treated.

There are relatively few uncomplicated routes for entry into the bicyclo[3.3.1]nonane series.[4-6] A simple pathway was recently reported[6,7] *via* rearrangement of 1-*N*,*N*-dichloroaminoadamantane in the presence of aluminum chloride. Subsequent exposure to aqueous acid afforded *endo*-7-aminomethylbicyclo[3.3.1]nonan-3-one (**1**) in 70–80% yield (eq 1). Prior work[6,8] has shown that **1** can serve as a versatile precursor for a variety of derivatives in this series by reactions which generally take place in high yield.



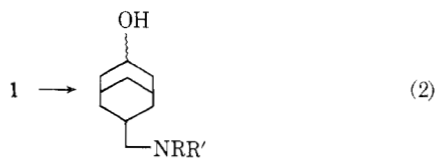
(1)

1a **1**

The objective of the present work was to investigate the behavior of **1** under diverse reducing conditions. In addition, attention was given to the stereochemical and mechanistic aspects. In previous, related studies involving **1**, Wolff–Kishner reduction[6] provided *endo*-3-bicyclo[3.3.1]nonylmethylamine, and $LiAlH_4$ gave 4-azahomoadamantane.[7]

Results and Discussion

Hydride Reduction. Initially, our attention was focused on reduction of **1** with sodium borohydride in various alcoholic solvents. In all cases, reaction provided an endo–exo mixture of *endo*-7-aminomethylbicyclo[3.3.1]nonan-3-ols, generally in very good yields (eq 2). The ratio of **2** to **3**, determined by glpc, was found to vary with change in solvent, but in all cases isomer **2** predominated as expected.



(2)

endo OH **2**, R = R′ = H **4**, R = H; R′ = C_2H_5 **6**, R = R′ = C_2H_5

exo OH **3**, R = R′ = H **5**, R = H; R′ = C_2H_5 **7**, R = R′ = C_2H_5

From Table I it can be seen that there is a systematic increase in the per cent of **2** as the solvent is changed from isopropyl alcohol to ethanol to methanol. A similar solvent effect was observed earlier for reduction of 3-cholestanone[9] and tropinone.[10] This type of correlation was attributed to formation of methoxyborohydrides *in situ*.

Table I
Reduction of 1 with $NaBH_4$

Solvent	Yield, %	2:3 ratio
MeOH	90–95	95:5
MeOH–H_2O[a]	40–50	95:5
95% EtOH	90–95	75:25
Absolute EtOH	90–95	75:25
i-PrOH	80–85	63:37
Pyridine	60–65	70:30
MeOH[b]	80–85	93:7

[a] 1:1 molar ratio. [b] $NaB(OCH_3)_3H$ as reducing agent.

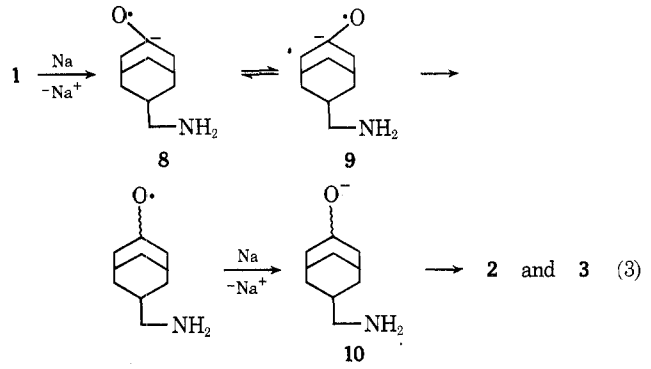
These bulkier reducing entities would favor approach from the less hindered side of the carbonyl group. Thus, the predominance of **2** is rationalized in terms of steric control to attack by hydride resulting in the thermodynamically less stable isomer. The results in Table I are in accord with the relative acidities of *i*-PrOH, EtOH, and MeOH toward sodium borohydride. To test this hypothesis, sodium trimethoxyborohydride was used to reduce **1**, giving essentially the same isomer ratio as did sodium borohydride in methanol, in line with the analogous result[9] of Vail and Wheeler with 3-cholestanone. When $NaBH_4$ was allowed to react with methanol for 0.5 hr before addition of **1**, no reduction of the amino ketone occurred, indicating that all of the hydrides were replaced by methoxyl groups. This type of exchange is well documented.[11]

A high degree of selectivity was also obtained when the acetamide of **1** was reduced with sodium borohydride in methanol. The resulting product was shown to be essentially 100% endo alcohol by hydrolysis and subsequent glpc analysis. The added bulk on nitrogen would lend additional driving force to exo attack by the reducing species.

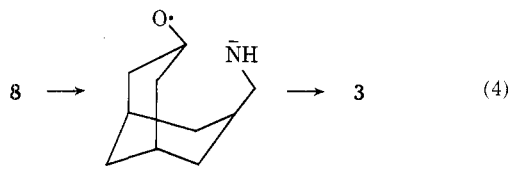
Reduction with Sodium and Alcohols. Reduction of **1** with sodium and ethanol provided **3** contaminated with substantial amounts of unchanged ketone which could be removed by conversion to the oxime followed by a simple extraction procedure. Similar results were obtained with isopropyl alcohol. However, best yields of **3** (75%) were realized with *tert*-butyl alcohol. It is evident that a decreased rate of reaction between sodium and the alcohol (EtOH > *i*-PrOH > *t*-BuOH) produces an overall beneficial effect.

The pronounced selectivity merits comment. Dissolving metal reductions of this type are believed[12] to involve initial formation of an anion radical, which is then protonated (eq 3). Applying this concept to **1**, one can visualize

the existence of exo (8) and endo (9) forms of the anion radical.



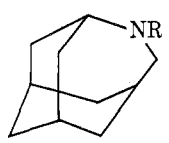
One plausible route would entail intramolecular abstraction of a proton which would be favored in the case of the exo form (8) (eq 4).



Alternatively, prior work[12] has shown that the more stable alcohol is frequently the predominant product. Apparently, the generated alkoxide, *e.g.* **10**, can interact with substrate ketone, similar to the Meerwein–Ponndorf–Verley reduction, to produce the isomeric alkoxide in an equilibrium situation which usually favors the more stable product (eq 5).

$$10\ (\text{endo}) + 1 \rightleftharpoons 10\ (\text{exo}) + 1 \qquad (5)$$

Catalytic Hydrogenation. When **1** was hydrogenated in ethanol with Raney nickel catalyst, products were obtained resulting from carbonyl reduction, N-alkylation, and reductive cyclization. At 100° and about 2000 psi, **4** and **5** were isolated in a ratio of 35:65. The ring-closed material was found to be *N*-ethyl-4-azahomoadamantane (**11c**). In addition, a small amount of an unknown substance was present.



11a, R = H
b, R = CH_3
c, R = C_2H_5

Alcohols **4** and **5** were identified by comparison with authentic materials.[13] The structure of **11c** was established by spectral comparison with **11b**,[6] and by alternate synthesis involving reduction by $LiAlH_4$ of the acetyl derivative of **11a**.

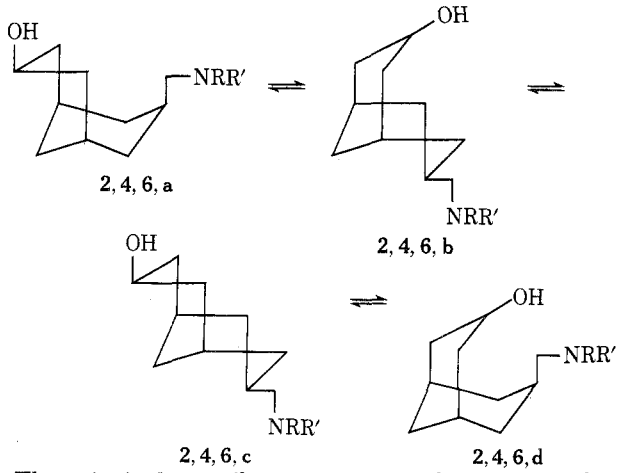
When the temperature of reaction was increased to 130°, **11c** and the minor, unidentified product were again produced. However, the N-alkylated alcohols were found to be a mixture of **6** and **7** in 4:96 ratio, whose structures were assigned on the basis of microanalyses, spectral evidence, and independent synthesis. The mass spectra displayed a weak, parent peak at *m/e* 225 and a base peak at *m/e* 86. The presence of two *N*-ethyl groups and the exo or endo configuration at C-3 are in accord with the nmr spectra. Dialkylation of **3** with ethyl iodide provided an alternate route to **7**. Compound **6**, as well as **7**, was also prepared by acetylation of the *N*-ethyl derivative[13] of **1** with subsequent reduction by $LiAlH_4$. Temperatures of 165–175° produced a complex mixture from hydrogenation.

It has been reported that N-alkylation during hydrogenation of ketones containing primary or secondary amino groups is an undesirable side reaction when low molecular weight alcohols are present with Raney nickel catalyst.[14a] Whereas this type of reaction occurred at 100–130° in our case, previous investigators used temperatures in excess of 150° with their systems.[14] In other, prior work,[15] primary and secondary amines were found to undergo alkylation by alcohols and hydrogen at 180–250° in the presence of Raney nickel or copper chromite. Since tertiary alcohols did not function, the proposal was advanced that dehydrogenation of the alcohol occurs, the resultant carbonyl compound reacts with the amine, and finally hydrogenation to the end product takes place. Excellent yields from reductive alkylation of pyridine bases with alcohols were realized with rhenium sulfide and hydrogen.[16] A related example may be cited in the conversion of 2-amino-2-methyl-1-propanol to 2,2,5,5-tetramethylpiperazine on exposure to hydrogen and Raney nickel.[17]

The mechanistic scheme previously advanced[14-16] serves to rationalize the presence of **4**, **5**, **6**, and **7**. Three possible routes can be visualized for formation of **11c**. Hydrogenolysis might occur with **1a** or the *N*-ethyl derivative of **1a**. Alternatively, intramolecular dehydration of **1** could conceivably generate the strained bridgehead imine. Subsequent steps would consist of hydrogenation to **11a** and then N-alkylation.

Stereochemistry. Amino alcohols **2** and **3** were identified by microanalytical and spectral means. The nmr spectra were especially helpful in assigning exo and endo configurations to the hydroxyl functions as described[13] for the corresponding *N*-ethyl derivatives, **4** and **5**. As anticipated, **3** displayed a larger vicinal coupling constant for the C-3 carbinyl proton than did the endo isomer.

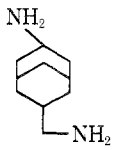
In addition, the nmr spectra indicate that **2** and **3** exist in different conformations. Most notable is the appearance of the CH_2N signal, a singlet for **2** in contrast to a doublet for **3**. Similar results were observed for **4** *vs.* **5** and **6** *vs.* **7**. Conformational preferences for bicyclo[3.3.1]nonane derivatives have been discussed.[4,13,18,19] Peters and coworkers provided[18] a detailed treatment of the 3,7-disubstituted compounds, which is quite pertinent to the present work. Various conformations for the endo,endo case are illustrated.



The principal contributors appear to be the chair–boat forms **a** and **b**. The double-boat conformation (**c**) seems to play an increasing role as the bulk of the substituents increases, and **d** purportedly participates to only a small extent. For the corresponding exo alcohols, the population would mainly consist of the chair–boat forms.

Possibilities for hydrogen bonding in our case may complicate the conformational picture. For **6** and **7** in chloroform, both free and bonded absorptions (3600 and 3300 cm^{-1}, respectively) are present, whereas a neat sample of **7** showed absorption in this region only at 3300 cm^{-1}. Molecular models indicate that **2** might exist as a hydrogen-bonded monomer in conformation **b** and as a hydrogen-bonded dimer in conformations **a**, **b**, and **c**. The exo isomers **3**, **5**, and **7**, can apparently undergo only linear hydrogen bonding.

Reduction to Diamine. Dissolving metal reduction[20,21] of the oxime of **1** with sodium and ethanol afforded *exo*-3-amino-*endo*-7-aminomethylbicyclo[3.3.1]nonane (**12**) in reasonable yield.



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Since the free base was quite sensitive to atmospheric exposure, more complete characterization was carried out with the dibenzamide derivative. The rather sharp melting points of the benzamide and the freshly purified amine suggest the presence of essentially one isomeric form. The nmr data, including similarity to the spectra of **3**, **5**, or **7**, indicate an exo configuration for the 3-amino group. Hence, a mechanism analogous to that discussed (see above) for the corresponding reduction of **1** seems plausible.

Attempts to reduce the oxime with $LiAlH_4$ in refluxing ether for periods up to 46 hr gave mostly unchanged starting material. The sluggishness of this type of reducing system has been noted previously.[22] The Leuckart reaction was investigated as a possible direct method. Several runs under various conditions yielded only a small amount (about 10%) of the diamine, in addition to recovered **1**.

Experimental Section

Melting points are uncorrected. Infrared spectra were obtained with Beckman IR-8, IR-20A, and Perkin-Elmer 137 instruments, calibrated with the 1601-cm^{-1} band of polystyrene. Varian T-60 and HA-100 instruments were used to obtain nmr data, which are reported in parts per million relative to tetramethylsilane as internal standard. Gas chromatography was carried out with a Varian Aerograph instrument (A-90-P, 1700, or 1800) with a 15 ft × 0.25 in. column of 15% Carbowax 20M and 10% NaOH on Chromosorb P (30/60), or a 10 ft × 0.25 in. column of 20% Carbowax 20M and 10% NaOH on Chromosorb P (30/60) at 225°.

Solutions were dried over Na_2SO_4. Sodium trimethoxyborohydride was obtained from Alfa Inorganics. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill., Baron Consulting Co., Orange, Conn., Mr. A. Gasiecki, and Mr. R. White.

2 and 3 from 1 and Sodium Borohydride. The following procedure is illustrative. A solution of **1** (8 g, 0.48 mol) and $NaBH_4$ (2.3 g, 0.06 mol) in 100 ml of dry methanol was stirred at room temperature for 24 hr. Then 50 ml of 20% saline was added and stirring was continued for a few minutes longer. After the volatile material was removed under reduced pressure, the residue was extracted with methylene chloride. The combined, dried extract was freed of solvent to yield 7.7 g (95%) of a mixture of **2** and **3** as a white solid which can be further purified by recrystallization from cyclohexane and/or sublimation at 70–80° (<1 mm). The ratio of **2**:**3** was found to be 95:5 by glpc. Analytical samples were obtained by preparative glpc followed by sublimation.

Alcohol **2** had mp 93–94.5°; ir ($CHCl_3$) 3650 and 3250 (NH, OH) and 1125 cm^{-1} (CO); nmr ($CDCl_3$) δ 4.12 (m, 1, $J_{AX} \cong J_{BX}$ = 3 Hz, CHOH), 2.54 (m, 2, CH_2N), 1.8 (m, 16, CH, CH_2, NH_2, OH); mass spectrum *m/e* (rel intensity) 169 (3), 152 (2), 151 (5), 30 (100).

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.27. Found: C, 71.29; H, 11.42, N, 8.19.

Alcohol **3** had mp 107–108°; ir ($CHCl_3$) 3650 and 3250 (NH, OH) and 1050 cm^{-1} (CO); nmr ($CDCl_3$) δ 3.91 (m, 1, J_{AX} = 5, J_{BX} = 16 Hz, CHOH), 2.48 (d, 2, CH_2N), 1.5 (m, 15, CH, CH_2, NH_2, OH); mass spectrum *m/e* (rel intensity) 169 (2), 151 (6), 30 (100).

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.27. Found: C, 70.74; H, 11.40; N, 8.04.

Essentially the same procedure was employed when other alcohols were used as solvents for the reduction of **1**. Lesser quantities of **1** (generally 1–2 g) were used. A drying tube was attached to the apparatus when the solvent was anhydrous. A control experiment showed that the ratio of **2**:**3** was not significantly altered during the work-up and purification procedures.

Reduction of 1 with Sodium Trimethoxyborohydride. To a solution of **1** (1 g, 0.006 mol) in 25 ml of dry methanol was added 2.3 g (0.018 mol) of sodium trimethoxyborohydride in one portion. The mixture was stirred for 12 hr, and then 5 ml of 10% saline was added, followed by a few minutes of stirring. The solvents were removed under reduced pressure, the residue was extracted with CH_2Cl_2, and then solvent was removed from the dried solution to yield crude alcohol product, 0.9 g (90%). Glpc analysis indicated an endo–exo ratio of 93:7 for **2**:**3**.

***endo*-7-Acetamidomethylbicyclo[3.3.1]nonan-3-one from 1.** A mixture of **1** (5 g, 0.03 mol), anhydrous potassium carbonate (6 g, 0.04 mol), and 500 ml of dry benzene was cooled to 0°. Acetyl chloride (5.3 g, 0.07 mol) in 30 ml of dry benzene was added dropwise with stirring during 30 min. The mixture was then stirred for 1 hr at 0–10°, and then for 15 hr at room temperature. The resulting solid was collected by suction filtration and washed thoroughly with hot benzene. The filtrate and benzene washings were combined and washed first with 10% K_2CO_3, next with water, and then dried. Removal of benzene under reduced pressure gave a light yellow oil which crystallized on stirring with 20 ml of petroleum ether (bp 60–90°). The white solid was collected, washed with petroleum ether, and recrystallized from 1:1 benzene–petroleum ether to give 4.2 g (68%) of the amide: mp 113–114°; ir (KBr) 3310 (NH), 1700 (ketone), 1650 (amide), and 1560 cm^{-1} (NH); nmr ($CDCl_3$) δ 1.90 (s, 3, $COCH_3$), 3.0 (t, 2, CH_2N), 7.13 (s, 1, NH).

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.86; H, 9.21; N, 6.53.

***endo,endo*-7-Acetamidomethylbicyclo[3.3.1]nonan-3-ol.** A solution of the acetamide of **1** (7 g, 0.033 mol) in 70 ml of absolute methanol was cooled to 0°. Sodium borohydride (2.5 g, 0.067 mol) was added during 10 min. The mixture was stirred at ice-bath temperature for 2 hr and then at room temperature for 15 hr. After addition of water (20 ml), the solvents were removed under reduced pressure, yielding a clear oil which solidified upon addition of 30 ml of water. The solid was collected, dried, and repeatedly crystallized from benzene to yield 6.2 g (88%) of a white solid: mp 165–166°; ir (KBr) 3300–3100 (OH, NH), 1650 (amide), and 1750 cm^{-1} (amide); nmr (CD_3SOCD_3) δ 1.77 (s, 3, $COCH_3$), 2.83 (broad s, 2, CH_2N), 4.0 (broad s, 1, CHOH), 4.27 (d, 1, OH), 7.6 (broad s, 1, NH).

Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.44; H, 10.21, N, 6.56.

2 from Hydrolysis of the Acetamide of 2. A suspension of the acetyl derivative of **2** (2.1 g, 0.01 mol) in 200 ml of 10% NaOH was heated at reflux until complete solution was attained (1.5 hr). After an additional 1 hr at reflux, the mixture was cooled and extracted in portions with chloroform. Removal of solvent from the combined, dried extract yielded a clear oil which crystallized on standing. Sublimation (80°, 0.3 mm) gave 1.3 g (77%) of white solid, mp 95–96°, which was identical (ir, nmr) with **2** obtained from **1** and $NaBH_4$.

Reduction of 1 with Sodium and Alcohols. 1. Ethanol. In a 1-l. flask with condenser and drying tube were placed **1** (10 g, 0.06 mol) and 400 ml of absolute ethanol. The solution was brought to reflux and kept there by addition of sodium (16 g, 0.69 g-atom) over a 2-hr period. Water (25 ml) was added and the volatile solvents were removed. The residue was refluxed for 8 hr with 28 g of $NH_2OH \cdot HCl$ and about 250 ml of 50% ethanol. The ethanol was removed under reduced pressure, and 100 ml of 15% caustic was added. After the solution was extracted with CH_2Cl_2 in portions, the dried extract was freed of solvent. The residue was sublimed (80–85°, 0.3 mm), yielding 4.5 g (45%) of **3**. Recrystallization from cyclohexane provided a pure sample: mp 114–116°; ir ($CHCl_3$) 3600, 3250 (OH, NH), and 1050 cm^{-1} (CO); nmr ($CDCl_3$) δ 2.46 (d, 2, CH_2N), 3.96 (m, 1, CHOH).

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.70; H, 11.40; N, 8.15.

2. Isopropyl Alcohol. A mixture of **1** (3 g, 0.018 mol) in 70–75 ml of dry isopropyl alcohol was warmed until solution was complete. Sodium (4.1 g) was added in one portion, which caused the reaction mixture to reflux gently. After the initial reaction had subsided an additional 2 g of sodium and 25 ml of *i*-PrOH were added. The mixture was kept warm until all of the sodium was consumed and a white precipitate had formed. Water (50 ml) was added and the solvents were removed. An additional 100 ml of water was added, and the aqueous solution was extracted with CH_2Cl_2 in portions. Evaporation of solvent left 2.9 g of white solid which was heated at reflux with a 5-molar excess of $NH_2OH \cdot HCl$ and $NaHCO_3$ in 50% ethanol overnight. The volatile solvents were removed and the residue was made basic with 100 ml of 33% caustic. The basic solution was extracted repeatedly with CH_2Cl_2. The dried extract was evaporated to give a white solid, which was sublimed (80–90°, 0.2 mm) to give 1.5 g (50%) of **3**, mp 115–117°. The product was identical (ir and nmr spectra) with that obtained from the sodium–ethanol reduction.

3. *tert*-Butyl Alcohol. Compound **1** (3 g, 0.018 mol) was dissolved in 200 ml of warm *tert*-butyl alcohol. Sodium (6.2 g, 0.27 g-atom) was added in two equal portions at 1-hr intervals. The reaction mixture was agitated with gentle heating until all of the sodium was consumed (4–5 hr). After water (40 ml) was added, volatile material was removed under reduced pressure. Water (100 ml) was added to the residue, and the resulting solution was extracted repeatedly with methylene chloride. Following removal of solvent, the white, solid residue was heated at reflux with a 10-molar excess of hydroxylamine hydrochloride and sodium bicarbonate in 200 ml of 50% ethanol for 8–9 hr. The ethanol was removed under reduced pressure, and then 50 ml of 50% NaOH and 25 ml of water were added. The solution was extracted repeatedly with methylene chloride. The combined, dried extract was freed of solvent, leaving a white solid, which was sublimed (85°, 0.5 mm) to yield 2.1 g (70%) of **3**. Crystallization from cyclohexane gave material melting at 115–118°. The ir and nmr spectra were essentially identical with those of the product from Na–EtOH reduction.

Hydrogenation (Ni-C_2H_5OH) of 1. 1. At 100°. An autoclave was charged with **1** (7 g, 0.04 mol), Raney nickel (10–20 g), and 100–125 ml of absolute ethanol. The reaction mixture was agitated at 100° under a hydrogen pressure of 1800–2000 psi for about 24 hr. The catalyst was removed by gravity filtration and washed with alcohol. Solvent removal afforded an intractable, viscous liquid. After addition of excess 18% HCl, evaporation to dryness yielded 8.4 g of white solid. Glpc analysis (Carbowax 20M), after conversion to the free base, indicated the presence of **4** and **5** (39–41%), **11c** (49–51%), and an unidentified component (8–9%). Compound **4** was identified by glpc peak enhancement with authentic material.[13] Compound **5** had mp 131–132.5° after purification by preparative glpc and vacuum sublimation (lit.[13] mp 131.5–133°). Compound **11c**, purified by preparative glpc, had bp 250° (736 mm) (uncorrected, micro technique); $n^{24}D$ 1.5090; nmr (CCl_4) δ 1.0 (t, 3, CH_2CH_3), 2.58 (q, 2, CH_2CH_3), 2.75 (d, 2, CH_2N), 3.0 (m, 1, CHN), 1.67 (m, 13, rest of H).

Anal. Calcd for $C_{12}H_{21}N$: C, 80.38; H, 11.81; N, 7.81. Found: C, 80.51; H, 11.71; N, 7.63.

11c HCl had mp 258–260°.

Anal. Calcd for $C_{12}H_{22}NCl$: C, 66.80; H, 10.28; N, 6.49. Found: C, 66.56; H, 10.16; N, 6.49.

2. At 130°. The procedure in the preceding section was followed at 130°. After work-up, 6.6 g of hydrochloride salt was obtained (from 5 g of **1**), which was treated with caustic. After extraction with CH_2Cl_2, solvent removal from the dried extract afforded a viscous oil which turned yellow on standing. Glpc analysis revealed the following components (% composition): *N*-ethyl-4-azahomoadamantane (50–52%), unidentified material (about 9%), and a mixture of **6** and **7** (39–41%) in a ratio of 4:96.

Compound **6** was identified by glpc peak enhancement with authentic material. Compound **7**, purified by preparative glpc followed by sublimation at 60–70° (0.1 mm), had mp 69.5–71.5°; ir ($CHCl_3$) 3550, 3350 (OH), and 1050 cm^{-1} (CO); nmr ($CDCl_3$) δ 0.96 (t, 6, CH_2CH_3), 2.21 (s, 1, exchangeable with D_2O), 2.51 (q, 4, CH_2CH_3), 3.95 (m, 1, J_{AX} = 5, J_{BX} = 15 Hz, CHOH), 1.9 (m, rest of H); mass spectrum *m/e* (rel intensity) 22 (1.4), 87 (13), 86 (100), 58 (10.3).

Anal. Calcd for $C_{14}H_{27}NO$: C, 74.61; H, 12.08; N, 6.21. Found: C, 74.58; H, 11.88; N, 6.22.

6 from *N*-Ethyl-7-aminomethylbicyclo[3.3.1]non-3-one. The synthesis was carried out by acetylation (CH_3COCl–C_6H_6–C_5H_5N, room temperature) of the *N*-ethyl derivative[13] of **1**, followed by $LiAlH_4$ reduction. Glpc analysis indicated that **6** and **7** were present in a ratio of 72:28. The endo isomer **6** was separated by preparative glpc and then sublimed under vacuum: mp 69–70°; ir ($CHCl_3$) 3600 and 3300 (OH), 1125 cm^{-1} (CO); nmr ($CDCl_3$) δ 0.99 (t, 6, CH_2CH_3), 1.53 (s, 1, OH, exchangeable with D_2O), 2.50 (q, 4, NCH_2CH_3), 4.13 (m, 1, $J_{AX} \cong J_{BX}$ = 3 Hz, CHOH); mass spectrum *m/e* (rel intensity) 225 (3.5), 87 (13), 86 (100), 58 (9.9), 30 (8.4).

Anal. Calcd for $C_{14}H_{27}NO$: C, 74.61; H, 12.08; N, 6.21. Found: C, 74.35; H, 11.87; N, 6.16.

7 from 3. Crude **3** (4 g) from the sodium–ethanol reduction of **1** (4 g, 0.023 mol) was dissolved in 30 ml of CH_2Cl_2. After the addition of 2,6-lutidine (5.35 g, 0.05 mol) and freshly distilled ethyl iodide (8.6 g, 0.055 mol), the reaction mixture was stirred for about 8 hr at room temperature. Sodium hydroxide (15%, 25 ml) was added, the layers were separated, and the basic portion was extracted with several portions of CH_2Cl_2. The dried, combined organic fraction was freed of solvent. The desired product was separated from the dark brown residue by preparative glpc. Sublimation provided **7** which was identical in all respects with the corresponding product obtained from catalytic hydrogenation of **1** at 130°.

Oxime of 1. A solution of Na_2CO_3 (2.3 g, 0.044 mol) and $NH_2OH \cdot HCl$ (3.1 g, 0.044 mol) in 20 ml of H_2O was refluxed for 5 min to degas the solution. Compound **1** (3.7 g, 0.022 mol) in 20 ml of 95% EtOH was added. After 15 hr at reflux, the solvents were removed under reduced pressure, and the residue was extracted with hot benzene and petroleum ether (bp 30–60°). The solid from filtration of the cooled, combined extract was recrystallized from benzene, 3.4 g (85%), mp 140–141°. The analytical sample was obtained by sublimation at 90–110° (0.1 mm) and recrystallization from benzene, ir (KBr) 3400–3200 (OH, NH) and 1665 cm^{-1} (CN).

Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.90; H, 9.95; N, 15.37. Found: C, 66.16; H, 10.08; N, 15.48.

12 from Oxime of 1. A solution of the oxime of **1** (4.3 g, 0.023 mol) in 60 ml of absolute ethanol was degassed by boiling for 5 min. After heating was discontinued, sodium (6 g, 0.27 g-atom) was added so as to maintain rapid reflux. The mixture was then stirred for 30 min. Water (30 ml) was added, the solution was stirred for 20–30 min, and then the cooled solution was acidified (litmus) with 18% HCl. After the ethanol was removed under reduced pressure, the remaining aqueous solution was basified with 50% caustic. The product was extracted with $CHCl_3$. Removal of solvent from the dried extract under reduced pressure provided a solid which was purified by sublimation at 40–50° (0.2 mm) to yield 2.4 g (60%) of diamine: mp 40–42°; ir ($CHCl_3$) 3500–3100 (NH) and 1600 cm^{-1} (NH); nmr ($CDCl_3$) δ 1.37 (s, 4, NH, exchangeable with D_2O), 2.48 (d, 2, CH_2N), 3.02 (m, 1, CHN), 1.4 (m, rest of H). Since the product is very sensitive to atmospheric CO_2, it was characterized as the dibenzamide derivative.

Dibenzamide of 12. After freshly sublimed diamine **12** (0.52 g, 0.003 mol) was dissolved in 20 ml of dry pyridine, 1 ml of benzoyl chloride was added dropwise with stirring. The solution was stirred at room temperature for 15 min and then at 60–70° for 45 min. After the cooled mixture was poured into 100 ml of water, the filtered solid was recrystallized from benzene, affording 0.74 g (70%) of the dibenzamide: mp 208–209°; ir (KBr) 3300 (NH), 1650 (C=O), and 1550 cm^{-1} (NH); nmr ($CDCl_3$) δ 3.26 (t, 2, CH_2N), 4.43 (broad s, 1, CHN), 6.10 (broad d, 1, NH), 6.63 (broad m, 1, NH), 7.41 (m, 5, Ar), 7.80 (m, 5, Ar).

Anal. Calcd for $C_{24}H_{28}N_2O_2$: C, 76.55; H, 7.51; N, 7.44. Found: C, 76.45; H, 7.54; N, 7.50.

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Registry No.—**1**. 34650-78-7; **1** acetamide, 50361-63-2; **1** (*N*-ethyl), 34913-38-7; **1** oxime, 50361-65-4; **2**, 50361-66-5; **2** acetamide, 50361-67-6; **3**, 50361-68-7; **6**, 50361-69-8; **7**, 50361-70-1; **11c**, 50361-71-2; **11c** hydrochloride, 50529-57-2; **12**, 50361-72-3; **12** dibenzamide, 50361-73-4; sodium borohydride, 16940-66-2; sodium trimethoxyborohydride, 16940-17-3.

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Studies Related to the Conversion of 9,10-Anthraquinones to Anthracenes

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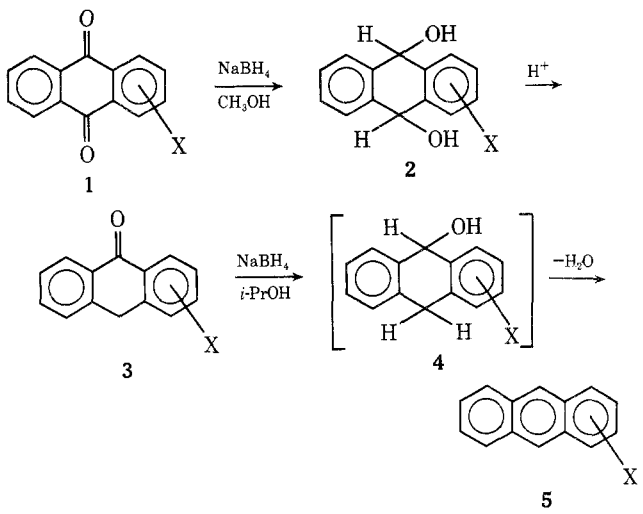
A facile method for the conversion of certain 9,10-anthraquinones to anthracenes *via* successive heterogeneous alcoholic sodium borohydride reductions and dehydrations has been developed. Several halo- and methyl-substituted anthracenes have been prepared by this procedure and the intermediate 9,10-dihydroxy-9,10-dihydroanthracenes and anthrones have been isolated and characterized. Ir and nmr spectroscopy have been employed for determination of the isomer distribution of 9,10-dihydroxy-9,10-dihydroanthracenes and unsymmetrically substituted anthrones.

The reduction of an appropriately substituted anthraquinone provides a potential route to many anthracene derivatives which are otherwise difficult to obtain. We wish to report that sodium borohydride in a lower alcohol is an effective reagent for this purpose. The intermediates formed during this reduction have been identified and their conformational and keto–enol relationships studied.

Sodium borohydride reduction of anthraquinones in diglyme under widely different reaction conditions has been reported. In one instance,[1] the difficult-to-purify products contained boron, whereas anthrahydroquinone was the product reported in the second case.[2] Later investigators[3,4] claimed 35–50% yields of anthracenes for the reduction of the corresponding anthraquinones in refluxing sodium borohydride–diglyme solutions. Evidence was also given for the formation of some anthracene derivatives (50–70%) when the reduction was run in the presence of boron trifluoride or aluminum chloride. Under these conditions, anthraquinone gave a mixture of anthracene and 9,10-dihydroanthracene. More recently,[5,6] sodium borohydride in methanol has been used to obtain 9,10-dihydroxy-9,10-dihydroanthracenes from the corresponding anthraquinones. Reductions wherein lithium aluminum hydride has been used have given conflicting results.[7,8]

We have found that a three-step procedure involving two reduction–dehydration sequences using sodium borohydride in methanol or 2-propanol converts many anthraquinones (**1**) to anthracenes (**5**) in a straightforward fashion, *via* the successive formation of 9,10-dihydroxy-9,10-dihydro intermediates, anthrones, and 9-hydroxy-9,10-dihydro intermediates. The steps are schematically represented wherein X represents one or more substituents on either or both end rings.



Procedures described in the Experimental Section have been generalized and represent a skeletal framework from which one can adapt procedures for specific anthraquinones. Table I lists the pertinent data for a number of anthraquinones. An additional specific procedure for the synthesis of 1,4-dimethoxyanthracene (**5j**) is included, because the literature preparation[9] for **5j** is not readily reproducible in our hands. Compound **5j** has been shown to be a useful diagnostic tool for detecting the presence of benzyne intermediates,[10] and satisfactory yields are not obtained by the general stepwise procedure discussed above.

The yield of 9,10-dihydroxy-9,10-dihydroanthracene (**2a**) was lower than the yields for **2** from substituted anthra-