# Bridged Azapolycyclic Alcohols from Intramolecular Epoxide Ring Openings by Amides

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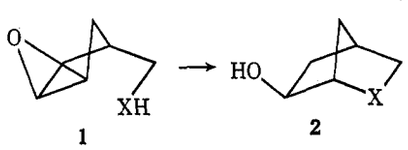
An epoxide ring opening by an intramolecular nucleophilic attack of an amide group was utilized to synthesize 2-azanorbornan-6-ols and 2-azaadamantan-4-ols. The spectral identification of these compounds is described.

In the courses of our studies of heteronorbornanes[3,4] and 2-adamantyl derivatives[5] we were led to devise synthetic routes to the 2-aza analogs of these two types of bridged polycyclic skeleta. The main requisite in both cases lay in the versatility of the synthetic method with regard to substituent variation on the ring-incorporated nitrogen. Fortunately, a single reaction type sufficed as the culminating step in the syntheses of both 2-azanorborn-6-yl derivatives and 2-azaadamant-4-yl derivatives. The reaction, a ring closure effected through an intramolecular epoxide ring opening, had been applied previously in the syntheses of 2-oxanorbornan-6-ol[3] (**2a**) and 2-thianorbornan-6-ol[6] (**2b**) from *trans*-3,4-epoxycyclopentylmethyl alcohol (**1a**) and thiol (**1b**), respectively. Interestingly, it failed com-

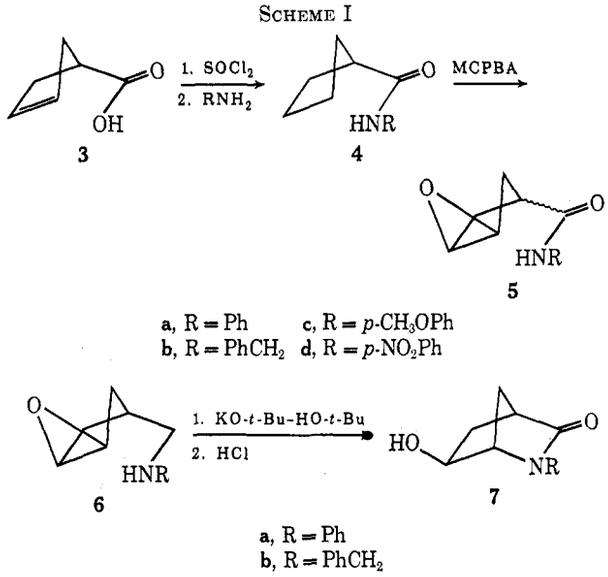


**a**, X = O
**b**, X = S
**c**, X = NR

pletely for syntheses of the amine analogs **2c**, owing to an inability to epoxidize the requisite olefins for preparation of **1c**.

As the latter difficulty could only be attributed to the amine nitrogen, several epoxy amides (**5**) were prepared by conventional procedures from $\Delta^3$-cyclopentenecarboxylic acid[7] (**3**) (Scheme I). Separations of the trans epoxides (**6**) were accomplished by recrystallization. Cyclizations of **6a** and **6b** were smoothly effected by potassium *tert*-butoxide in *tert*-butyl alcohol at reflux. Infrared analyses of the crude products showed the disappearance of epoxide absorptions, appearance of hydroxyl absorptions, and a shift of the amide C=O stretching frequency to the higher wavenumber characteristic of the lactam.[8] The nmr spectra of the purified lactams substantiated the structural assign-

SCHEME I

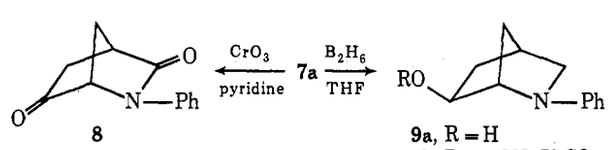


**a**, R = Ph **c**, R = *p*-$CH_3OPh$
**b**, R = $PhCH_2$ **d**, R = *p*-$NO_2Ph$

**a**, R = Ph
**b**, R = $PhCH_2$

ments, as did those of subsequent conversion products (Table I).

For further characterization the *N*-phenyl hydroxylactam **7a** was converted to its corresponding ketone **8**



**9a**, R = H
**b**, R = *p*-$NO_2PhCO$
**c**, R = $CH_3CO$

by chromium trioxide–pyridine oxidation. In addition, **7a** underwent facile reduction with a diborane–tetrahydrofuran mixture to afford crystalline amino alcohol **9a**, which along with its *p*-nitrobenzoate (**9b**) and acetate (**9c**) derivatives, was structurally identified on the basis of its well-defined nmr spectrum (Table I).

The preparation of **9a** confirmed the viability of the synthetic technique and indicated its having met the previously stated criterion as a general method for preparation of 2-substituted 2-azanorbornan-6-ols. This success led to our investigation of the ring closure method for preparation of azaadamantanols of similar structural relationship between hydroxyl and ring nitrogen.

*N-endo*-Bicyclo[3.3.1]non-6-en-3-ylbenzamide (**11**) was prepared from the related carboxylic acid[9] **10** by a conventional series of reactions[10] (see Scheme II).

(1) (a) Taken in part from the Ph.D. thesis of R. J. Schultz, Brown University, 1971; (b) Taken in part from the Ph.D. thesis of W. H. Staas, Brown University, 1973.

(2) Alfred P. Sloan Fellow, 1973–1975.

(3) L. A. Spurlock and R. G. Fayter, Jr., *J. Amer. Chem. Soc.*, **94**, 2707 (1972).

(4) L. A. Spurlock and R. G. Fayter, Jr., Abstracts, 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, ORGN 108; L. A. Spurlock, R. D. Gleim, and R. J. Schultz, Abstracts, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, ORGN 133.

(5) L. A. Spurlock and K. P. Clark, *J. Amer. Chem. Soc.*, **94**, 5349 (1972); **92**, 3289 (1970).

(6) C. R. Johnson, J. E. Keiser, and J. C. Sharp, *J. Org. Chem.*, **34**, 860 (1969).

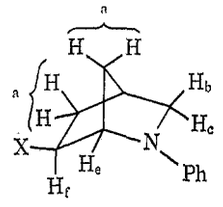
(7) K. C. Murdock and R. B. Angier, *J. Org. Chem.*, **27**, 2395 (1962).

(8) The cyclizations of *trans*-**5c** and **5d** gave similar apparent results; however, the crude products in these cases were characterized only by their infrared spectra and no further attempt was made to utilize these materials.

(9) T. Sasaki, S. Eguchi, and T. Toru, *J. Org. Chem.*, **35**, 4109 (1970).

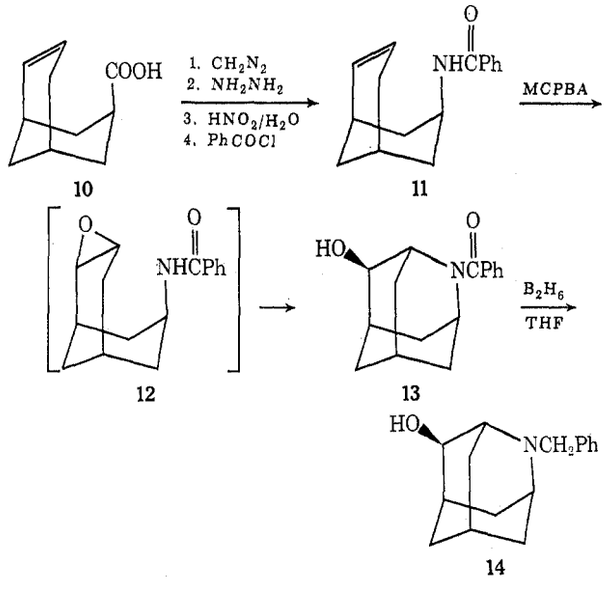
(10) The reaction sequence proceeded from **10** *via* diazomethane esterification, conversion to the hydrazide, Curtius rearrangement to the endo amine, and benzoylation to give **11**. Experimental details will be given in a subsequent publication.

TABLE I
CHEMICAL SHIFTS ($\delta$) OF *N*-PHENYL-*exo*-6-SUBSTITUTED 2-AZANORBORNYL DERIVATIVES



| Proton | 7a | 9a |
|---|---|---|
| $H_a$ | 1.43–2.36 (m) | 1.15–2.00 (m) |
| $H_b$ | 2.80 (m) | 2.53 (br s) |
| $H_c$ | | 2.53 (d) |
| $H_d$ | | 3.28 (d tr) |
| $H_e$ | 4.23 (br s) | 3.87 (br s) |
| $H_f$ | 4.29 (dd) | 3.86 (dd) |
| | **9b** | **9c** |
| $H_a$ | 1.82, 1.98 (br s) | 1.70, 1.81 (br s) |
| $H_b$ | 3.72 (m) | 2.62 (d) |
| $H_c$ | 2.73 (d) | 2.62 (d) |
| $H_d$ | 3.45 (d tr) | 3.38 (dq) |
| $H_e$ | 4.31 (br s) | 4.13 (br s) |
| $H_f$ | 5.05 (dd) | 4.77 (dd) |

SCHEME II




Treatment of the olefin **11** with *m*-chloroperbenzoic acid in methylene chloride at room temperature (the procedure utilized in preparation of **5**) afforded a product in 80% yield which, on the bases of its infrared and nmr spectra, was assigned the ring-closed structure, *N*-benzoyl-2-azadamantan-*anti*-4-ol (**13**). This unexpectedly facile closure of epoxyamide **12** apparently resulted from the unusual proximity of the amide nitrogen to the back side of the epoxide-bearing ring carbon.[11] Quite happily we were thus provided with a highly efficient means of obtaining the desired synthetic goal of an azaadamantanol with possibilities (hydrolysis and alkylation or direct reduction) for easy substituent variation at the nitrogen. One of these variants, the *N*-benzylazaadamantanol **14**, was, in fact, achieved by reduction of **13** with diborane in tetrahydrofuran. Its structure could likewise be confirmed by infrared and nmr spectra.

The further application of this technique to heteropolycyclic systems will be reported later, as will the developments of the azapolycyclic derivatives already prepared.

(11) This is one of several examples which we have observed of unusually enhanced reactivity at the former double bond sites of this endo-substituted bicyclic ring system. All are seemingly related to proximity effects.

## Experimental Section[12]

**$\Delta^3$-Cyclopentenecarboxylic Acid (3).**—The procedure of Murdock and Angier[7] was utilized to convert 156 g (1.25 mol) of *cis*-1,4-dichloro-2-butene and 200 g (1.25 mol) of diethyl malonate to 24.75 g of pure **3**, bp 98–99° (7.5 mm) [lit.[7] bp 83–84° (2 mm)].

**$\Delta^3$-Cyclopentenecarbonyl Chloride.**—To 67.2 g (0.600 mol) of **3** being stirred and cooled with an ice bath was added dropwise 55 ml of thionyl chloride. The reaction mixture was then stirred overnight at room temperature. The crude mixture was distilled at 51 mm, giving 76.9 g (98.2%) of the desired product, bp 79–80° [lit.[7] bp 95–96° (55 mm)].

**General Procedure for Preparation of Amides.**—A solution of $\Delta^3$-cyclopentenecarbonyl chloride (0.025 mol) dissolved in 50 ml of anhydrous ether was added dropwise to a solution of 0.05 mol of primary amine dissolved in 50 ml of ether being stirred at 5°. Upon completion of the addition, the reaction mixture was stirred at room temperature overnight. The amine hydrochloride was removed by filtration and thoroughly washed with ether. The combined ether solutions were dried over magnesium sulfate and concentrated. In this fashion the following secondary amides were prepared, with solvents for recrystallization and yields indicated: *tert*-butyl, mp 127.5–128.5° (78.8%); phenyl, **4a**, mp 139.5–140.5° from $CHCl_3$–pentane (75.8%) (lit.[7] mp 140°); benzyl, **4b**, mp 112–113° from $CH_2Cl_2$–pentane (77.3%); *p*-nitrophenyl, **4d**, mp 121–123° from $CHCl_3$ (74.7%); and *p*-methoxyphenyl, **4c**, mp 138–140° (79.4%).

***cis*- and *trans*-3,4-Epoxycyclopentenecarboxamides (5).**—In a typical procedure, 0.341 mol of amide **4** was dissolved in 725 ml of chloroform and stirred at 5°. To this solution was added dropwise 83.1 g of 85% *m*-chloroperbenzoic acid dissolved in 950 ml of chloroform. After the addition was complete, the mixture was allowed to come to room temperature and was stirred overnight. The excess peracid was destroyed by the addition of 10% sodium sulfite solution and the reaction mixture was filtered. The chloroform solution was washed with 5% sodium hydroxide solution, dried over magnesium sulfate, and concentrated to give the crude epoxide mixture.

In the case of the *p*-nitrophenyl and *p*-methoxyphenyl compounds, only partial separation of isomers was achieved. Trituration of the crude *p*-nitrophenyl reaction product with chloroform left a yellow, crystalline solid, mp 225–230° (53.1%). Addition of pentane to the chloroform solution deposited a pale yellow, fluffy solid, mp 161–168° (32.3%). The same procedure was applied to the crude *p*-methoxyphenyl product, giving a fluffy white, chloroform-insoluble solid, mp 182–185° (32.5%). From the chloroform solution was obtained a light tan solid, mp 142–145° (50.8%).

The crude material from epoxidation of the phenyl amide **4a** was completely soluble in chloroform but upon addition of pentane deposited a 55.4% yield of the trans epoxide **6a** as a white, crystalline solid: mp 169–170°; nmr (DMSO-$d_6$) $\delta$ (TMS) 1.52–2.89 (5 H, m), 3.56 (1 H, s), 6.70–7.78 (5 H, m). The filtrate from **6a** was concentrated and the residue was recrystallized from ether–pentane, giving the cis epoxide as a fluffy, white solid: mp 112–114° (35.8%); nmr ($CDCl_3$) $\delta$ (TMS) 1.72–3.23 (5 H, m), 3.62 (2 H, s), 6.72–7.75 (6 H, m).

Treating a chloroform solution of the crude *N*-benzyl epoxide mixture with pentane gave, on cooling, a 45.7% yield of the trans isomer **6b** as a white solid: mp 140.0–141.5°; ir (Nujol) 3275, 1640, 1540, 1218, 1050, and 845 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ (TMS) 1.78–2.50 (5 H, m), 3.40 (2 H, s), 4.28 (2 H, d), 6.42 (1 H, br s), 7.15 (5 H, s). Concentration of the filtrate gave impure cis epoxide as a yellow oil, ir (film) 3300, 1650, 1545, and 840 $cm^{-1}$.

(12) Infrared spectra were determined on a Perkin-Elmer Model 337 grating infrared spectrometer using sodium chloride optics. Nmr determinations were carried out on a Varian Associates A-60A spectrometer; approximately 20% solutions in a deuterated solvent ($CDCl_3$ or DMSO-$d_6$) were employed with tetramethylsilane as the internal standard. Analyses were carried out by Micro-Analysis, Inc., Wilmington, Del.

*N*-Phenyl-*exo*-6-hydroxy-2-azabicyclo[2.2.1]heptan-3-one (7a).—To a hot solution of 14.8 g (0.378 g-atom) of potassium in 1150 ml of *tert*-butyl alcohol was added in small portions over a period of 30 min 38.4 g (0.198 mol) of **6a**. The resulting orange solution was heated at reflux for 14 hr, after which time approximately 700 ml of *tert*-butyl alcohol was removed by distillation. The cooled solution was acidified with concentrated hydrochloric acid (39 ml) and filtered. The filtrate was concentrated to approximately 200 ml and then dissolved in 300 ml of chloroform. The chloroform solution was washed seven times with 100-ml portions of water and once with saturated sodium chloride solution, dried, and concentrated, giving 30.5 g (79.4%) of crude product as a dark tan solid. An analytical sample of **7a** was obtained after five recrystallizations from absolute ethanol: mp 120.5–122.0°; ir ($CHCl_3$) 3440, 1700, 1600, 1500, 1280, 1160, 1078, 1068, 990, and 947 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ (TMS) 1.43–2.36 (4 H, m), 2.80 (1 H, m), 3.97 (1 H, br s), 4.23 (1 H, br s), 4.29 (1 H, dd), and 5.88–7.64 (5 H, m).

*Anal.* Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.03; H, 6.54; N, 6.92.

*N*-Benzyl-*exo*-6-hydroxy-2-azabicyclo[2.2.1]heptan-3-one (7b).—The preparation was carried out in a similar fashion to that of **7a**. The trans epoxy amide **6b**, 29.6 g (0.136 mol), was treated with a hot solution of 10.67 g (0.273 g-atom) of potassium in 850 ml of *tert*-butyl alcohol. On work-up, 26.7 g of a dark oil was obtained. Crystallization was accomplished by trituration of the oil with ether. In this fashion a light tan solid was obtained: mp 105–107°; ir (Nujol) 3350, 1680, 1410, 1225, 1075, 970, 750, and 700 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ (TMS) 1.28–2.22 (4 H, m), 2.61 (1 H, m), 3.46 (1 H, br s), 3.70–4.22 (3 H, m), 4.47 (1 H, d), 7.13 (5 H, s).

*N*-Phenyl-*exo*-6-hydroxy-2-azabicyclo[2.2.2]heptane (9a).—Treatment of 14.21 g (0.07 mol) of crude **7a** dissolved in 75 ml of tetrahydrofuran with 117 ml of approximately 1 *M* borane in tetrahydrofuran, utilizing the reductive method of Brown and Heim,[13] gave 17 g of crude material as an orange oil. A portion of the crude product was distilled at 124.5–127.0° (0.1 mm), affording the amino alcohol as a colorless oil which slowly solidified to a white, waxy solid, mp 80.5–83.0°. Four recrystallizations from ether–pentane gave pure **9a** as fluffy, white needles: mp 85.0–85.5°; ir ($CHCl_3$) 3650, 3465, 1600, 1500, 1146, 1080, 1010, 920, and 690 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ (TMS) 1.15–2.00 (4 H, m), 2.53 (1 H, br s), 2.53 (1 H, d), 2.70 (1 H, s), 3.28 (1 H, d tr), 3.86 (1 H, dd), 3.87 (1 H, br s), 6.33–7.38 (5 H, m).

*Anal.* Calcd. for $C_{12}H_{15}NO$: C, 76.16; 7.99; N, 7.40. Found: C, 75.98; H, 7.96; N, 7.40.

The *p*-nitrobenzoate **9b** was recrystallized from ether, giving red needles: mp 141–142.5°; ir ($CDCl_3$) 1720, 1600, 1525, 1280, 1120, 1105, 1018, and 1000 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 1.82 (2 H, br s), 1.98 (2 H, br s), 2.73 (1 H, m), 2.73 (1 H, d), 3.45 (1 H, d tr), 4.31 (1 H, br s), 5.05 (1 H, dd), 6.52–7.44 (5 H, m), 8.25 (4 H, s).

*Anal.* Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.45; H, 5.44; N, 8.43.

The acetate **9c** was obtained as a colorless oil: bp 126–127° (0.1 mm); ir (film) 1730, 1590, 1370, 1240, 1140, 1045, and 740 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ (TMS) 1.70 (2 H, br s), 1.81 (2 H, br s), 2.00 (3 H, s), 2.62 (1 H, d), 2.62 (1 H, d), 2.62 (1 H, d), 3.38 (1 H, dq), 4.13 (1 H, br s), 4.77 (1 H, dd), 6.48–7.38 (5 H, m.).

*N*-Phenyl-2-azabicyclo[2.2.1]heptane-3,6-dione (8).—The amino alcohol **7a**, 2.03 g (0.01 mol), was oxidized with chromium trioxide and pyridine in methylene chloride according to the procedure of Ratcliffe and Rodehorst.[14] The crude product was recrystallized from ether, giving 1.493 g (74.3%) of pure **8** as white needles: mp 105–106°; ir ($CHCl_3$) 1770 1720, 1600, 1500, 1365, 1291, 1127, 1100, and 980 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ (TMS) 1.68–2.63 (4 H, m), 3.05 (1 H, m), 4.22 (1 H, dd), 6.88–7.62 (5 H, m).

*Anal.* Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.41; H, 5.74; 6.93.

*N*-Benzoyl-2-azaadamantan-4-ol (13).—To 4.04 g (0.02 mol) of 85% *m*-chloroperbenzoic acid dissolved in 40 ml of methylene chloride was added dropwise a solution of 4.8 g (0.02 mol) of **11**[10] dissolved in 40 ml of methylene chloride. The temperature was maintained below 25° during the addition. Afterward, the solution was allowed to stir at room temperature overnight. The excess oxidizing agent was destroyed by washing with 10% sodium bisulfite solution and the resulting solution was washed with saturated sodium bicarbonate solution and then with water until neutral. The solution was dried and concentrated to give 5.1 g of colorless oil which crystallized upon treatment with a single drop of ethanol. The resultant oily solid was slurried with hexane and filtered to give 4.2 g (82.5%) of **13** as a white, crystalline solid. An analytical sample was prepared by recrystallization from benzene–hexane: mp 143–145°; ir ($CHCl_3$) 3320, 2930, 2850, 1590, 1570, 1445, 1375, 1080, 1025, 970, 920, 790, 735, and 700 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ (TMS) 1.18–2.54 (10 H, m), 3.45 (1 H, s), 3.80 (2 H, m), 4.75 (1 H, m), 7.34 (5 H, s).

*Anal.* Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.85; H, 7.29; N, 5.46.

*N*-Benzyl-2-azaadamantan-4-ol (14).—Reduction of **13** was effected using the method of Brown and Heim.[13] A 1.28-g (0.005 mol) sample of **13** in 25 ml of tetrahydrofuran was treated with 10 ml of an approximately 1 *M* solution of diborane in tetrahydrofuran. Standard work-up gave 1.1 g (90%) of **14** as a white, crystalline solid. An analytical sample was prepared by recrystallization from cyclohexane–pentane: mp 94.5–96°; ir (mull) 3340, 2930, 2850, 1500, 1455, 1360, 1150, 1080, 1050, 1035, 1000, 740, and 700 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ (TMS) 1.18–2.33 (11 H, m), 2.67 (2 H, m), 3.81 (2H, s), 4.0 (1H, m), 7.24 (5H, br s).

*Anal.* Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.69; H, 8.58; N, 5.61.

**Registry No.**—**4** (R = *t*-Bu), 40810-34-2; **4a**, 7686-79-5; **4b**, 40810-36-4; **4c**, 40810-37-5; **4d**, 40810-38-6; *cis*-**5c**, 40810-39-7; *trans*-**5c**, 40810-40-0; *cis*-**5d**, 40810-41-1; *trans*-**5d**, 40810-42-2; **6a**, 40810-43-3; *cis*-**6a**, 40810-44-4; **6b**, 40810-45-5; *cis*-**6b**, 40810-46-6; **7a**, 40810-47-7; **7b**, 38318-60-4; **8**, 40810-49-9; **9a**, 40810-50-2; **9b**, 40810-51-3; **9c**, 40810-52-4; **11**, 40923-03-3; **13**, 40810-53-5; **14**, 40810-54-6; $\Delta^3$-cyclopentenecarbonyl chloride, 3744-80-7.

(13) H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, **86**, 3566 (1964).

(14) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).