Ring Opening of Azetidinols by Phenols: Regiochemistry[1a] and Stereochemistry[1b]

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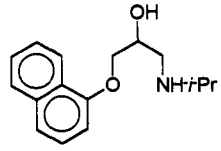
Ring opening of a series of 1-alkyl- and 1-benzyl-3-azetidinols by 4-bromophenol without added base is reported. Opening of *trans*-2-methyl- and *cis*- and *trans*-2-phenyl-3-azetidinols is highly regioselective, if not regiospecific. The 2-methyl compounds open by cleavage of the N–C4 bond and the 2-phenyl compounds by cleavage of the N–C2 bond in a highly stereoselective, if not stereospecific, manner, which involves inversion of configuration at C2. The results are rationalized in terms of nucleophilic ring opening of the azetidinium ions.

Introduction

Since 1967, when Gaertner[2] reported that primary amines react with epichlorohydrin to produce azetidinols, there have been several reports indicating ring openings of azetidinols;[3] however, there have been no systematic investigations of this phenomenon, presumably due to difficulties in the preparation of the azetidinols and the separation and isolation the ring-opened products. Recent advances in the preparation of azetidinols[4-6] have largely overcome the former problem.

Since the early 1970's, there have been numerous patents[7] describing the reactions of phenols with azetidinols at elevated temperature in the presence of a catalytic quantity of base under an inert atmosphere to produce compounds structurally related to the powerful β-adrenolytic compound propranolol.



Propranolol

Results and Discussion

Since a rather large variety of 1-alkyl- and 1-benzyl-3-azetidinols is available,[5,6] it seemed advantageous to do much of the initial chemistry with these azetidinols. 4-Bromophenol was chosen for the ring-opening reactions since most products (**2a–h**, see Figure 1) should be solids, the aromatic region of the ^{1}H NMR spectra of the ring-opened 1-benzylazetidinols (**2d–f**) should have minimal overlap between the two aromatic moieties present, and the phenoxide should be transparent in the aliphatic region of the ^{1}H NMR spectra.

If ring opening involves nucleophilic attack on the basic azetidinol, it seems likely that it should be facilitated by use of a full equivalent of phenoxide rather than by a catalytic quantity. When **1b** was heated with 1 equiv of sodium 4-bromophenoxide, thin-layer chromatography indicated at least five components with the expected **2b** being a minor component (*ca.* 5–10% by ^{1}H NMR analysis). In a separate experiment, **2b** was found to be stable to these conditions, indicating the additional products did not arise by decomposition of **2b**. It seems likely that the mechanism involves protonation of the azetidinol followed by nucleophilic attack at C2 and/or ring opening to a carbocationic intermediate.[8]

This presented an interesting and mechanistically revealing study involving opening 2-substituted azetidinols. Bimolecular nucleophilic attack normally occurs more readily at the least substituted atom, although acid-catalyzed ring opening of oxiranes, aziridines, and oxetanes often occurs at the more substituted atom by VanderWerf's "push–pull" mechanism.[9-11] If 2-substituted azetidinols gave ring-opening products which result from N–C4 cleavage, it may be deduced that bond cleavage and bond formation are occuring in a concerted fashion with little, if any, carbocationic character in the transition state (Scheme 1, path A). If, however, ring-opened products result from N–C2 cleavage, it may be deduced that bond cleavage is running ahead of bond formation and that at least some carbocationic character is present in the transition state (Scheme 1, path B).

Preparation of 2-Substituted Azetidinols. Gaertner[2] isolated and characterized **4a** from the reaction of *tert*-butylamine with **3** (Figure 2). A few years later, the second isomer, **5a**, was isolated and the configurations of the two isomers were assigned on the basis of their ^{1}H NMR spectra (primarily by chemical shift data[12]) with

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(2) Gaertner, V. R. *J. Org. Chem.* **1967**, *32*, 2972.

(3) See, for example: (a) Chen, T.-Y.; Sanjiki, T.; Kato, H.; Ohta, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2401. (b) Gaertner, V. R. *J. Heterocycl. Chem.* **1969**, *6*, 273. (c) Frehel, D.; Heymes, A.; Maffrand, J. P.; Eloy, F.; Aubert, D.; Rolland, F. *Eur. J. Med. Chem., Chim. Theor.* **1977**, *12*, 447.

(4) Jenkins, H.; Cale, A. D. German Offen. 1,932,219, 1970; *Chem. Abstr.* **1970**, *72*, 100478s.

(5) Higgins, R. H.; Eaton, Q. L.; Worth, L., Jr.; Peterson, M. V. *J. Heterocycl. Chem.* **1987**, *24*, 255.

(6) Higgins, R. H.; Watson, M. R.; Faircloth, W. J.; Eaton, Q. L.; Jenkins, H., Jr. *J. Heterocycl. Chem.* **1988**, *25*, 383.

(7) See, for example: Imperical Chemical Industries Ltd., *Japan Kokai 75*, 32135; *Chem. Abstr.* **1977**, *86*, P21001m. Laboratorio Martin Cuatress S.A. *Span.* 453,367; *Chem. Abstr.* **1977**, *86*, P72437. Tucker, H. *Brit.* 1,456,525; *Chem. Abstr.* **1977**, *87*, P5625p.

(8) Ring opening was shown not to involve thermal decomposition since **1b** was recovered in 98% yield after heating a xylene solution at 130 °C for 24 h.

(9) Feldstein, A.; VanderWerf, C. A. *J. Am. Chem. Soc.* **1954**, *76*, 1626.

(10) Fuchs, R.; VanderWerf, C. A. *J. Am. Chem. Soc.* **1954**, *76*, 1631.

(11) See: Paquette, L. A. *Principles of Modern Heterocyclic Chemistry*; W. A. Benjamin, Inc.: New York, 1968; pp 25–34 and 89–95.

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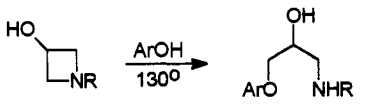


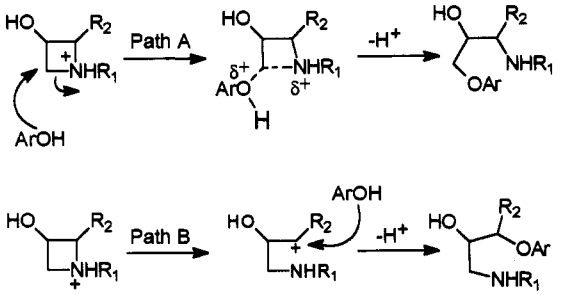
1 2

Ar = p-BrC$_6$H$_4$

	R	%
a	*i*-Pr	64
b	*t*-Bu	47
c	*cyclo*-C$_6$H$_{11}$	31
d	Bn	75
e	*p*-Me-Bn	12
f	*p*-F-Bn	8
g	*p*-Cl-Bn	80
h	*m*-MeO-Bn	18

Figure 1. Ring opening of various azetidinols by 4-bromophenol.

Scheme 1



later substantiation by use of a shift reagent.[13] While treatment of **3** with *tert*-butylamine affords a 2:1 mixture of **4a** and **5a**, respectively, treatment of **3** with cyclohexylamine affords almost exclusively **5b**.[12]

In view of our success in the preparation of azetidinols by cyclization of trimethylsilyl ethers of 1-(alkylamino)-3-chloro-2-propanols followed by cleavage of the resulting trimethylsilyl ethers,[5,6] we wished to investigate whether this method could be extended to the preparation of **4a–c** and **5a–c**. When **3** was condensed with *tert*-butylamine, with cyclohexylamine, and with benzylamine in acetonitrile, the resulting mixtures were silylated by treatment with (trimethylsilyl)imidazole (prepared *in situ*) and triethylamine and then ring closed in the usual manner;[6] mixtures with a trans–cis ratio of about 10:1 were obtained from which the *trans* compounds (**5a–c**) were separated by simple crystallization after methoxide-catalyzed cleavage.

Okutani[14] and co-workers isolated **4d** and **5d** from treatment of **6** and **7** with cyclohexylamine. Use of **6** stereoselectively provides **4d** in excellent yield, while use of **7** provides a somewhat better yield of **5d**, see Figure 2.

Stereochemical Assignment of 2-Substituted Azetidinols. The 60-MHz spectra of **4a,d** and **5a–d** alone

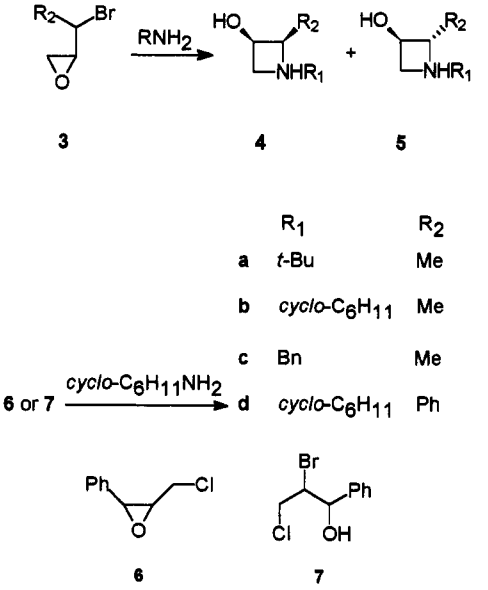


Figure 2. Preparation of 2-substituted azetidinols.

provide little criteria for absolute configurational assignments. In fact, the assignment of protons in the ^{1}H NMR spectra of azetidines is rarely trivial. Doomes and Cromwell[15] assigned configurations to 1-alkyl-2-phenyl-3-aroylazetidines based upon the somewhat smaller coupling constant observed between the protons at C2 and C3 in the *trans*-isomers, as well as upon chemical and mass spectral evidence. The assignment of the C4 protons of *cis*-isomers was based upon the size of the coupling constants between these protons and that at C3—that is, $J_{3\text{-}4trans}$ was noticeably smaller than was $J_{3\text{-}4cis}$. The complexity of the 60-MHz spectra of the *trans*-isomers prevented such an assignment for the C4 protons resulting in an erroneous assignment for these protons. A few years later, the C4 protons of the *trans*-isomers were reassigned[16] based a more complete evaluation of conformational preferences and dispersion effects.[17] The initial assignment of configurations to **4a** and **5a,b** was even more challenging. The original configurational assignments of these were based primarily on chemical shift data in their ^{1}H NMR spectra.[12] In a subsequent report it was stated that the configurational assignments to these had been supported by use of tris(2,2,6,6-tetramethyl-3,5-heptanedionato)europium(III),[13] without elaboration. This reagent, which is not transparent in the region of interest, was also employed by Okutani, Morimoto, Kaneko, and Masuda for the configurational assignment of **4d** and **5d**.[18]

The use of shift reagents has been reviewed.[19,20] It has been observed[21] that there is a linear relationship between the change in the chemical shift of protons of *cis*-4-*tert*-butylcyclohexanol and the concentration of the shift reagent; furthermore, slopes of these plots are dependent upon the distance between the protons and the europium atom.[19,21]

(12) Higgins, R. H.; Cromwell, N. H. *J. Heterocycl. Chem.* **1971**, *8*, 1059.
(13) Higgins, R. H.; Cromwell, N. H. *J. Am. Chem. Soc.* **1973**, *95*, 120.
(14) Okutani, T.; Morimoto, A.; Kaneko, T.; Masuda, K. *Chem. Pharm. Bull. Jpn.* **1974**, *22*, 1490.
(15) Doomes, E.; Cromwell, N. H. *J. Org. Chem.* **1969**, *34*, 310.
(16) Higgins, R. H.; Doomes, E.; Cromwell, N. H. *J. Heterocycl. Chem.* **1971**, *8*, 1063.
(17) Higgins, R. H.; Cromwell, N. H.; Paudler, W. W. *J. Heterocycl. Chem.* **1971**, *8*, 961.
(18) Okutani, T.; Morimoto, A.; Kaneko, T.; Masuda, K. *Tetrahedron Lett.* **1971**, 1115.
(19) Kime, K. A.; Sievers, R. E. *Adrichimi. Acta* **1977**, *10*, 54.
(20) Sievers, R. E., Ed. *Nuclear Magnetic Resonance Shift Reagents*; Academic Press: New York, 1973.
(21) Demarco, P. V.; Elzey, T. K.; Lewis, R. B.; Wenkert, E. *J. Am. Chem. Soc.* **1970**, *92*, 5734.

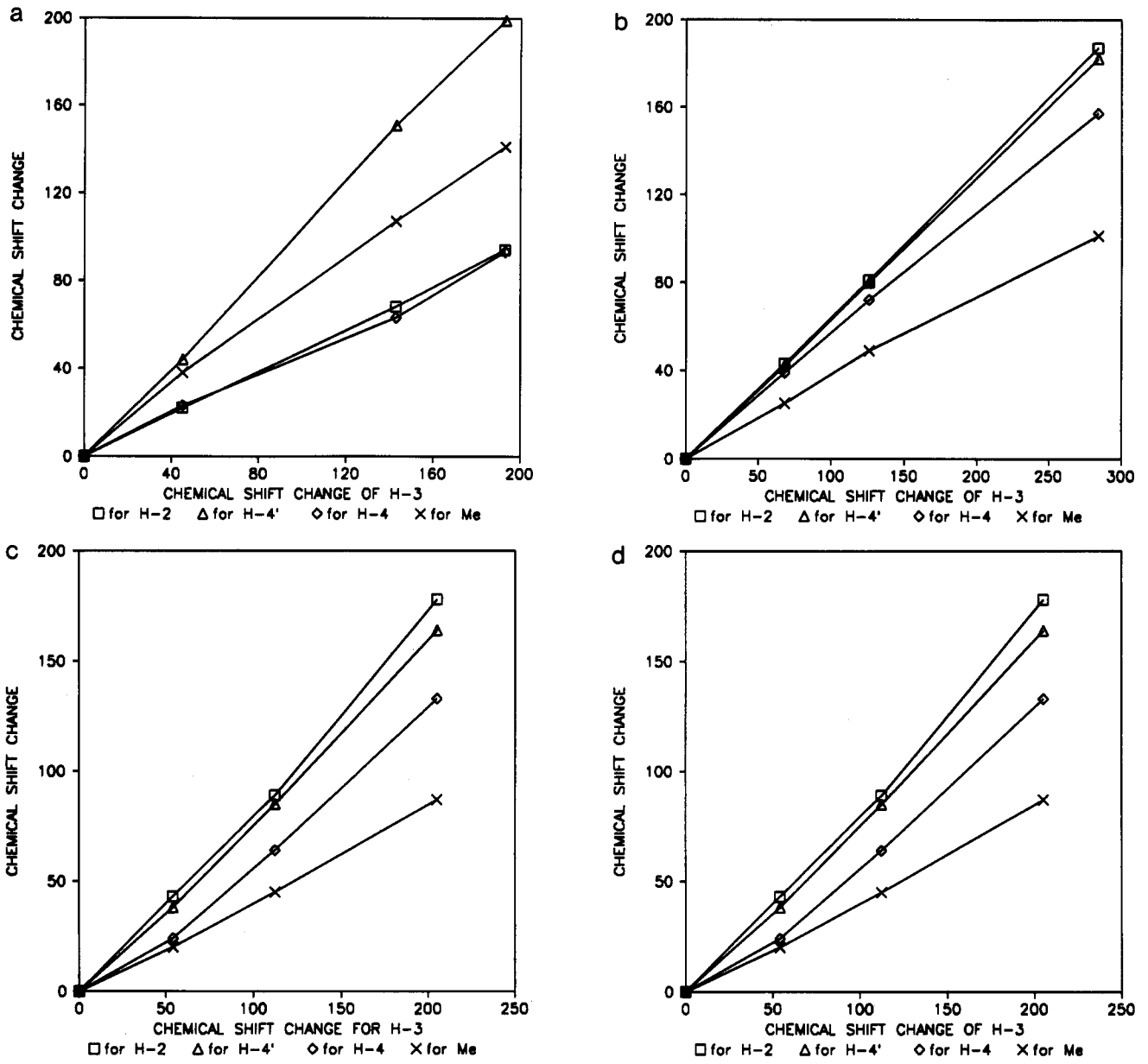


Figure 3. Chemical shift changes (in Hz) of various protons (a) for **4a**, (b) for **5a**, (c) for **5b**, and (d) for **5c**.

The details of the previously reported[13] shift reagent experiments for **4a**, **5a**, and **5b** are no longer available. The shift reagent, tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium(III), Eu(fod)$_3$, was chosen for this investigation since it is more transparent in the region of interest than is tris(2,2,6,6-tetramethyl-3,5-heptanedianoto)europium(III). This reagent could complex at either the hydroxyl position or at the nitrogen atom. The fact that the greatest shift occurs with the hydroxyl proton followed by that at C3 indicates complexation at the hydroxyl in agreement with results obtained with **4d** and **5d** and Eu(thd)$_3$.[18]

That the change in chemical shift for protons is directly proportional to the concentration of shift reagent[21] provides a convenient method for graphically establishing configurations for azetidinols. Since the change in chemical shift should vary linearly with the quantity of added shift reagent, plots of change in chemical shift of the various protons with that of the carbinol proton should be linear. Thus, additional undetermined quantities of shift reagent[22] were added to samples which were then again subjected to ^{1}H NMR analysis.[23] Indeed, straight line plots were obtained for all azetidinols examined (Figure 3).

The following convention is used for the assignment of protons at C4 in Figure 3. The C4 proton which is *cis* to the proton at C2 (*i.e.*, *trans* to the substituent at C2) is designated H4, while the epimeric proton is designated H4′. One C4 proton in the spectra of each of the 2-substituted azetidines, **4a** and **5a–c**, undergoes changes in chemical shift which are nearly parallel to those experienced by H2. It seems safe to conclude that this proton is H4 since H2 and H4 should be essentially equidistant from the europium atom and should experience similar effects.

Once the C4 protons have been assigned with respect to the 2-substituent, the final step is to assign these protons with respect to the 3-hydroxyl substituent. In the *trans*

(22) Commercial (Aldrich Chemical Co.) Eu(fod)$_3$ was employed without purification. It contained a small amount of insoluble residue preventing quantification and eventually to significant deterioration of spectral quality.

(23) Decoupling of the 2-methyl substituent aided in the assignment of the proton at the 2-position.

isomers **5a–c**, where H2 and H4 are *cis* to, and therefore closer to, the hydroxyl, the slopes of plots for H2 and H4 should be larger than for H4′. In the *cis* isomers **4a–c**, where H2 and H4 are *trans* to, and therefore farther from, the hydroxyl, the slopes of the plots for H2 and H4 should be smaller than for H4′. The assignments derived by this method are identical with those previously reported for **4a** and **5a,b**.[12,13]

Further support for this assignment is gained by the fact that in **4a**, the methyl protons are more sensitive to variations in the quantity of added shift reagent than are H2 and H4, while the opposite is true for the *trans*-isomers **5a–c**.

Following this method of reasoning, the major diastereomer obtained in the treatment of **3** with benzylamine (with or without silation of the intermediate 1-(benzylamino)-3-bromo-2-butanol) is assigned as *trans* (**5c**).

Ring Opening of Azetidinols. Since the primary purpose for preparing **2a–h** was for spectral comparisons and since this investigation focuses on the mechanism of the ring opening, no concerted attempts were made to maximize yields of **2a–h**. When **1a–h** were treated with excess 4-bromophenol at 130 °C for 5 h under an argon atmosphere and the excess phenol removed by extraction of a benzene solution of the products with aqueous sodium hydroxide, the ^{1}H NMR spectra of the crude products were indicative of high purity. Purification by recrystallization afforded **2a–h** in the yields reported in Figure 1.

When **5b** was subjected to ring opening by 4-bromophenol under the same conditions as had been applied to **2a–h** (*i.e.*, heating an intimate mixture of the azetidinol and the phenol at 130 °C for 5 h) the ^{1}H NMR spectrum of the crude product indicated only about 50% reaction. Consequently, the reaction times for ring opening of the 2-substituted azetidinols (**4a,d**, **5a–d**) were extended to 16–24 h. When the usual workup was employed, the crude products were weighed and ^{1}H NMR spectra determined. In this manner, mass balance of 80–95% were obtained with the 60-MHz spectra of the crude products being nearly identified with those of the purified products.

Regiochemistry of Ring Opening of 2-Substituted Azetidinols. The 60-MHz ^{1}H NMR spectra of the crude products resulting from ring openings of **5a–c**, even though poorly resolved, were indicative of **9a–c** rather than the isomeric **11–c**; see Figure 4.[24] Comparisons with 60-MHz spectra of the purified products suggested that the crude products were of high purity.

The 400-MHz spectra of the purified products of **5a–c** consist of the following: 1H complex multiplets (appears to be a well-defined pentuplet for **9a**, essentially a pentuplet for **9b**, and a rather well-defined quartet of doublets for **9c**) centered at about δ 3.0 ppm which collapse to doublets upon irradiation of the methyl protons. The three remaining glycidylamine protons are observed in the δ 3.75–4.0 ppm region of the spectra. The δ 3.0 ppm protons of **9a–c** are obviously attached to the nitrogen-bearing carbons, and the fact that they are coupled to the methyl protons provides unequivocal evidence that these products are **9a–c**.

These products indicate that ring opening occurs by N–C4 cleavage, *i.e.*, attack at the *least* substituted carbon. The fact that the ring opening of **5b** occurs at only about

(24) We have thus far been unable to obtain a crystalline product from the ring opening of **4a**.

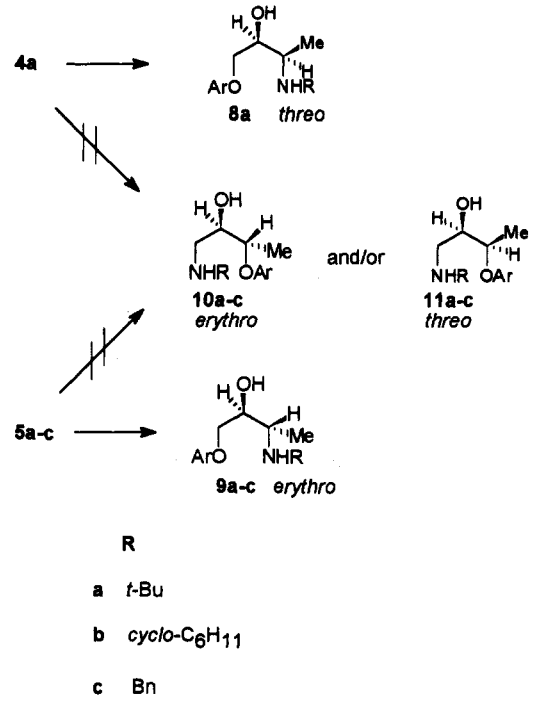


Figure 4. Ring opening of 2-methylazetidinols.

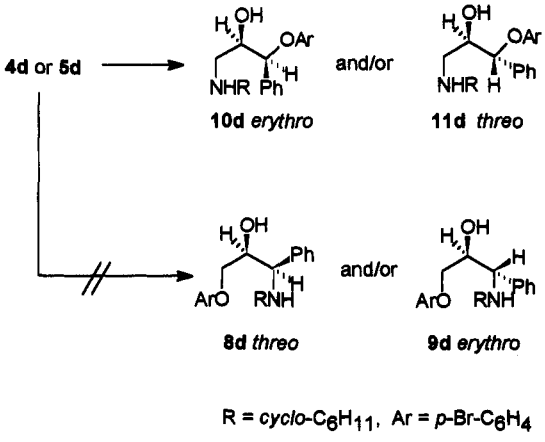


Figure 5. Ring opening of 2-phenylazetidinols.

half the rate of that of **1b** is consistent with this finding, since it has only one primary carbon attached to the nitrogen atom while **1b** has two identical carbons capable of undergoing facile attack.

Ring openings of **4d** and **5d** also provide for regiochemistry. If the reactions involve N–C4 cleavage as observed with **4a** and **5a–c**, then **8d** and **9d**, respectively, would result while if N–C2 cleavage is involved then **10d** and/or **11d** would result (see Figure 5). The 60-MHz ^{1}H NMR spectra of the crude products consist of a complex pattern in the δ 2–4 ppm region and a doublet centered about δ 5.1 ppm with different patterns obtained from ring opening of **4d** and **5d**. The doublet centered at δ 5.1 ppm is clearly consistent only with **10d** or **11d** and, therefore, with N–C2 bond cleavage.

Stereochemistry of Ring Opening of 2-Phenylazetidinols. The fact that ring openings of the 2-phenylazetidinols **4d** and **5d** occur with at least a high degree of stereoselectivity, if not complete stereospecificity, providing different diastereomers from each of the *cis–trans* pair, argues convincingly against free carbocationic intermediates. Configurational analysis based upon the 400-

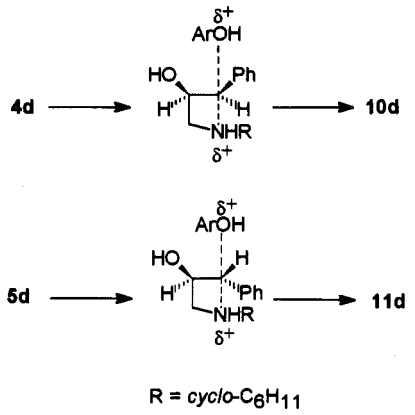
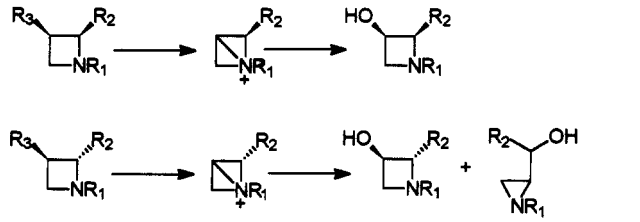


Figure 6. Mechanism of ring opening of 2-phenylazetidinols.



R_1	R_2	R_3	Ref.
t-Bu	Me	OTs	13
cyclo-C_6H_{11}	Ph	OMes	27

Figure 7. Ring opening of 2-substituted azabicyclo[1.1.0]-butonium ions.

MHz ^{1}H NMR spectra of the ring-opened products, **10d** and **11d**, is at best nontrivial and is further complicated by the presence of rotational isomers.[25]

The presence of the hydroxyl substituent at the 3-position prevents one from automatically assuming that the reaction involves retention of configuration, although it is difficult to envision anchimeric assistance by the hydroxyl being of significant importance since the transition state for this type of reaction in **4d** and **5d** could certainly not obtain the necessary linear N–C–O triad. Conclusive evidence that rupture of the N–C2 bond involves inversion of configuration was obtained from X-ray analysis[26] of the ring-opened products.

The regiochemistry and stereochemistry (Figure 6) of the ring opening of 2-substituted azetidinols by phenols is reminiscent of solvolysis of 2-methyl-3-azetidinyl tosylates and 2-phenyl-3-azetidinyl mesylates (Figure 7). In both types of sulfonates, the products dictated that anchimeric assistance (in the first of two steps, both involving inversion yielding overall retention) was involved in formation of azabicyclo[1.1.0]butonium ion intermediates.[13,27] 2-Phenylazabicyclo[1.1.0]butonium ions also gave overall retention of configuration when N–C3 cleavage occurred but also underwent some ring opening *via* N–C2 cleavage giving aziridinyl products,[27] which did not occur in the 2-methyl compounds.[13]

Apparently in azetidinium and azabicyclobutonium ions, 2-phenyl substituents provide sufficient stability to the transition states leading to formation of the developing benzylic carbocations such that N–C2 bond cleavage may be important, while 2-methyl substituents do not provide sufficient stabilization to this mode of ring opening and alternative mechanisms—N–C3 cleavage in azabicyclobutonium ions (to relieve the most strain) and N–C4 cleavage of azetidinols by phenols—occur exclusively.

In summary, the mechanism of ring opening of azetidinols by phenols seems to involve proton transfer to form the azetidinium ions, followed by nucleophilic attack by the phenol (or phenoxide) at the 2- and/or 4-positions of the ring. A 2-methyl substituent effectively shields C2 from attack by the nucleophile (presumably for steric reasons and the inability of the methyl to sufficiently stabilize carbocationic character in the transition state leading to N–C2 bond cleavage), thereby giving N–C4 cleavage. While carbocationic intermediates do not appear to be operative in the ring opening of the 2-phenylazetidinols, it appears that N–C2 bond cleavage bond is running sufficiently ahead of O–C2 bond formation in the transition state such that C2 in the transition state has developed significant carbocationic character.

Experimental Section

Melting points are uncorrected, and yields are probably not optimized. All NMR spectra were determined in chloroform-*d* solution to which a drop or two of deuterium oxide has been added. All shift reagent studies were conducted at 60 MHz. All ^{13}C data reported are for proton-decoupled experiments. Elemental analysis were performed by Galbraith Laboratories, Knoxville, TN.

Compounds **3**,[12] **6**,[14] **7**,[14] **1a–h**,[5,6] **4d**,[14] and **5d**[14] were prepared following literature procedures.

General Method for Preparation of 2-Methyl-3-azetidinols 4a and 5a–c. To a solution of 30.2 g (0.20 mol) of **3** in 200 mL of petroleum ether was added 0.20 mol of the appropriate amine. The solution was stirred for the specified time period at rt, and then the petroleum ether was removed *in vacuo* with minimal heating.

In a separate flask maintained in an ice–water bath, 25.4 g (0.20 mol) of chlorotrimethylsilane (Aldrich Chemical Co.) was added in a dropwise manner to a solution of 13.6 g (0.20 mol) of imidazole (Aldrich) in 400 mL of acetonitrile and 81.0 g (0.20 mol) of triethylamine. Upon completion of the addition, the resulting mixture was added to the crude aminobromobutanols above. The resulting mixtures were stirred at reflux for 3 d and filtered, and the solvent was removed *in vacuo*. The residue remaining after solvent removal was triturated twice with petroleum ether, and the petroleum ether was removed *in vacuo*.

The crude 2-methyl-3-(trimethylsiloxy)azetidines were then isolated by vacuum distillation. In all cases, the 60-MHz ^{1}H NMR spectra of the distillate indicated a 4:5 ratio of 1:10 or less. The azetidinols were obtained by desilylation in methanol containing a catalytic quantity of sodium methoxide[6] for 4 h.

1-*tert*-Butyl-2-methyl-3-azetidinols (4a and 5a). These compounds were prepared by published methods.[2,12] The 60-MHz ^{1}H NMR spectrum on the crude distilled product indicated a **4a**:**5a** ratio of about 2:1. When method A was followed at twice the mole scale with 23 d allowed for the condensation of *tert*-butylamine with **3**, distillation afforded 28.45 g (33%) of the silylated azetidinols (bp 76–120 °C at 15 Torr (mostly bp 98–100 °C)). Desilylation of 6.98 g (0.032 mol) in 30 mL of methanol afforded 1.08 g (23.6%) of **5a**, after recrystallization, mp 69.5–72 °C (lit.[11] mp 65–66 °C).

(25) Our investigation of conformational effects in products resulting from ring opening of various azetidinols is nearing completion and will be the subject of a forthcoming paper.

(26) The authors have deposited atomic coordinates for structures **10d** and **11d** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(27) Okutani, T.; Masuda, K. *Chem. Pharm. Bull. Jpn.* **1974**, *22*, 1498.

***trans*-1-Cyclohexyl-2-methyl-3-azetidinol (5b).** This compound (on the 0.20 mol scale with a condensation time of 72 h) gave a higher yield of more easily purified product by the general method than by that previously reported.[12] After distillation (bp 81–100 °C at 0.8 Torr) 18.66 g (38.7%) of the silyl ether was obtained. The 60-MHz ^{1}H NMR spectrum indicated a **4b**:**5b** ratio of 1:10 or less. Desilylation in 60 mL of methanol with two recrystallizations from ether–petroleum ether followed by recrystallization from ether afforded 5.21 g (15.4% overall) of **5b**, mp 74–76 (lit.[12] mp 80–81.5 °C).

***trans*-1-Benzyl-2-methyl-3-azetidinol (5c).** A solution of 30.18 g (0.20 mol) of **3** and 21.44 g (0.20 mol) of benzylamine in 40 mL of dimethyl sulfoxide was condensed for 24 h in a water-cooled bath and then at 60 °C for an additional 96 h. After cooling, the solution was made basic with 100 mL of 10% sodium hydroxide and extracted twice with equal volumes of ether. The combined ethereal layers were washed twice with equal volumes of 5% sodium hydroxide solution and dried over calcium carbonate.

For ease of purification, the product was silylated in preparation for distillation by addition of 26.90 g (0.205 mol) of (trimethylsilyl)acetamide (Aldrich Chemical Co.) and refluxing for 3 h. After being cooled to rt, the mixture was filtered and the solvent removed *in vacuo*. The residue was triturated with petroleum ether with solvent removal *in vacuo*. Distillation, bp 100–130 °C at 0.8 Torr, afforded 8.93 g (17.9%) of the trimethylsilyl ethers. The 60-MHz ^{1}H NMR spectrum of this material appeared to be identical with that obtained by the general method, *vide infra*. Consequently, it was combined with that obtained from the general method before desilylation.

Following the general method (condensation time of 120 h), distillation afforded 8.88 g (17.8%) of silylated azetidinols (bp 85–110 °C at 0.8 Torr). Desilylation of the combined silyl ethers, *vide supra* (17.8 g, 0.0715 mol), in 60 mL of methanol with recrystallization from ether afforded **5c**, 3.30 g (26.1% from the silyl ether), mp 55–57 °C. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.56; H, 8.69; N, 7.92. ^{1}H NMR δ: 1.22 (double-d, 3H), 2.81 (doublet-t, 1H), 3.13 (m, 1H), 3.68 (double-d, 1H), 3.74 (m, 1H), 3.84 (double-d, 1H), 4.13 (m, 1H), 7.35–7.5 (m, 5H).

General Method for Ring Opening of Azetidinols. An intimate mixture of the azetidinol (**1a–h**) and typically a 3- to 6-fold excess of 4-bromophenol was heated in a silicon oil bath at 130 °C for 5 h (16–24 h for **4a,d** and **5a–d**, see below) under an argon atmosphere. Upon cooling, the mixture was dissolved in benzene and the excess phenol was removed by extraction with 10% sodium hydroxide solution. After the solution was dried over sodium carbonate or sodium sulfate, the benzene was removed *in vacuo* and the resulting (bromophenoxy)propanolamine recrystallized from petroleum ether–benzene.

When **5b** was subjected to the above procedure, the ^{1}H NMR spectrum of the crude resulting mixture indicated only about 50% reaction. Therefore, reaction times for the opening of **4a,d** and **5a–d** were extended to 16–24 h (probably an unnecessary extension of time for **4d** and **5d**).

3-(4-Bromophenoxy)-1-(isopropylamino)-2-propanol (2a). From 1.15 g (0.010 mol) of **1a** and 10.0 g (0.058 mol) of 4-bromophenol was obtained 1.84 g (64%) of **2a**, mp 100–102 °C. Anal. Calcd for $C_{12}H_{18}NO_2Br$: C, 50.01; H, 6.29; N, 4.86. Found: C, 50.12; H, 6.40; N, 4.89. ^{1}H NMR δ: 1.05 (d, 6H), 2.65 (double-d, 1H), 2.78 (septuplet, 1H), 2.82 (double-d, 1H), 3.89 (m, 2H), 3.95 (m, 1H), 6.75 (d, 2H), 7.35 (d, 2H). ^{13}C NMR δ: 23.0, 23.1, 48.9, 50.2, 68.4, 70.8, 113.2, 116.4, 132.2, 157.8.

3-(4-Bromophenoxy)-1-(*tert*-butylamino)-2-propanol (2b). From 1.29 g (0.010 mol) of **1b** and 10.0 g (0.058 mol) of 4-bromophenol was obtained 1.43 g (47%) of **2b**, mp 111–112.5 °C. Anal. Calcd for $C_{13}H_{23}NO_2Br$: C, 51.67; H, 6.67; N, 4.64. Found: C, 51.78; H, 6.76; N, 4.47. ^{1}H NMR δ: 1.14 (s, 9H), 2.62 (double-d, 1H), 2.80 (double-d, 1H), *ca.* 3.9 (m, 3H), 6.82 (d, 2H), 7.38 (d, 2H). ^{13}C NMR δ: 29.2, 44.5, 50.3, 68.6, 70.8, 113.1, 116.4, 132.2, 157.9.

3-(4-Bromophenoxy)-1-(cyclohexylamino)-2-propanol (2c). From 1.55 g (0.010 mol) of **1c** and 10.0 g (0.058 mol) of 4-bromophenol was obtained 1.01 g (31%) of **2c**, mp 112–113 °C. An analytical sample melted at 115–116 °C. Anal. Calcd for $C_{15}H_{22}NO_2Br$: C, 54.88; H, 6.76; N, 4.27. Found: C, 55.02; H, 6.85; N, 4.12. ^{1}H NMR δ: 0.9–2.5 (m, 11H), 2.68 (m, 1H), 2.86 (m, 1H), *ca.* 3.9 (m, 3H), 6.76 (d, 2H), 7.34 (d, 2H). ^{13}C NMR δ: 25.0, 26.0, 33.7, 33.9, 48.7, 56.7, 68.3, 70.8, 113.1, 116.4, 132.2, 157.9.

3-(4-Bromophenoxy)-1-(benzylamino)-2-propanol (2d). From 1.51 g (0.010 mol) of **1d** and 10.0 g (0.058 mol) of 4-bromophenol was obtained 2.51 g (75%) of **2d**, mp 95.5–97 °C. Anal. Calcd for $C_{16}H_{18}NO_2Br$: C, 57.16; H, 5.40; N, 4.17. Found: C, 57.52; H, 5.61; N, 4.34. ^{1}H NMR δ: *ca.* 2.75 (m, 1H), 2.85 (m, 1H), 3.78 (d, 1H), 3.82 (d, 1H), 3.91 (d, 2H), 4.06 (m, 1H), 6.78 (d, 2H), 7.2–7.4 (m, 7H). ^{13}C NMR δ: 51.1, 53.8, 68.3, 70.7, 113.2, 116.3, 127.2, 128.1, 128.5, 132.2, 139.8, 157.8.

3-(4-Bromophenoxy)-1-[(4-methylbenzyl)amino]-2-propanol (2e). From 1.10 g (0.0062 mol) of **1e** and 5.26 g (0.030 mol) of 4-bromophenol was obtained 0.25 g (12%) of **2e**, mp 101–102 °C. Anal. Calcd for $C_{17}H_{20}NO_2Br$: C, 58.29; H, 5.76; N, 4.00. Found: C, 58.43; H, 6.00; N, 4.09. ^{1}H NMR δ: 2.27 (s, 3H), 2.73 (double-d, 1H), 2.83 (double-d, 1H), 3.74 (d, 1H), 3.77 (d, 1H), 3.89 (d, 2H), 4.01 (m, 1H), 6.76 (d, 2H), 7.1–7.4 (m, 6H). ^{13}C NMR δ: 21.1, 51.0, 53.5, 68.2, 70.7, 113.2, 116.4, 128.1, 129.2, 132.3, 136.8, 136.8, 157.8.

3-(4-Bromophenoxy)-1-[(4-fluorobenzyl)amino]-2-propanol (2f). From 2.36 g (0.0093 mol) of **1f** and 10.0 g (0.058 mol) of 4-bromophenol was obtained 0.14 g (8%) of **2f**, mp 116–117 °C. Anal. Calcd for $C_{16}H_{17}NO_2BrF$: C, 54.25; H, 4.84; N, 3.96. Found: C, 54.67; H, 4.98; N, 3.87. ^{1}H NMR δ: 2.72 (double-d, 1H), 2.82 (double-d, 1H), 3.75 (d, 1H), 3.78 (d, 1H), 3.91 (d, 2H), 4.02 (m, 1H), 6.75 (d, 2H), 6.9–7.4 (m, 6H). ^{13}C NMR δ: 51.0, 53.1, 68.4, 70.7, 113.3, 115.2, 115.4, 116.4, 128.3, 129.6, 129.7, 132.3, 135.6, 157.7, 163.2.

3-(4-Bromophenoxy)-1-[(4-chlorobenzyl)amino]-2-propanol (2g). From 1.00 g (0.0051 mol) of **1g** and 5.26 g (0.030 mol) of 4-bromophenol was obtained 1.51 g (80%) of **2g**, mp 95–96 °C. Anal. Calcd for $C_{16}H_{17}NO_2BrCl$: C, 51.84; H, 4.62; N, 3.78. Found: C, 52.20; H, 4.82; N, 3.87. ^{1}H NMR δ: 2.72 (double-d, 1H), 2.81 (double-d, 1H), 3.74 (d, 1H), 3.78 (d, 1H), 3.90 (t?, 2H), 4.02 (m, 1H), 6.75 (d, 2H), 7.2–7.4 (m, 6H). ^{13}C NMR δ: 51.1, 53.1, 68.5, 70.7, 113.3, 116.4, 128.6, 129.4, 132.3, 132.9, 138.4, 157.8.

3-(4-Bromophenoxy)-1-[(3-methoxybenzyl)amino]-2-propanol (2h). From 1.00 g (0.0052 mol) of **1h** and 5.26 g (0.030 mol) of 4-bromophenol was obtained 0.35 g (18%) of **2h**, mp 90.5–91.5 °C. Anal. Calcd for $C_{17}H_{20}NO_3Br$: C, 55.75; H, 5.50; N, 3.83. Found: C, 55.57; H, 5.73; N, 3.72. ^{1}H NMR δ: 2.72 (double-d, 1H), 2.84 (double-d, 1H), 3.77 (m, 2H), 3.9 (t?, 2H), 4.02 (m, 1H), 6.7–6.9 (m, 5H), 7.21 (m, 1H), 7.32 (d?, 2H). ^{13}C NMR δ: 51.1, 53.7, 55.2, 68.3, 70.7, 112.5, 113.2, 116.4, 120.4, 129.5, 132.2, 141.5, 157.8, 159.8.

***erythro*-1-(4-Bromophenoxy)-3-(*tert*-butylamino)-2-butanol (9a).**[28] From 1.00 g (0.0070 mol) of **5a** and 3.6 g (0.021 mol) of 4-bromophenol (reaction time 18 h) was obtained 1.80 g (81%) of crude **9a**. Two recrystallizations afforded 0.72 g (34%) of **9b**, mp 91–91 °C. Anal. Calcd for $C_{14}H_{22}NO_2Br$: C, 53.17; H, 7.01; N, 4.43. Found: C, 53.07; H, 7.11; N, 4.41. ^{1}H NMR δ: 1.06 (d, 3H), 1.15 (s, 9H), 2.99 (m, 1H), 3.73 (m, 1H), *ca.* 3.9 (m, 2H), 6.76 (d, 2H), 7.33 (d, 2H). ^{13}C NMR δ: 18.4, 30.1, 48.8, 51.1, 69.8, 74.1, 113.0, 116.4, 132.2, 157.0.

***erythro*-1-(4-Bromophenoxy)-3-(cyclohexylamino)-2-butanol (9b).**[28] From 2.00 g (0.012 mol) of **5b** and 6.14 g (0.036 mol) of 4-bromophenol (reaction time 18 h) was obtained 3.40 g (83%) of crude **9b**. Recrystallization from benzene afforded 2.05 g (50%) of **9b**, mp 124–125 °C. Anal. Calcd for $C_{16}H_{24}NO_2Br$: C, 56.14; H, 7.07; N, 4.09. Found: C, 56.29; H, 7.29; N, 3.89. ^{1}H NMR δ: 1.03 (d, 3H), 0.9–2.5 (m, 11H), 3.00 (m, 1H), 3.84 (m, 1H), *ca.* 3.93 (m, 2H), 6.75 (d, 2H), 7.33 (d, 2H). ^{13}C NMR δ: 15.9, 25.0, 25.1, 26.0, 34.2, 34.4, 51.3, 53.7, 70.0, 70.3, 113.1, 116.3, 132.2, 157.9.

***erythro*-1-(4-Bromophenoxy)-3-(benzylamino)-2-butanol (9c).**[28] From 2.00 g (0.011 mol) of **5c** and 5.90 g (0.034 mol) of 4-bromophenol (reaction time 24 h) was obtained 3.40 g (90%)

(28) Since the chiral atoms of the ring-opened products have at least two immediately attached elements in common, C and H (those from the 2-phenyl compounds have three in common (C, H, and O), our conventions in assigning *erythro* and *threo* are with respect to the immediately attached atoms.

of crude **9c**. Recrystallization afforded 1.78 g (46%) of **9c**, mp 90.5–91 °C. Anal. Calcd for $C_{17}H_{20}NO_2Br$: C, 58.29; H, 5.76; N, 4.00. Found: C, 57.98; H, 5.97; N, 3.96. ^1H NMR δ: 1.09 (d, 3H), 2.95 (m, 1H), 3.76 (d, 1H), 3.84 (d, 1H), *ca.* 3.96 (m, 3H), 6.75 (d, 2H), 7.2–7.4 (m, 7H). ^{13}C NMR δ: 15.3, 51.4, 54.2, 69.8, 70.4, 113.2, 116.4, 127.1, 128.1, 128.5, 132.3, 140.1, 157.8.

***erythro*-1-(4-Bromophenoxy)-3-(cyclohexylamino)-1-phenyl-2-propanol (10d).**[26,28] From 0.35 g (0.0015 mol) of **4d** and 0.78 g (0.0045 mol) of 4-bromophenol (reaction time 17 h) was obtained 0.56 g (92%) of crude **10d**. Recrystallization afforded 0.35 g (58%) of **10d**, mp 130.5–131.5 °C. Anal. Calcd for $C_{21}H_{26}NO_2Br$: C, 62.37; H, 6.48; N, 3.46. Found: C, 62.65; H, 6.62; N, 3.45. ^1H NMR δ: 0.9–2.4 (m, 11H), 2.75 (double-d, 1H), 2.86 (double-d, 1H), 3.86 (m, 1H), 5.06 (d, 1H), 6.68 (d, 2H), 7.2–7.4 (m, 7H). ^{13}C NMR δ: 25.0, 26.0, 33.6, 33.8, 47.3, 56.7, 72.9, 82.5, 113.2, 117.7, 126.9, 128.1, 128.6, 132.1, 137.8, 157.0.

***threo*-1-(4-Bromophenoxy)-3-(cyclohexylamino)-1-phenyl-2-propanol (11d).**[26,28] From 0.50 g (0.0022 mol) of **5d** and 1.12 g (0.0065 mol) of 4-bromophenol (reaction time 16 h) was obtained 0.80 g (90%) of crude **11d**. Recrystallization afforded 0.45 g (51%) of **11d**, mp 114–115 °C. Anal. Calcd for $C_{21}H_{26}NO_2Br$: C, 62.37; H, 6.48; N, 3.46. Found: C, 62.34; H, 6.78; N, 3.18. ^1H NMR δ: 0.8–2.3 (m, 11H), 2.55 (double-d, 1H), 2.61 (double-d, 1H), 3.94 (m, 1H), 5.05 (d, 1H), 6.71 (d, 2H), 7.15–7.4 (m, 7H). ^{13}C NMR δ: 24.9, 25.0, 26.1, 33.5, 33.8, 47.7, 56.7, 73.6, 82.7, *ca.* 113, 117.9, 127.0, 128.3, 128.7, 132.2, 137.4, *ca.* 157.

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