Hydroboration–Carbon Monoxide Insertion of Bis-Olefinic Amine Derivatives. Synthesis of δ-Coniceine, Pyrrolizidine, (±)-Heliotridane, and (±)-Pseudoheliotridane

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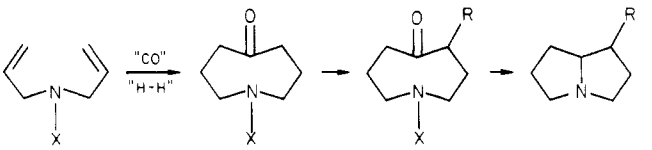
The hydroboration–carbon monoxide insertion of several bis-olefinic amine derivatives has provided facile preparations of *N*-(carbomethoxy)-5-azacylooctanone (**6**), *N*-(carbobenzyloxy)-5-azacyclooctanone (**9**), and *N*-(carbobenzyloxy)-5-azacyclononanone (**18**). Of the hydroboration protocols examined, thexylborane–cyanidation proved to be the most useful. Reductive ring closure of **9** and of **18** gave **26** and **27**, respectively. Methylation of **9** followed by reduction afforded **29** and **30**.

The preparation of medium-sized, heterocyclic ketones from acyclic precursors remains a difficult synthetic transformation owing to entropy losses upon cyclization.[2] The only existing ring closure routes to such systems are the Dieckman condensation[3] or the acyloin reaction.[4] In the course of studies directed toward the synthesis of pyrrolizidine alkaloids, we sought a convenient, nonhigh-dilution route to make 5-azacyclooctanone precursors for 1-azabicyclo[3.3.0]octanes via reductive ring closure.[5,6]

Formally, these medium-sized aza ketones could arise from reductive addition of a carbon monoxide synthon across the termini of a bis(olefinic) amine (Scheme I). Of the known methods for net carbon monoxide (CO) addition to olefins[7,8] only hydroboration–CO insertion[7a] and Friedel–Crafts acylation[7e] have been applied to the synthesis of medium-sized rings. The former route to these heterocycles offers three potential advantages over the traditional procedures.[3,4] (1) The starting bis-olefinic amines are readily available. (2) The borane intermediates obtained from the initial hydroboration offer the potential for boron nitrogen interaction. This positive interaction would decrease entropy losses during the cyclization steps leading to the aza ketone. (3) The inclusion of a nitrogen atom with sp^2 character decreases the internal rotation of the acyclic diene. Therefore, the entropy loss on cyclization is minimized.[9] Despite extensive literature about hydroboration, this technique has seldom been applied to carbon–carbon bond formation in natural product synthesis.[10] In fact, serious problems with functional group compatability have been encountered.[10a]

Scheme I



In this work we have subjected a series of *N,N*-bis-olefinic amines to two different hydroboration–carbon monoxide insertion methods, fulfilling the goal outlined in Scheme I.[11,12] These recently developed methods for hydroboration–CO insertion have not previously been applied to compounds containing nitrogeneous functional groups. The first method, as developed by Brown,[13] involved treating a dialkyl methoxyborane with a selective CO synthon, dichloromethyl methyl ether (DCME procedure). Second, we examined the specific two-migration cyanoborate process (cyanidation) on dialkylthexylboranes,[14] a CO equivalent reported by Pelter.[15] These sequences have led to a selective synthesis of both eight- and nine-membered-ring compounds without high-dilution conditions. These examples establish the effectiveness of borane-mediated CO insertion in the presence of a reducible functional group. Ketones **9** and **18**, the first medium-sized heterocycles to be obtained by any CO insertion process, have also served as precursors to four alkaloids.

Results of Hydroboration

Chloroborane. Pyrrolizidine synthesis via Scheme I requires the preparation of an eight-membered-ring intermediate. Using their haloborane–DCME protocol, Brown and Zaidlewicz[13] converted 1,6-heptadiene into a 75% yield of cyclooctanone, 2-methylcycloheptanone, and 2-ethylcyclohexanone in a 4:1:1 ratio. Application of the chloroborane sequence to dienes containing other functional groups has not been reported. Our results with amino dienes are summarized in Table I (method A). *N*-Benzyl-*N,N*-diallylamine (**1**) failed to react at ambient temperature according to the established DCME proce-

(1) (a) Taken from the Ph.D. Thesis of J.N.B., University of California—San Diego, 1980. (b) Undergraduate research participant, summers 1977–1980.
(2) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.
(3) Schaefer, J. P.; Bloomfield, J. J. *Org. React.* **1967**, *15*, 1.
(4) Bloomfield, J. J.; Owsley, D. C.; Nelke, J. M. *Org. React.* **1976**, *23*, 259.
(5) Leonard, N. J.; Sato, T. *J. Org. Chem.* **1969**, *34*, 1066.
(6) (a) Wilson, S. R.; Sawicki, R. A. *Tetrahedron Lett.* **1978**, 2969. (b) Glass, R. S.; Deardorff, D. R.; Gains, L. H. *Ibid.* **1978**, 2965.
(7) (a) Boron: Brown, H. C. "Organic Syntheses via Boranes", Wiley-Interscience: New York, 1975. (b) Cobalt: Heck, R. F. *J. Am. Chem. Soc.* **1963**, *85*, 3116. Falbe, J.; Korte, F. *Chem. Ber.* **1965**, *98*, 1928. (c) Rhodium: Suggs, J. W. *J. Am. Chem. Soc.* **1979**, *101*, 489. Larock, R.; Oertle, K.; Potter, G. F. *Ibid.* **1980**, *102*, 190. (d) Iron: Collman, J. P. *Acc. Chem. Res.* **1975**, *8*, 342. (e) Friedel–Crafts: Comer, W. T.; Catt, J. D.; Matier, W. L.; Combs, C. M.; Dykstra, S. J. *J. Heterocycl. Chem.* **1973**, *10*, 519. (f) Recent lactone syntheses might be applied to lactams: Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743.
(8) For related applications of cobalt and rhodium see: Garst, M. E.; Lukton, D. *J. Org. Chem.* **1981**, *46*, 4433.
(9) Shaw, B. *J. Am. Chem. Soc.* **1975**, *97*, 3856.
(10) (a) Murphy, R.; Prager, R. H. *Aust. J. Chem.* **1976**, *29*, 617. (b) Bryson, T. A.; Reichel, C. J. *Tetrahedron Lett.* **1980**, 2381. (c) Bryson, T. A.; Pye, W. E. *J. Org. Chem.* **1977**, *42*, 3214. (d) Reichert, C. F.; Pye, W. E.; Bryson, T. A. *Tetrahedron* **1981**, *37*, 2441.
(11) Garst, M. E.; Bonfiglio, J. N. *Synth. Commun.* **1981**, *11*, 231. Structure **4** in this paper is incorrect. Although the two samples of "**4**" have comparable NMR and IR spectra, they exhibit different CI mass spectra with either ammonia or isobutane reagent gas.
(12) Garst, M. E.; Bonfiglio, J. N. *Tetrahedron Lett.* **1981**, 2075.
(13) Brown, H. C.; Zaidlewicz, M. *J. Am. Chem. Soc.* **1976**, *98*, 4917.
(14) Negishi, E.; Brown, H. C. *Synthesis* **1974**, 77.
(15) Pelter, A.; Smith, K.; Hutchings, M. G.; Rowe, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 129, 138, 142, 145.

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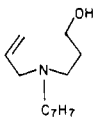
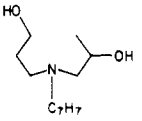
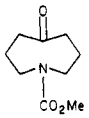
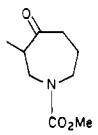
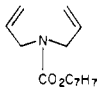
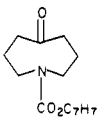
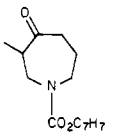
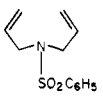
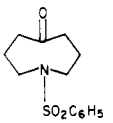
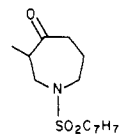
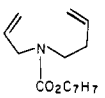
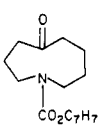
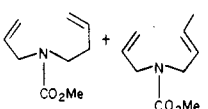
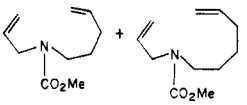
Table I. Hydroboration–CO Insertion with Bis-Olefinic Amine Derivatives

entry	diene	method[a]	products	ratio	% yield
I	 1	A[b]	 2		90
II	1	B	2		
III	1	B[b]	$C_7H_7N((CH_2)_3OH)_2$ (3) +  4	4:1 (3/4)	80
IV	 5	A	 6		20–31
V	5	B	6 +  7	1:1	30
VI	 8	A	alcohols[c,d]		
VII	8	B	 9 +  10	1:1	30
VIII	8	C	9 + $C_7H_7O_2CN((CH_2)_3OH)_2$ (11) + $C_7H_7O_2CNH(CH_2)_3OH$ (12)	2:5:1 (9/11/12)	
IX	 13	B	 14 +  15	1:1	80
X	13	C	$C_6H_5SO_2N((CH_2)_3OH)_2$ (16)		
XI	 17	B	 18		25
XII	 19 20	A	3 isomeric ketones[d]		15
XIII	17	C	alcohols[c,d]		
XIV	 21 22	A–C	alcohols[c,d]		

[a] Method A: hydroboration with chloroborane–dimethyl sulfide and polymer cracking followed by DCME treatment. Method B: hydroboration with thexylborane at room temperature followed by cyanidation. Method C: hydroboration with thexylborane at room temperature, equilibration at 135 °C, and cyanidation. [b] Hydroboration at 100 °C. [c] A complex mixture of alcohols containing no CO insertion products. [d] Determined by GC/MS.

dure,[16-18] while at 100 °C **1** gave olefinic alcohol **2** in 90% yield. *N*-(Carbomethoxy)-*N*,*N*-diallylamine (**5**) provided the desired ketone, azacyclooctanone **6**, and alcohols. Although the yield of **6** was modest (20–30%), the absence of ketone isomers makes this reaction attractive.

The factors limiting the production of **6** were determined by product analysis after each step of the chloroborane–DCME multistage sequence.[19] These experiments confirmed that cracking the initially formed polymer limited the yield. After numerous attempts to overcome these difficulties, we completed hydroboration at high dilution with $H_2BCl{\cdot}SMe_2$, other chloroborane complexes, bromoborane, and iodoborane.[19,20] Ketone **6** was never formed in greater than 10% yield. Increasing the scale of the preparation of **6** drastically decreased the yield.

Despite the moderate yield of **6** and the problems with its preparation, we examined the other substrates **8** and **19–22** to determine the generality of this cyclization. The treatment of either butenyl diene **19** or crotyl diene **20** with the DCME procedure gave low yields of at least three isomeric ketones. Olefins **21** and **22** afforded only diols. The more versatile *N*-(carbobenzyloxy)-*N*,*N*-diallylamine (**8**) and $H_2BCl{\cdot}SMe_2$ gave a polymer which could not be cracked; consequently, ketone **9** was not obtained from it.[19]

Although diene **5** was converted to **6** in 20–30% yield on a millimole scale, the failure to increase the scale of the reaction and the failure with diene **8** led us to pursue alternative borane procedures. The selective formation of **6** from **5** does establish the chloroborane protocol for synthesis of eight-membered heterocyclic ketones.[11]

Thexylborane. A carbonyl group insertion into olefins with thexylborane was developed by Pelter[15] and has been applied to several examples.[10a,22] To our knowledge this method has not been utilized in the synthesis of medium-sized rings.

The reactions of thexylborane and allylamine derivatives are also summarized in Table I (method B). Hydroboration of *N*-benzyl-*N*,*N*-diallylamine (**1**) at 65 °C followed by cyanidation gave diols **3** and **4** in a 4:1 ratio. *N*-Benzyl-5-azacyclooctanone was prepared by the method of Leonard and Sato[5] and shown to be absent in this crude reaction mixture. At ambient temperature both carbamate **5** and sulfonamide **13** gave a 1:1 mixture of seven- and eight-membered-ring ketones (**6**, **7** and **14**, **15**) in 30% and 80% yields, respectively. Surprisingly, *N*-(2-propenyl)-*N*-(3-butenyl) carbamate **17** yielded nine-membered-ring ketone **18** in 16–35% yield with greater than 95% isomeric purity[12] accompanied by alcohols. Dienes **20–22** gave only alcohols.[19]

This cyanidation method offers three major advantages: there is no polymer to crack, thexylborane can be prepared easily in high purity, and the reaction is a one-pot, technically simple procedure. The utility of the Pelter CO insertion method in heterocyclic synthesis is firmly established by the preparation of **18**. A minor detraction of this protocol is the formation of two ketones from **5**, **8**, and **13**. This disadvantage could be alleviated by isomerization of the seven-membered borane intermediate **24** into eight-membered ring **23**.

23, R′ = $CO_2C_7H_7$; R = C_6H_{13}
25, R′ = $CO_2C_7H_7$; R = H

24

We assumed that borane **23** was more stable than isomer **24**. Heterocycle **23** is a nonbranched borane capable of an unstrained, transannular boron–nitrogen interaction. Upon being heated, thexyldialkylboranes such as **23** and **24** could equilibrate or could lose the thexyl group.[23] Pyrolysis of the initial trialkylborane mixture from thexylborane and **8** for 2 h at 135 °C followed by the cyanidation procedure gave ketone **9** in 18–35% yield, *N*,*N*-bis(3-hydroxypropyl) carbamate **11** (40–50%), and *N*-(3-hydroxypropyl) carbamate **12** (10%).[24] This equilibration was not noticeably catalyzed by added borane or oxygen. Pyrolysis of the borane from **13** followed by cyanidation afforded diol **16** (>90% yield) and 2,3-dimethyl-2-butene (thexene, 30% yield). "Equilibration" of the boranes from carbamates **17** and **20–22** also afforded only alcohols.[19]

The formation of alcohols such as **11** and **16** from olefinic carbamates after thermal equilibration suggested that secondary boranes such as **25** might be formed. Secondary boranes do not undergo cyanidation to provide ketones.[24] These normally reactive boranes might be stabilized by a strong boron–nitrogen interaction. Secondary dialkyl boranes can be converted into ketones by using the phenolate–DCME protocol.[19,25] Application of this sequence to the pyrolyzate from **8** yielded less than 5% of **9**. Similarly, sulfonamide **13** again afforded only diol **16**.[26,27]

The specific generation of eight-membered-ring ketones by using the cyanidation procedure could be "scaled up" and applied to the versatile benzyl carbamate **8**. The ketones **9** or **18** can be purified by sequential oxidation of the crude reaction mixture with Jones reagent and base extraction. The borane-mediated synthesis of **6**, **9**, and **18** are the first examples of hydroboration–CO insertion in the presence of functional groups reduced by borane.[28] This medium-sized ring synthesis does not require high-dilution conditions.

Discussion of Hydroboration

Although the DCME procedure and the cyanidation procedure involve different reagents for net CO insertion, mechanistic similarities do exist. Both reactions form a cyclic borane during the key ring-forming step. The treatment of either borane intermediate with a CO

(16) (a) Brown, H. C.; Ravindran, N. *Inorg. Chem.* **1977**, *16*, 2938. (b) Brown, H. C.; Campbell, J. B. *J. Org. Chem.* **1980**, *45*, 389.

(17) The equilibration process to prepare chloroborane–dimethyl sulfide has been problematic. We were never able to obtain $ClBH_2{\cdot}SMe_2$ in greater than 85% purity. This purity can be determined by boron NMR or by converting styrene into 1,5-diphenyl-3-pentanone.

(18) We are grateful to Professor David Evans (California Institute of Technology) for sharing the details of numerous BH_3–BCl_3 equilibration experiments completed in his laboratory.

(19) The details of most of these experiments have not been included; we will be pleased to provide them on request. See also: Bonfiglio, J. N. Ph.D. Dissertation, University of California San Diego, 1980.

(20) Kinberger, K.; Siebert, W. *Z. Naturforsch. B: Anorg. Chem., Org. Chem.* **1975**, *30*, 55.

(21) We converted styrene into 1,5-diphenyl-3-pentanone in good yield using this reagent.

(22) For transformation of dialkylthexylboranes into ketones with carbon monoxide at elevated pressures see: Brown, H. C.; Negishi, E. *J. Am. Chem. Soc.* **1967**, *89*, 5285, 5477; *Chem. Commun.* **1968**, 594.

(23) (a) Brown, H. C.; Negishi, E.; Katz, J. *J. Am. Chem. Soc.* **1972**, *94*, 5893. (b) Brown, H. C.; Negishi, E. *Tetrahedron* **1977**, *33*, 2331. (c) Pelter, A. In "Rearrangements in Ground and Excited States"; DeMayo, P., Ed.; Academic Press: New York, 1980; Vol. 2, pp 95–147.

(24) Under these mild conditions, cyanidation of tris(2-phenylethyl)-borane afforded only 2-phenylethanol.

(25) Carlson, B. A.; Brown, H. C. *Synthesis* **1973**, 776.

(26) The 9-BBN hydroboration–borane equilibration procdure[27] on **5** afforded only trace amounts of **6**.

(27) Burke, P. L.; Negishi, E.; Brown, H. C. *J. Am. Chem. Soc.* **1973**, *95*, 3654.

equivalent yields comparable product mixtures.

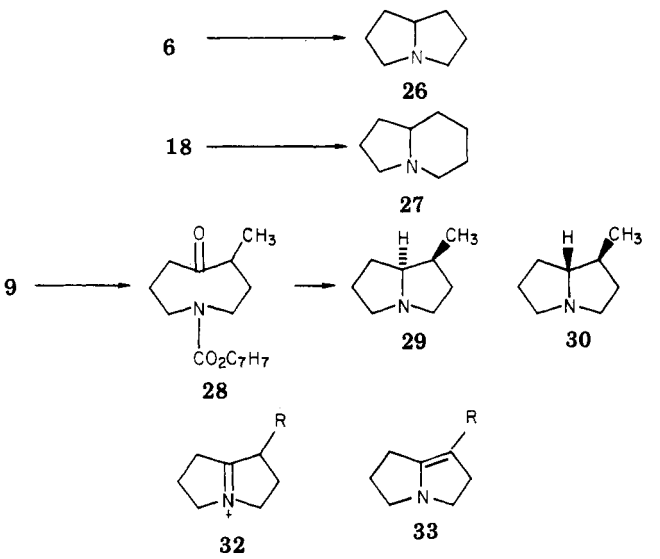
Ketone formation from carbamate **5** occurs with greater regioselectiveity albeit in lower yield than from 1,6-heptadiene. The introduction of a nitrogen into the diene creates at least six differences between the two substrates. The allylic heteroatom may alter the regiochemistry of the initial hydroboration.[29] The coordinating effects[30-33] and conformational restrictions of the amide derivatives can direct the kinetic ring closure. The transannular nitrogen–boron interaction in the eight-membered-ring product **13** may actually increase the thermodynamic stability of it in relation to smaller azaborane rings. Finally, boranes such as **23** and **24** possess two irreversible decomposition pathways. The seven-membered-ring borane heterocycle **24** can undergo a well-documented β cleavage[9a,28] to provide propene and an aminoborane. At any stage, unspent chloroborane or thexylborane might reduce the carbamate.[28]

Our experiments clarify these variables for both hydroboration sequences. Kinetic hydroboration of these nitrogeneous olefins occurs by addition of boron to the least hindered carbon as observed in simple olefins. Addition of boron at other positions followed by CO insertion and oxidation would give secondary alcohols, unsubstituted urethanes, or piperidinones. Only small quantities of secondary alcohols were observed. The absence of piperidinones suggests that six-membered aminoboranes are less stable than the seven- or, especially, the eight-membered aminoboranes. From the minor amounts of alcohol **12** we infer that β fragmentation is not a major decomposition pathway. The formation of **16** in high yield from **13** under equilibrating conditions is also incompatible with β cleavage. The thermodynamic stability of the eight-membered-ring borane is indicated by the formation of azacyclooctanones **6** and **10** under equilibrating conditions. Finally, carbamate reduction did not appear to be a serious problem although incomplete mass balance forces us to concede as much as 10% reduction.

The formation of and stability of dialkylchloroboranes and dialkylthexylboranes leading to medium-sized heterocyclic ketones is finely balanced. The chloroborane cracking process must yield a thermodynamically stable borane as must the thexylborane–equilibration sequence. In both cases, eight-membered rings are the only cyclic boranes formed. Other larger cyclic boranes cannot be prepared under equilibrating conditions. Furthermore, even the thexyl-substituted eight-membered rings require some stabilization from the transannular nitrogen. The carbamates **5** and **8** yield **6** and **9**, respectively, while the sulfonamide **13** and the carbamate **17** undergo other reactions upon equilibration. Recently, Pelter has shown that nitrogen groups can stabilize thexylborane.[30]

The kinetic or nonequilibrating hydroboration has only been successful with thexylborane. Seven- and eight-membered rings form with equal probabilty from carbamates **5** and **8** and from sulfonamide **11**. However, nine-membered-ring **18** is produced with great regioselectivity. Larger rings could not be detected under a variety of conditions. From these observations and others in our laboratory,[31] we conclude that a boron–nitrogen interaction

Scheme II



does not direct the second hydroboration. Minimization of the rotational entropy of the starting diene does facilitate this cyclization. Under kinetic conditions the formation of azaboranes occurs at comparable rates. The generation of **23** must be sterically hindered by an amount energetically comparable to the formation of α-branched borane **24**. The nine-membered ring lacks this steric inhibition. Larger ring precursors have too much rotational entropy to permit facile ring closure and yield azaboranes without sufficient transannular nitrogen–boron stabilization.

Alkaloid Synthesis

To utilize carbamates **9** and **18** in alkaloid synthesis, we examined the reactions illustrated in Scheme I. For instance, hydrogenolysis of **9** and of **28** afforded pyrrolizidine **26** and the indolizidine alkaloid δ-coniceine (**27**)[11,34] in good yield (Scheme II). The successful reductive ring closure indicated the potential for these medium-sized keto carbamates in alkaloid sythesis. In fact this synthesis of δ-coniceine compares favorably with other preparations of **27**.[34] The precursors for this two-step synthesis are readily available, and the ring closure sequence does not require high-dilution reaction conditions.

To extend this scheme to complex pyrrolizidines, we attempted to functionalize the aza ketone **9** using standard enolate chemistry. The enolate of **9** was generated under strong base conditions and was trapped with chlorotrimethylsilane or with methyl iodide.[35] The reductive ring

(28) Amide reduction by borane has been reported: Russ, P. L.; Caress, E. A. *J. Org. Chem.* **1976**, *41*, 149 and references cited therein.

(29) Brown, H. C.; Gallivan, R. M., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 2906.

(30) Pelter reports that thexylborane–diethylaniline is a stable, active hydroborating reagent. Pelter, A.; Ryder, D. J.; Sheppard, J. H. *Tetrahedron Lett.* **1978**, 4715.

(31) To support the lack of boron–nitrogen direction, we completed a series of experiments to probe hydroboration selectivity in ω-amino and ω-mercapto olefins. Dimethyl sulfide–boranes[17] and more recently thexylborane–diethyl aniline[30] are hydroborating reagents. If these "ate" complexes add to olefins prior to dissociation, intramolecular directing effects should be observed. Treatment of a homologous series of ω-olefins, anilines, or ω-olefinic phenylthio ethers with thexyl borane/THF at 78 °C, dilution with hexane, warming, and oxidation afforded starting olefin and primary alcohol. We did not detect any secondary alcohols. Heteroatom–boron coordination should have altered the directionality of borane addition.[32,33]

(32) Still, W. C.; Darst, K. P. *J. Am. Chem. Soc.* **1980**, *102*, 7385.

(33) We are grateful to Ms. V. Paul for completing some of these experiments.

(34) For syntheses of δ-coniceine see: (a) Pezzorno, M. T.; Albonico, S. M. *J. Org. Chem.* **1977**, *42*, 909. (b) Stevens, R. V.; Luh, Y.; Sheu, J. T. *Tetrahedron Lett.* **1976**, 3799. (c) Wilson, S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, *44*, 330. (d) Khatri, N. A.; Schmitthenner, H. F.; Shringapure, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6387. (e) Lukes, R.; Vesely, *Collect. Czech. Chem. Commun.* **1959**, *24*, 944. (f) Lellman, E. *Justus Liebigs Ann. Chem.* **1890**, *259*, 193.

(35) Numerous other electrophiles failed to react with the enolate from **9** or with the silyl enol ether from **6** or **9** (see ref 19).

closure of **28** was expected to yield heliotridane (**29**)[5,36] stereoselectively. Hydrogenation of **28** over 10% Pd/C in ethanol with or without added acid cleanly provided **19** and **30**[36,37] in a 2:3 ratio.

The failure to observe stereoselective ring closure of **28** was unexpected when compared with the stereoselectivity reported by Leonard[5] for 2-(carboethoxy)-*N*-benzyl-5-azacyclooctanone (**31**). Consideration of the mechanism of this reduction offers an explanation. Hydrogenolysis of **28**, loss of CO_2, condensation, and dehydration would provide immonium ion **32**. Ion **32** is nearly planar, permitting addition of hydrogen from either face. Deprotonation of **32** would afford **33**. This acid–base reaction of **32** could compete with reduction of **32** when R is a good electron-withdrawing group. The cis addition of hydrogen to **33** can only afford the stereochemistry of **29**. After completion of our work, Miyano et al.[38] reported similar observations.

Conclusions

We have demonstrated that hydroboration–carbonyl group insertion of bis-olefinic amines can be useful for the synthesis of medium-sized azacyclanones **6**, **9**, and **18**. The presence of the nitrogen has a major effect on the products obtained from either hydroboration–CO insertion sequence. The choice of the third nitrogen substituent is critical for the success of either scheme. The initial hydroboration step occurs at the least substituted end of the olefin. The intermediate eight-membered-ring boracycle is the thermodynamically favored product, affording ketones **6** and **9**. Thexylborane–cyanidation can be used to make a nine-membered ring (**18**) in high specificity and moderate yield. Azacyclanones larger than nine membered could not be formed from any of the reactions examined. These keto carbamates are formed without high-dilution conditions from readily available precursors. Purification can be effected by sequential Jones oxidation–base extraction. The preparation of **6**, **9**, and **18** also demonstrates that hydroboration–CO insertion can occur in the presence of a readily reduced functional group (carbamate). Finally, we have shown that the medium-sized rings produced in these sequences can be useful alkaloid precursors.

Experimental Section

General Methods. Details about instrumentation, isolation, and purification have been described.[39] Low-resolution mass spectra were obtained from an LKB 9000 or a Finnigan 4021 GC/MS at an ionizing voltage of 70 eV or of 16–20 eV. High-resolution spectra were performed at the California Institute of Technology Analytical Laboratory, at the UCLA mass spectral facility, at the Berkeley Chemistry Department mass spectral facility or at the Mass Spectrometry Resource, Space Sciences Laboratory, Berkeley.

Reagents and Solvents. Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl immediately prior to use. Pentane was washed with sulfuric acid and distilled from calcium hydride. Borane/THF and borane/methyl sulfide were purchased from Aldrich Chemical Co. 2,3-Dimethyl-2-butene (thexene) was purchased from numerous suppliers and its purity analyzed by GC. Pure thexene was stored at 0 °C under argon. Exposure to air promoted extensive isomerization. All amines were purchased from Aldrich Chemical Co. and were distilled from barium oxide under nitrogen prior to use. Olefinic halides were obtained from Columbia Organics and used as received after verification of purity. Methanol was dried by distillation from methoxymagnesium and then stored over activated 3-Å molecular seives under argon. All other organic reagents were purchased from Aldrich Chemical Co. All inorganic reagents and all solvents were purchased from Mallinkrodt Chemical. Unless specified, all of these materials were used as received. Compounds **1**, **5**, **8**, and **13** were prepared as described from diallylamine.[40]

Methyl *N*-(2-Propenyl)-*N*-(2-butenyl)carbamate (20), Methyl *N*-(2-Propenyl)-*N*-(4-pentenyl)carbamate (21), and Methyl *N*-(2-Propenyl)-*N*-(5-hexenyl)carbamate (22). The procedure reported by Nordlander[41] was used. From 11.2 g (9.7 × 10^{-2} mol) of methyl *N*-(2-propenyl)carbamate,[42] 10.8 g (9.7 × 10^{-2} mol) of 4-chloro-2butene, and 4.9 g (1.20 × 10^{-1} mol) of potassium hydride[43] there was obtained 8.7 g (43%) of **20**: bp 120–122 °C (1.6 kPa); IR 1695, 1470, 1270 cm^{-1}; NMR δ 1.7 (d, *J* = 5.1 Hz, 3 H), 3.7 (s, 3 H), 3.9 (m, 4 H) 5.1–5.9 (m, 5 H).

From 4-pentenyl bromide was obtained **21**: bp 65–67 °C (0.026 kPa); IR 2950, 1710, 1400 cm^{-1}; NMR δ 1.6 (m, 2 H), 2.0 (m, 2 H), 3.2 (t, *J* = 3.5 Hz, 2 H), 3.7 (s, 3 H), 3.8 (d, *J* = 3 Hz), 5.1 (m, 4 H), 5.7 (m, 2 H); high-resolution mass spectrum, obsd *m/z* 183.124976, $C_{13}H_{17}NO_2$ requires 183.125 47.

From 5-hexenyl bromide was obtained **22**: bp 80–82 °C (0.03 kPa); IR 2960, 1710, 1400 cm^{-1}; NMR δ 1.5 (m, 4 H), 2.0 (m, 2 H), 3.2 (t, *J* = 3.2 Hz, 2 H), 3.5 (s, 3 H), 3.7 (d, *J* = 3 Hz, 2 H), 5.1 (m, 4 H), 5.7 (m, 2 H); high-resolution mass spectrum, obsd *m/z* 197.140 912, $C_{11}H_{19}NO_2$ requires 197.141 07.

Methyl *N*-(2-Propenyl)-*N*-(3-butenyl)carbamate (19) and Benzyl *N*-(2-Propenyl)-*N*-(3-butenyl)carbamate (17). Allylamine (50.0 g, 0.9 mol) and 12.0 g (0.1 mol) of 4-bromo-1-butene in ether afforded *N*-(2-propenyl)-*N*-(3-butenyl)amine: bp 40–43 °C (1.6 kPa); NMR δ 1.3 (s, 1 H, NH), 2.3 (m, 2 H), 2.6 (m, 2 H), 3.3 (dd, *J* = 7.1 Hz, *J* = 2.0 Hz, 2 H), 5.1 (m, 4 H, vinyl), 5.7 (m, 2 H). Acylation as before with methyl chloroformate afforded **19** in 51% yield from bromobutene: bp 60–63 °C (0.03 kPa); IR 2925, 1695, 1410 cm^{-1}; NMR δ 2.3 (m, 2 H), 3.3 (t, *J* = 5.1 Hz, 2 H), 3.7 (s, 3 H), 3.8 (d, *J* = 3.1 Hz), 5.2 (m, 4 H, vinyl), 5.7 (m, 2 H, vinyl).[44,45]

Diene **17** was prepared in comparable yield: bp 112–115 °C (0.01 kPa); IR 2925, 1695 (br), 1410 cm^{-1}; NMR δ 2.3 (m, 2 H), 3.3 (t, *J* = 7.1 Hz, 2 H), 3.8 (d, *J* = 6.4 Hz, 2 H), 5.0–5.2 (m, 2 H), 7.3 (s, 5 H, aromatic); high-resolution mass spectrum, obsd *m/z* 245.140 92, $C_{15}H_{19}NO_2$ requires 245.141 48.

Method A: *N*-(Carbomethoxy)-5-azacyclooctanone (6). Upon addition of 2.20 mL (0.02 mol) of $BH_2Cl{\cdot}SMe_2$[16–18] to 40 mL of dry ether, the solution turned cloudy with the formation of a small amount of white precipitate. Diene **5** (3.10 g, 0.02 mol) was added over 15 min, and the resulting solution was stirred for 2.5 h. After removal of the solvent under N_2, the residual white polymeric glass was distilled at 0.03 kPa by using a Wood's metal bath with an initial temperature of 150–170 °C. The heating bath temperature was increased to 220 °C and the apparatus warmed with a heat gun to complete the distillation within 1 h. This distillate (35% yield of chlorodialkylborane) was diluted with 10 mL of dry THF containing 0.8 mL of dry methanol and stirred for 12 h. After the solvent was evaporated, the residue was cooled

(36) Heliotridane is a degradation product from trachelanthamidine. Warren, F. L.; Von Klemperer, M. E. *J. Chem. Soc.* **1958**, 4574. Leonard, N. J.; Felley, D. L. *J. Am. Chem. Soc.* **1950**, *72*, 2537.

(37) Psuedoheliotridane is a degradation product from the pyrrolizidine base isoretronecanol. Men'shikob, H. P.; Bordino, J. *J. Gen. Chem. USSR (Engl. Transl.)* **1945**, *15*, 225. Men'shikob, H. P. *Ibid.* **1946**, *16*, 1311.

(38) Miyano, S.; Fujii S.; Yamishita, O.; Toraishi, N.; Sumoto, K.; Satoh, F.: Masuda, T. *J. Org. Chem.* **1981**, *46*, 1737.

(39) Garst, M. E.; Bonfiglio, J. N.; Grudoski, D.; Marks, J. *J. Org. Chem.* **1980**, *45*, 2307.

(40) Matsoyan, S. G. *Ind. Eng. Chem.* **1954**, *46*, 587.

(41) Nordlander, J. E.; Catalane, D. B.; Eberlein, T. H.; Farkas, L. B.; Howe, R. S.; Stevens, R. M.; Tripoulas, N. A.; Stansfield, R. E.; Cox, J. L.; Payne, M. J.; Viehbeck, A. *Tetrahedron Lett.* **1978**, 4987.

(42) Childs, A. F.; Goldsworthy, L. J.; Harding, G. F.; Plant, S. G. P.; Weeks, G. A. *J. Chem. Soc.* **1948**, 2320.

(43) Other bases afforded only *N,N*, N-tris(2-propenyl)-1,3,5-triazene-2,4,6-trione: NMR 3.8 (d, *J* = 8 Hz, 2), 5.2 (m, 2), 5.7 ppm (m, 1); mass spectrum (70 eV), *m/z* 249 (M^+). Cf.: Hisao, K. *Chem. Abstr.* **1972**, *77*, 75760.

(44) Attempted N-alkylation of *N*-allylcarbamate with 1-bromo-3-butene afforded only elimination. The sulfonamide, diphenylphosphinamide (Coulton, S.; Moore, G. A.; Ramage, R. *Tetrahedron Lett.* **1976**, 4005), and diphenylphosphoramidate (Zwierzak, A.; Byrlikowska-Piotrowicz, J. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 107) also afforded elimination.

(45) This problem has been noted with 1-halo-3-butenes: Coates, R. M.; Pigott, H. O.; Ollinger, J. *Tetrahedron Lett.* **1974**, 3955.

to 0 °C and treated with 10 mL of dry THF, 0.98 mL (0.01 mol) of dichloromethyl methyl ether (DCME), and 20 mL (0.02 mol) of 1 M lithium triethylcarboxide solution in THF. The reaction was brought to room temperature for 2.5 h. The mixture was then treated with 20 mL of a 3.8 M KOH solution in 95% ethanol followed by the dropwise addition of 12 mL of 30% hydrogen peroxide. The reaction mixture was then refluxed for 2 h and subjected to the standard workup to give 0.95 g of a light yellow oil. Further purification by column chromatography (neutral alumina, 60:40 EtOAc/hexane) afforded 0.81 g (21%) of **6**: IR 2950, 1710 (br), 1450 cm^{-1}; NMR δ 2.1 (m, 4 H), 2.3 (m, 4 H), 3.4 (m, 4 H), and 3.8 (s, 3 H); high-resolution mass spectrum obsd m/z 185.105, $C_9H_{15}NO_3$ requires 185.106.

On several duplications of this experiment, the yields ranged from 20% to 31%. Application of the sequence on a 0.1-mol scale afforded a maximum 15% yield of **6** (five attempts).

Method A: *N*-(3-Hydroxypropyl)-*N*-(2-propenyl)-*N*-benzylamine (2). A solution of 1.87 g (0.01 mol) of **1** provided 2.0 g (89%) of **2** when the initial hydroboration was conducted at 100 °C: IR 3300 cm^{-1}; NMR δ 1.65 (d, $J \approx 6$ Hz, 2), 2.55 (t, $J \approx 6$ Hz, 2), 3.05 (d, $J \approx 6$ Hz, 2), 4.55 (s, 2), 4.60 (t, $J \approx 6$ Hz, 2), 5.10 (m, 2), 5.80 (dt, $J \approx 15$, 6 Hz, 1), 7.20 (2, 5); mass spectrum (70 Ev), m/z 201 (M^+).

Method B: *N*-(Carbomethoxy)-5-azacyclooctanone (6) and *N*-(Carbomethoxy)-2-methyl-4-azacycloheptanone (7). Thexylborane was synthesized by following the method of Brown.[14] The reagent was kept at 0 °C for at least 2 h but less than 4 h before use.

A solution of 1.55 g (0.01 mol) of diene **5** in 5 mL of dry THF was added by syringe to 0.01 mol of thexylborane over 20 min. After the mixture was stirred at room temperature for 4 h, 0.70 g (0.01 mol) of finely divided potassium cyanide[46] was added in one batch. The reaction was then stirred for 6 h or until most of the solid had dissolved. The mixture was cooled to −78 °C and treated with 1.68 mL (0.01 mol) of trifluoroacetic anhydride. The reaction mixture was allowed to warm to room temperature and was then stirred for 2 h. Oxidation was effected by the addition of 10 mL of a 3.8 M KOH in 95% ethanol solution and of 5 mL of 30% hydrogen peroxide and then by reflux for 1 h. Completion of the standard workup gave 2.10 g of a viscous yellow oil. GLC analysis (3% Hi-Eff 8 Bp) showed ketones **6** and **7** to be present in a 1:1 ratio (~30% combined yield). Analytical samples were obtained by preparative GC. Ketone **6**: IR 2950, 1710, 1410 cm^{-1}; NMR δ 2.0 (m, 4 H), 2.3 (m, 4 H), 3.3 (m, 4 H), 3.6 (s, 3 H); high-resolution mass spectrum, obsd m/z 185.106, $C_9H_{15}NO_3$ requires 185.105. Ketone **7**: IR 2950, 1710, 1410 cm^{-1}; NMR δ 1.1 (d, J = 8.1 Hz, 3 H), 1.7 (m, 2 H), 2.4–3.1 (m, 7 H), 3.6 (s, 3 H); high-resolution mass spectrum, obsd m/z 185.106, $C_9H_{15}NO_3$ requires 185.105. Likewise, diene **8** provided **9** and **10**.

Method B: *N*-Benzenesulfonyl-5-azacyclooctanone (14) and *N*-Benzenesulfonyl-2-methyl-4-azacycloheptanone (15). Sulfonamide **13** provided ketones **14** and **15** in a 1:1 ratio in an 80% yield: IR 1700–1710, 1300, 1160 cm^{-1}; NMR δ 1.20 (d, $J \approx$ 9 Hz, 3), 2.5–3.4 (m, 17), 3.7 (m, 4), 7.65 (m, 6), 7.80 (m, 4); high-resolution mass spectrum, obsd m/z 267.094, $C_{13}H_{17}NO_3S$ requires 267.093.

Method B: *N*,*N*-Bis(3-hydroxypropyl)benzylamine (3) and *N*-(3-Hydroxypropyl)-*N*-(2-hydroxypropyl)benzylamine (4). Completion of the hydroboration at 65 °C on 1.87 g (0.01 mol) of **1** yielded 1.8 g (80%) of **3** and **4** in a 4:1 ratio: IR 3400 cm^{-1}; NMR δ 1.05 (d, $J \approx 8$ Hz, 0.6), 1.7 (m, 3.6), 2.2 (d, $J \approx 8$ Hz, 0.4), 2.4 (t, $J \approx 8$ Hz, 3.6), 2.75 (m, 0.2), 4.6 (m, 5.6), 7.2 (s, 5); mass spectrum (70 eV), m/z 205 ($M_+ - H_2O$). Authentic *N*-benzyl-5-azacyclooctanone[5] was not present in the crude product.

Method B: *N*-(Carbobenzyloxy)-5-azacyclononanone (18). From 4.90 g (0.020 mol) of diene **17** there was obtained 7.12 g of crude oil. Treatment of this mixture with excess Jones reagent[47] in acetone followed by base extraction left 1.5 g of neutral material. Chromatography (silica gel, 50:50 EtOAc/hexane) yielded 1.30 g (24%) of the ketone **18** contaminated by less than 5% of an unknown isomer: IR 2910, 1750, 1710, 1410 cm^{-1}; NMR δ 1.7–2.2 (m, 6 H), 2.4 (m, 4 H), 3.3 (m, 4 H), 5.1 (s, 2 H), 7.3 (s, 5 H); mass spectrum (70 eV), m/z 275 (M^+), 91 (base); high-resolution mass spectrum, obsd m/z 275.150899, $C_{16}H_{21}NO_3$ requires 275.15209.

In five additional separate runs, isolated yields of ketone **18** varied from 16% to 35%.

Method C: *N*-(Carbobenzyloxy)-5-azacyclooctanone (9). A solution of 6.93 g (0.03 mol) of diene **8** in 10 mL of dry THF was added to 0.03 mol of thexylborane over 20 min. The reaction was stirred for 4–6 h. The solvent was then removed under an N_2 atmosphere. The remaining oil was heated at 135 °C for 2 h, cooled to room temperature, and diluted with 50 mL of dry THF. Cyanidation, as before, afforded 8.10 g of viscous yellow oil containing **9**, **11**, and **12**.

Oxidation of the crude product with Jones reagent[47] and basic extraction left 2.1 g of a light oil which was mainly **9**. Further purification by column chromatography (silica gel, 50:50 ethyl acetate/hexane) gave 1.4 g (18%) of a colorless oil which solidified on standing: mp 44–47 °C; IR 2970, 1795, 1415 cm^{-1}; NMR δ 2.2 (m, 4 H), 2.3 (m, 4 H), 3.4 (m, 4 H), 5.1 (s, 2 H, benzylic), 7.3 (s, 5 H, aromatic), 7.3 (s, 5 H, aromatic); mass spectrum (70 eV), m/z 261 (M^+), 233 ($M^+ - 28$), 91 (base); high-resolution mass spectrum, obsd m/z 261.1374, $C_{15}H_{19}NO_3$ requires 261.1383. Other runs afforded **9** in 18–33% yield.

In a separate preparation the crude reaction mixture was treated with an excess of acetic anhydride in pyridine at 0 °C for 2 h. Chromatography of the resulting oil led to the isolation of two additional compounds. Diacetate of **11**: 45% yield; IR 2970, 1730, 171/ (br), 1410 cm^{-1}; NMR δ 2.0 (s, 6 H), 3.4 (t, J = 8.1 Hz, 4 H), 4.1 (t, J = 8.1 Hz, 4 H), 5.1 (s, 2 H), 7.3 (s, 5 H); mass spectrum (16 eV), m/z 351 (M^+), 91 (base). Monoacetate of **12**: 10% yield; IR 3310, 2910, 1730, 1710 (br), 1410 cm^{-1}; NMR δ 2.1 (s, 3 H), 3.4 (m, 2 H), 4.1 (t, J = 7.5 Hz, 2 H), 5.1 (s, 2 H), 7.3 (s, 5 H).

An authentic sample of this monoacetate was prepared from 3-aminopropanol by the standard procedure.[40]

Method C: *N*,*N*-Bis(3-hydroxpropyl)benzenesulfonamide (16). Sulfonamide **13** (2.4 g, 0.01 mol) gave 2.6 g of viscous yellow oil which was assigned structure **16**: IR (film) 3450, 1330, 1160 cm^{-1}; NMR δ 1.70 (m, 4), 3.2 (t, $J \approx 6$ Hz, 4), 3.6 (t, $J \approx 6$ Hz, 4), 7.2 (m, 6), 7.8 (m, 4).

Pyrrolizidine (26). This procedure was adapted from a procedure by Leonard and Sato.[5] A solution of 0.05 g (1.9×10^{-4} mol) of ketone **9**, 0.002 g of 10% Pd/C, 2 drops of 70% perchloric acid, and 3 mL of methanol was stirred under 101.35 kPa of hydrogen for 6 h. The acid was neutralized and the solution subjected to the standard workup to leave 0.02 g (95% yield) of **29**: mass spectrum (70 eV), m/z 111 (M^+), 83 (base) and 55.[48,49] A picrate salt was formed from this oil: 73% yield; mp 251–255 °C (from ethanol) (lit.[5] mp 258–260 °C).

δ-Coniceine (27). A solution of 0.180 g (6.54×10^{-4} mol) of ketone **16** and 0.05 g of 10% Pd/C in 10 mL of absolute MeOH was shaken under 355 kPa of hydrogen in a Paar apparatus for 24 h. The solution was then filtered and passed over a small pad of alumina. Removal of the solvent afforded 0.068 g (83%) of **25**: mass spectrum (70 eV), m/z 125 (M^+), 124, 97, 83 (base), 69.[49] A picrate was formed: 78% yield; mp 228–231 °C (from methanol) (lit.[34b] mp 230–231 °C).

(±)-Heliotridane (29) and (±)-Pseudoheliotridane (30). Lithium hexamethyldisilazide was prepared from 0.12 mL (2.7×10^{-4} mol) of 2.1 M *n*-butyllithium and 0.06 mL (2.7×10^{-4} mol) of hexamethyldisilazane in 3 mL of THF and 0.05 mL (2.7×10^{-4} mol) of HMPA at −78 °C. Ketone **9** (0.07 g, 2.7×10^{-4} mol) in 1 mL of dry THF was added over 15 min. After 15 min at −78 °C the solution was warmed to 0 °C for 15 min and quenched with 0.02 mL (2.7×10^{-4} mol) of methyl iodide. The THF was removed on the rotary evaporator. The standard workup of the oily residue provided 0.07 g of a light yellow oil from which PLC

(46) After completion of this work, Professor A. Pelter recommended drying the KCN at 100 °C before use. Pelter, A., private communication.

(47) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.

(48) For a discussion of this diagnostic fragmentation see: (a) Bull, L. B.; Culvenor, C. C. J.; Dick, A. T. "The Pyrrolizidine Alkaloids"; North-Holland Publishing Co.: Amsterdam, 1968; pp 54–6. (b) Robbins, D. J. *Adv. Heterocycl. Chem.* **1979**, *24*, 282–3. (c) Abdullaev, U. A.; Rashkes, Y. V.; Shakhidoyatov, K.; Yunosov, S. Y. *Khim. Prir. Soedin.* **1972**, 634.

(49) This spectrum was identical with a published spectrum: Stenhagen F.; Abrahamsson, S.; McLafferty, F. W. "Registry of Mass Spectral Data"; Wiley: New York, 1974; Vol. 1, pp 313, 203.

(silica gel, 1:1 ethyl acetate/pentane) gave 0.04 g (51%) of **28**: IR 2950, 1700, 1415 cm^{-1}; NMR δ 1.1 (m, 3 H), 2.0 (m, 4 H), 2.3–2.5 (m, 3 H), 3.2–3.4 (m, 4 H), 5.1 (s, 2 H), 7.3 (s, 5 H); mass spectrum, (20 eV), 275 (M^+), 91 (base); high-resolution mass spectrum, obsd m/z 275.151 795, $C_{16}H_{21}NO_3$ requires 275.152 09.

A solution containing 0.16 g (5.82×10^{-4} mol) of **28**, 0.8 g of 10% of Pd/C, and 2 drops of 70% aqueous perchloric acid in 10 mL of absolute methanol was stirred under 101 kPa of hydrogen for 2 h. This solution was passed through a small pad of activated basic alumina (Brockman) with ether to afford 0.056 g (78% yield) of **29** and **30**. GC analysis on 3% Dexsil indicated that **30** and **29** were in a 3:2 ratio, with the lower boiling **30** eluting first. A picrate salt was formed directly: 0.146 g (91% yield); mp 228–239 °C; NMR δ 1.14 (d, J = 5 Hz), 1.23 (d, J = 6 Hz), 1.78 (brd m),2.15 (brd m), 2.35 (brd m), 2.64 (brd m), 2.82 (brd m), 2.98 (brd m), 3.12 (brd m), 3.68 (brd m), 3.90 (brd m), 4.04 (brd m), 4.28 (brd m), 4.40 (brd m), 8.89 (s);[50] GC/MS [using a 3% SE-30 column at 110 °C for 2 min and then programmed at 20 °C/min] (70 eV), for t_R = 2 min (from Et_2O), m/z 125 (M^+), 97, 83 (base), 55,[48] for t_R - 2.5 min, m/z 125 (M^+), 97, 83 (base), 55.[48] In a separate experiment, part of the product was converted to the picrates, which were combined with the above and repeatedly crystallized from methanol, enriching **29**: mp 239–241 °C (lit.[36] mp (**29**) 243–244 °C; mp (**30**) 234–236 °C); GC/MS, t_R = 2.5 min, mass spectrum identical with that above. The pooled methanol mother liquors were evaporated, and the residue was crystallized from ethanol to yield mainly **30**: mp 229–231 °C; GC/MS, t_R = 2.0 min, mass spectrum identical with that above.

(50) We are grateful to Ms. Victoria Roberts for obtaining this 360-MHz spectrum. Unfortunately, the exceptionally broad, ill-defined multiplets precluded meaningful decoupling experiments.

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Registry No. **1**, 4383-26-0; **2**, 80662-79-9; **3**, 5279-23-2; **4**, 80662-80-2; **5**, 78805-03-5; **6**, 80662-81-3; **7**, 80662-82-4; **8**, 25070-76-2; **9**, 80662-83-5; **10**, 80662-84-6; **11**, 80662-85-7; **11** diacetate, 80662-86-8; **12**, 34637-22-4; **12** monoacetate, 80662-87-9; **13**, 25630-24-4; **14**, 80662-88-0; **15**, 80662-89-1; **16**, 80662-90-4; **17**, 80248-99-3; **18**, 80249-00-9; **19**, 80662-91-5; **20**, 80662-92-6; **21**, 80662-93-7; **22**, 80662-94-8; **26**, 643-20-9; **26** picrate, 14129-07-8; **27**, 13618-93-4; **27** picrate, 5210-66-2; (±)-**28**, 80662-95-9; (±)-**29**, 17463-81-9; (±)-**29** picrate, 17463-80-8; (±)-**30**, 76548-10-2; (±)-**30** picrate, 76548-11-3; *N*-(Z-propenyl)-*N*-(3-butenyl)amine, 80662-96-0.

New Heterocyclic Rearrangement: Transformation of 1-Substituted 4-(Alkylamino)-1*H*-pyrrolo[3,2-*c*]pyridines into 1-Substituted 4-(Alkylamino)-1*H*-pyrrolo[2,3-*b*]pyridines (5-Aza- to 7-Azaindoles)

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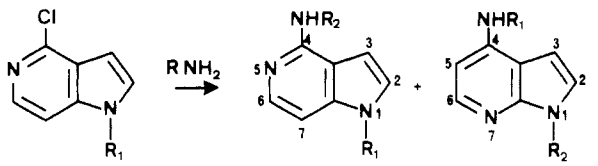
Substitution of 1-alkyl-4-chloro-1*H*-pyrrolo[3,2-*c*]pyridines by primary alkylamines in excess afforded the expected 1-alkyl-4-(alkylamino)-1*H*-pyrrolo[3,2-*c*]pyridines and their 1-alkyl-4-(alkylamino)-1*H*-pyrrolo[2,3-*b*]pyridine isomers resulting from the reversible isomerization of the preceding compounds.

In 1970 we described[1] a synthesis of 1-substituted 4-chloro-1*H*-pyrrolo[3,2-*c*]pyridines (5-azaindoles). Nucleophilic displacement of the chlorine atom was then reported to give the expected 4-substituted products, and this reaction was used to prepare various 4-anilino-1*H*-pyrrolo[3,2-*c*]pyridines.[2] The structure of a derivative of 1-benzyl-4-amino-1*H*-pyrrolo[3,2-*c*]pyridine obtained by reduction of the corresponding hydrazine was established by X-ray crystallography,[3] and the structure of various 4-substituted 1-alkyl-1*H*-pyrrolo[3,2-*c*]pyridine derivatives seemed to be unambiguous.

Surprisingly, a recent experiment showed that substitution of 1-methyl-4-chloro-1*H*-pyrrolo[3,2-*c*]pyridine by benzylamine and other primary alkylamines can afford a mixture of two isomeric compounds. Reinvestigation of this reaction allowed us to establish conditions which lead to normal substituted 1*H*-pyrrolo[3,2-*c*]pyridines and their 1*H*-pyrrolo[2,3-*b*]pyridine (7-azaindoles) isomers and to specify in what cases isomerization can be observed.

Substitution of 1-methyl-4-chloro-1*H*-pyrrolo[3,2-*c*]-pyridine (**1**) by various primary alkylamines in excess takes place by boiling the mixture in 2-methoxy- or 2-ethoxyethanol (Scheme I). For completion of the reaction, heating with benzylamine, 2-hydroxypropylamine, and 3-hydroxypropylamine required at least 1 week. In every

Scheme I[a]



1 **2** **3**

[a] a, $R_1 = CH_3$, $R_2 = CH_2C_6H_5$; b, $R_1 = CH_3$, $R_2 = CH_2CH(OH)CH_3$; c, $R_1 = CH_3$, $R_2 = CH_2CH_2CH_2OH$; d, $R_1 = R_2 = CH_2C_6H_5$.

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