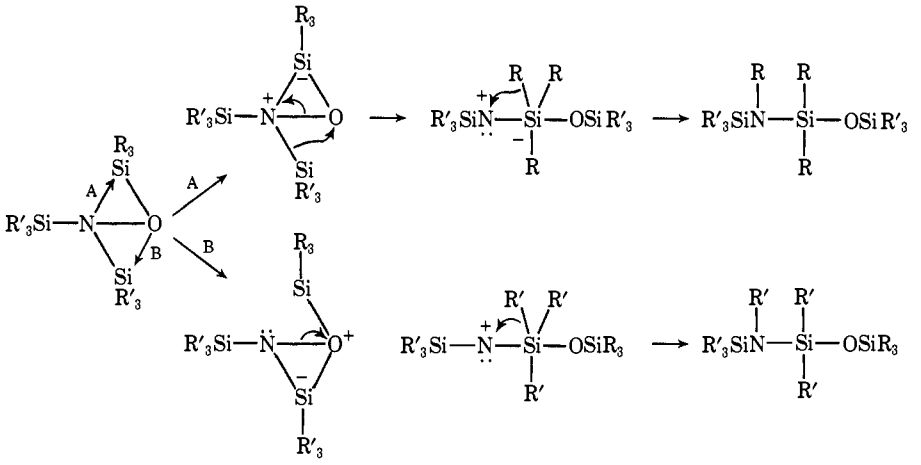
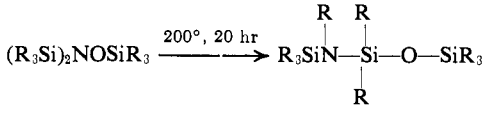
Scheme I



the trimethylsilyl group in the anion of *N,O*-bis(trimethylsilyl)hydroxylamine (**1**) provided the first example of a 1,2 O → N anionic rearrangement. In the course of follow-up studies of this rearrangement we have synthesized several tris(organosilyl)hydroxylamines[3,4] by treating deprotonated **1** with various triorganochlorosilanes. To our surprise, we find that tris(organosilyl)hydroxylamines, when heated to 200°, undergo an intramolecular rearrangement involving (1) the insertion of a silicon moiety into the bond between nitrogen and oxygen, and (2) the transfer of an alkyl group from silicon to nitrogen, to form silylaminosiloxanes.



2, R = Me
3, R = Et

4, R = Me
5, R = Et

Tris(trimethylsilyl)hydroxylamine (**2**) and tris(triethylsilyl)hydroxylamine (**3**) were prepared by the method of Wannagat and Smrekar.[4] When placed in a sealed tube under nitrogen and heated for 20 hr, **2** is converted almost quantitatively to trimethylsilylaminopentamethylsiloxane (**4**). The structure is proposed on the basis of nmr and ir spectral data and elemental analyses. The nmr of **4** in benzene shows a single resonance with relative intensity 1.0 at τ 7.52, the usual region for *N*-methyl protons, and three absorptions in the Si–C–H region at τ 9.75, 9.76, and 9.77 with relative intensities 3.0:2.0:3.0, consistent with the proposed structure. The infrared spectrum of **4** shows a strong band at 1060 cm^{-1}, diagnostic for siloxanes (ν_{as} Si–O–Si), giving strong support to our structure rather than the isomers, $Me_3SiSi(Me)_2N(Me)OSiMe_3$ and $Me_3SiN(Me)OSi(Me)_2SiMe_3$.[5] When treated in a similar manner, **3** converts to **5**, also in nearly quantitative yield.[6]

The high yields and lack of condensation products suggest an intramolecular mechanism for the thermolyses of **2** and **3**. When a mixture of the two is heated to 200° for 20 hr only **4** and **5** are isolated and no crossover products could be observed when the product mixture was analyzed by vpc.

A rearrangement of this kind is unique in both silicon and carbon chemistry. It provides the first example of the insertion of a silicon moiety into a bond between nitrogen and oxygen and is also the first case in which an alkyl group is transferred from silicon to nitrogen.[7] The ease with which the tris(organosilyl)hydroxylamines convert to silylaminosiloxanes leads us to believe that the reaction takes place through a formation of pentacoordinate silicon atoms. Two possible pathways are shown in Scheme I.

The thermolysis products of selected tris(organosilyl)hydroxylamines possessing silicon moieties with different alkyl groups will be investigated in an effort to clarify the mechanism. Thermolyses of alkyl-substituted organosilylhydroxylamines are also under investigation.[9]

(3) All compounds reported gave satisfactory analyses for C, H, N, and Si.

(4) U. Wannagat and O. Smrekar, *Monatsh. Chem.*, **100**, 750, 760 (1969).

(5) We have prepared several *N,O*-bis(organosilyl)-*N*-methylhydroxylamines and their infrared spectra do not show strong absorptions in the 1040–1070-cm^{-1} region.

(6) The thermolyses of **3** and **4** can be carried out within 15 min by passing them through a 15 ft × 3/8 in. column of 20% SE-30 on Chromosorb W at 260°. Samples of **5** and **6** collected in this manner need no further purification.

(7) No analogous rearrangements are known to occur in carbon compounds, although the thermal rearrangements of some oxaziridines[8] have similar features such as cleavage of the bond between nitrogen and oxygen and an alkyl group transfer (from carbon to nitrogen).

(8) For a review of the thermal rearrangements of oxaziridines see M. Lamchen in "Mechanisms of Molecular Migrations," Vol. 1, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1968, Chapter 1.

(9) *N,O*-Bis(trimethylsilyl)-*N*-methylhydroxylamine forms hexamethyldisiloxane and polymer when heated to 200° for 20 hr. This suggests that alkyl-substituted organosilylhydroxylamines may decompose by a different mechanism.

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Epimeric 3-Vinyl-4-piperidineacetic Acids, Synthetic Precursors of Cinchona and Indole Alkaloids

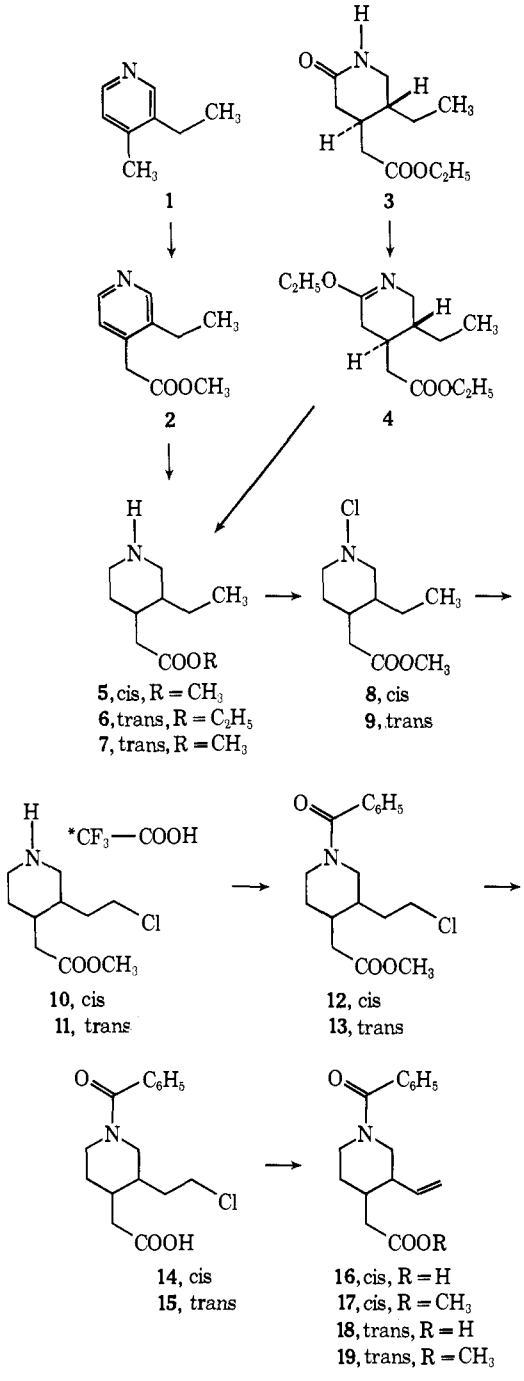
Sir:

The *cis*-3-vinyl-4-piperidineacetic acid, known as meroquinine,[1] was recently described as a synthetic precursor of the quinuclidine ring of quinine and quinidine.[2] Further investigations in our laboratories have revealed that this compound and its trans epimer can also be used as practical synthetic substitutes for bio-

(1) W. Koenigs, *Chem. Ber.*, **27**, 900, 1501 (1894); W. E. Doering and J. D. Chanley, *J. Amer. Chem. Soc.*, **68**, 586 (1946).

(2) M. Uskoković, J. Gutzwiller, and T. Henderson, *ibid.*, **92**, 203 (1970); J. Gutzwiller and M. Uskoković, *ibid.*, **92**, 204 (1970); M. Gates, B. Sugavanam, and W. L. Schreiber, *ibid.*, **92**, 205 (1970).

Scheme I



genetic, terpene-derived "C_9–C_{10}" precursors of the indole alkaloids.[3] This is exemplified by the syntheses of the heteroyohimbine alkaloids ajmalicine, tetrahydroalstonine, and akuammigine, and the indole–cinchona alkaloid cinchonamine, which are described in the accompanying communications.[4,5] In this communication we report the preparation of the *N*-benzoyl derivatives of *cis*- and *trans*-3-vinyl-4-piperidineacetic acids from the corresponding saturated intermediates. The conversion of the ethyl groups into vinyl side chains was achieved by means of the photolytic Löffler-Freytag reaction followed by dehydrohalogenation.

The saturated *cis*-amino ester **5** was obtained from β-collidine (**1**) (Scheme I). Methoxycarbonylation of **1** with dimethyl carbonate and lithium diisopropylamide in tetrahydrofuran gave the ester **2** [bp 98° (0.04 mm); ir ($CHCl_3$) 1730, 1160 cm^{-1}; nmr ($CDCl_3$) δ 3.67 (s, 3 H, $-OCH_3$); mass *m/e* 179 (M^+)] in 88% yield. Hydrogenation of the corresponding hydrochloride (mp 167–168°) with platinum catalyst led stereoselectively to the cis compound **5**[6] [hydrochloride, mp 133–135°; ir (KBr) 2750, 1730, 1230, 1170 cm^{-1}; mass *m/e* 185 (M^+ of the free base)] in 82% yield. This racemate was resolved with *d*- and *l*-tartaric acid to give the pure (3*R*),(4*S*)[7] [**5**, mono-*d*-tartrate, mp 143–143.5°; hydrochloride, mp 174.5–175.5°; $[\alpha]^{25}D$ −8.3° (*c* 1.0, CH_3OH)] and (3*S*),(4*R*) [**5**, mono-*l*-tartrate, mp 143–143.5°; hydrochloride, mp 174.5–175.5°; $[\alpha]^{25}D$ +8.4 (*c* 1.0, CH_3OH)] enantiomers, respectively. Chlorination of the racemic or (3*R*),-(4*S*) compound **5** with *N*-chlorosuccinimide in ether produced in 92% yield the corresponding *N*-chloramines **8**, which were subjected without purification to photolysis by a 200-W Hanovia medium-pressure mercury lamp in trifluoroacetic acid solution. The resulting crude trifluoroacetate salts **10** were benzoylated under neutral conditions to give the chloroethyl derivatives **12** [84% yield; purified by column chromatography; oils; mass *m/e* 323 (M^+), 288 (M − Cl), 105 (base peak); the (3*R*),(4*S*) enantiomer, $[\alpha]^{23}D$ 0°, $[\alpha]_{546}^{23}$ +4.8° and $[\alpha]_{365}^{23}$ +42.2° (*c* 1.0, CH_3OH)]. Hydrolysis of **12** with methanolic potassium hydroxide at room temperature furnished quantitatively the *N*-benzoyl acid **14** [racemic mp 121–124°; ir ($CHCl_3$) 3500, 1715 cm^{-1}; mass *m/e* 309 (M^+); the (3*R*),(4*S*) enantiomer, mp 124–126°; $[\alpha]^{25}D$ +28.71 (*c* 0.9055, CH_3OH)]. Elimination of hydrogen chloride was effected with potassium *tert*-butoxide in DMSO–benzene at 70°. *N*-Benzoylmeroquinene (**16**) was obtained in 87% yield [racemic, oil; the (3R),(4*S*) enantiomer, mp 115–117°; $[\alpha]^{25}D$ +49.77° (*c* 1.0368, CH_3OH); nmr ($CDCl_3$) δ 4.87–5.33 (m, 2 H, $-CH=CH_2$), 5.87 (m, 1 H, $-CH=CH_2$), 10.70 (s, 1 H, $-COOH$); mass *m/e* 273 (M^+)]. Esterification with diazomethane gave *N*-benzoylmeroquinene methyl ester [**17**; racemic mp 57–58°; ir ($CHCl_3$) 1735 and 1178 ($COOCH_3$), 1636 (amide), 1012 and 933 cm^{-1} (vinyl); nmr ($CDCl_3$) δ 3.65 (s, 3 H, OCH_3), 4.9–6.2 (m, 3 H, $CH=CH_2$); mass *m/e* 287 (M^+); the (3*R*),(4*S*) enantiomer, oil; $[\alpha]^{25}D$ +49.72° (*c* 0.9955, CH_3OH)]. The cis esters **17** were utilized as starting materials in the syntheses of quinine,[2,5a] quinidine,[2,5a,c] and tetrahydroalstonine.[4]

In the trans series the saturated amino ester **7** was obtained from the racemic *trans*-piperidone **3**.[8] Treatment of **3** with triethyloxonium fluoroborate

(3) R. Thomas, *Tetrahedron Lett.*, 544 (1961); E. Wenkert, *J. Amer. Chem. Soc.*, **84**, 98 (1962); A. R. Battersby, *Pure Appl. Chem.*, **14**, 117 (1967); A. I. Scott, *Accounts Chem. Res.*, **3**, 151 (1970).

(4) J. Gutzwiller, G. Pizzolato, and M. Uskoković, *J. Amer. Chem. Soc.*, **93**, 5907 (1971).

(5) (a) G. Grethe, H. L. Lee, T. Mitt, and M. Uskoković, *ibid.*, **93**, 5904 (1971); (b) C. Chang-pai, R. P. Evstigneeva, and N. A. Preobrazhenskii, *Zh. Obshch. Khim.*, **30**, 2085 (1960); (c) R. L. Augustine and S. F. Wanat, *Syn. Commun.* in press.

(6) The corresponding ethyl ester was synthesized by G. Stork and S. M. McElvain, *J. Amer. Chem. Soc.*, **68**, 1053 (1946).

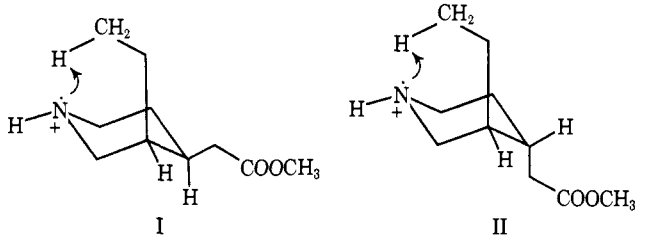
(7) Hydrolysis with hydrochloric acid gave (3*R*)-ethyl-(4*S*)-piperidineacetic acid [hydrochloride, mp 192–194°, $[\alpha]^{25}D$ −44.63° (*c* 1.0082, CH_3OH], which is known as cincholoipon, a degradation product of cinchona alkaloids.

(8) R. P. Evstigneeva, R. S. Livshic, M. S. Bainova, L. I. Zaharkin, and N. A. Preobrazenskii, *Zh. Obshch. Khim.*, **22**, 1467 (1952); R. P. Evstigneeva, J. F. Malina, and N. A. Preobrazenskii, *Izv. Vyssh. Ucheb. Zaved. Khim. Khim. Tekhnol.*, **No. 5**, 46 (1958); R. J. Sundberg, and F. O. Holcombe, *J. Org. Chem.*, **34**, 3273 (1969).

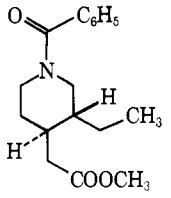
gave the imino ether **4**, which on reduction with sodium borohydride[9] furnished the racemic *trans*-ethyl ester **6** in nearly quantitative overall yield [bp 91–92° (bath) (0.5 mm); nmr ($CDCl_3$) δ 0.85 (distorted t, 3 H, $-CH_2CH_3$), 1.26 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.71 (s, 1 H, NH), 4.13 (q, 2 H, J = 7 Hz, OCH_2CH_3); mass m/e 199 (M^+)]. Saponification and reesterification with methanolic hydrogen chloride gave the methyl ester **7**.

Photolysis of the *trans*-*N*-chloramine **9**, followed by benzoylation, resulted in only 35% yield of the desired rearranged product **13** [oil, mass m/e 323 (M^+), 288 (M − Cl), 105 (base peak)]. Competitive photolytic dechlorination[10] followed by benzoylation led to racemic *trans*-*N*-benzoyl-3-ethyl-4-piperidineacetic acid methyl ester (**20**) in 25% yield [mass m/e 289 (M^+)].

Scheme II



I II



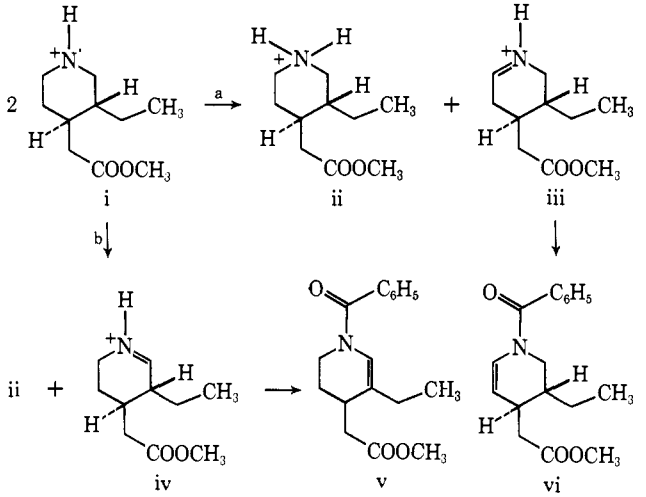
20

The low rearrangement yield in this case is due to a higher energy transition state in the hydrogen abstraction step, which involves chair conformation II with two axial substituents. This is contrasted with chair conformation **I** for the corresponding transition state in the cis series, which bears only one axial substituent (Scheme II). It was noted on the basis of several experiments that lower temperatures during photolysis favored dechlorination instead of rearrangement.

Hydrolysis of **13** afforded quantitatively the chloro acid **15** [mp 122–124°; ir ($CHCl_3$) 3520, 1716 cm^{-1}; mass m/e 309 (M^+)]. Subsequent elimination then gave racemic *trans*-*N*-benzoylmeroquinene [**18**; mp 137–141°; nmr ($CDCl_3$) δ 4.9–5.8 (m, 3 H, $CH{=}CH_2$), 7.36 (s, 5 H, phenyl); mass spectrum m/e 273 (M^+)] in 97% yield. The methyl ester **19** was obtained in high yield on treatment with diazomethane [oil, nmr ($CDCl_3$) δ 3.64 (s, 3 H, $-OCH_3$), 4.9–5.8 (m, 3 H, $CH{=}CH_2$), 7.37 (s, 5 H, phenyl); mass m/e 287 (M^+)]. This ester was utilized in the synthesis of ajmalicine and **19**-epiajmalicine.[4,11]

(9) R. F. Borch, *Tetrahedron Lett.*, 61 (1968).

(10) Dechlorination is probably due to disproportionations a and b of the intermediate aminium radical i



Compounds v and vi were isolated from the benzoylation reaction, and their structures were supported by spectra. The yield of v and vi together was equal to the yield of **20**, which resulted from the benzoylation of ii.

(11) Correct analytical figures have been obtained for all compounds for which physical and spectral data are given.

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Synthesis of Cinchona Alkaloids *via* Quinuclidine Precursors

Sir:

We report a new total synthesis of the cinchona alkaloids quinine, quinidine, and their dihydro analogs. It differs from previous syntheses[1] in that quinuclidine derivatives properly functionalized at C-2 and C-5 are used as intermediates. These compounds were prepared from 1,1-dichloro-3-piperidinylpropan-2-ols synthesized by two complementary methods (Scheme I).

In method A, applicable only to the dihydro series, β-collidine (**1**)[2] was condensed with chloral[3] and the crystalline reaction product was subsequently resolved with *l*- and *d*-tartaric acid into the enantiomers **2** [mp 132–134° (ether); $[\alpha]^{25}D$ −43.6° (*c* 1.123, EtOH)][4] and **3** [mp 132–134° (ether); $[\alpha]^{25}D$ +43.2° (*c* 1.1075, EtOH)]. Hydrogenation of **2** in 5% aqueous hydrochloric acid over a platinum catalyst gave after fractional crystallization the diastereoisomers **4** [mp 169–171° (acetone); $[\alpha]^{25}D$ −25.2° (*c* 0.931, MeOH); ir (KBr) 3340 cm^{-1} (OH); nmr (D_2O) δ 4.54 (m, 1, CHOH), 6.52 (d, 1, J = 3 Hz, $CHCl_2$)] and **5** [mp 232–233° (EtOH); $[\alpha]^{25}D$ −28.3° (*c* 1.024, MeOH); ir (KBr) 3390 cm^{-1} (OH); nmr (D_2O) δ 4.52 (m, 1, CHOH), 6.49 (d, 1, J = 3 Hz, $CHCl_2$)]. Under identical conditions the enantiomer **3** yielded **6** [mp 169–171° (acetone); $[\alpha]^{25}D$ +25.3° (*c* 1.014, MeOH)] and **7** [mp 232–233° (EtOH); $[\alpha]^{25}D$ +29.6° (*c* 1.095, MeOH)]. The hydrogenation yields were high, and none of the trans isomers was isolated. The cis configuration of the products **4**–**7** was

(1) (a) P. Rabe, W. Huntenberg, A. Schultze, and G. Vogler, *Chem. Ber.*, **64**, 2487 (1931); (b) M. Prošenik and V. Prelog, *Helv. Chim. Acta*, **26**, 1965 (1943); (c) R. B. Woodward and W. E. Doering, *J. Amer. Chem. Soc.*, **67**, 860 (1945); (d) M. Uskoković, T. Henderson, and J. Gutzwiller, *ibid.*, **92**, 203 (1970); J. Gutzwiller and M. Uskoković, *ibid.*, **92**, 204 (1970); (e) M. Gates, B. Sugavanam, and W. E. Schreiber, *ibid.*, **92**, 205 (1970); (f) G. Grethe, J. Gutzwiller, H. L. Lee, and M. Uskoković, to be published.

(2) An efficient three-step synthesis of β-collidine has been developed in these laboratories (unpublished results).

(3) E. Koenigs and W. Ottmann, *Chem. Ber.*, **54**, 1343 (1921).

(4) All new compounds gave correct microanalyses and their structural assignments were supported by physical data.