Table I. Silaoxazolidones **1**

No.	R	R′	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % Si	Found, % C	Found, % H	Found, % N	Found, % Si
1a[a]	H	C_6H_5	84–86	66.9	5.6	5.2		66.7	5.7	5.2	
1b	CH_3	C_6H_5	115–117								
1c[b]	CH_3	C_6H_5	125–128	67.8	6.1	5.0	9.9	67.7	6.1	5.0	9.9
1d	$C_6H_5CH_2$	C_6H_5	128–130	73.5	5.9	3.9	7.8	73.5	6.1	4.0	7.6
1e	C_6H_5	C_6H_5	171–175	73.0	5.5	4.1	8.1	73.3	5.6	3.8	8.6
1f	$(CH_3)_2CH$	C_6H_5	109–112	69.4	6.8	4.5		69.0	7.1	4.3	
1g[c]	$(CH_3)_2CH$	C_6H_5	120–125								
1h[d]	$(CH_3)_2CH$	C_6H_5	115–118								
1i[e]	CH_3	XC_6H_4									

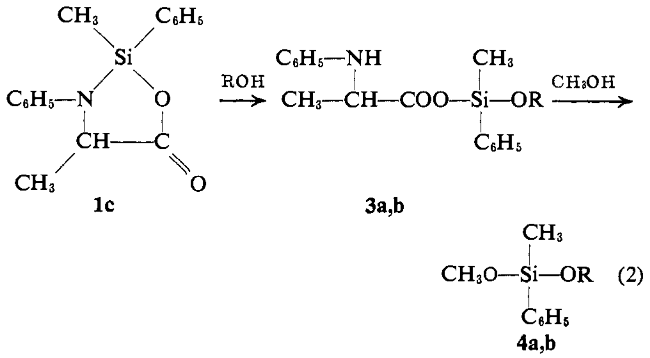
[a] Mol wt: calcd, 269; found, 268. [b] $[\alpha]^{25}D$ $-27.5°$. [c] $[\alpha]^{25}D$ $-38.0°$. [d] $[\alpha]^{25}$ D $+32.6°$. [e] X = *p*-CH_3O, *p*-CH_3, *p*-Cl, *p*-NO_2, *m*-NO_2 (pairs of diastereomers which have not crystallized to date).

The predominant diastereomer gave rise to the upfield silicon methyl peak in all cases except in those derived from N-phenylphenylglycine (**1e**) and N-phenylvaline (**1f–h**), where the signal remaining after crystallization was the downfield one of the original pair.

Since it was possible that the downfield silicon methyl absorbance was due to the silicon having the opposite configuration from that of the alanine derivative, N-phenylvaline was resolved through the quinine salt ($[\alpha]^{25}D$ $+85°$ (*c* 5, EtOH)). The silaoxazolidone **1g** was prepared as in the alanine case, mp 120–125°, $[\alpha]^{25}D$ $-38.0°$ (*c* 8.7, benzene). Its antipode, **1h**, starting with N-phenylvaline ($[\alpha]^{25}D$ $-80°$), was also prepared, mp 115–118°, $[\alpha]^{25}D$ $+32.6°$.

Reactions of 2-Methylphenylsila-3-phenyl-4-alkyloxazolidone-5. The silicon–nitrogen bond in the silaoxazolidone would be expected to be much more reactive than the silicon–oxygen bond. This suggested that successive reactions of the silaoxazolidone with two different alcohols could lead to separation of the optically active silicon from the carbon asymmetric center if both cleavage reactions were stereospecific.

Reaction of the 3-methylsilaoxazolidone **1c** with 2-propanol and methanol in successive steps led to the expected isopropoxymethoxymethylphenylsilane (**4a**) (eq 2).



1c **3a,b** **4a,b** (2)

a, R = $(CH_3)_2CH$; b, R = α-naphthyl

The specific rotation of **4a** was very small ($[\alpha]^{25}D$ $-0.4°$). From examination of the change of optical rotation during this reaction sequence we concluded that the silyl ester **3a** racemized rapidly during the reaction even though the two diastereomers of **3a** could not be detected by nmr. However, when 1-naphthol was used in the ring opening, the formation of two diastereomeric esters **3b** was readily determined by nmr which made it possible to choose reaction conditions that minimize the racemization. When an equivalent amount of 1-naphthol was added to silaoxazolidone **1c** (20% in benzene), the reaction was essentially complete at room temperature in 20 min. A short time later a new Si–CH_3 singlet appeared and grew at the expense of the original product. At equilibrium the two Si–CH_3 signals were of about equal intensity. The isomerization was accompanied by a change in specific rotation from $+36.5°$ at 0.5 hr to $+53.0°$ at 7 hr after addition of the 1-naphthol.

These results indicated that while a stereospecific ring opening could be achieved, any subsequent reaction must not only also be stereospecific but sufficiently rapid to minimize racemization. When a fivefold excess of methanol was added to the naphthoxysilyl ester **3b** the reaction was more than 90% complete in 3 min at 40°; less than 10% isomerization of **3b** was detected.

The isolated optically active naphthoxymethoxymethylphenylsilane **4b** had a specific rotation of $+21.9°$ (*c* 5, benzene). *Anal.* Calcd for $C_{18}H_{20}SiO_2$: C, 73.45; H, 6.16; Si, 9.54. Found: C, 73.21; H, 6.08; Si, 9.75. (This compound is the first known case of an optically active silane with two oxygen atoms attached to silicon.) Previous preparations of optically active silanes have been limited to compounds having at most one Si–O bond. Sommer, *et al.*,[7] report a specific rotation of $+16.5°$ for methoxymethylphenylnaphthylsilane.

A similar set of experiments was carried out using the silaoxazolidone derived from (+)-N-phenylvaline. Since the racemization of the naphthoxysilyl ester was considerably faster than in the case of the N-phenylalanine derivative, optical purity of the methoxynaphthoxymethylphenylsilane has not been high; $[\alpha]^{25}D$ $-4.9°$ (*c* 19.5, benzene). However, the opposite configuration was obtained as expected from the nmr spectrum.

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Effect of Substituents on the Proton–Proton Coupling Constants of Monosubstituted Benzenes

Sir:

It has been well established experimentally that, among the several factors which determine the size of the vicinal coupling constants between a proton bonded

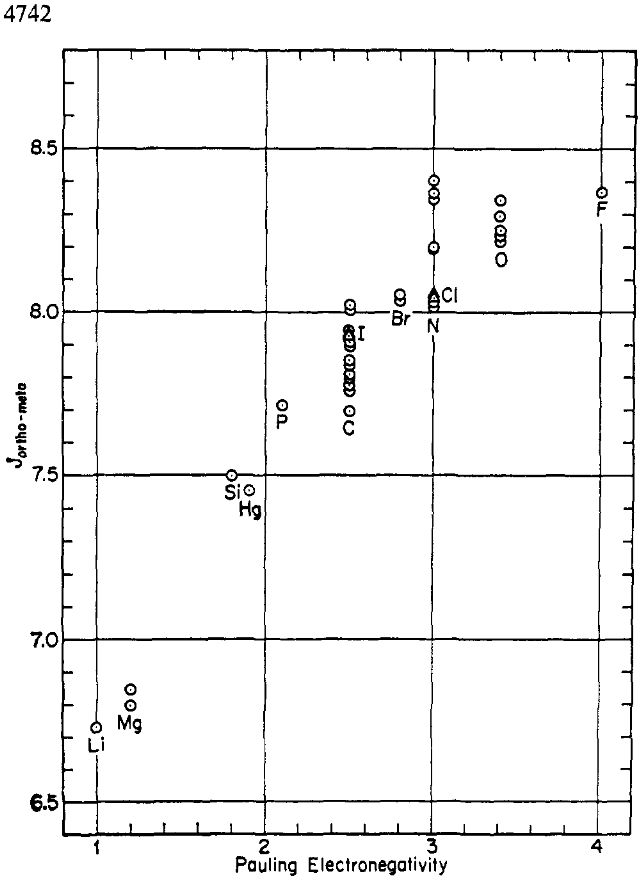

Figure 1. Correlation between the vicinal coupling constant $J_{ortho-meta}$ and the Pauling electronegativity of the atom of the substituent bonded to the aromatic ring in a series of monosubstituted benzenes.

to a carbon bearing a substituent and those attached to a carbon α to it, the electronegativity of the substituent plays an important role: an increase in the electronegativity of the substituent causes an algebraic decrease in the magnitude of the vicinal coupling constants.[1] This behavior has been observed in various series of monosubstituted ethylenes[2-4] and of monosubstituted ethanes,[5-7] and several other convincing examples may be found throughout the chemical literature of the past years.[1] This behavior has been explained theoretically in terms of the rehybridization of the carbon atom bearing the substituent and in terms of the inductive effect.[8] According to current theories[9] both effects should attenuate rapidly and monotonically along the carbon skeleton of alicyclic or cyclic hydrocarbons, and therefore the electronegativity of the substituents should cause smaller changes, but always in the same direction, in the vicinal coupling constants, among the protons attached to the carbons α and β to the one bearing the substituent. Yet there is evidence that this is not the case. Previous work on the nmr spectra of 3-substituted fluoropropenes,[10] for example, showed, contrary to expectation, that an increase in the number of fluorine substituents causes the *cis* and *trans* coupling constants between the vinyl protons to increase. Similar anomalous trends have also been reported by Cohen and Schaefer,[11] who have carried out an extensive and critical survey of the data appearing in the literature. Since previously published data show that this alternating effect of the electronegativity of the substituent on the vicinal coupling constants is very small, or, in some cases undetectable, because of the experimental errors, Cohen and Schaefer suggested that a test of this trend may possibly be obtained from the nmr spectra of monosubstituted benzenes.

Independently we had already undertaken such a study and present in this communication some of our results which confirm the above earlier observations. In Figure 1 the vicinal coupling constants between the *ortho* and *meta* protons ($J_{12} = J_{45}$ in our nomenclature, which corresponds to the labeling of the protons from 1 to 5 around the ring) of 35 monosubstituted benzenes[12] are plotted *vs.* the Pauling electronegativity of that atom of the substituents bonded to the benzene ring. A pronounced increasing trend of J_{12} with the electronegativity is observed. Of the remaining coupling constants only the ones connecting the *ortho* protons to the other protons in the ring show clearly definite trends with the electronegativity. In particular, a similar plot of J_{15} is nearly parallel to that of J_{12}, increasing monotonically from a value of 0.740 cps (R = Li) to a value of 2.744 cps (R = F). The coupling constants $J_{13} = J_{35}$ and $J_{14} = J_{25}$ display instead decreasing trends, their values ranging from 1.538 and 0.774 cps (R = Li) to 1.059 and 0.401 cps (R = F), respectively. A less definite and more scattered behavior is shown by the plot of J_{24}; the other vicinal coupling constant $J_{23} = J_{34}$ remains almost stationary with maximum variation of ±0.20 cps randomly distributed over the whole

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(1) For a review on the subject, see A. A. Bothner-By in "Advances in Magnetic Resonance," Vol. 1, Academic Press Inc., New York, N. Y., 1965, p 195, and literature quoted therein.

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(12) These data were obtained by complete analyses of the nmr spectra of the neat liquids (n) and/or of the solutions (s) of a series of monosubstituted benzenes (PhR). Carbon tetrachloride was used as solvent in most of the cases; acetone (a), diethyl ether (d), tetrahydrofuran (t), and carbon disulfide (c) were also employed occasionally. The concentrations most commonly used in the preparation of the samples were 10% (1) and 5% (2) w/w; for a few compounds different concentrations were used and they have been[13-16] or will be reported in the final publications.[17]

In the plot of Figure 1 a single point often represents experimental data corresponding to several compounds which are enclosed in brackets in the list given below. From left to right and from bottom to top of Figure 1, the monosubstituted benzenes to which this communication refers, are R = ···: Li (s1d); MgBr (s1d); MgBr (s1t); [$Si(Ph)_2Cl$ (s1, s2)]; HgPh (s1c); $PO(OCH_3)_2$ (s1); COH (n); $C\equiv CH$ (n); [$C\equiv CH$ (s); 2-phenyl-*trans*-ethenyl (sc)]; [Ph (s1), $C\equiv C—Ph$ (s1); $C\equiv N$ (s1)]; [COPh (s); $C\equiv C—Ph$ (s2); 2-phenyl-*trans*-ethenyl (s); Ph (s2)]; [$CH=CH_2$ (s1); $C\equiv N$ (n)]; [COOPh (s1); $CH=CH_2$ (n); $COOCH_3$ (n, s1); $CONH_2$ (s1a)]; [picolinoyl (s1); $COCH_3$ (n); COF (s1); $CONH_2$ (s2a)]; [COF (n); 2-pyridyl (s1)]; [I (n, s1)]; $COCH_3$ (s1); [COBr (n, s1); 2-methyl,4-phenyl,6-*sym*-triazinyl (s)]; [COCl (n, s1)]; Br (n); Br (s1); NH_2 (n); NH_2 (s1); Cl (s1); Cl (n); $NHCH_3$ (n); $NHCH_3$ (s1); NO_2 (n); NO_2 (s1); [$N(CH_3)_2$ (n, s1)]; OCOPh (s1); OPh (n); OPh (s1); OCH_3 (s1); OCH_3 (n); F (n).

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(17) We acknowledge the collaboration of Dr. B. L. Shapiro and Dr. N. F. Hepfinger in the study of the spectra of phenyllithium and phenylmagnesium bromide, of Dr. H. Dreeskamp in the study of the spectrum of diphenylmercury, and of Mr. R. Kostelnik in the study of some of the other monosubstituted benzenes.

range of electronegativity. Analogous trends for some of the coupling constants were already reported for various compounds in the series of *ortho*-[18,19] and *para*-disubstituted[20,21] benzenes. It was however, impossible from those data to dissect the observed effect into contributions surely attributable to each substituent separately. It may be interesting to report that by direct interpolation of the experimental data, the following values of the coupling constants for the protons of benzene are obtained: $J_{ortho} = 7.72, 7.65$ cps $[J_{12}, (J_{12} + J_{34})/2]$; $J_{meta} = 1.38, 1.46$ cps $[(J_{13} + J_{24})/2, (J_{13} + J_{24} + J_{15})/3]$; $J_{para} = 0.60$ cps $[J_{14}]$.

It is difficult, on the basis of current theories alone, to explain the observed trend of $J_{ortho-meta}$ or for that matter, those of all the other coupling constants with the electronegativity of the substituent in the series of monosubstituted benzenes. Our experimental results establish, however, that, as far as the magnitude of the coupling constants is concerned, the perturbation introduced by the substituent attenuates rapidly and is not appreciable beyond the *ortho* carbons as expected for an inductive effect. The algebraic variations observed for the $J_{ortho-meta}$ coupling constants are, however, of opposite sign to the ones that would have been predicted from the results obtained in the series of monosubstituted ethanes and ethylenes. Any correct formulation of the mechanism of the coupling between vicinal protons should take into account and explain this alternating effect of the electronegativity of the substituents. Perhaps the real clue toward the solution of this problem is furnished by the observation that, by decreasing the electronegativity of the substituent in the series of monosubstituted benzenes, the magnitudes of all the coupling constants move consistently and unambiguously toward the corresponding values found in pyridine. In view of the isoelectronic character of the phenyl anion and pyridine, this convergence of the experimental results appears quite natural in retrospect. The possibility of formulating quantitative correlations in this direction is presently under study.

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Biosynthesis of the Cinchona Alkaloids. The Incorporation of Geraniol-3-^{14}C into Quinine[1]

Sir:

It has been suggested[2] that quinine (**6**) and related alkaloids found in *Cinchona* species are derived from a corynantheine-type indole alkaloid (**3**) as indicated briefly in Figure 1. Loss of a carbon atom at C_{16}, bond cleavage between N_4 and C_5, and bond formation between C_{17} and N_4 affords the carbon skeleton of the alkaloid cinchonamine (**5**). Finally ring expansion of the indole moiety of cinchonamine involving the side chain at C_3 yields the quinoline nucleus present in quinine. Our previous tracer experiments[3] have supported the latter part of this scheme relating to the origin of the quinoline ring. The origin of the 10-carbon atom unit indicated with heavy lines in formula **3** has been the subject of much discussion and speculation. However it has recently been established[4–7] that this unit and related structures found in the indole alkaloids of *Vinca rosea* are derived from geraniol (**1**). The pattern of labeling found in these alkaloids was consistent with the intermediate formation of a cyclopentano monoterpene (**2**) which then underwent bond cleavage to the unit **4** as suggested 5 years ago by Thomas[8] and Wenkert.[9]

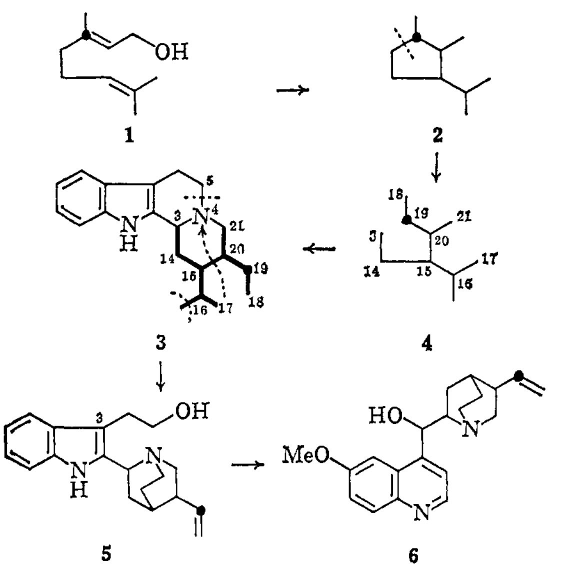

Figure 1. Biosynthesis of quinine (^{14}C indicated with a heavy dot).

We have now tested this hypothesis for the origin of the quinuclidine ring of quinine by feeding geraniol-3-^{14}C[7] (**1**, 17.6 mg, 75 μcuries), emulsified in water with Tween 80, to three 2-month-old *Cinchona succirubra* plants by means of cotton wicks inserted in the stems. After 3 weeks the plants were harvested and radioactive quinine (8.1×10^4 dpm/mmole) isolated without dilution by chromatography of the crude alkaloids on alumina followed by thin layer chromatography on silica gel.[10] Dihydroquinine (7.5×10^4 dpm/mmole), obtained on hydrogenation of the vinyl group, was subjected to a Kuhn–Roth oxidation affording a mixture of acetic and propionic acids. These acids were separated on silicic acid,[11] assayed as their α-naphthylamides,[12] and had specific activities of 7.5 and 7.9×10^4 dpm/mmole, respectively. A Schmidt reaction on the acetic acid afforded carbon dioxide collected as barium carbonate having an activity of

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