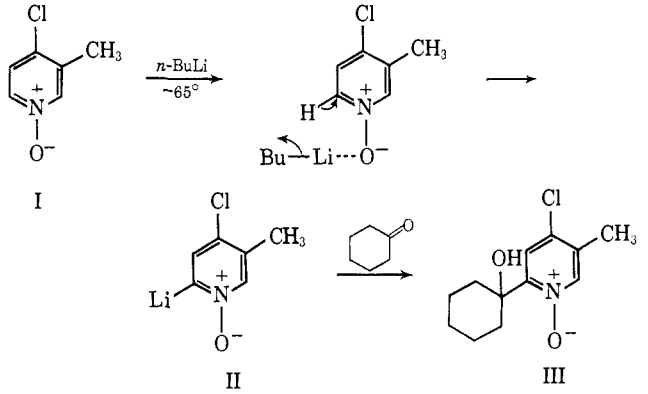
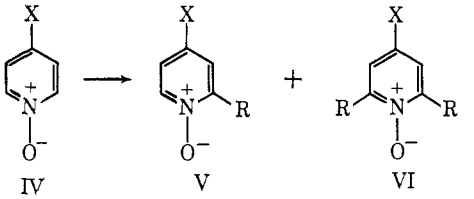
has been verified quantitatively.[3] For example, 3-bromopyridine 1-oxide undergoes H–D exchange readily with 0.1 *N* NaOD in D_2O, the order of reactivities being 2- > 6- > 4- >> 5-.[3] By making use of this principle we have now uncovered a facile alkylation and acylation of pyridine N-oxides in which the oxide group is retained. No simple direct introduction of such groups into this ring system has been available previously.

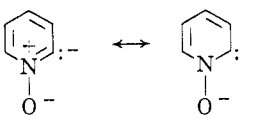
Treatment of 4-chloro-3-methylpyridine 1-oxide (I) with *n*-BuLi at −65° in ether gave the organolithium derivative II which, with cyclohexanone, gave 2-(1′-hydroxycyclohexyl)-4-chloro-5-methylpyridine 1-oxide (III) (38%), mp 164°. The nmr spectrum confirmed the structure and was as expected for pyridine N-oxides[4] [τ: 2.02 (1 H, singlet, C_6–H), 2.82 (1 H, singlet, C_3–H), 7.73 (3 H, singlet, CH_3–Ar)]. The infrared spectrum and microanalysis[5] were in agreement with structure III. No product resulting from the formation of the carbanion at C_2 was detected. Treatment of II with CO_2 gave 4-chloro-3-picoline-6-carboxylic acid 1-oxide (24%), mp 160°. The activating (−*I*) influence of the 4-chloro substituent was not required for proton abstraction as 3,4-lutidine 1-oxide gave a 6-lithio derivative which reacted with cyclohexanone to give 2-(1′-hydroxycyclohexyl)-4,5-dimethylpyridine 1-oxide (84%), mp 121–122°. Since the relative rates of deuterium–hydrogen exchange at C_2 and C_6 of 3-picoline methiodide with NaOD in D_2O are in the ratio $k_2:k_6 = 1.2$,[3] formation of the 2-lithio derivative in both the above N-oxides might have been expected to predominate slightly over the formation of the 6-lithio compound. That none of the former was detected indicates that steric hindrance by the 3-methyl group may be important in these metalations.[6] *The results described in this paper provide incontrovertible evidence for the proton-abstraction mechanism via a carbanion intermediate for the base-catalyzed H–D exchange in pyridine N-oxides.*[3]



A number of 4-substituted pyridine N-oxides reacted in a similar manner. Tetrahydrofuran was a suitable solvent for those N-oxides which were too insoluble in ether. In the absence of a 3-substituent disubstitution at C_2 and C_6 also occurred to give VI as well as V. Thus, when X = OEt, V (R = 1′-hydroxycyclohexyl) (20%), mp 127–128°, and VI (R = 1′-hydroxycyclohexyl) (12%), mp 166–167°, were obtained. Similarly, when X = CH_3, V (R = 1′-hydroxycyclohexyl) (21%), mp 115°, and VI (R = 1′-hydroxycyclohexyl) (27%), mp 198–199°, were obtained. On the other hand, treatment of the lithium derivative of 4-chloropyridine 1-oxide with CO_2 only gave the known[8] 4-chloropicolinic acid 1-oxide (V, R = CO_2H) (49%), mp 135–136°. 4-Picoline 1-oxide yielded the 2,6-dicarboxylic acid, mp 160°. Pyridine N-oxide itself gave VI (R = 1′-hydroxycyclohexyl) (15%), mp 158°. Treatment of the intermediate organolithium derivatives with nitriles or amides gave interesting ketones whose structures and reactions will be discussed in a subsequent publication.



The action of other electrophilic reagents is now under study as are ring systems other than the pyridine N-oxides and pyridinium salts. It is anticipated that the reaction will prove to be a general one for suitable six-membered heteroaromatic compounds. The carbanions can be looked upon as being stabilized by resonance with the carbene structure (VII) which would be another example of the so-called nucleophilic carbenes.[3,9]



Acknowledgments. This research was supported by a grant from the National Research Council of Canada and also, in part, by a grant from Merck & Co., for both of which we are grateful. We also thank Reilly Tar and Chemical Co. for the gift of some pyridine N-oxides.

(3) R. A. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem Commun.*, 55 (1967).
(4) R. A. Abramovitch and J. B Davis, *J. Chem. Soc., Sect. B*, 1137 (1966).
(5) Satisfactory analyses and infrared and nmr spectra were obtained for all new compounds described in this paper.
(6) Steric hindrance may account for the fact that some 3,4- but no 2,3-pyridyne 1-oxide was detected in the reaction of 3-chloropyridine 1-oxide with piperidine in benzene.[7]
(7) T. Kauffmann and R. Wirthwein, *Angew. Chem.*, 76, 993 (1964).
(8) E. Profft and W. Steinke, *J. Prakt. Chem.*, 13, 58 (1961).
(9) B. Capon, M. J. Perkins, and C. W. Rees, "Organic Reaction Mechanisms. 1965," Interscience Publishers Ltd., London, 1966, p 233.
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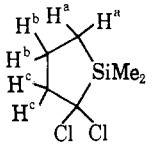
Insertion of CCl_2 into the Silicon–Carbon Bond of Silacyclobutanes

Sir:

We wish to report a new reaction which is noteworthy for two reasons: it represents the first reported CCl_2 insertion into a silicon–carbon bond as well as the first

reported insertion of CCl_2 (with ring expansion) into a strained cyclic system.[1]

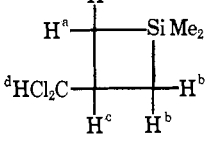
When a mixture of 10 mmoles of 1,1-dimethyl-1-silacyclobutane[2] (I) and phenyl(bromodichloromethyl)-mercury[3] in 15 ml of benzene was stirred at reflux for 2 hr (under nitrogen), phenylmercuric bromide precipitated (isolated in 93% yield). The filtered solution was distilled at 0.02 mm into a trap at −78°. Glpc analysis (Apiezon L on Chromosorb W, 40–105° temperature program) showed that in addition to starting silane (20%) and tetrachloroethylene (6%) there were present two other compounds. The product with a 14.1-min retention time was identified as 1,1-dimethyl-2,2-dichloro-1-silacyclopentane (II), and quantitative glpc showed that it had been formed in 58% yield. The structure of II, a volatile solid, mp 61.5–63.5°, was determined by means of its infrared and nmr spectra. Its nmr spectrum (CCl_4; in parts per million) showed a six-proton singlet at 0.4 (Si–CH_3), a two-proton triplet (J = 7.5 cps) at 0.9 (H^a), a two-proton quintet at 1.9 (H^b), and a two-proton triplet (J = 7 cps) at 2.45 downfield from internal TMS (H^c). Its infrared spectrum did not contain a strong band at 1120–1130 cm^{-1}; such strong absorption is characteristic of the silacyclobutane system.[4,5] (*Anal.*



II

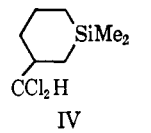
Calcd for $C_6H_{12}Cl_2Si$: C, 39.34; H, 6.61; Cl, 38.71. Found: C, 39.14; H, 6.64; Cl, 38.71.

The second product, a liquid formed in 12% yield (16.2-min retention time), was identified as 1,1-dimethyl-3-dichloromethyl-1-silacyclobutane (III). Its nmr spectrum (CCl_4; in parts per million) showed the $Si(CH_3)_2$ group at 0.4, H^a and H^b as a four-proton complex pattern at 1.1–1.5, H^c as a multiplet centered at 2.9, and H^d as a doublet (J = 6 cps) at 5.77.[6] The

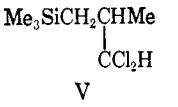


III

infrared spectrum of III showed a strong band at 1120 cm^{-1}, and its mass spectrum and elemental analysis were in agreement with this structure.



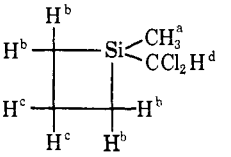
IV



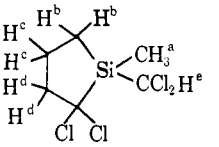
V

Reaction of I with $C_6H_5HgCCl_2Br$ in 3:1 molar ratio gave II and III in yields of 63 and 16%, respectively, while these yields were 56 and 14% when this reactant ratio was decreased to 1.5.

The reaction of 1-methyl-1-silacyclobutane (VI) with an equimolar quantity of $C_6H_5HgCCl_2Br$ in benzene at 71° gave 1-dichloromethyl-1-methyl-1-silacyclobutane (VII)[7] as major (68%) product (*i.e.*, the already familiar[8] insertion of CCl_2 into the Si–H bond), but a higher boiling by-product (6% yield) was 1-dichloromethyl-1-methyl-2,2-dichloro-1-silacyclopentane (VIII), bp 79–80° (0.8 mm), $n^{25}D$ 1.5246. The nmr



VII



VIII

spectrum (CCl_4; in parts per million) established the structure of the latter: H^a, singlet at 0.62; H^b, multiplet at 0.83–1.33; H^c, multiplet at 1.6–2.20; H^d, multiplet at 2.25–2.64; H^e, singlet at 5.49. *Anal.* Calcd for $C_6H_{10}Cl_4Si$: C, 28.59; H, 4.00; Cl, 56.28. Found: C, 28.61; H, 3.95; Cl, 56.27.

In an experiment in which VI was allowed to react with 2 molar equiv of $C_6H_5HgCCl_2Br$, the yields of VII and VIII were 28 and 61%, respectively.

Similar insertion of CCl_2 into the ring Si–C bond of 1-chloro-1-methyl-1-silacyclobutane has been observed. In contrast to these results with silacyclobutanes, it was found that 1,1,3,3-tetramethyl-1,3-disilacyclobutane was completely inert toward $C_6H_5HgCCl_2Br$-derived CCl_2. In one such attempted insertion reaction the starting disilacyclobutane was recovered in 97% yield and the only CCl_2-derived product that could be identified was tetrachloroethylene.

Dichlorocarbene insertion into a silicon–carbon bond has not been reported previously. The action of mercurial-derived CCl_2 on tetraalkylsilanes and on larger silacycloalkanes resulted in CCl_2 insertion into a C–H bond β with respect to the silicon atom, *e.g.*, to form products such as IV and V in the case of 1,1-dimethyl-1-silacyclohexane and *n*-propyltrimethylsilane, respectively.[6]

Among the known silacycloalkanes the silacyclobutane ring system is the only one for which a strain-free conformation is not available, and a great diversity of reagents is able to effect ring opening.[2,9,10] Such increased strain should result in increased p character of the Si–C bonds of the silacyclobutane ring and in increased s

(1) Dichlorocarbene (*via* $CHCl_3$ + base) has been reported to react with methyl bicyclobutane-1-carboxylate, but the products isolated were $CCl_2{=}CHCH_2C(CO_2Me){=}CH_2$ and $CH_2{=}CHCH_2C(CO_2Me){=}CCl_2$. The reaction of CH_2 with bicyclobutane gave a ~1% yield of bicyclo[1.1.1]pentane in addition to a large amount of 1,4-pentadiene: K. B. Wiberg, G. M. Lampman, R. P. Ciula, D. S. Connor, P. Schertler, and J. Lavanish, *Tetrahedron*, **21**, 2749 (1965).

(2) L. H. Sommer and G. A. Baum, *J. Am. Chem. Soc.*, **76**, 5002 (1954).

(3) D. Seyferth and J. M. Burlitch, *J. Organometal. Chem.*, (Amsterdam), 4, 127 (1965).

(4) J. Laane, *J. Am. Chem. Soc.*, **89**, 1144 (1967).

(5) N. S. Nametkin, V. D. Oppengeim, V. I. Zav'yalov, K. S. Puschevaya, and V. M. Vdovin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1547 (1965).

(6) The CCl_2H absorption in IV and V occurred at 5.70 and 5.59 ppm, respectively: D. Seyferth and S. S. Washburne, *J. Organometal. Chem.* (Amsterdam), **5**, 389 (1966).

(7) $n^{25}D$ 1.4901; analysis satisfactory; nmr (ppm): H^a, singlet at 0.45; H^b, multiplet at 0.9–1.45; H^c, multiplet at 1.8–2.4; H^d, singlet at 5.33 (note Et_3SiCCl_2H at 5.44[8]). The infrared spectrum contains a strong band at 1125 cm^{-1}.

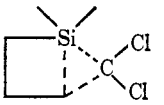
(8) D. Seyferth and J. M. Burlitch, *J. Am. Chem. Soc.*, **85**, 2667 (1963).

(9) C. Eaborn, "Organosilicon Compounds," Butterworth & Co. (Publishers) Ltd., London, 1960, pp 370–371.

(10) For recent references see D. Seyferth and R. B. King, "Annual Surveys of Organometallic Chemistry," Elsevier Publishing Co., Amsterdam: Vol. 1, 1965, p 97, and Vol. 2, 1966, p 120.

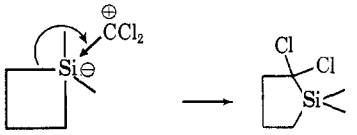
character in the Si–CH_3 and Si–H bonds of I and VI.[11] Thus the Si–C ring bonds in the silacyclobutane system should be weaker (and more reactive) than the Si–C ring bonds in the larger silacycloalkanes. On this basis CCl_2 insertion into ring Si–C bonds of I and VI to give the less strained silacyclopentane system is understandable. Molecular models show that the 1,3-disilacyclobutane system is significantly less strained than the silacyclobutanes, and thus its lack of reaction with CCl_2 is explained.

We have no evidence concerning the nature of this CCl_2 insertion process. One may consider as possible alternatives an electrophilic attack by CCl_2 at the reactive Si–C ring bond with a transition state IX or a process in which nucleophilic attack by CCl_2 (a



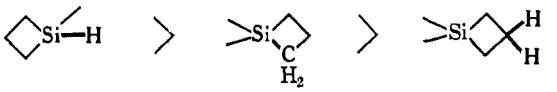
IX

possibility we have offered for consideration before[6]) at silicon is followed by migration of $-CH_2$ from silicon to CCl_2. Hopefully, further studies will shed some



light on this question.

It is apparent that the order of reactivity of silicon functionality toward CCl_2 is



Further investigations of reactions of CCl_2 with strained organometallic and organic ring systems are in progress.

Acknowledgments. The authors are grateful to the Directorate of Chemical Sciences, Air Force Office of Scientific Research, for generous support of this work and to Dow Corning Corporation for gifts of chemicals. This work was supported in part by Public Health Service Fellowship No. 5-F1-GM-24,781 (to R. D.).

(11) Spectroscopic results are in agreement with this view (expressed previously by Sommer[12]). A correlation to the effect that increase in s character of an Si–H bond leads to an increased ν_{Si-H} has been established;[13] ν_{Si-H} in VI (2130 cm^{-1}) is to be compared with that in Et_3SiH (2097 cm^{-1}).

(12) L. H. Sommer, "Stereochemistry, Mechanism and Silicon," McGraw-Hill Book Co., Inc., New York, N. Y., 1965, p 157.

(13) A. L. Smith and N. C. Angelotti, *Spectrochim. Acta*, **15**, 412 (1959).

(14) Alfred P. Sloan Foundation Fellow, 1962–1966.

(15) National Institutes of Health Predoctoral Fellow, 1964–1967.

(16) Union Carbide Fellow, 1966–1967.

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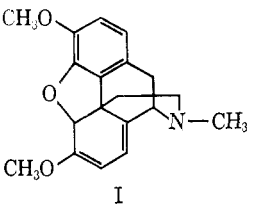
Received January 9, 1967

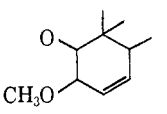
Codeinone as the Intermediate in the Biosynthetic Conversion of Thebaine to Codeine[1]

Sir:

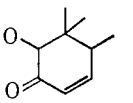
The final steps in the biosynthesis of morphine have been established[2] as conversion of thebaine (I) to codeine (IV), which is then demethylated to morphine. Formation of codeine from thebaine must involve an additional intermediate, since two processes occur, reduction and demethylation. The nature of this intermediate will depend upon which process occurs first. Thebaine could be reduced to codeine methyl ether (II), followed by demethylation to codeine; or demethylation could occur first, yielding codeinone (III),[3] followed by reduction to codeine. Neither codeine methyl ether nor codeinone has been isolated from fresh plants; however, codeine methyl ether has been found in opium.[4] We have now found evidence that codeinone is the intermediate in the biosynthetic conversion of thebaine to codeine.



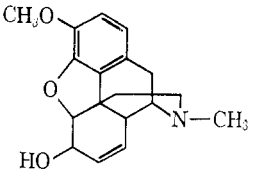
I



II



III



IV

Both codeine methyl ether and codeinone were considered as possible intermediates. Primary evidence was sought from short exposures to $^{14}CO_2$, the principal requirement being that the specific activity of the intermediate, if isolable, should be between those of thebaine and codeine. Supporting evidence was sought in feeding experiments, the assumption being that a true precursor should be converted to codeine.

All experiments were done with 60-day-old *Papaver somniferum* plants. Single plants were used for the $^{14}CO_2$ exposures (30 mcuries of $^{14}CO_2$) for a period of 4 hr.[5] Codeine methyl ether and codeinone were fed *via* the roots, and the alkaloids were isolated after 24 hr.[2] The alkaloids fed were only nuclear labeled so as to avoid any confusion arising from transmethylation.

(1) Sponsored in part by the U. S. Atomic Energy Commission and Grant MH 12797 from the National Institutes of Health, U. S. Public Health Service.

(2) F. R. Stermitz and H. Rapoport, *J. Am. Chem. Soc.*, **83**, 4045 (1961).

(3) Neopinone, the β,γ-unsaturated isomer, may be involved in a tautomeric equilibrium with codeinone; we shall comment on this question in a future publication.

(4) E. Brochmann-Hanssen and B. Nielsen, *J. Pharm. Sci.*, **54**, 1393 (1965).

(5) H. Rapoport, F. R. Stermitz, and D. R. Baker, *J. Am. Chem. Soc.*, **82**, 2765 (1960).