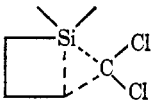
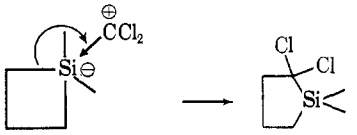
character in the Si–CH_3 and Si–H bonds of I and VI.[11] Thus the Si–C ring bonds in the silacyclobutane system should be weaker (and more reactive) than the Si–C ring bonds in the larger silacycloalkanes. On this basis CCl_2 insertion into ring Si–C bonds of I and VI to give the less strained silacyclopentane 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



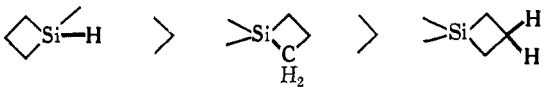
IX

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.

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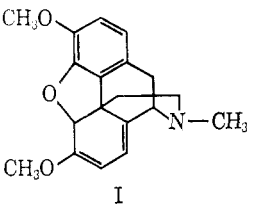
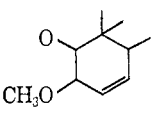
Codeinone as the Intermediate in the Biosynthetic Conversion of Thebaine to Codeine[1]

Sir:

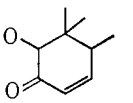
The final steps in the biosynthesis of morphine have been established[2] as conversion of thebaine (I) to codeine (IV), which is then demethylated to morphine. Formation of codeine from thebaine must involve an additional intermediate, since two processes occur, reduction and demethylation. The nature 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.



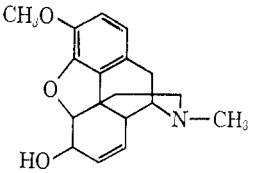
I



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).

Codeine methyl ether and codeinone were synthesized from randomly labeled biosynthesized morphine. The morphine was converted to normorphine[6] and thence to codeine methyl ether.[7] For the preparation of codeinone, normorphine was N-methylated to morphine *via* O^3,N-dicarbethoxynormorphine and subsequent reduction with lithium aluminum hydride,[8] and then O^3-methylated (diazomethane) to codeine, which was oxidized with silver carbonate to codeinone.[9]

Isolation of the nonphenolic alkaloids[5] was followed by thin layer and gas chromatography to separate codeine, codeine methyl ether, and thebaine into pure fractions; codeinone was separated from the other nonphenolic alkaloids *via* its bisulfite addition product.[10] Codeinone decomposed on gas chromatography; therefore it was converted by hydrogenation to dihydrocodeinone[11] or by borohydride to codeine.[12] Specific activities were determined with a gas chromatograph–flow counter system[13] in the $^{14}CO_2$ exposures when no carrier alkaloids were added during the isolation. In the feeding experiments, when carriers were added, the pure alkaloids were analyzed by liquid scintillation counting. To ensure the absence of any artifact during isolation, radioactive codeine and thebaine and inactive codeinone were added to a plant mash; reisolation showed only a trace of activity in the codeinone fraction (analyzed as dihydrocodeinone).

The results of the feeding experiments are presented in Table I. Both codeine methyl ether and codeinone, fed hydroponically through the roots, were converted to codeine. However, with codeine methyl ether, only 4.7% of the incorporated activity was converted to codeine whereas 51.5% was recovered as unchanged codeine methyl ether. With codeinone, 14.5% was converted to codeine and only 14% was recovered as codeinone, indicating a much more versatile metabolism for codeinone.

Results of the $^{14}CO_2$ exposures are given in Table II. Codeine methyl ether could not be detected, either *via* mass or radioactivity. Considering the analytical sensitivity of our method, this means that codeine methyl ether, if present at all, must have been present to an extent <0.02% of thebaine, assuming a specific activity close to that of thebaine as a small pool size would require.[14] On the other hand, radioactive codeinone was easily detected (>1% of thebaine), and its specific activity was between those of thebaine and codeine and closer to that of thebaine. As confirmation, similar $^{14}CO_2$ biosyntheses were conducted in which inactive carrier alkaloids were added to the isolates. Again, the codeine methyl ether was inactive and the codeinone was active (total activity 5% of that of thebaine).

The data from the $^{14}CO_2$ exposures provide strong evidence that codeinone is the intermediate in the biosynthetic conversion of thebaine to codeine. The slight incorporation of root-fed codeine methyl ether may be the result of general or induced demethylating action by the plant.[15]

Table I. ^{14}C-Labeled Alkaloid Feeding Experiments

Compd fed	mg/100 g of plant	Activity incorpd, dpm	% of incorpd activity in compounds isolated: Thebaine	Codeine	Morphine
Codeine methyl ether[a]	12.1	53,500	..	4.7	3
Codeinone[b]	7.8	309,000	..	14.5	2.8

[a] 51.5% of the incorporated codeine methyl ether was recovered unchanged. [b] 14% of the incorporated codeinone was recovered unchanged.

Table II. Specific Activities of Alkaloids Isolated after $^{14}CO_2$ Exposures[a]

Expt	Alkaloid isolated	Spec act., dpm/μmole
1[b]	Thebaine	8.65×10^6
	Codeine methyl ether	*c*
	Codeine	1.03×10^6
2[d]	Thebaine	9.1×10^3
	Codeinone[e]	8.2×10^3
	Codeine	5.7×10^3

[a] Exposures were for 2 hr in the light followed by 2 hr in the dark. [b] For the detection of codeine methyl ether. [c] Below detection limit (both mass and radioactivity) of the gas chromatograph–flow counter. [d] For the detection of codeinone. [e] Converted to codeine for analysis.

(6) J. von Braun, *Ber.*, 47, 2312 (1914).
(7) C. Mannich, *Arch. Pharm.*, **254**, 349 (1916).
(8) C. Elison, H. W. Elliott, M. Look, and H. Rapoport, *J. Med. Chem.*, 6, 237 (1963).
(9) H. Rapoport and H. N. Reist, *J. Am. Chem. Soc.*, 77, 490 (1955).
(10) H. Rapoport, C. H. Lovell, H. R. Reist, and M. E. Warren, *ibid.*, in press.
(11) C. Mannich and H. Loewenheim, *Arch. Pharm.*, **258**, 295 (1920).
(12) M. Gates, *J. Am. Chem. Soc.*, **75**, 4340 (1953).
(13) R. O. Martin, M. E. Warren, and H. Rapoport, *ibid.*, **86**, 4726 (1964).
(14) The plant (34 g) contained 535 μg of codeine and 67 μg of thebaine.
(15) The possibility exists of multiple pools and paths, with codeine methyl ether as an intermediate present in undetectable quantity or never free as such. The positive results with codeinone argue against this unnecessary complication.
(16) National Institutes of Health Predoctoral Fellow.

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