was found to be linearly proportional to the strength of the magnetic field (6.4 hertz at 60 Mhertz; 10.7 hertz at 100 Mhertz),[10] the splitting of the aromatic resonances cannot be due to spin-spin interactions. (2) Although a dissociation–recombination mechanism would also bring about interconversion of the diastereomers, the resulting phosphine radicals should have caused significant broadening of the spectral lines. Diphosphines are known to cleave by thermal means.[11] In the present situation, however, a dissociation would have to be followed by rapid, intramolecular recombination, since the spectral changes are reversible. Such a process, if exceedingly rapid, would be practically indistinguishable by nmr methods from inversion. This mechanism is not favored because line broadening was not appreciable (Table I) and irreversible radical reactions were not apparent. (3) Of the six rotational isomers that may be written for each diphosphine diastereomer, three do not contain eclipsed interactions.[8] Of these, either *gauche* conformation would be of much higher energy than the *trans* form (II, III), which minimizes not only the nonbonded interactions between substituents, but also the lone pair–lone pair repulsions.[12] Our conclusions require either that diphosphines are frozen into the *trans* conformation or that there is free rotation about the phosphorus–phosphorus bond. The equivalence of all the protons in P_2H_4 is consistent with this model.[8,13] Furthermore, the ^{31}P spectra of numerous diphosphines of the type R_2P-PR_2 or $R_2P-PR'_2$, for which rotamers, but not diastereomers, can exist, have never been reported to exhibit multiple resonances, except from chemically distinct species.[4,14] Coalescence of the phenyl resonances at elevated temperatures is therefore best explained in terms of phosphorus inversion, rather than equilibration of rotamers. Studies with related polyphosphine systems are continuing.

(10) We are grateful to Professor M. R. Willcott of the University of Houston for measuring the 100-Mhertz spectra.
(11) R. S. Davidson, R. A. Sheldon, and S. Trippett, *J. Chem. Soc. (Org.)*, 722 (1966).
(12) C. A. Coulson, "Valence," Oxford University Press, New York, N. Y., 1961, pp 178–179.
(13) R. M. Lynden-Bell, *Trans. Faraday Soc.*, **57**, 888 (1961).
(14) K. Moedritzer, L. Maier, and L. C. D. Groenweghe, *J. Chem. Eng. Data*, **7**, 307 (1962); E. Fluck and K. Issleib, *Ber.*, **98**, 2674 (1965).
(15) National Science Foundation Undergraduate Research Participant, 1965–1966.

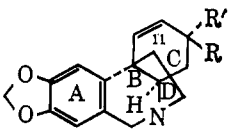
Joseph B. Lambert, David C. Mueller[15]
Department of Chemistry, Northwestern University
Evanston, Illinois 60201
Received May 20, 1966

A Total Synthesis of (±)-Crinine

Sir:

Crinine (I)[1a] and epicrinine (II)[1b] are representatives of one of the more widely occurring groups of Amaryllidaceae alkaloids,[2] the 5,10b-ethanophenanthridines.

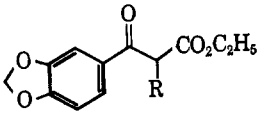
While several communications have appeared in the past few years concerning the synthesis of various



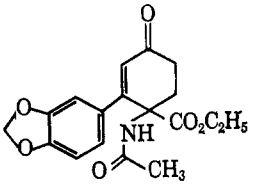
I, R = H; R′ = OH
II, R = OH; R′ = H

5,10b-ethanophenanthridine alkaloids,[3] no total syntheses have been reported. We now wish to report the first total synthesis of (±)-crinine (I) and (±)-epicrinine (II) and to describe a versatile pathway with potential for the elaboration of structurally similar alkaloids.

Ethyl piperonylacetate (III)[4] was nitrosated (sodium nitrite–acetic acid) and then reduced and acetylated (zinc–acetic acid–acetic anhydride) to ethyl N-acetylpiperonylglycinate (IV) (mp 122–123°).[5] Condensation of IV with methyl vinyl ketone (Triton B–benzene) followed by cyclization of the Michael adduct (1,4-diazabicyclo[2.2.2]octane, piperidine, acetic acid, and xylene)[6] gave the α,β-unsaturated ketone V (mp 176–178°). Saponification and decarboxylation of V led to VIa (mp 197–199°) in 59% over-all yield based on III.



III, R = H
IV, R = NHCOCH$_3$



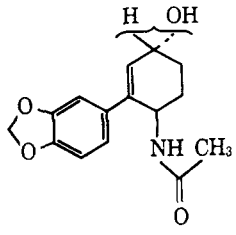
V

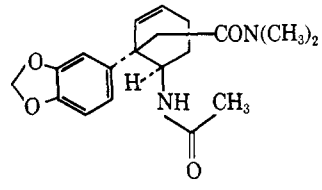
VIa, R = COCH$_3$
b, R = H
c, R = COCH$_2$CO$_2$CH$_3$

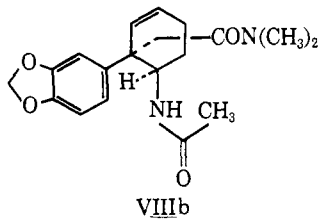
Reduction of VIa with sodium borohydride gave a nearly quantitative yield of a mixture of epimeric alcohols VII (mp 166–170°). Refluxing the mixture VII in benzene or toluene with 1,1-dimethoxy-1-dimethylaminoethane[7] gave the diamides VIIIa and b[8] (45% after chromatography),[9] accompanied by a 50% yield of the diene IX[10] (mp 137–138°; $\lambda\lambda_{max}^{ethanol}$ mμ

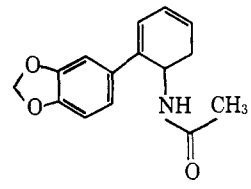
(1) (a) W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 2567 (1958); (b) R. E. Lyle, E. A. Kielar, J. R. Crowder, and W. C. Wildman, *ibid.*, **82**, 2620 (1960).
(2) For a review, see W. C. Wildman in "The Alkaloids," Vol. VI, R. H. F. Manske, Ed., Academic Press Inc., New York N. Y., 1965, p 290; K. W. Bentley, "The Alkaloids," Vol. VII, Interscience Publishers, Inc., New York, N. Y., 1965, p 54.
(3) H. W. Whitlock, Jr., and G. L. Smith, *Tetrahedron Letters*, 1389 (1965); J. B. Hendrickson, C. Foote, and N. Yoshimura, *Chem. Commun.*, 165 (1965).
(4) T. Kametani and H. Iida, *J. Pharm. Soc. Japan*, **73**, 681 (1953).
(5) Satisfactory analytical data have been obtained for all new compounds reported, and all compounds were characterized by ultraviolet, infrared, and nuclear magnetic resonance spectroscopy. Melting points were taken on a Kofler hot-stage microscope.
(6) H. Muxfeldt, *Angew. Chem.*, **74**, 825 (1962).
(7) H. Meerwein, W. Florian, N. Schön, and G. Stopp, *Ann.*, **641**, 1 (1961); A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *Helv. Chim. Acta*, **47**, 2425 (1964).
(8) We wish to propose that this modification of the Claisen rearrangement be known as the Meerwein–Eschenmoser reaction.
(9) These isomeric amides were only slightly separated on thin layer chromatography.
(10) The formation of this sensitive compound is notable. Applications of this alternate course of the reaction are under investigation.

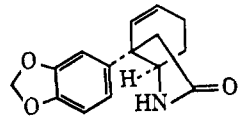
(ε) 322 (14,700) and 220 (11,300)). Treatment of the noncrystalline mixture of VIIIa and b with 10% sodium hydroxide (2-ethoxyethanol–water, 1:4, reflux) gave a 40% yield of a single lactam X (mp 206–207°) as well as some unreacted VIIIb.[11] Catalytic hydrogenation of X gave the dihydro derivative XI (mp 144–145°).

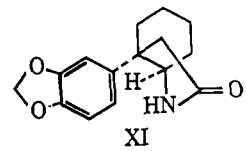

VII


VIIIa


VIIIb


IX


X

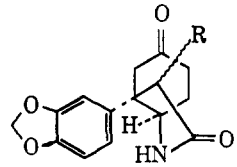

XI

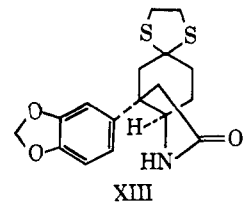
Unambiguous demonstration of the configuration of X was desired. Therefore the amine VIb was prepared by treatment of VIa with Meerwein's reagent[12] followed by hydrolysis of the imino ether hydrofluoroborate in aqueous tetrahydrofuran. Reaction of VIb with carbomethoxyacetyl chloride afforded the amide VIc (mp 90–91°; $\lambda\lambda_{max}^{ethanol}$ mμ (ε) 342 (11,500), 300 (7900), 250 (13,100), and 242 (13,100)). Treatment of VIc with sodium hydride in refluxing tetrahydrofuran led in quantitative yield to XIIa (mp 183–190°; $\lambda\lambda_{max}^{ethanol}$ mμ (ε) 287 (3600) and 237 (3300)), identified by nmr as a 1:1 mixture of the C-11 epimers.[13] Kinetic and thermodynamic factors demand that the ring junction which results from an intramolecular Michael addition of VIc be *cis*. Saponification of XIIa (0.5 *N* methanolic sodium hydroxide) resulted in the quantitative formation of the acid XIIb which was not purified but decarboxylated (lithium iodide in diglyme) to XIIc (mp 179–182°). Reaction of XIIc with 1,2-ethanedithiol gave the thioketal XIII (mp 265–268°) which, upon treatment with Raney nickel (refluxing dioxane), afforded the lactam XI (mp 144–145°). This material was shown to be identical in all respects with the lactam obtained from the catalytic reduction of X. Thus the C,D ring fusion of X is established as *cis*. This was further confirmed by reduction of XI with lithium aluminum hydride followed by Pictet–Spengler cyclization (formalin, hydrochloric acid) to the previously known (±)-crinane (XIV, mp 94–97°, lit.[1a] 97–99°).

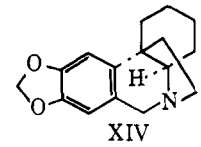
(11) The amide VIIIb (mp 200–201°) isolated from this reaction mixture could not be transformed to a lactam under the conditions mentioned above.

(12) H. Meerwein, G. Hinz, P. Hofmann, E. Kroning, and E. Pfeil, *J. Prakt. Chem.*, [2] **147**, 257 (1937).

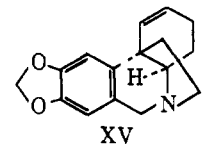
(13) All carbon atoms in the intermediates are numbered in the manner described for I.

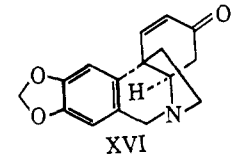

XIIa, R = CO_2CH_3
b, R = CO_2H
c, R = H


XIII


XIV

With the configuration of X firmly established, the conversion into (±)-crinine was investigated. Reduction of X with lithium aluminum hydride followed by Pictet–Spengler cyclization gave (±)-α-desoxycrinine (XV, mp 76–78°)[14] in 70% yield based on X. Oxidation of XV with selenium dioxide (acetic acid–acetic anhydride, reflux) and saponification of the resulting acetate gave (±)-crinine (I, mp 173–175°) after purification *via* its picrate (mp 203–204°). This material is identical in every respect with (±)-crinine of natural origin prepared by mixing (−)-crinine and (+)-crinine (vittatine).[15]


XV


XVI

Oxidation of I (chromium trioxide–pyridine) afforded (±)-oxocrinine (XVI, mp 172–173°, lit.[1b] 177–178°). Finally, reduction of XVI with sodium borohydride gave (±)-epicrinine (II, mp 235.5–237°, lit.[1b] 239°).

Acknowledgment. The authors are grateful to Professor W. C. Wildman for an authentic sample of (±)-crinine and to the National Science Foundation (Grant No. GP-3696) for generous financial support.

(14) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 4395 (1958). Professor W. C. Wildman has confirmed the identity of XV with a sample of α-desoxycrinine previously known as a degradation product of powelline.

(15) H. G. Boit and H. Ehmke, *Chem. Ber.*, **90**, 369 (1957).

(16) National Institutes of Health Predoctoral Fellow, 1963–1966.

(17) National Aeronautics and Space Administration Trainee, 1964–1966.

Hans Muxfeldt, Richard S. Schneider,[16] Jared B. Mooberry[17]
Chemistry Research Building, University of Wisconsin
Madison, Wisconsin 53706
Received June 20, 1966

The Stereochemistry of the Thermally Induced Isomerization of N-Substituted Pyrroles

Sir:

Recent kinetic studies on the thermal isomerization of N-alkylpyrroles have indicated that the isomerization is a homogeneous unimolecular process[1] in which the 2

(1) (a) I. A. Jacobson, Jr., H. H. Heady, and G. V. Dinneen, *J. Phys. Chem.*, **62**, 1563 (1958); (b) I. A. Jacobson, Jr., and H. B. Jensen, *ibid.*, **66**, 1245 (1962); (c) I. A. Jacobson, Jr., and H. B. Jensen, *ibid.*, **68**, 3068 (1964).