gases was used, a significant isotopic discrimination was observed in favor of the formation of the hydrogenated product over the deuterated product (Table I). This result indicates that in reactions 2 and 2a the formation of dihydride IIa is preferred over the formation of dideuteride II, and neither reaction is rate controlling.

That no exchange occurs before addition is shown by the absence of deuterated species in partially reduced sorbate. This result and the stereochemical requirement of the suggested intermediate III are consistent with the unusually high selectivity of this catalyst system.

The tricarbonylchromium complex should have practical utility in tracer studies to label olefins specifically with deuterium or possibly tritium.

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was first interpreted in terms of the transfer step being rate determining and was explained by considering differences in the activated complex.[4a] Later when solvent displacement was considered rate determining, secondary isotopic effects were invoked.[4b]

[12] This is a laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Mention of firm names or trade products is made for information only and does not constitute endorsement by the U. S. Department of Agriculture.

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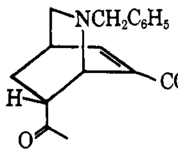
*Received February 10, 1968*

## The Total Synthesis of Velbanamine

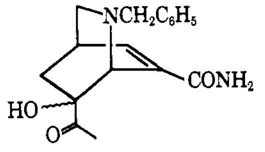
*Sir:*

The oncolytic agents vinblastine and vincristine[1,2] are "dimeric" alkaloids containing a pentacyclic indoline and a tetracyclic indole moiety. Fragmentation into these structural units is brought about readily by reduction in acidic media which in the case of vinblastine gives desacetylvindoline[3] and velbanamine (**14**).[4] These fragments are obvious intermediates in a synthesis of vinblastine, and we now describe the first total synthesis[5] of velbanamine (**14**).

Oxygenation[6] of the isoquinuclidine **1**[7] in *t*-butyl alcohol-monoglyme saturated with potassium *t*-butoxide at −20° gave the hydroxy ketone **2**,[8] mp 156–158°. The corresponding diol **3**, mp 182–183°, prepared by reduction of the hydroxy ketone with sodium borohydride, was cleaved with sodium metaperiodate in aqueous methanol to give the ketone **4**, mp 109–112° (ethyl acetate solvate). The latter was transformed to the ketal **5**, mp 163–165°, by treatment with a mixture of methyl orthoformate and methanol in the presence of *p*-toluenesulfonic acid at reflux during 24 hr. Hofmann reaction[9] followed by hydrolysis with sodium carbonate in methanol-water gave the ketone **6**, mp 121–123°. Hydrogenolytic debenzylation of the hydrochloride of **6** over a palladium catalyst proceeded smoothly, and condensation of the crude secondary amine hydrochloride with sodium indoleacetate in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride[10] in water gave the amide **7**, mp 106–112° (benzene solvate). Cyclization with 1.1 equiv of *p*-toluenesulfonic acid in refluxing benzene[11] during 30 min yielded the pentacyclic methoxy ketone **8**, mp 282–284°. In agreement with structure **8** the nmr spectrum ($CDCl_3$) displayed an AB quartet centered at $\delta$ 3.94, a one-proton singlet at 4.83, and a three-proton singlet at 3.09 which were assigned to the methylene group adjacent to the indole ring, the bridgehead hydrogen atom next to the amide nitrogen, and the methoxy group, respectively.



**1**



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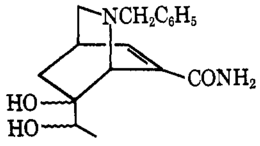

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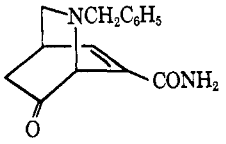

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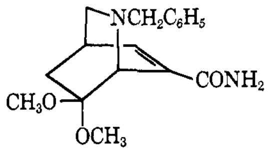

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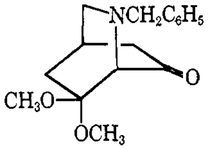

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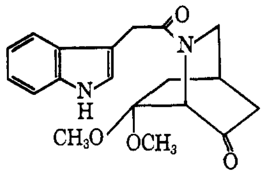
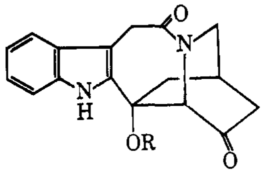


**7**



**8**, R = $CH_3$
**9**, R = H

Cleavage of the methyl ether **8** in acetic acid containing 6% perchloric acid[12] at room temperature during 24 hr furnished the hydroxy ketone **9**, mp 262–264°. A solution of the aldol **9** in *t*-butyl alcohol containing potassium *t*-butoxide displays ultraviolet absorption at 350 m$\mu$ indicating the presence of the anion derived from the 2-acylindole **10**. Quenching with acetic acid gave a solution of the unstable 2-acylindole **10** (uv absorption at 316 m$\mu$) which was buffered at pH 6 and sodium borohydride was added. Work-up followed by chromatography on silica gel gave the diol **11**, mp 272–275°, convertible to the alcohol **12**, mp 270–273°, by reduction with tin and

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(1) J. W. Moncrief and W. N. Lipscomb, *J. Am. Chem. Soc.*, **87**, 4963 (1965).

(2) N. Neuss, M. Gorman, W. Hargrove, N. J. Cone, K. Biemann, G. Büchi, and R. E. Manning, *ibid.*, **86**, 1440 (1964).

(3) M. Gorman, N. Neuss, and K. Biemann, *ibid.*, **84**, 1058 (1962).

(4) N. Neuss, M. Gorman, H. E. Boaz, and N. J. Cone, *ibid.*, **84**, 1509 (1962).

(5) Substances containing the carbon skeleton present in velbanamine have been synthesized previously: J. P. Kutney, W. J. Cretney, P. Le Quesne, B. McKague, and E. Piers, *ibid.*, **88**, 4756 (1966); J. Harley-Mason, Atta-ur-Rahman, and J. A. Beisler, *Chem. Commun.*, 743 (1966); J. Harley-Mason and Atta-ur-Rahman, *ibid.*, 208 (1967); 1048 (1967).

(6) E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *J. Chem. Soc.*, 1578 (1962).

(7) G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *J. Am. Chem. Soc.*, **88**, 3099 (1966).

(8) All compounds were characterized by ir, uv, nmr, and mass spectra.

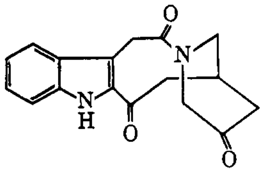
(9) S. Archer and M. R. Bell, *ibid.*, **82**, 4642 (1960).

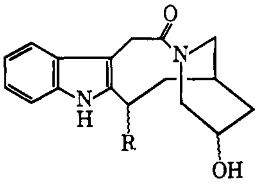
(10) J. C. Sheehan, J. Preston, and P. A. Cruickshank, *ibid.*, **87**, 2492 (1965).

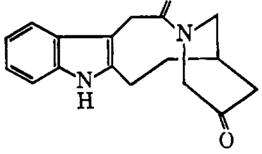
(11) W. Nagata, S. Hirai, K. Kawata, and T. Okumura, *ibid.*, **89**, 5046 (1967).

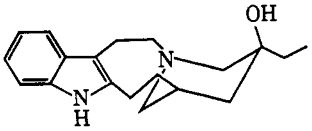
(12) A. J. Birch and J. S. Hill, *J. Chem. Soc.*, 419 (1966).

stannous chloride in hot acetic acid containing $p$-toluenesulfonic acid.[4] Oxidation[13] to the ketone **13**, mp 250–252°, followed by successive treatments with ethylmagnesium bromide in ether and with lithium aluminum hydride gave mainly the axial alcohol **14** in 0.4% yield based on **1**. Its infrared and mass spectra were identical with those of velbanamine prepared from vinblastine.[14] Further, racemic velbanamine (**14**) gave a di-$p$-toluoyl-$l$-tartrate, mp 140–140.5°, identical with the salt of "natural" velbanamine, mp 140–140.5°; mixture melting point not depressed.


**10**


**11**, R = OH
**12**, R = H


**13**


**14**

**Acknowledgment.** The mass spectra were measured in the National Institutes of Health supported mass spectrometry facility at Massachusetts Institute of Technology (Grant FR 00317) under the direction of Professor K. Biemann. We are indebted to the National Institutes of Health (GM 09686) for generous financial support.

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(13) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5670 (1965).

(14) We are indebted to Dr. N. Neuss, Eli Lilly and Co., for a sample of velbanamine.

(15) National Institutes of Health Predoctoral Fellow, 1965–1967.

(16) National Institutes of Health Predoctoral Fellow, 1965–present.

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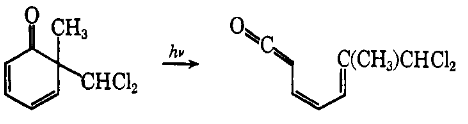
*Received March 6, 1968*

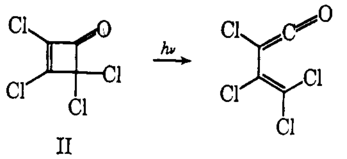
## Direct Observation of Ketene Intermediates in Photochemical Reactions[1]

*Sir:*

Ketenes have been invoked as intermediates in many photochemical reactions of unsaturated ketones. For example, irradiation of 2,4-cyclohexadienones or cyclobutenones in the presence of nucleophiles gives acyclic adducts.[2] Evidence for the involvement of ketenes as intermediates in these reactions is indirect. We now wish to report the direct observation of ketenes as primary photoproducts of 6-methyl-6-dichloromethyl-2,4-cyclohexadienone (I)[3] and perchloro-2-cyclobuten-1-one (II), and the unexpected intrusion of a thermally unstable ketene intermediate in the interconversion of III and IV.



I



II

The infrared spectrum of the mixture produced by irradiation[4] of I as a liquid nitrogen cooled glass is shown in Figure 1. The 2118-cm$^{-1}$ band is readily recognizable as the C=O stretch of the ketene.[5] The low-frequency region suggests that the initially formed diene ketene is the *cis*-diene ketene in accord with earlier postulates.[2] Irradiation[4] of II gave a new compound with a ketene carbonyl band at 2145 cm$^{-1}$.

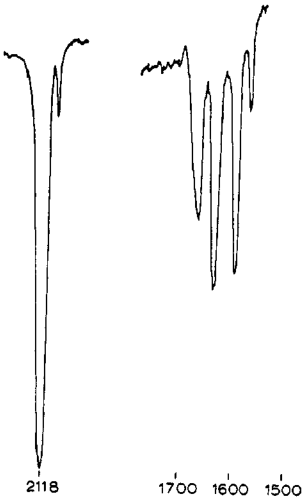


Figure 1. Low-temperature infrared spectrum of the carbonyl region after 45-min irradiation[4] of 6-methyl-6-dichloromethyl-2,4-cyclohexadienone (I).

The photochemical rearrangement of III to IV has been described.[6] Labeling of positions 4 and 6 with alkyl groups defined the rearrangement of atoms as shown. It was suggested[6] that electronic excitation of III, 4,6-bond formation, rearrangement (V → VI), and electron redistribution gave IV. This mechanistic rationalization satisfactorily accounted for related rearrangements reported later.[7] We wish to describe evidence for a path from III to IV which implicates a thermally unstable ground-state intermediate.

Irradiation[4] of III gave rise to a new product with a

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(1) Photochemical Transformations. XXVI.

(2) D. H. R. Barton, *Helv. Chim. Acta*, **42**, 2604 (1959); D. H. R. Barton and G. Quinkert, *J. Chem. Soc.*, 1 (1960); J. E. Baldwin and M. C. McDaniels, *J. Am. Chem. Soc.*, **89**, 1537 (1967); P. M. Collins, and H. Hart, *J. Chem. Soc.*, 1197 (1967); G. Quinkert, *Angew. Chem. Intern. Ed. Engl.*, **4**, 211 (1965).

(3) The sample of 6-methyl-6-dichloromethyl-2,4-cyclohexadienone was provided by Professor John Baldwin. The photochemical transformations of I in the presence of nucleophiles will be reported shortly by J. Baldwin and M. McDaniel.

(4) Neat glasses were irradiated in a liquid nitrogen cooled infrared cell mounted in a vacuum shroud with sodium chloride windows. Pyrex filters were used for all irradiations.

(5) The weak band at 2060 cm$^{-1}$ is due to the natural abundance $^{13}$C=O ketene band as in the spectrum of ketene: W. F. Arendale and W. H. Fletcher, *J. Chem. Phys.*, **26**, 793 (1957).

(6) W. G. Dauben, K. Koch, S. L. Smith, and O. L. Chapman, *J. Am. Chem. Soc.*, **85**, 2616 (1963); **83**, 1768 (1961).

(7) T. Mukai and T. Miyashi, *Tetrahedron*, **23**, 1613 (1967); T. Mukai and T. Shishido, *J. Org. Chem.*, **32**, 2744 (1967).