

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.

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

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## The Total Synthesis of Velbanamine

Sir:

The oncolytic agents vinblastine and vincristine<sup>1,2</sup> 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<sup>3</sup> and velbanamine (14).<sup>4</sup> These fragments are obvious intermediates in a synthesis of vinblastine, and we now describe the first total synthesis<sup>5</sup> of velbanamine (14).

Oxygenation<sup>6</sup> of the isoquinuclidine 1<sup>7</sup> in *t*-butyl alcohol-monoglyme saturated with potassium *t*-butoxide at  $-20^\circ$  gave the hydroxy ketone 2,<sup>8</sup> 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

(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).

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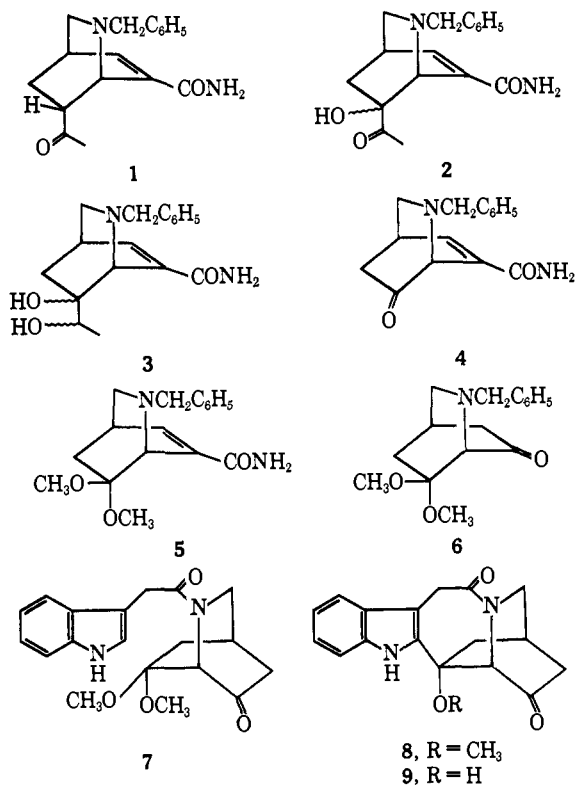
(5) Substances containing the carbon skeleton present in velbanamine have been synthesized previously: J. P. Kutney, W. J. Cretney, P. Le Quesne, B. McKague, and E. Piers, *ibid.*, **88**, 4756 (1966); J. Harley-Mason, Atta-ur-Rahman, and J. A. Beisler, *Chem. Commun.*, 743 (1966); J. Harley-Mason and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

during 24 hr. Hofmann reaction<sup>9</sup> followed by hydrolysis with sodium carbonate in methanol-water gave the ketone 6, mp 121–123°. Hydrogenolytic debenzoylation 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<sup>10</sup> in water gave the amide 7, mp 106–112° (benzene solvate). Cyclization with 1.1 equiv of *p*-toluenesulfonic acid in refluxing benzene<sup>11</sup> during 30 min yielded the pentacyclic methoxy ketone 8, mp 282–284°. In agreement with structure 8 the nmr spectrum (CDCl<sub>3</sub>) 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.



Cleavage of the methyl ether 8 in acetic acid containing 6% perchloric acid<sup>12</sup> 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

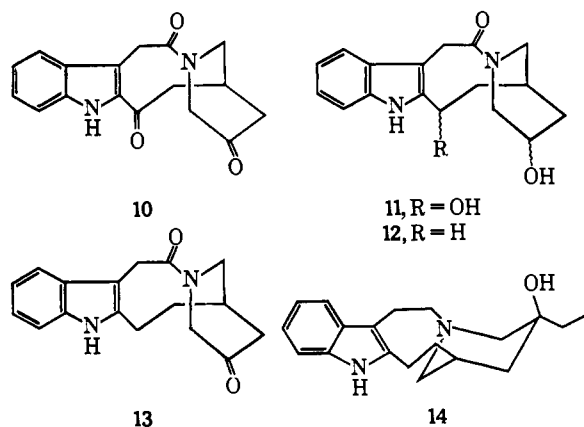
(9) S. Archer and M. R. Bell, *ibid.*, **82**, 4642 (1960).

(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.<sup>4</sup> Oxidation<sup>13</sup> 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.<sup>14</sup> 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.



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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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## Direct Observation of Ketene Intermediates in Photochemical Reactions<sup>1</sup>

Sir:

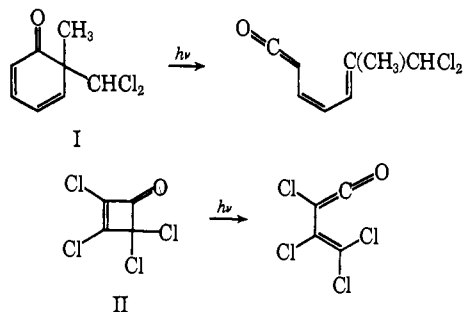
Ketenes have been invoked as intermediates in many photochemical reactions of unsaturated ketones. For example, irradiation of 2,4-cyclohexadienones or cyclobutenones in the presence of nucleophiles gives acyclic adducts.<sup>2</sup> Evidence for the involvement of ketenes as intermediates in these reactions is indirect. We now wish to report the direct observation of ketenes as primary photoproducts of 6-methyl-6-dichloromethyl-2,4-cyclohexadienone (**I**)<sup>3</sup> and perchloro-2-cyclobuten-1-

(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 trans-

one (**II**), and the unexpected intrusion of a thermally unstable ketene intermediate in the interconversion of **III** and **IV**.



The infrared spectrum of the mixture produced by irradiation<sup>4</sup> of **I** as a liquid nitrogen cooled glass is shown in Figure 1. The 2118-cm<sup>-1</sup> band is readily recognizable as the C=O stretch of the ketene.<sup>5</sup> The

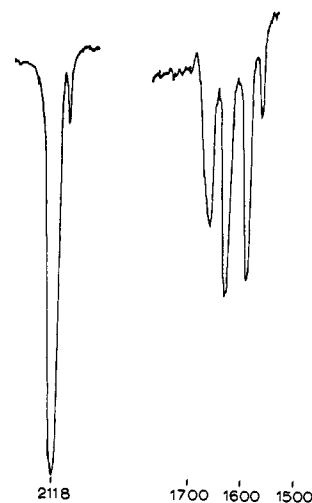


Figure 1. Low-temperature infrared spectrum of the carbonyl region after 45-min irradiation<sup>4</sup> of 6-methyl-6-dichloromethyl-2,4-cyclohexadienone (**I**).

low-frequency region suggests that the initially formed diene ketene is the *cis*-diene ketene in accord with earlier postulates.<sup>2</sup> Irradiation<sup>4</sup> of **II** gave a new compound with a ketene carbonyl band at 2145 cm<sup>-1</sup>.

The photochemical rearrangement of **III** to **IV** has been described.<sup>6</sup> Labeling of positions 4 and 6 with alkyl groups defined the rearrangement of atoms as shown. It was suggested<sup>6</sup> 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.<sup>7</sup> We wish to describe evidence for a path from **III** to **IV** which implicates a thermally unstable ground-state intermediate.

Irradiation<sup>4</sup> of **III** gave rise to a new product with a

formations 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<sup>-1</sup> is due to the natural abundance <sup>13</sup>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).