[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE UNIVERSITY OF SCIENCE AND TECHNOLOGY, AMES, IOWA]

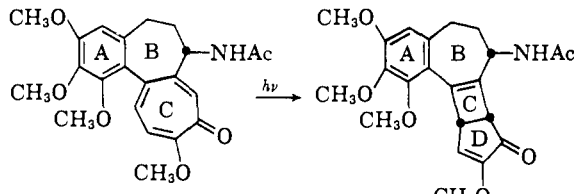
The Structure of β-Lumicolchicine[1]

BY O. L. CHAPMAN, H. G. SMITH AND R. W. KING

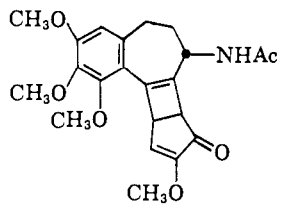
RECEIVED AUGUST 20, 1962

The structure of β-lumicolchicine has been rigorously established by nuclear magnetic resonance studies using solvent effects, double resonance techniques and deuteration on β-lumicolchicine, γ-lumicolchicine and the alcohols obtained by sodium borohydride reduction of these ketones.

Irradiation of colchicine (I) gives three crystalline photoproducts, α-, β- and γ-lumicolchicine.[2-4] Structures II and III have been suggested for β- and γ-

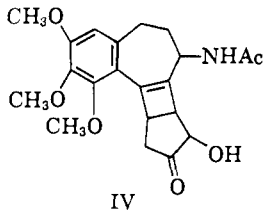


I II

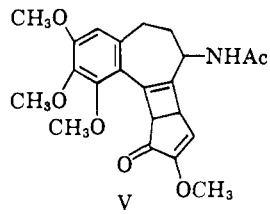


III

lumicolchicine.[4,5] Recently, α-lumicolchicine has been shown to be a dimer of β-lumicolchicine.[6] In connection with our investigation of the structure of α-lumicolchicine[6] it is of primary importance that the structure of β-lumicolchicine be established beyond question. Evidence previously presented for structure II,[2,4,5] although reasonably interpretable on the basis of this structure, is by no means rigorous. Specifically, the following problems are posed: (1) No evidence is available that ring B of colchicine remains intact in the colchicine to β-lumicolchicine transformation.[4] (2) Evidence for bridging ring C of colchicine to form rings C and D of II is limited to the infrared carbonyl absorption of desmethyldihydro-β-lumicolchicine (IV)[4] and the ambiguous observation that a dialdehyde obtained from a glycol derived from desmethyldihydro-β-lumi-

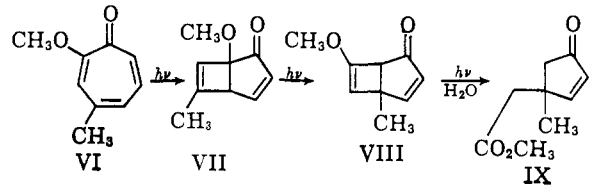


IV



V

colchicine did not cyclize[4] as does the dialdehyde obtained by reduction and cleavage of ring C of colchicine. (3) No evidence is available to exclude V from consideration. The complex photoisomerizations of simple tropolones (*e.g.*, VI–IX)[7] show that photoisomerization of colchicine need not be simple, and structure V must be



VI VII VIII IX

seriously considered. (4) The stereochemical assignment of structures II and III to β- and γ-lumicolchicine is equivocal.[8]

The nuclear magnetic resonance spectra of β-lumicolchicine (Fig. 1) and γ-lumicolchicine (Fig. 2) integrate for 25 protons and show in each case four methylene protons and one methine (on the carbon bearing nitrogen) in essentially the same positions as the four methylene protons and the methine proton of ring B in colchicine. Ring B is therefore intact in the photoproducts. The nuclear magnetic resonance spectra of β-lumicolchicine and γ-lumicolchicine could accommodate structure II, III or V for either of these compounds. The high-field bridgehead proton which is not visible in the nuclear magnetic resonance spectrum of β-lumicolchicine can be observed by use of pyridine as solvent (Fig. 3). The diamagnetic anisotropy of this solvent produces remarkable shifts of certain protons.[9] The methyl group of the enol ether is shifted to higher field as is one of the aromatic methoxyl groups. The bridgehead protons are essentially unchanged, and the shift of the enol ether methyl groups clearly reveals the second bridgehead proton at 6.37 τ. The methylene resonance at 7.29 τ in β-lumicolchicine is shifted to lower field as is the proton on nitrogen. The latter shift is probably a result of hydrogen bonding to pyridine. The aromatic proton is shifted to lower field and now overlaps the olefinic proton resonance. *These highly specific shifts to both higher and lower field positions indicate that the shielding effect of pyridine, as suggested by Slomp,[9] arises from coördination of pyridine molecules at specific sites on the β-lumicolchicine molecule, not from an average effect of the solvent as a whole.* Observation of the olefinic proton and the two bridgehead protons provides strong support for bridging of the tropolone ring in the formation of β-lumicolchicine. Rigorous evidence that the olefinic proton is coupled to a bridgehead proton comes from a double resonance experiment in which saturation of the lower field bridgehead proton collapses the olefinic proton doublet to a singlet (Fig. 4). The rigorous establishment of the nature of rings C and D is now complete. The nuclear magnetic resonance spectrum as well as the chemical evidence, however, still does not permit a choice between structures II, III and V.

(1) Part IV of the Photochemical Transformations series; see O. L. Chapman, D. J. Pasto, G. W. Borden and A. A. Griswold, *J. Am. Chem. Soc.*, **84**, 1220 (1962), for part III.

(2) R. Grewe and W. Wulf, *Ber.*, **84**, 621 (1951).

(3) F. Šantavý, *Biol. Listy*, **31**, 246 (1950).

(4) E. J. Forbes, *J. Chem. Soc.*, 3864 (1955).

(5) P. D. Gardner, R. L. Brandon and G. R. Haynes, *J. Am. Chem. Soc.*, **79**, 6334 (1957).

(6) O. L. Chapman and H. G. Smith, *ibid.*, **83**, 3914 (1961); O. L. Chapman, H. G. Smith and R. W. King, *ibid.*, **85**, 806 (1963).

(7) W. G. Dauben, K. Koch, O. L. Chapman and S. L. Smith, *ibid.*, **83**, 1768 (1961).

(8) The base-catalyzed epimerization of β-lumicolchicine to γ-lumicolchicine[5] we cannot reproduce. Professor Gardner has informed us that he has been unable to reproduce this experiment. The remaining evidence for the stereochemical assignments is based on the effect of concentration on extinction coefficient in the ultraviolet spectra of the tetrahydro derivatives of β-lumicolchicine and γ-lumicolchicine. The stereochemistry of the tetrahydro derivatives is not established and has been assigned on the basis of arguments concerning the mode of reduction.[5] The demonstration (in this paper) that the dihydro derivatives of β-lumicolchicine and γ-lumicolchicine both show strong intramolecular hydrogen bonds renders the distinction between the tetrahydro derivatives somewhat tenuous.

(9) G. Slomp and F. MacKellar, *J. Am. Chem. Soc.*, **82**, 999 (1960).

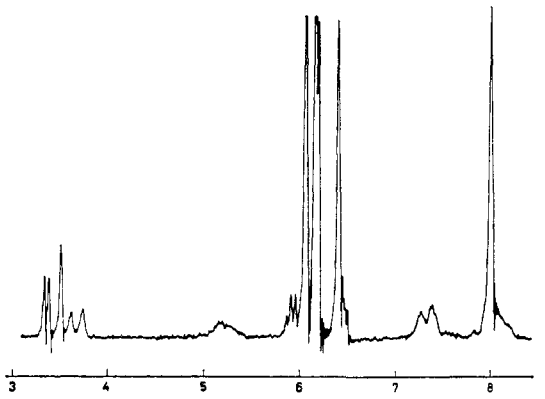


Fig. 1.—Nuclear magnetic resonance spectrum of β-lumicolchicine. The scale is calibrated in τ-units.

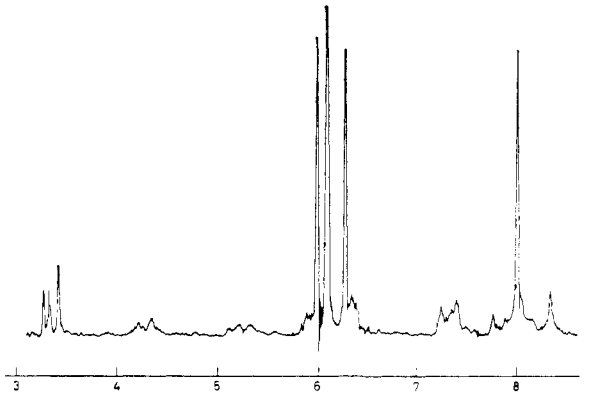


Fig. 2.—Nuclear magnetic resonance spectrum of γ-lumicolchicine.

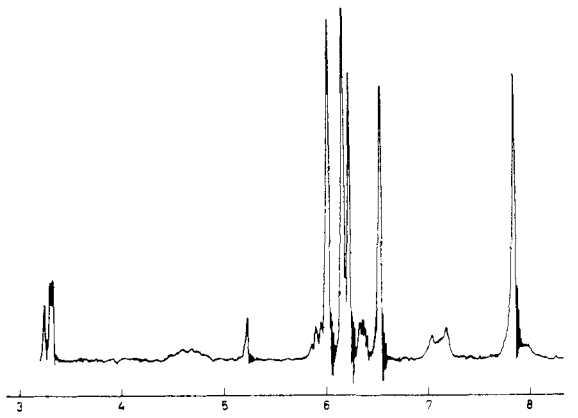
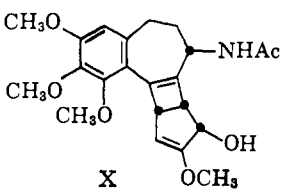


Fig. 3.—Nuclear magnetic resonance spectrum of β-lumicolchicine in pyridine.

Reduction of β-lumicolchicine with sodium borohydride[4] in tetrahydrofuran gives a homogeneous alcohol



X

which will be shown (see below) to be X. Reduction of the ketone should give an alcohol in which hydride has been delivered to the most accessible side of the molecule.[10] In the reduction of β-lumicolchicine this would lead to the partial stereochemistry XI regardless of the gross structure of the remainder of the molecule. Reduction of γ-lumicolchicine with sodium borohydride in tetrahydrofuran gives a mixture of alcohols which we could not separate. Reduction of γ-lumicolchicine

(10) O. L. Chapman, D. J. Pasto, G. W. Borden and A. A. Griswold, *J. Am. Chem. Soc.*, **84**, 1220 (1962).

TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA[a]

Compound	Solvent	H, C=C	—NH	H, N, C	H, O, C	—OH	Bridge-head protons	Arom. —OMe	OMe, C=C	Amide —Me	—CH2—	Arom. H
β-Lumicolchicine (II)	$CDCl_3$	3.32	3.64	5.16	..	...	5.90, 6.37	6.01, 6.19	6.37	7.95	7.29, 7.95	3.49
β-Lumicolchicine (II)	Pyridine	3.26	[c]	4.64	..	...	5.93, 6.37	6.01, 6.16, 6.23	6.53	7.85	6.96, 7.85	3.32
β-Lumicolchicine alcohol (X)	$CDCl_3$	4.97	1.40 (1.87)[b]	5.67	5.26	5.53 (7.30)[b]	6.27, 6.51	6.27	6.44	8.05	7.39, 8.05	3.55
β-Lumicolchicine alcohol (X)	CCl_4	5.12	1.30	5.80	5.38	5.00	6.22, 6.48	6.19, 6.26	6.48	8.13	7.50, 8.13	3.68
Desmethyl-β-lumicolchicine alcohol (IV)	$CDCl_3$	..	2.21	5.55	5.55	5.80	6.01, 6.31	6.15	..	8.02	7.51	3.52
γ-Lumicolchicine (III)	$CDCl_3$	3.30	4.30	5.24	..	...	5.97, 6.30	6.03, 6.10	6.24	7.98	7.25, 7.98	3.44
γ-Lumicolchicine alcohol	$CDCl_3$	5.02	3.32 (4.58)[b]	5.25	5.25	4.60(5.05)[b]	6.17, 6.79	6.17	6.47	7.97	7.29, 7.97	3.59

[a] Resonance positions are given as τ-values relative to internal tetramethylsilane. [b] Values obtained by extrapolation to infinite dilution. [c] The N–H resonance is lost in the pyridine absorption.

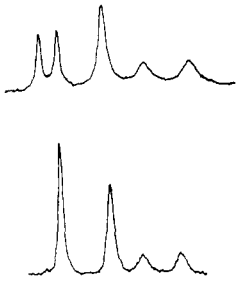
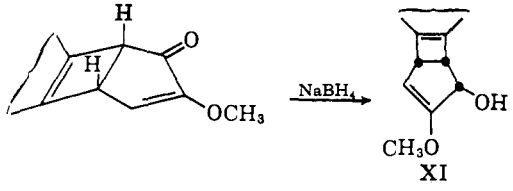


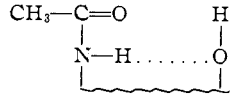
Fig. 4.—Double resonance experiment. Upper spectrum shows (from left to right) the olefinic proton doublet (J = 3.2 c.p.s.), the aromatic proton singlet and the N–H doublet. Lower spectrum shows the same region with the adjacent bridgehead proton (151 c.p.s. upfield) saturated. Note collapse of the olefinic doublet to a singlet.

with sodium borohydride in methanol,[4] however, gives a homogeneous, crystalline alcohol analogous to that obtained from β-lumicolchicine. Comparison of the nuclear magnetic resonance spectra of the alcohols derived from β-lumicolchicine and γ-lumicolchicine (Fig.



XI

5 and 6) show general similarity except that the alcohol from β-lumicolchicine shows an anomalously low-field (relative to β-lumicolchicine, γ-lumicolchicine and dihydro-γ-lumicolchicine) N–H absorption. This low-field N–H strongly suggests that a new *intramolecular* hydrogen bond is possible in the alcohol which is not possible in β-lumicolchicine. It is necessary to establish the intramolecular nature of the hydrogen bond. This can most easily be done by extrapolation of the N–H resonance position (as a function of concentration) to infinite dilution. Such extrapolation gives 488 c.p.s. (relative to internal tetramethylsilane at 60 Mc.) for the resonance of the N–H of the alcohol from β-lumicolchicine at infinite dilution in both deuteriochloroform and carbon tetrachloride. Similar extrapolation for the N–H resonance of the alcohol derived from γ-lumicolchicine gives 325 c.p.s. The N–H resonance of β-lumicolchicine alcohol (X) shows a much smaller shift on dilution (23 c.p.s.) than the N–H of γ-lumicolchicine alcohol (76 c.p.s.). The difference of 163 c.p.s. in the position of the N–H resonance lines of the two alcohols at infinite dilution and the small shift of the N–H resonance of β-lumicolchicine alcohol leave no doubt that a strong hydrogen bond exists between the acetamido group and the newly introduced hydroxyl function in the alcohol derived from β-lumicolchicine. *Such a hydrogen bond is possible only if the acetamido group and the hydroxyl function are on the same side of the molecule in close proximity.* These requirements are met only in structure X. This evidence rigorously eliminates structure V for β-lumicolchicine and at the same time rigorously establishes the stereochemistry of β-lumicolchicine as II. The nature of the actual hydrogen bond is established as



by the following facts: (1) Shaking the sample with D_2O exchanges the hydroxyl hydrogen for deuterium without significantly affecting the position of the N–H

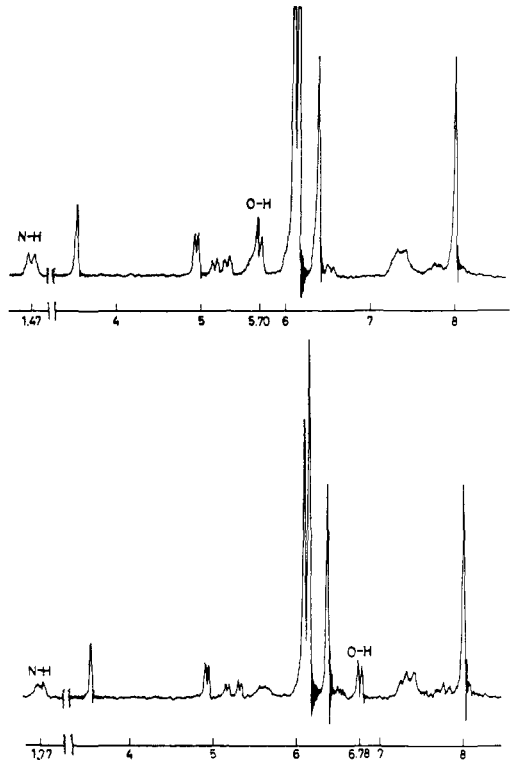


Fig. 5.—Upper spectrum shows the nuclear magnetic resonance spectrum of the alcohol derived from β-lumicolchicine at normal concentration. Lower spectrum shows the same sample after fourfold dilution. Note the large shift in the resonance position of the hydroxyl proton and the much smaller shift of the N–H resonance.

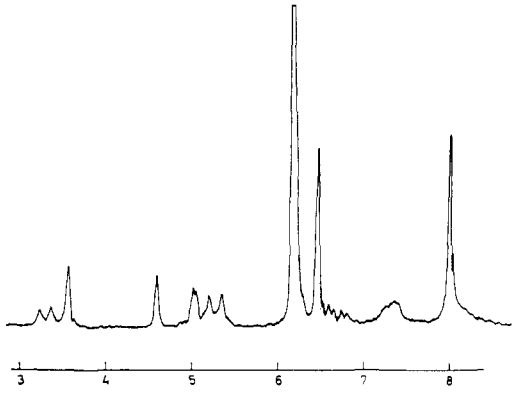
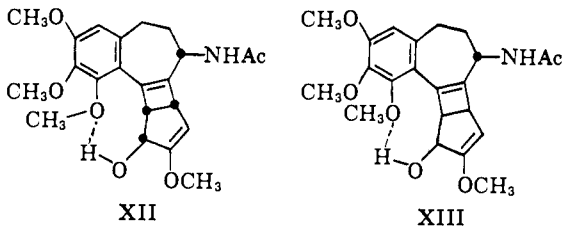


Fig. 6.—Nuclear magnetic resonance spectrum of the alcohol derived from γ-lumicolchicine.

resonance. (2) Extrapolation of the O–H resonance position to infinite dilution shows a change in resonance location (268 to 162 c.p.s.) indicative of intermolecular hydrogen bonding of this proton.

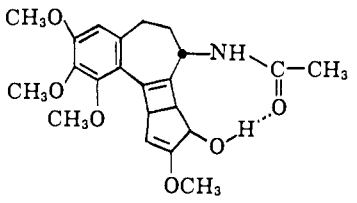
The alcohol from γ-lumicolchicine shows an intramolecularly hydrogen bonded hydroxyl function (in contrast to the alcohol obtained from β-lumicolchicine). This hydroxyl resonance is still at low field (297 c.p.s.) after extrapolation to infinite dilution. Only three possible hydrogen bonded structures (XII, XIII and XIV) are possible. No definitive choice among these structures is possible, although on the basis of the rigorously established structure of β-lumicolchicine, structure XIV may seem more plausible. The observation of a photochemical conversion of β- to γ-lumicolchicine[11] cannot be considered direct evidence in support

(11) G. O. Schenck, H. J. Kuhn and O.-A. Neumüller, *Tetrahedron Letters*, **1**, 12 (1961).



XII

XIII



XIV

of structure XIV in view of the photochemical transformations of simple tropolones.[7] The virtual identity of the infrared, ultraviolet and nuclear magnetic resonance spectra of β-lumicolchicine and γ-lumicolchicine coupled with the firm assignment of structure II to β-lumicolchicine supports structure III for γ-lumicolchicine and XIV for the alcohol derived from it. This assignment, however, cannot be considered rigorous and the two stereoisomers of V must be considered possibilities.

Experimental

Nuclear Magnetic Resonance Spectra.—The nuclear magnetic spectra were run in deuteriochloroform using a Varian Associates, HR-60 spectrometer (60 Mc.). Spectra were calibrated by the side band technique. Extrapolation to infinite dilution was based on four dilutions covering a factor of 8 in concentration. The extrapolation was carried out graphically. Deuteration of each sample (by shaking *ca.* 30 seconds with D_2O)[12] identified the hydroxyl protons by their disappearance. The proton on nitrogen did not exchange with deuterium under these conditions.

β-Lumicolchicine Double Resonance Experiment.—A field-modulation apparatus similar to those of Kaiser[13] and of Freeman[14] was used. The lower-field bridgehead proton was irradiated with a radiofrequency field H_2 of 1.1 milligauss. Optimum decoupling of the olefinic proton was achieved with a modulation-frequency of 151 c.p.s.

Dihydro-β-lumicolchicine.[4]—A solution of β-lumicolchicine (600 mg.) in pure tetrahydrofuran (15 ml.) was treated with sodium borohydride (200 mg.). The mixture was refluxed for 60 min. and then stirred overnight at room temperature. After dilution with water and removal of the tetrahydrofuran under reduced pressure, extraction with benzene gave dihydro-β-lumicolchicine as a colorless resin which crystallized from aqueous ethanol; m.p. 194–196° (lit.[4] 195°); infrared absorption 6.04, 6.07 and 6.28 μ.

Hydrolysis of dihydro-β-lumicolchicine by the method of Forbes[4] gave desmethyldihydro-β-lumicolchicine, m.p. 210–212° (lit.[4] 208°); infrared absorption 5.73, 6.07 and 6.27 μ.

Dihydro-γ-lumicolchicine.[4]—A solution of γ-lumicolchicine (450 mg.) and sodium borohydride (200 mg.) in tetrahydrofuran (30 ml.) was refluxed for 60 min. After cooling, water (3 ml.) was added, and the mixture was stirred for 4 hr. at room temperature. The mixture was diluted with water, and the tetrahydrofuran was removed under reduced pressure at 80°. The product was isolated by extraction with benzene. Evaporation of the benzene after drying over potassium carbonate gave the product as a colorless resin which could not be crystallized. The nuclear magnetic resonance spectrum of the resinous product showed two N-H absorptions at 3.37 and 3.73 τ of unequal area strongly suggestive of the presence of isomeric products.

Reduction of γ-lumicolchicine as above except using aqueous methanol as solvent gave dihydro-γ-lumicolchicine as colorless needles, m.p. 200–202° (lit.[4] 204°); infrared absorption 6.03-(sh), 6.08 and 6.29 μ.

Acknowledgment.—This investigation was supported by a grant (CA-04253) from the National Institutes of Health, Department of Health, Education and Welfare.

(12) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, p. 71.
(13) R. Kaiser, *Rev. Sci. Instr.*, **31**, 963 (1960).
(14) R. Freeman, *Mol. Phys.*, **3**, 435 (1960).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE UNIVERSITY OF SCIENCE AND TECHNOLOGY, AMES, IOWA]

The Structure of α-Lumicolchicine: Some Examples of Diamagnetic Shielding by the Carbon–Oxygen Double Bond[1]

BY O. L. CHAPMAN, H. G. SMITH AND R. W. KING

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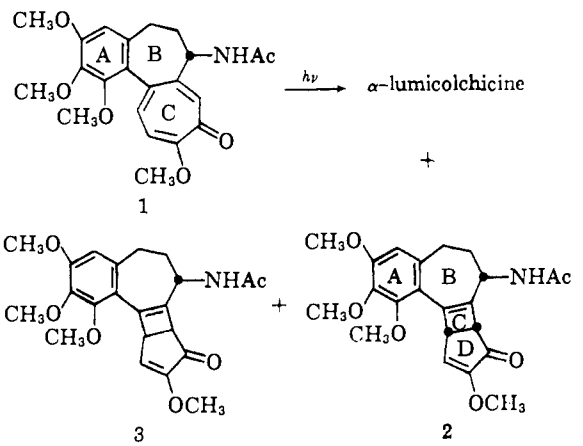
α-Lumicolchicine has been shown to be a head-to-head dimer of β-lumicolchicine. The nuclear magnetic resonance spectra of α-lumicolchicine and its derivatives provide rare examples of diamagnetic shielding by the carbon–oxygen double bond. An intramolecular hydrogen bond between the acetamido nitrogen and the hydroxyl group of the diol (detected by a shift of the N-H resonance to lower field) gives the stereochemistry of the reduced derivatives of α-lumicolchicine.

Irradiation of colchicine (1) gives three crystalline photoproducts, α-lumicolchicine, β-lumicolchicine and γ-lumicolchicine.[2–4] The structure 2 suggested for β-lumicolchicine[4,5] has been firmly established.[6] γ-Lumicolchicine is probably 3,[3–6] but structure 4 cannot be eliminated on the basis of the available evidence. Structure 5 has been suggested for α-lumicolchicine,[7] but evidence to be presented below eliminates this structure from consideration.

The principal difficulty in the investigation of α-lumicolchicine was preparation of this substance. We encountered the same difficulty on solar irradiation of colchicine as Gardner and co-workers.[8] β-Lumicolchi-



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(1) A preliminary account of this investigation has been published: O. L. Chapman and H. G. Smith, *J. Am. Chem. Soc.*, **83**, 3914 (1961). This is part V of the Photochemical Transformations series; see ref. 6, 9 and 16 for earlier papers in this series.
(2) R. Grewe and W. Wulf, *Ber.*, **84**, 621 (1951).
(3) F. Šantavý, *Biol. Listy*, **31**, 246 (1950).
(4) E. J. Forbes, *J. Chem. Soc.*, 3864 (1955).
(5) P. D. Gardner, R. L. Brandon and G. R. Haynes, *J. Am. Chem. Soc.*, **79**, 6331 (1957).
(6) O. L. Chapman, H. G. Smith and R. W. King, *ibid.*, **85**, 803 (1963).
(7) G. O. Schenck, H. J. Kuhn and O.-A. Neumüller, *Tetrahedron Letters*, No. 1, 12 (1961).
(8) Other workers have reported this method of preparation using a different filter.[7]