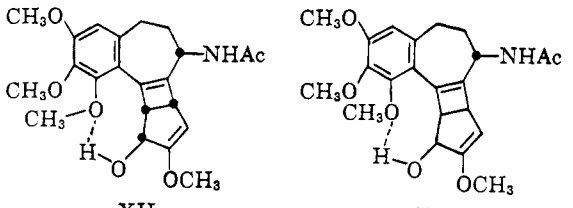
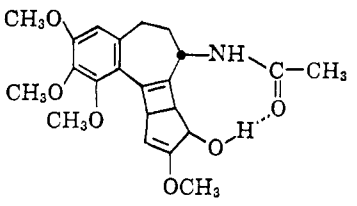


XII

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]

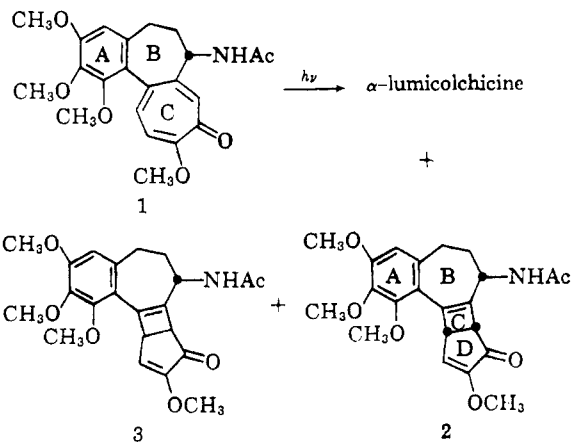
BY O. L. CHAPMAN, H. G. SMITH AND R. W. KING

RECEIVED AUGUST 20, 1962

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



1

3 2

encountered the same difficulty on solar irradiation of colchicine as Gardner and co-workers.[8] β-Lumicolchi-

(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**, 6334 (1957).

(6) O. L. Chapman, H. G. Smith and R. W. King, *ibid.*, **85**, 803 (1963).

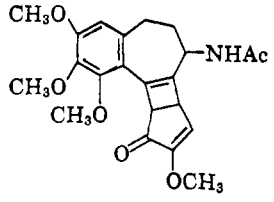
(7) G. O. Schenck, H. J. Kuhn and O.-A. Neumüller, *Tetrahedron Letters*, No. 1, 12 (1961).

(8) Other workers have reported this method of preparation using a different filter.[7]

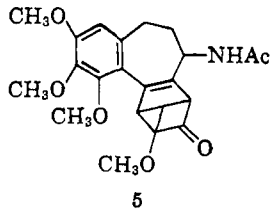
TABLE I

ULTRAVIOLET SPECTRA

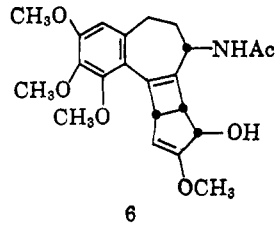
Compound	Solvent	Spectrum, mμ (log ε)
α-Lumicolchicine (10)	95% EtOH	215 (4.69), 230 (sh., 4.65), 282 (4.64)
β-Lumicolchicine alcohol (6)	95% EtOH	226 (4.37), 278 (4.24)
α-Lumicolchicine diol (12a)	MeOH	227 (4.59), 278 (4.57)
α-Lumicolchicine diol diacetate (12b)	MeOH	228 (4.66), 280 (4.63)
α-Lumicolchicine diol monoacetate (12c)	MeOH	228 (4.58), 279 (4.59)
Ketoalcohol 13a	MeOH	217 (sh., 4.59), 228 (sh., 4.59) 279 (4.57)
Ketoacetate 13b	MeOH	217 (4.61), 228 (sh., 4.59), 281 (4.57)
α,β-Dihydro-β-lumicolchicine (8)		215 (4.30), 229 (sh., 4.26), 283 (4.30)



4



5



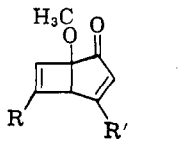
6

cine and γ-lumicolchicine were obtained in good yield, but no α-lumicolchicine could be isolated. Irradiation of colchicine in a Pyrex vessel using an unfiltered mercury arc gave similar results. Use of a cyanine dye filter solution with a mercury arc finally permitted selective formation of α-lumicolchicine in approximately 20–30% yield.[8] Our α-lumicolchicine was identical in infrared, ultraviolet and nuclear magnetic resonance absorption to a sample kindly provided by Professor R. Grewe.[2] Irradiation of β-lumicolchicine also gives α-lumicolchicine. α-Lumicolchicine tends to crystallize as a solvate from benzene, but can be obtained solvent free from absolute ethanol.

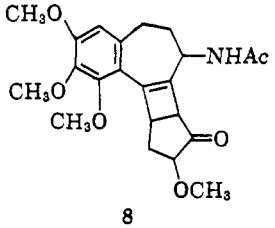
Earlier investigations have demonstrated that α-lumicolchicine is inert to catalytic hydrogenation under conditions in which β-lumicolchicine and γ-lumicolchicine each absorb two equivalents of hydrogen.[2] Combustion analysis of α-lumicolchicine shows it to be an isomer of colchicine.[2] α-Lumicolchicine is inert to normal carbonyl reagents,[2] whereas β-lumicolchicine and γ-lumicolchicine form carbonyl derivatives.[4] It is interesting, and perhaps significant, that three separate groups have described α-lumicolchicine without mentioning the infrared spectrum.[2,4,7] Heating α-lumicolchicine to its melting point or above 100° in solution gives essentially quantitative yields of β-lumicolchicine.[1,7] In fact α-lumicolchicine does not depress the melting point of β-lumicolchicine.[2] It has been reported that the optical rotation of the material obtained by heating α-lumicolchicine does not correspond to either the rotation of α-lumicolchicine or β-lumicolchicine.[2] This is not the case in our hands. The β-lumicolchicine obtained by heating α-lumicolchicine is identical in optical rotation, nuclear magnetic resonance spectrum, infrared spectrum and ultraviolet spectrum with authentic β-lumicolchicine.

The infrared spectrum of α-lumicolchicine shows a strong carbonyl band at 5.78 μ and an amide carbonyl bond at 6.0 μ. The 6.2 μ band due to the enol ether double bond of β-lumicolchicine has disappeared. The ultraviolet spectrum of α-lumicolchicine is very similar to that of the alcohol 6 obtained by sodium borohydride reduction of β-lumicolchicine[4b] (see Table I), tetrahydro-β-lumicolchicine[5] and tetrahydro-γ-lumicolchicine,[5] but differs substantially from the ultraviolet spectra of β-lumicolchicine and γ-lumicolchicine.[2] This observation suggests that the only chromophore in α-lumicolchicine capable of producing high intensity maxima is a trimethoxystyryl chromophore like that present in 6. The nuclear magnetic resonance spectrum of α-lumicolchicine (Fig. 1) is remarkably similar to that of β-lumicolchicine (Fig. 2) with three important differences: (1) the single olefinic proton (3.32 τ) of β-lumicolchicine is missing in α-lumicolchicine, (2) α-lumicolchicine shows one more aliphatic proton than β-lumicolchicine (integration of the α-lumicolchicine spectrum shows 25 protons relative to the single aromatic proton in agreement with the analytical data) and (3) the methoxyl group on the enol ether double bond of β-lumicolchicine (6.37 τ) has shifted to an unusually high field position (6.98 τ) in the α-lumicolchicine spectrum. The presence of a 5.78 μ band and the absence of the enol ether double bond at 6.2 μ in the infrared, the presence of only the trimethoxystyryl chromophore in the ultraviolet and the absence of olefinic proton resonance in the nuclear magnetic resonance spectrum of α-lumicolchicine leave absolutely no doubt that the 5-membered ring D of β-lumicolchicine is a saturated cyclopentanone in α-lumicolchicine. Saturation of ring D in the formation of α-lumicolchicine cannot be the result of addition of water or another small molecule to the double bond because this is inconsistent with the analysis and the proton count on the nuclear magnetic resonance spectrum. An attractive solution to the dilemma is the formation of a photodimer of β-lumicolchicine.

Four photodimers of β-lumicolchicine are theoretically possible. Consideration of the abnormally high field methoxyl resonance of α-lumicolchicine also leads to the conclusion that α-lumicolchicine is a photodimer and moreover permits a unique selection among the four structural possibilities (Fig. 3). The shift of the methoxyl resonance from low to high field suggests that it is now on a saturated carbon, a conclusion consistent with the formation of a photodimer. Examination of the location of methoxyl groups in suitable model compounds 7a,b,c (6.4–6.6 τ)[9] shows, however, that the methoxyl resonance (6.98 τ of α-lumicolchicine) is quite



7a, R = R' = H
b, R = CH3; R' = H
c, R = R' = CH3



8

significantly higher than anticipated. A closer model for the α-lumicolchicine saturated methoxyl group is 8,

(9) W. G. Dauben, K. Koch, O. L. Chapman and S. L. Smith, *J. Am. Chem. Soc.*, **83**, 1768 (1961).

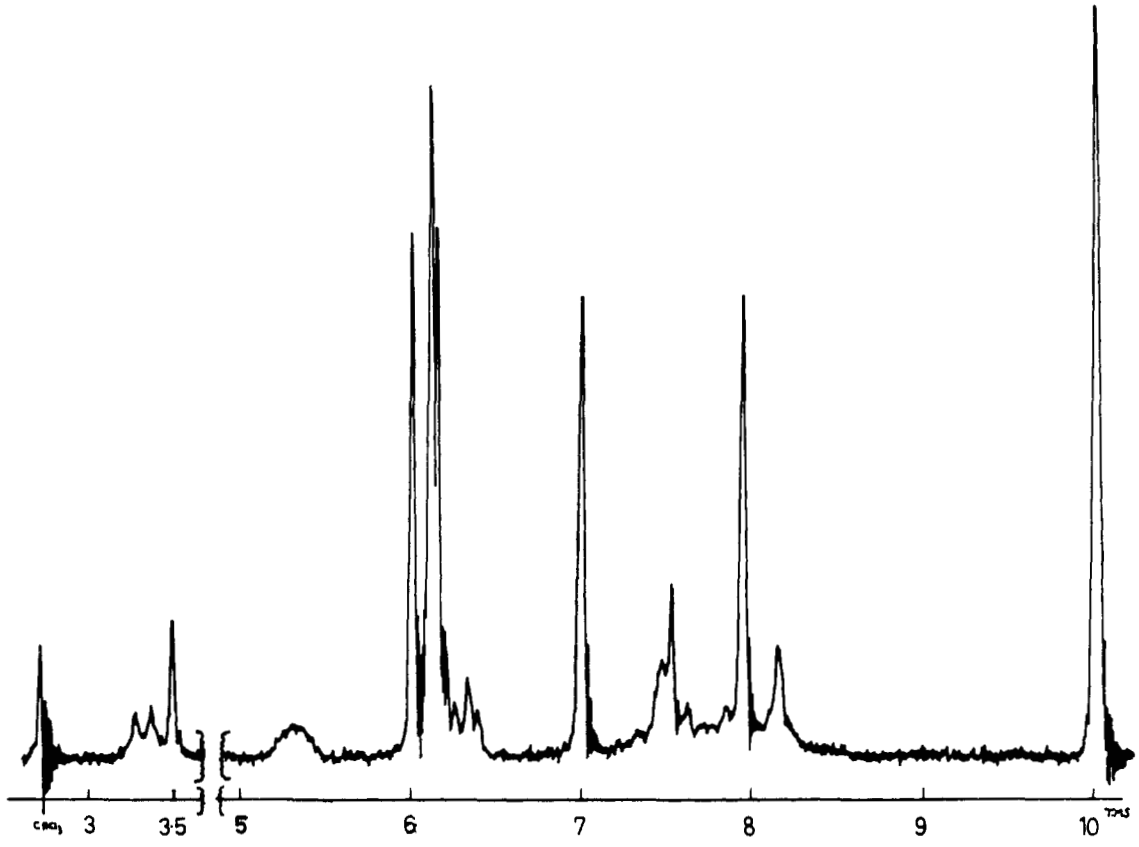


Fig. 1.—Nuclear magnetic resonance spectrum of α-lumicolchicine; scale is calibrated in τ-units.[21]

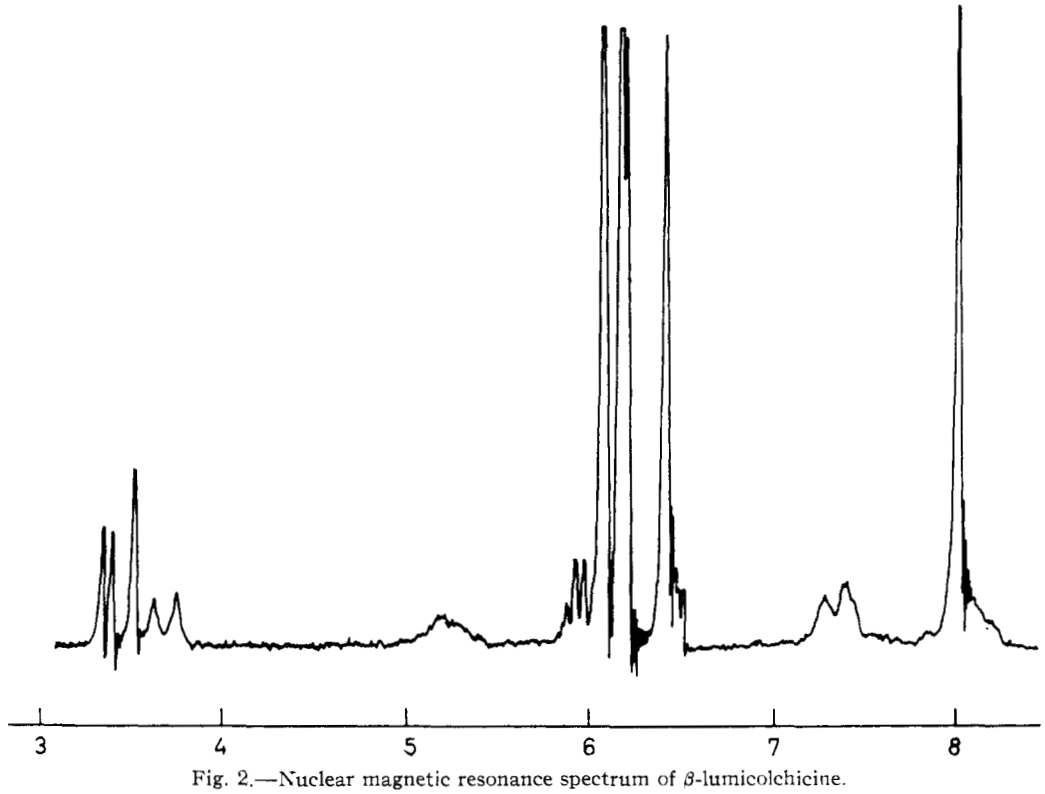


Fig. 2.—Nuclear magnetic resonance spectrum of β-lumicolchicine.

prepared by careful catalytic reduction of β-lumicolchicine. This model shows a saturated methoxyl resonance at 6.60 τ in agreement with the other model compounds. The saturated methoxyl resonance of α-lumicolchicine (6.98 τ) is even higher than the methoxyl resonance of dimethyl ether (6.76 τ). This must mean that the abnormally high field position of the saturated methoxyl group is the result of diamagnetic shielding by some unsaturated group in the α-lumicolchicine molecule.[10] The observation of a normal resonance position for the saturated methoxyl group of 8 shows

(10) For a discussion of diamagnetic and paramagnetic shielding by unsaturated groups see J. A. Pople, W. G. Schneider and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 175 ff., and L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, pp. 14–20, 121–129.

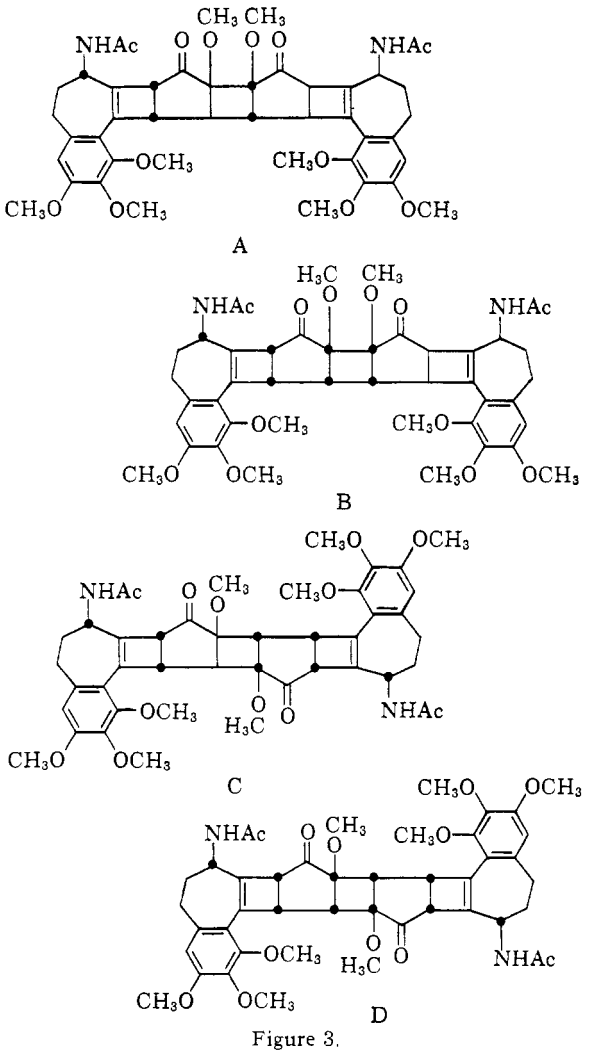
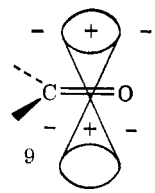


Figure 3.

that the unsaturated group responsible for the diamagnetic shielding cannot be present in the same half of the photodimer as the methoxyl group but must, in fact, be in the other half of the dimer. Further reflection shows that in any of the four dimer structures only the ketone group in the other half of the dimer will ever be in sufficiently close proximity to the methoxyl group to be effective in shielding this group. The theory of diamagnetic shielding by carbon–oxygen double bond has been discussed.[11] Nuclei in a roughly conical area above and below the plane of the carbon–oxygen double bond (*cf.* 9) will experience diamagnetic shielding, while nuclei outside this area will experience paramagnetic



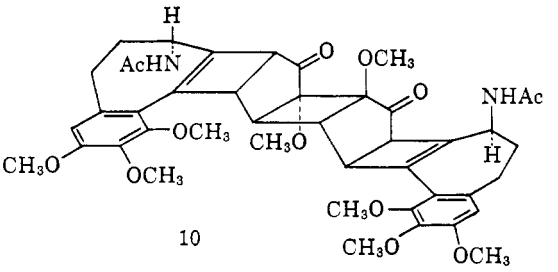
9

shielding.[11] Examples of paramagnetic shielding (*cf.* the low field position of aldehydic protons) by carbon–oxygen double bond are abundantly available. Examples of diamagnetic shielding by the carbon–oxygen double bond are limited to those described in this paper and B/C *cis*-rotenoids.[12] Diamagnetic shielding of the methoxyl group by the ketone group will be possible only in the head-to-head dimer structure with *trans* fusion of the β-lumicolchicine molecules, structure 10.

(11) L. M. Jackman, ref. 10, pp. 121–125.

(12) L. Crombie and J. W. Lown, *Proc. Chem. Soc.*, 299 (1961).

The saturated methoxyl groups in structure 10 are each so situated that in rotation they pass directly over the carbonyl group in the other half of the molecule and thus pass through the region of maximum shielding. The origin of the diamagnetic shielding in the ketonic carbonyl groups is confirmed by the disappearance of this shielding on reduction of the ketonic carbonyls. Chemical transformations of α-lumicolchicine and physical properties of derivatives described below unequivocally establish structure 10.



10

Molecular weight measurements on α-lumicolchicine pose problems. Cryoscopic determinations are difficult because of the tendency of α-lumicolchicine to crystallize at lower temperatures. Rast determinations in camphor give monomeric molecular weights because α-lumicolchicine decomposes to β-lumicolchicine above 100°. Molecular weight measurements on the reduced derivatives (which without exception show greater thermal stability than α-lumicolchicine) give values within a few per cent of those calculated for dimeric structures. The facile thermal conversion of α-lumicolchicine to β-lumicolchicine strongly supports the head-to-head dimer structure. Both carbonyl groups[13] as well as the two ether groups appear to be necessary for stabilization of the transition state 11, since reduction of one or both ketone groups greatly enhances the thermal stability. Reduction of α-lumicolchicine with excess sodium borohydride in aqueous tetrahydrofuran gives a diol (12a, mol. wt. 850 (Rast), 788 (Signier)) which is thermally stable under conditions in which α-lumicolchicine is quantitatively converted to β-lumicolchicine. The diol 12a gives α-lumicolchicine on oxidation. The diol shows the expected changes in the nuclear magnetic resonance spectrum: (1) a low field resonance due to the proton on the carbon bearing the hydroxyl function and (2) the shift of the saturated methoxyl resonance to a normal position (6.74 τ; *cf.* dimethyl ether 6.76 τ). The return of the saturated methoxyl resonance to a normal position firmly identifies the ketonic carbonyl function as the source of the diamagnetic shielding observed in α-lumicolchicine. Acetylation of the diol with acetic anhydride and sodium acetate gives the diacetate 12b (mol. wt. 786,

(13) It is not immediately obvious that a carbonyl group stabilizes an odd electron on an α-carbon. Recent observations (D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, **84**, 199 (1962)) suggest that sufficient stabilization is available to permit addition of a C-19 radical to the double bond in i which does not occur in ii.

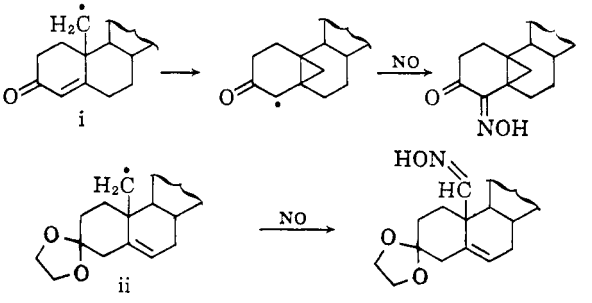
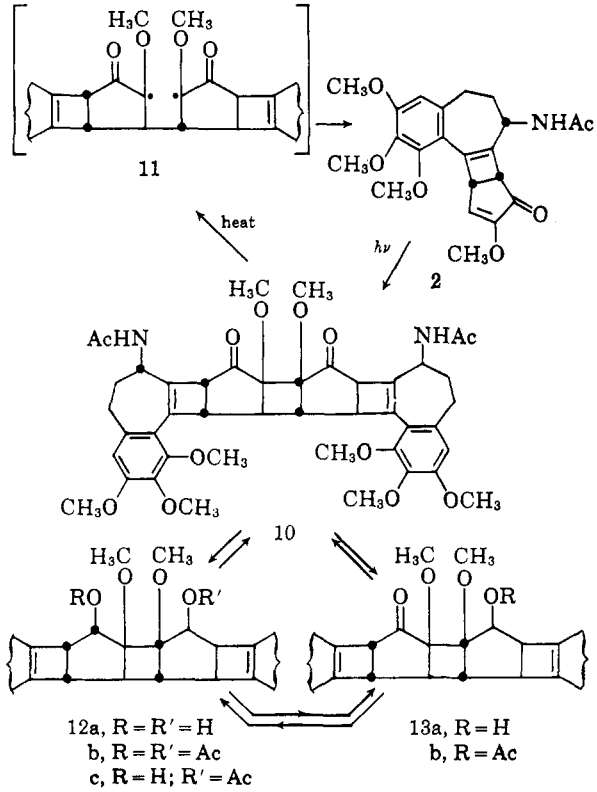


TABLE II

NUCLEAR MAGNETIC RESONANCE SPECTRA[a]

Compound	H C=C	NH	C H N	C H OH	C H OAc	OH	Arom. OMe	Satd. OMe	Amide Me	Acetate Me	Arom. H	OMe C=C
							6.00					
α-Lumicolchicine (10)		3.28					6.10	6.98	7.94		3.46	
		(3.33)[b]	5.32				6.14					
β-Lumicolchicine (2)	3.32	3.64	5.16				6.01		7.95		3.49	6.37
							6.19					
α,β-Dihydro-β-lumicol-							6.10					
chicine (8)		3.64	5.65				6.14	6.60	8.02		3.46	
α-Lumicolchicine diol		1.87				6.01	6.10					
(12a)		(2.05)[b]	5.68	5.44		(6.93)[b]	6.15	6.74	8.03		3.52	
α-Lumicolchicine diol		1.67				5.88		6.45				
monoacetate (12c)		(1.67)[b]	5.60	5.60	4.49	(6.25)[b]	6.12	6.87	7.92	8.02	3.48	
		3.35										
		(3.38)[b]										
α-Lumicolchicine diol							6.10					
diacetate (12b)		3.40	5.63		4.41		6.14	6.54	7.90	7.95	3.50	
Ketoalcohol 13a		1.97										
		(2.15)[b]	5.65	5.29		6.49	6.03	6.81	7.98			
		3.76				(6.87)[b]	6.06	6.95	8.04		3.50	
		(3.87)[b]					6.13					
Ketoacetate 13b		3.17	5.64		4.43		6.02	6.77	7.93	7.97	3.46	
		3.88					6.07	6.91				
							6.13					

[a] Spectra were run in deuteriochloroform using a Varian Associates HR-60 spectrometer operating at 60 Mc.; resonance positions are τ-values[21] relative to internal tetramethylsilane. [b] Extrapolated to infinite dilution.



5.73 μ).[14] Acetylation of the diol with acetic anhydride and pyridine for a limited time gives primarily the monoacetate (12c mol. wt. 810); 5.74 μ; C–CH_3, calcd. 5.34, found 5.13). The nuclear magnetic resonance spectrum of the monoacetate shows all of the expected features (see Table II). Reduction of α-lumicolchicine with one equivalent of sodium borohydride in aqueous tetrahydrofuran gives the ketoalcohol 13a (5.82 μ).[15]

Oxidation of the ketoalcohol 13a gives α-lumicolchicine. The ketoalcohol 13a has also been prepared by partial oxidation of α-lumicolchicine diol (12a). The nuclear magnetic resonance spectrum of the ketoalcohol, in accord with expectation, shows one high field methoxyl resonance (6.95 τ) and one normal methoxyl resonance (6.81 τ). Acetylation of the ketoalcohol 13a with acetic anhydride and sodium acetate gives the ketoacetate 13b (mol. wt. 748; 5.74, 5.84 μ).[15] Reduction of the ketoacetate with sodium borohydride gives the monoacetate 12c. Oxidation of the monoacetate 12c gives the ketoacetate 13b. The nuclear magnetic resonance spectrum of the ketoacetate also shows a shielded (6.91 τ) and a normal methoxyl group (6.77 τ). The formation of a monoacetate 12c, a ketoalcohol 13a and a ketoacetate 13b establishes α-lumicolchicine as a photodimer.

All derivatives (12a, b, c and 13a, b) of α-lumicolchicine described above show the same trimethoxystyryl chromophore in the ultraviolet (see Table I) as the alcohol 6 derived from β-lumicolchicine, the dihydroderivative 8 of β-lumicolchicine, tetrahydro-β-lumicolchicine[5] and tetrahydro-γ-lumicolchicine.[5] It is interesting to note, however, that in each case in which there is a ketone function in the five-membered ring (8, 10, 13a, b) an absorption maximum in the 215–217 mμ region appears suggesting a definite interaction between the isolated ketone function and the trimethoxystyryl chromophore. Non-classical interaction of similarly placed double bonds has been observed previously in the bicyclo[3.2.0]hepta-3,6-dien-2-one system.[9,16]

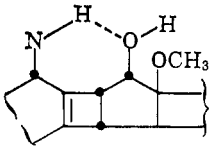
The nuclear magnetic resonance spectra of α-lumicolchicine and its derivatives show one additional feature of interest which permits assignment of the complete stereochemistry to the derivatives. The N–H resonance (at infinite dilution, see Table II) of the diol (2.05 τ) appears at much lower field than the N–H resonance of α-lumicolchicine (3.33 τ). The

(14) Acetylation of the hydroxyl group shifts one methoxyl resonance to lower field. This is probably due to paramagnetic shielding of the adjacent methoxyl group by the acetate carbonyl group.

(15) This carbonyl absorption is at slightly higher wave length than expected, but rearrangement is precluded by interconversion of the diol, the monoacetate, the ketoalcohol, the ketoacetate and α-lumicolchicine.

(16) O. L. Chapman and D. J. Pasto, *J. Am. Chem. Soc.*, **82**, 3642 (1960).

nonoacetate 12c shows one low field N–H (1.67 τ) and one high field N–H (3.38 τ). The ketoalcohol 13a also shows one low field N–H (2.15 τ) and one high field N–H (3.87 τ). The low field N–H resonance of the diol 12a, the monoacetate 12c and the ketoalcohol 13a is due to an intramolecular hydrogen bond between the N–H and the nearest hydroxyl group. The hydrogen bonds must be intramolecular, since the values reported were obtained by extrapolation to infinite dilution. It is also significant that the intramolecularly hydrogen bonded N–H resonances shift only slightly on dilution (see Table II). The hydrogen bonding of the N–H and hydroxyl groups coupled with the stereochemistry of α-lumicolchicine leads unambiguously to the stereochemistry shown in 12a, b, c and 13a, b. The exact nature of the hydrogen bond is fixed as shown in 14 by the observations: (1) The hydroxyl proton of the diol

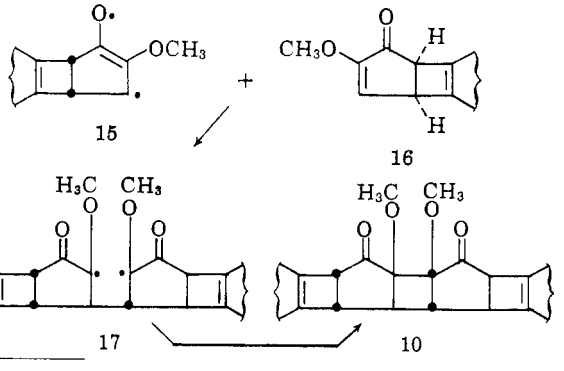


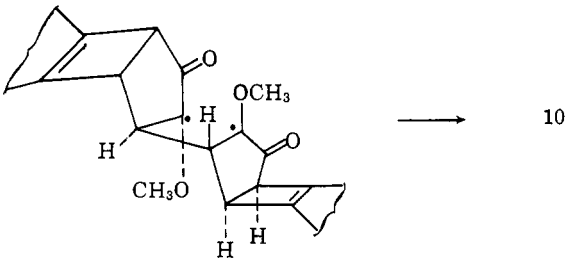
14

shifts significantly (56 c.p.s.) on dilution showing that it is intermolecularly hydrogen bonded. (2) Shaking the diol with deuterium oxide which exchanges the hydroxyl protons for deuterons does not affect the position of the low field N–H. (3) Acetylation of the hydroxyl function which significantly lowers the electron density on the oxygen atom disrupts the hydrogen bond and shifts the N–H resonance well up field (3.40 τ in the diacetate 12b) as expected.

Nuclear magnetic resonance has not been used as much as it should for the detection of intramolecular hydrogen bonds. The magnitude of the effect observed (a shift of more than 100 c.p.s. in the present work) for intramolecularly hydrogen bonded *versus* intermolecularly hydrogen bonded structures at infinite dilution is easily measurable and unmistakable. It is far easier experimentally and considerably more reliable (because of the magnitude of the shift measured) than the customary infrared measurements in which shifts are of the order of a few reciprocal centimeters.

The stereospecific formation of a single dimer in the photodimerization of β-lumicolchicine is a striking observation in view of the fact that photodimerization of cyclopentenone gives roughly equal amounts of *trans* fused head-to-head and head-to-tail dimers.[17] It is also significant that γ-lumicolchicine does not dimerize under conditions in which β-lumicolchicine is readily converted to α-lumicolchicine. The head-to-head dimer would be favored in addition of a diradical type excited state (15) to an unexcited molecule (16) by stabilization of the odd electron on the carbon bearing methoxyl and carbonyl groups (17).[18] Addition of the excited molecule to the least hindered side of the non-excited molecule (18) leads to the observed stereochemistry. Before such a picture of the stereospecific





18

photodimerization is accepted it will be necessary to show (by use of selected wave lengths for irradiation) that other photodimers which happen to be photo-labile under the present conditions are not being formed and destroyed.

Experimental

α-Lumicolchicine from Colchicine.—Carefully purified colchicine (11.5 g.) in methanol (200 ml.) was flushed with nitrogen for 30 min. This solution was then irradiated with an immersion type mercury arc lamp (Hanovia type A) in a Pyrex vessel. A solution of cyanine dye (see below) containing 40 mg. of dye per 100 ml. of water was used as coolant and filter. The cooling jacket was such that light from the lamp was required to pass through a 5-mm. thickness of the filter solution. The filter solution was circulated with a finger pump and passed through a water-cooled coil to provide efficient cooling. After 15 hr. irradiation the precipitated α-lumicolchicine (1.3 g.) was collected by filtration. Irradiation of the filtrate for 18 hr. gave an additional 1.6 g. of α-lumicolchicine. The combined crude product was purified by refluxing in absolute methanol (100 ml.) for 15 min.[19] and then recrystallization from absolute ethanol. This treatment gives α-lumicolchicine (2.47 g.), m.p. 161–163°. Further recrystallization raised the melting point to 164–165.5° $[\alpha]^{29}D$ +80° (*c* 1.5 in $CHCl_3$); $\lambda_{max}^{95\%\ EtOH}$ 282 mμ (4.64), 230 mμ (shoulder, 4.65) 215 mμ (4.69).

Anal. Calcd. for $C_{44}H_{50}N_2O_{12}$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.02; H, 6.48; N, 3.35.

Recrystallization of α-lumicolchicine from benzene gives a benzene solvate of α-lumicolchicine, m.p. 139–141°. The presence of benzene is readily detected by the intense 2.7 τ absorption in the nuclear magnetic resonance spectrum.

Filter Solution.[20]—Acetylacetone (5 ml.) and ethylenediamine (5 ml.) were heated together for 2 min. at 120° Glacial acetic acid (5 ml.) was added slowly in portions, and the solution was heated at 120–130° for an additional 10 min. After cooling, water (20 ml.) was added, then 20% hydriodic acid (30 ml.). Evaporation of the solvent under reduced pressure gave the crude cyanine iodide as a brown crystalline mass which was triturated with acetone and filtered. The crystals (8.1 g.) thus obtained were recrystallized from aqueous acetone. The filter solution was prepared by dissolving 40 mg. of the pure cyanine iodide in 100 ml. of water (2 l. of this solution was used as filter and coolant in the preparation of α-lumicolchicine).

Photodimerization of β-Lumicolchicine.—Pure β-lumicolchicine (2.0 g.) in methanol (20 ml.) was flushed with nitrogen and irradiated with a General Electric UA-3 mercury arc lamp in a Pyrex vessel (with internal cooling) at a distance of 6 in. from the lamp. After 64 hr. irradiation, the precipitate was collected, washed with cold methanol and digested for 5 min. with boiling methanol (15 ml.). The product was collected and washed with cold methanol giving pure α-lumicolchicine (0.25 g.) identical in infrared absorption and mixed melting point with authentic α-lumicolchicine.

Thermal Conversion of α-Lumicolchicine to β-Lumicolchicine.—α-Lumicolchicine (170 mg.) in a 50-ml. erlenmeyer flask was heated at 180° (oil-bath) until it melted. The melt quickly resolidified and was heated for an additional 5 min. The solid thus obtained crystallized from benzene–petroleum ether as small heavy prisms, m.p. 208–210°, $[\alpha]^{27.5}D$ +311° (*c* = 0.48 in $CHCl_3$). The nuclear magnetic resonance, infrared and ultraviolet absorption of this substance were identical with that of β-lumicolchicine. A mixture melting point with authentic β-lumicolchicine was undepressed.

α,β-Dihydro-β-lumicolchicine (8).—A solution of β-lumicolchicine (3.0 g.) in absolute ethanol (200 ml.) was hydrogenated using 10% palladium-on-charcoal (500 mg.). The reaction was stopped after one equivalent of hydrogen had been absorbed. The solution was filtered and evaporated. The residue in ben-

(17) P. E. Eaton, *J. Am. Chem. Soc.*, **84**, 2344 (1962).
(18) P. E. Eaton, *ibid.*, **84**, 2454 (1962).
(19) α-Lumicolchicine is insoluble in refluxing methanol.
(20) M. Kasha, *J. Opt. Soc. Am.*, **38**, 929 (1948).

zene was chromatographed on neutral alumina (150 g.). Elution with benzene–chloroform (1:1) and chloroform gave α,β-dihydro-β-lumicolchicine (2.3 g.) as an oil which readily crystallized as the hydrate from aqueous ethanol; m.p. 97–103° and after resolidification 142–147°.

Anal. Calcd. for $C_{22}H_{27}NO_6 \cdot H_2O$: C, 63.00; H, 6.96. Found: C, 62.59; H, 6.94.

Removal of the water of crystallization from the hydrate with benzene gave anhydrous α,β-dihydro-β-lumicolchicine, m.p. 150–152°; λ_{max}^{MeOH} 283 mμ (4.30), 229 mμ (shoulder, 4.26), 215 mμ (4.30); $\nu_{max}^{CHCl_3}$ 5.76 μ (cyclopentanone carbonyl) 6.01 μ (amide carbonyl).

Anal. Calcd. for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78. Found: C, 65.49; H, 6.75.

α-Lumicolchicine Diol (12a).—A solution of sodium borohydride (150 mg.) in water (10 ml.) was added to a stirred suspension of α-lumicolchicine (600 mg.) in pure tetrahydrofuran (30 ml.). The mixture gradually became homogeneous, and after 15 hr. the solution was neutralized to pH 7 with dilute hydrochloric acid. Removal of the solvent under reduced pressure gave the diol as a viscous oil which solidified readily on warming with water at 80–90° for 10 min. Recrystallization from aqueous ethanol gave the pure diol (500 mg.); colorless needles, m.p. 284–286°, $[\alpha]^{28}D$ −210° (*c* 2.2 in $CHCl_3$); λ_{max}^{MeOH} 278 mμ (4.57), 227 mμ (4.59); mol. wt. 850 (Rast), 788 (Signier).

Anal. Calcd. for $C_{44}H_{54}N_2O_{12}$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.76; H, 6.67; N, 3.71.

Recrystallization of the diol from benzene gives a benzene solvate, m.p. 174–176° (resolidifies at 190° and melts at 278–286°).

Oxidation of Diol 12a.—A solution of diol (12a, 100 mg.) in pyridine (2 ml.) was added slowly to the chromic oxide–pyridine complex (from chromic oxide (100 mg.) and pyridine (2 ml.)), and the mixture was allowed to stand 20 hr. at room temperature. Dilution with water followed by chloroform extraction gave 80 mg. of crude α-lumicolchicine. The crude product in benzene was chromatographed on neutral alumina (7 g.). Elution with chloroform and chloroform containing 2% methanol gave α-lumicolchicine (70 mg.) which crystallized from ethanol; m.p. 155–160°, mixture melting point was undepressed by authentic α-lumicolchicine. The product was identical in infrared absorption to authentic α-lumicolchicine.

α-Lumicolchicine Diol Diacetate (12b).—A solution of α-lumicolchicine diol (12a, 500 mg.) and anhydrous sodium acetate (500 mg.) in acetic anhydride (7 ml.) was stirred and heated at 100° for 18 hr. The solution was cooled, poured onto ice and after standing extracted with benzene. Removal of the benzene after washing with dilute sodium bicarbonate solution and water and then drying gave crude diacetate (400 mg.) as an almost colorless resin. The crude product in benzene was chromatographed on neutral alumina (35 g.). Elution with benzene–chloroform gave the pure diacetate as a colorless resin (300 mg.) which crystallized from aqueous ethanol giving pure α-lumicolchicine diol diacetate (12b), m.p. 167–178°, $[\alpha]^{28}D$ −90° (*c* 0.88 in $CHCl_3$); λ_{max}^{MeOH} 280 mμ (4.63), 228 mμ (4.46); mol. wt. 786 (Rast).

Anal. Calcd. for $C_{48}H_{55}N_2O_{14}$: C, 65.00; H, 6.59; N, 3.16. Found: C, 64.88; H, 6.54; N, 3.25.

α-Lumicolchicine Diol Monoacetate (12c).—A solution of α-lumicolchicine diol (12a, 800 mg.) and pure acetic anhydride (8 ml.) in pyridine (14 ml.) was heated at 100–110° for 3 hr., cooled and poured onto ice. After standing for 30 min. the product was isolated by extraction with benzene. The benzene extract was washed with 10% sodium bicarbonate solution and water and then dried over anhydrous magnesium sulfate. Removal of the solvent gave the crude monoacetate (940 mg.) as a pale yellow resin. The crude product in benzene was chromatographed on neutral alumina (60 g.). Elution with chloroform–benzene (1:1) gave the monoacetate (450 mg.) as an almost colorless resin. Crystallization of the monoacetate from aqueous methanol gave α-lumicolchicine diol monoacetate (12c), m.p. 172–175°, $[\alpha]^{29}D$ −157° (*c* 0.82 in $CHCl_3$); λ_{max}^{MeOH} 279 mμ (4.59), 228 mμ (4.58); mol. wt. 810 (Rast).

Anal. Calcd. for $C_{46}H_{56}N_2O_{13}$: C, 65.40; H, 6.60; N, 3.32; C-methyl, 5.34. Found: C, 65.22; H, 6.60; N, 3.49; C-methyl, 5.13.

Ketoalcohol 13a.—A solution of sodium borohydride (15 mg.) in water (1 ml.) was added to a stirred suspension of α-lumicolchicine (1.0 g.) in pure tetrahydrofuran (30 ml.). Water (2 ml.) was added, and the suspension was stirred overnight. After dilution with water the mixture was acidified with 3 *N* hydrochloric acid (5–8 drops), and the solvent was removed under reduced pressure. The residue was filtered, sucked dry and digested with boiling methanol (40 ml.) for 5 min. The mixture was filtered to remove unreacted α-lumicolchicine (400 mg.). The filtrate was evaporated to dryness, triturated with lukewarm methanol (15 ml.) and filtered. Evaporation of the filtrate gave the crude ketoalcohol 13a as a colorless resin (500 mg.). The crude ketoalcohol (1.1 g.) from two preparations on the same scale was chromatographed on neutral alumina (75 g.). Elution with chloroform–benzene (1:1) gave the ketoalcohol (500 mg.) which crystallized from aqueous methanol as colorless needles, m.p. 225–228° $[\alpha]^{29}D$ +19° (*c* 1.9 in $CHCl_3$); λ_{max}^{MeOH} 279 mμ (4.57), 228 mμ (shoulder, 4.59), 217 mμ (shoulder, 4.59).

Anal. Calcd. for $C_{44}H_{52}N_2O_{12}$: C, 66.00; H, 6.55; N, 3.50. Found: C, 65.89; H, 6.71; N, 3.41.

Oxidation of Ketoalcohol 13a.—A solution of chromic oxide (22 mg.) in dilute sulfuric acid (2 drops of concentrated sulfuric acid plus 7 drops of water) was added with swirling to ketoalcohol 13a (220 mg.) in pure acetone (10 ml.). After 3 min. the solution was diluted with water and extracted with chloroform. The extract was washed with dilute sodium bicarbonate solution and water and dried over anhydrous magnesium sulfate. Removal of the chloroform gave crude α-lumicolchicine (180 mg.) which was purified by chromatography on neutral alumina (7 g.). Elution with benzene–chloroform (1:1) gave α-lumicolchicine (110 mg.) identical in infrared absorption, m.p. and mixed m.p. with authentic α-lumicolchicine. Elution with chloroform gave unreacted ketoalcohol (50 mg.) identified by infrared comparison.

Ketoacetate 13b.—A solution of the ketoalcohol (13a, 500 mg.) and fused, anhydrous sodium acetate (500 mg.) in pure acetic anhydride (10 ml.) was refluxed 10 min. under nitrogen and then heated for 3 hr. at 100°. The solution was cooled and poured onto ice (30 g.). After standing 60 min. the product was isolated by extraction with benzene. The benzene extract was washed with aqueous sodium bicarbonate solution and with water and then dried over anhydrous magnesium sulfate. Removal of the benzene gave the crude ketoacetate (430 mg.) as a yellow resin. The crude product in benzene was chromatographed on neutral alumina (40 g.). Elution with benzene–chloroform (3:1) gave the ketoacetate 13b which was twice recrystallized from aqueous methanol giving colorless crystals (290 mg.) of ketoacetate monohydrate, m.p. 174–182°, $[\alpha]^{29}D$ +46° (*c* 1.5 in $CHCl_3$); λ_{max}^{MeOH} 281 mμ (4.57), 228 mμ (shoulder, 4.58), 217 mμ (4.61); mol. wt. 748 (Rast).

Anal. Calcd. for $C_{46}H_{54}N_2O_{13} \cdot H_2O$: C, 64.20; H, 6.56; N, 3.26. Found: C, 64.14; H, 6.52; N, 3.00.

Oxidation of Monoacetate 12c.—A solution of the monoacetate (12c, 125 mg.) in pyridine (5 ml.) was added at 0° to a stirred suspension of chromic oxide–pyridine complex (from chromic oxide (100 mg.) and pyridine (2 ml.)). After the addition the mixture was stored at room temperature overnight. Dilution with water (40 ml.) followed by extraction with chloroform (4 × 15 ml.) gave the crude ketoacetate (120 mg.). The crude ketoacetate in benzene was chromatographed on neutral alumina (7 g.). Elution with chloroform–benzene (1:3) gave the ketoacetate as a colorless resin (100 mg.). This material was identical in infrared and nuclear magnetic resonance absorption to authentic ketoacetate 13b.

Reduction of Ketoacetate 13b.—A solution of sodium borohydride (50 mg.) in water (2 ml.) was added to a stirred solution of the ketoacetate 13b (100 mg.) in pure tetrahydrofuran (12 ml.). After 4 hr. stirring, water (5 ml.) was added, and the solution was stirred 3 hr. The tetrahydrofuran was removed at 80° under reduced pressure, and the solution was cooled and extracted with benzene. Removal of the benzene after drying over anhydrous magnesium sulfate gave α-lumicolchicine diol monoacetate (12c, 70 mg.) which was identical in infrared absorption to an authentic sample.

Partial Oxidation of Diol 12a.—A solution of α-lumicolchicine diol (12a, 500 mg.) in pure acetone (30 ml.) was treated with a solution of chromic oxide (42 mg., 1 equiv.) in dilute sulfuric acid (2 drops of concentrated sulfuric acid, 10 drops of water and 5 ml. of acetone). After standing for 15 min. the solution was diluted with water and extracted with chloroform. The extract was washed with dilute sodium bicarbonate solution and water and dried over magnesium sulfate. Evaporation of the solvent gave a yellow resin (440 mg.) which was chromatographed on neutral alumina (40 g.). Elution with chloroform gave the keto alcohol 13a (290 mg.) identical in infrared absorption to an authentic sample.

Nuclear Magnetic Resonance Spectra.—Nuclear magnetic resonance studies were performed with a Varian HR-60 instrument at 60 Mc./sec. Calibration was by the audio side-band technique using tetramethylsilane as internal reference. Audio frequencies were measured by an electronic counter. Chemical shifts are reported as τ-values.[21]

In a typical dilution experiment, 100 mg. of sample was dissolved in 0.35 ml. of deuteriochloroform and the spectrum recorded. The solution was successively diluted by a factor of two with deuteriochloroform until the signal became too weak for accurate measurement.

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

(21) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).