crystallization from benzene gave an analytical sample, mp 157–158°.

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.71; H, 7.51; N, 9.37.

1,2,3,4,5,8-Hexahydro-1-(indol-3-ylmethyl)-6-methoxy-2-methylisoquinoline (6).—To a solution of 12.0 g of 1,2,3,4-tetrahydro-1-(indol-3-ylmethyl)-6-methoxy-2-methylisoquinoline in 200 ml of tetrahydrofuran was added 400 ml of ammonia. Then 5.0 g of sodium and 24 ml of *t*-butyl alcohol were added alternately in six equal protions. One hour after this addition had been completed, 0.5 g of sodium was added and stirring was continued for 1 hr longer. The excess sodium was destroyed by the dropwise addition of methanol and the ammonia was allowed to evaporate. On pouring the reaction mixture into 600 ml of cold water, there was deposited 8.0 g (66%) of a crystalline solid, mp 137–139°. Recrystallization from benzene gave an analytical sample, mp 141–142°.

Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 77.76; H, 7.92; N, 9.16.

1,2,3,4,8,8a-Hexahydro-1-(indol-3-ylmethyl)-6(7H)-isoquinolone (7).—A solution of 1.0 g of 1,2,3,4,5,8-hexahydro-1-(indol-3-ylmethyl)-6-methoxyisoquinoline in 100 ml of methanol was mixed with a solution of 1.33 g of oxalic acid in 20 ml of water and was allowed to stand at room temperature for 135 min. The reaction mixture was poured into 200 ml of ether. The ethereal solution was washed with 10% sodium carbonate solution and water and was dried over sodium sulfate, and the solvent was removed. The residue was chromatographed on neutral alumina. Elution with 2% methanol in ether gave, after recrystallization from benzene, 0.10 g (10%) of a crystalline solid: mp 203–204°; $\nu_{max}^{CHCl_3}$ 1668 (C=O, conjugated), 1620 (C=C, conjugated) cm^{-1}.

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.32; H, 7.20; N, 9.91.

cis-**Cyclohex[*j*]indolo[2,3-*f*]morphan-15-one** (8).—A solution of 4.4 g of 1,2,3,4,5,8-hexahydro-(1-indol-3-ylmethyl)-6-methoxyisoquinoline and 45 ml of hydrochloric acid in 150 ml of methanol was refluxed for 1 hr. The reaction mixture was diluted with 45 ml of water and the methanol was stripped *in vacuo*. The solution was made basic with sodium hydroxide solution. Filtration gave a solid which, after recrystallization from ether, afforded 0.90 g (22%) of a crystalline solid, mp 201–201.5°.

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.08; H, 7.23; N, 9.74.

cis-**2-Methylcyclohex[*j*]indolo[2,3-*f*]morphan-15-one** (9).—A solution of 5.0 g of 1,2,3,4,5,8-hexahydro-1-(indol-3-ylmethyl)-6-methoxy-2-methylisoquinoline and 45 ml of hydrochloric acid in 125 ml of methanol was refluxed for 1 hr. The reaction mixture was diluted with 70 ml of water and the methanol was stripped *in vacuo*. The solution was made basic with 40% sodium hydroxide solution. Filtration gave a solid which, after recrystallization from benzene, afforded 3.2 g (67%) of a solid, mp 236–237°. Further recrystallization gave an analytical sample, mp 236.5–237.5°.

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.52; N, 9.52. Found: C, 77.56; H, 7.71; N, 9.52.

cis-**2-Methylcyclohex[*j*]indolo[2,3-*f*]morphan** (10).—A solution of 2.0 g of *cis*-2-methylcyclohex[*j*]indolo[2,3-*f*]morphan-15-one, 1.6 g of sodium hydroxide, and 30 g of hydrazine hydrate in 80 ml of ethylene glycol was refluxed for 1 hr. The overhead then was removed until the temperature of the distillate reached 192°, after which heating was continued for 3 hr. On pouring the reaction mixture into 750 ml of water, there was deposited 1.1 g (58%) of a solid, mp 131–138°. Recrystallization from Skellysolve B gave a sample, mp 139–141°, which was shown to be identical with an authentic sample[1] by the methods of mixture melting point and infrared analysis.

Registry No.—**1**, 13118-18-8; **2**, 13118-19-9; **3**, 13118-20-2; **4**, 13118-53-1; **5**, 13118-54-2; **6**, 13118-55-3; **7**, 13118-56-4; **8**, 13131-50-5; **9**, 13143-77-6; **10**, 13118-57-5.

Acknowledgment.—The authors are indebted to Mr. A. Lewis and his associates, to Mr. R. Puchalski for the spectral data, and to Mrs. U. Zeek for analytical determinations. We also wish to thank the Chemical Development Department under the supervision of Dr. A. W. Ruddy for the large-scale preparation of intermediates.

Spectroscopic Studies of Aromatic Isoprenoids. Application of Nuclear Resonance to the Structural Differentiation of Tocopherols[1]

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Received February 6, 1967

A novel nuclear magnetic resonance (nmr) approach for definitively characterizing phenolic isoprenoids that belong to the vitamin E family is discussed and evaluated in the context of the nmr properties of a large number of binary systems containing as principal components several of these tocopherols. The method depends on experimentally developed anisotropy indices based on predictable orientation effects in some of the binary systems. These indices facilitate the assignment of chemical shifts that can be characteristically identified with specific ring positions in the system-modified tocopherols and these shifts can then be used for structural identification. The method, which is used in this study to identify specifically five tocopherols, appears to be suitable not only for other unsaturated tocopherols where heretofore ambiguous identifications were more likely, but for members of the coenzyme Q group (after straightforward conversions to their respective chromanols or chromenols), various other classes of phenols, aromatic amines, and aromatic mercaptans.

Recent reviews of the chemistry of tocopherols (vitamin E family)[2–4] have pointed to experimental difficulties in unequivocally differentiating unsaturated and certain of the less abundant saturated tocopherols isolable from natural sources, as well as synthetic analogs. Physical measurements cited in one of these reviews, in particular detailed nuclear magnetic resonance data,[2] appeared to hold out no promising applicability to this problem. In reexamining this in the larger context of structural elucidation of related ring systems, including substituted quinones capable of facile reduction to tocopherol-like prototypes, it appeared to us that the significant electron-acceptor properties of the phenolic group might possibly be-

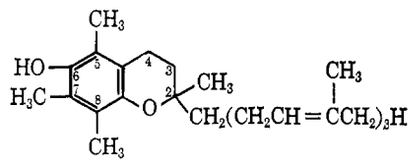
(1) Presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966.

(2) M. Kofler, P. F. Sommer, H. R. Bolliger, B. Schmidli, and M. Vecchi, "Vitamins and Hormones," Vol. 20, R. S. Harris and I. G. Wool, Ed., Academic Press Inc., New York, N. Y., 1962, p 407.

(3) O. Isler and M. Montavon, *Bull. Soc. Chim. France*, 2403 (1965).

(4) J. F. Pennock, F. W. Hemming, and J. D. Kerr, *Biochem. Biophys. Res. Commun.*, **17**, 542 (1964).

come the basis of a practicable nmr method for differentiating members within such related families. The tocopherols, of which 5,7,8-trimethyltocotrienol (I) exemplifies the structure of an unsaturated isoprenoid chromanol related to the well-established and biomolecularly significant chromanol, 5,7,8-trimethyltocol (containing a saturated side chain of the same skeletal structure), afford a useful series for a test of the proposed method.



I

Experimental Section

Spectra were measured at 60.005 MHz with a Varian Associates spectrometer (stabilized by external field frequency lock) and other Varian accessories. The requisite high order of precision of the nmr measurements taken in the aromatic spectral regions was facilitated both by the use of a memory scope with sweep triggered by tetramethylsilane (TMS) and by bracketing each group of measured lines at 8 Hz upfield and downfield with TMS side bands taken in the usual way from a Hewlett-Packard audio sine wave generator standardized against Hewlett-Packard audio calibration gear. Three successive superposable sweeps were required for each measurement, with the insertion of the side bands taking place during the final sweep. Chemical shifts, $-\Delta\nu$ Hz, where $\Delta\nu = \nu - \nu_{ref}$, are internally referenced from TMS. Precision of measurement is estimated to be ± 0.2 Hz.

Samples were examined in the usual precision-bore analytical tubes. Because of small concentration effects on the chemical-shift values noted in some instances in a study carried out to assess this effect and because the values should be available as reference standards, concentrations not exceeding 15 μmoles/ml were used in each examination. Variations in sample temperature by $\pm 10°$ of the 37° probe temperature did not significantly affect the aromatic methyl chemical shifts.

The reference tocopherols were obtained from commercial sources: 5,8-dimethyltocol, 7,8-dimethyltocol, and 5,7,8-trimethyltocol from Distillation Product Industries and 5,7-dimethyltocol from Pierce Chemical Co. The 5-methyltocol, 7-methyltocol, and 8-methyltocol were synthesized by the condensation of methylhydroquinone (0.92 g) and phytol (2.11 g) in 20 ml of a 1:1 mixture of benzene and formic acid by heating at 100° for 4 hr.[5] The 5-, 7-, and 8-methyltocols formed in this reaction were separated by a combination of thin layer and gas–liquid chromatographic techniques. The tocotrienols, which are usually extracted from natural sources, were a gift from Hoffmann-La Roche, Inc. Perdeuterated benzene, pyridine, and acetonitrile were obtained from the Ciba Corp., Merck Sharp and Dohme, Ltd., and Fluka, A.G. Furan (Matheson Chromatographic Quality), chlorobenzene, and carbon tetrachloride (both Eastman White Label) were vacuum distilled prior to use.

Results and Discussion

The principal bands of four of the naturally occurring and more readily obtainable tocopherols, determined at 60 MHz in carbon tetrachloride solutions, are listed in Table I, together with assignments of band origins based on readily available empirical information.[6] These standardized spectral data have a limited usefulness which, careful examination indicates, does not encompass possibilities for structural differentiation required in our present problem.

(5) P. Karrer and H. Fritzsche, *Helv. Chim. Acta*, **22**, 260 (1939).

(6) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press Inc., New York, N. Y., 1966, Appendix C, p 1131.

TABLE I

PRINCIPAL BANDS OF SOME TOCOPHEROLS IN CCl_4 SOLUTIONS AT 60 MHz

Bands,[a] Hz				
5,7,8-Trimethyltocol	5,8-Dimethyltocol	7,8-Dimethyltocol	5,7-Dimethyltocol	Assignments
51.3[b]	51.0[b]	52.6[b]	50.2[b]	Methyl, isoprenoid
71.0	71.6	71.8	69.5	Methyl, alicyclic, C-2
71.0	71.6	71.8	71.8	Methylene and methine, isoprenoid
121.7	121.6	122.7	123.4	Methyl, aromatic
124.5		123.6	127.6	Methyl, aromatic
153.3	154	156.1	152.0	Methylene, alicyclic, C-4
230.4	248.1	261.9	258.7	Phenolic, C-6
...	378.7	367.3	378.9	Ring hydrogen, aromatic

[a] All values are chemical shifts, except as noted. [b] Chemical shift is not readily determinable by spectral analysis; the indicated value is weighted band center.

The phenolic group affords a geometrically specific center for complexation by molecules having collateral electron-rich sites. By selecting donors which also contain sites having large diamagnetic anisotropies, a high probability of removing chemical shift degeneracies in the vicinity of the complexation center can be anticipated. The selection of a series of donors capable of predictably different geometries of mutual orientation with respect to the vitamin substrate should facilitate obtaining multiple sets of parameters useful as analytical indices because of the independent geometries to which they owe their differences.

There are essentially three types of binary systems in the five groups of tocopherol complexes examined: (1) those in which either a π-electron or an n-electron transfer takes place between donor and vitamin substrate, (2) those in which a predominantly π-electron transfer is involved, and (3) those in which a predominantly n-electron transfer is involved. Representing complex 1 are the chlorobenzene–tocopherol and the furan–tocopherol systems, complex 2 are the acetonitrile–tocopherol and the benzene–tocopherol systems, and complex 3 is the pyridine–tocopherol system. The results obtained for the aromatic methyl chemical shifts of the 20 complexes containing four tocopherols are presented in Table II. Spectra of the complexes and of the CCl_4 solution of one tocopherol, 5,7,8-trimethyltocol, are given in Figure 1.

One of the most obvious features apparent from Table II is the excellent resolution of each of the aromatic methyl signals for all the binary systems except certain of those containing acetonitrile. Because of the large magnetic anisotropies of the donors as well as the specificity of the receptor site, the anisotropic contribution to the chemical shift of the aromatic methyls becomes a significant one (compared with each of the many other features that go into the composition of the shielding values) and permits the reliable assignment of each of the aromatic methyl groups to a particular ring position.

Pyridine complexes to the tocopherol molecule by a lateral approach between the 5 and the 7 positions at the receptor site, consistent with the n-donor ac-

TABLE II
AROMATIC METHYL CHEMICAL SHIFTS OF SOME TOCOPHEROL COMPLEXES AT 60 MHz

Substrate	Chemical Shift, Hz				
	Pyridine-d_5 donor	Benzene-d_6 donor	Chlorobenzene donor	Furan donor	Acetonitrile-d_3 donor
5,7,8-Trimethyltocol	145.9	133.2	131.7	132.8	125.2
	142.3	119.8	130.0	129.6	122.3
	138.9	117.5	126.8	126.7	122.3
5,8-Dimethyltocol	140.6	135.6	131.0	130.8	127.8
	136.9	122.7	124.7	125.2	120.9
7,8-Dimethyltocol	143.7	131.7	135.4	130.8	123.3
	137.8	124.3	132.7	127.5	122.7
5,7-Dimethyltocol	145.4	119.5	124.1	126.5	126.6
	141.7	115.0	122.9	126.5	123.7

tivity of its nitrogen. Using "Framework Molecular Models,"[7] it is possible to show how easily the pyridine ring can orient itself so as to present an equipotential surface to the methyl groups at the 5 and 7 positions if these are so occupied. There is no severe steric strain involved in the complexation and since the equipotential position represents the potential minimum when both 5 and 7 positions are methyl substituted, it would be the preferred orientation. The anisotropic contribution[8,9] to the chemical shift of the methyl groups at the 5 and 7 positions will be principally dominated by the large diamagnetic anisotropy of the pyridine ring and this contribution will be approximately equal for both of the rotating methyl groups at the minimum potential geometry.

It is possible to estimate what this anisotropic contribution will be[10] if one makes a reasonable assumption regarding the N···H—O bond distances and measures the other vectors and angles from a framework model accurately constructed to scale using available microwave and X-ray data of closely related rings.[11] However, a more precise value would be obtainable from the experimental measurements of the complex itself if it were feasible to separate this contribution from the electronegative, steric, mesomeric, inductive, and intramolecular magnetic factors other than anisotropy that contribute to the chemical shifts of the methyl groups. Since these other factors will be approximately the same for both the noncomplexed and the complexed tocopherols, a measure of the anisotropic contribution can be obtained simply by determining the differences between corresponding methyl signals for the tocopherol–carbon tetrachloride binary systems and the tocopherol–pyridine binary systems.

The pyridine chemical shifts may now be assigned to specific ring positions. The differences between the 5,7-dimethyltocol–pyridine *vs.* 5,7-dimethyltocol–carbon tetrachloride shifts (obtained from Tables I and II) are 17.8 and 18.3 Hz, pairing the shifts so as to obtain the theoretically expected similar differences. Again, the appropriately paired differences for the 5,8-dimethyltocol complex *vs.* the CCl_4 solutions give 19.0 and 15.3 Hz. The chemical shifts resulting in the 15.3-Hz difference obviously correspond to the

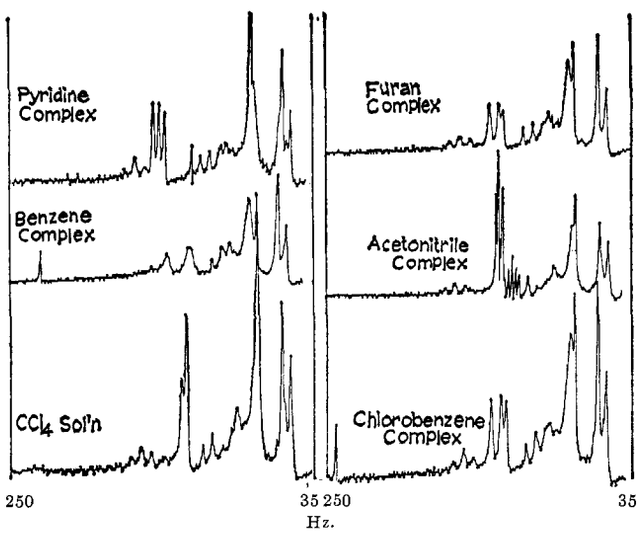


Figure 1.—Complexes and CCl_4 solution spectra of 5,7,8-trimethyltocol at 60 MHz. In some spectra the phenolic proton line is too broad for cursory recognition, has a chemical shift downfield from 250 Hz, or has substantially exchanged with ^2H.

8 position, since the other difference is much closer to the 5 and 7 differences. Proceeding similarly for 7,8-dimethyltocol, values of 20.1 and 15.1 Hz are obtained, which permit the assignment of the chemical shift at the 7 position. Table III tabulates the differences,

TABLE III
ANISOTROPY INDICES FOR PYRIDINE–TOCOPHEROL COMPLEXES AT 60 MHz

Substrate	Index at assigned Ring position, Hz		
	5-C	7-C	8-C
5,7,8-Trimethyltocol	20.6	21.4	17.2
5,8-Dimethyltocol	19.0	...	15.3
7,8-Dimethyltocol	...	20.1	15.1
5,7-Dimethyltocol	17.8	18.3	...

which may be considered as the aromatic methyl anisotropy indices, for the four pyridine–tocopherol complexes *vs.* the CCl_4 solutions; the ring position assignments of the aromatic methyl chemical shifts for each of the tocopherols are also listed. Table IV summarizes the mean ring-position assignments of the aromatic methyl chemical shifts of the CCl_4 solutions and of the benzene, furan, and acetonitrile as well as the pyridine complexes. The assignments for all the tocopherol complexes were made by first obtaining the respective indices as described in detail for the pyridine systems.

(7) "Framework Molecular Models," Prentice-Hall, Inc., Englewood Cliffs, N. J.

(8) J. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 176.

(9) Reference 6, Vol. 1, 1965, p 133.

(10) Reference 6, Vol. 1, 1965, p 135.

(11) L. E. Sutton, H. J. M. Bowen, J. Donohue, D. G. Jenkin, O. Kennard, P. J. Wheatley, and D. H. Whiffen, "Tables of Interatomic Distances and Configuration," The Chemical Society, London, 1958.

TABLE IV

RING POSITION ASSIGNMENTS AND MEAN CHEMICAL SHIFTS OF AROMATIC METHYL GROUPS IN COMPLEXED AND FREE TOCOPHEROLS AT 60 MHz

Ring position	Mean chemical shift, Hz: Pyridine-d_5 donor	Benzene-d_6 donor	Furan donor	Acetonitrile-d_3 donor	CCl_4 (noncomplexed)
C-5	141.5 ± 0.6	118.4 ± 2.9	126.1 ± 0.6	126.5 ± 0.9	122.2 ± 0.8
C-7	145.0 ± 0.9	121.2 ± 2.1	127.9 ± 1.2	122.9 ± 0.5	125.2 ± 1.6
C-8	137.9 ± 0.7	133.5 ± 1.4	131.5 ± 0.9	122.0 ± 0.7	122.0 ± 0.5

TABLE V

SIGNIFICANT BANDS AND STRUCTURAL ASSIGNMENTS OF SOME TOCOPHEROLS OF PROBLEMATIC ORIGIN (60 MHz)

Compound	Aromatic methyl chemical shifts, Hz: Acetonitrile-d_3 complex	Pyridine-d_5 complex	Position assignment	Isoprenoid methylene bands, Hz (CCl_4)	Isoprenoid assignment: saturated (S) or unsaturated (U)	Structural assignment
A	125.5	141.1	C-5			
	122.9[a]	137.8	C-8	117.4	U	5,7,8-Trimethyltocotrienol
	122.9[a]	145.2	C-7			
B	123.3	137.6	C-8	72.3	S	8-Methyltocol
C	125.0	141.9	C-5	71.9	S	5-Methyltocol
D	123.0	135.4	C-8			
				117.2	U	5,8-Dimethyltocotrienol
	125.4	138.8	C-5			
E	123.4	145.1	C-7	71.8	S	7-Methyltocol

[a] Integration of signal at this chemical shift indicates a count of six protons.

Each of the ring-position assignments is based on the data obtained from three tocopherols. The average deviations from the mean are smallest, percentagewise, for the pyridine systems and, of those complexes included in Table IV, are largest for the benzene systems. The scatter for the chlorobenzene is too great to allow for meaningful averages to be assigned to particular ring positions and they are not included in the table. The large average deviations for the benzene complexes can be understood on the basis of the π-bond character of the complex formed and the steric requirement that the donor ring be oriented perpendicularly to the acceptor O–H bond. The bonding energy is not necessarily a minimum when the π bond exactly coincides with the geometric hexad axis of the donor benzene ring and it is physically possible for an off-axis π bond to have the same bonding energy as one at the hexad axis. Moreover, when only the 5 or the 7 position of the substrate is occupied by a methyl group, then it becomes quite probable, owing to van der Waals forces, that the minimum bonding potential of the π bond will not coincide with the hexad axis. However, since the diamagnetic anisotropy is calculated from the donor center, it is clear how the same ring position in the various tocopherols can have rather different anisotropy contributions and consequently more widely scattered aromatic methyl chemical shifts.

The large scatter in values for the chlorobenzene complexes is best understood on the basis of the possibly different modes of bonding (π and n) for different tocopherols, depending on the steric situation. The possibility of differences in the mode of bonding would appear to be much greater for the chlorobenzene than for the furan ring because of the much larger size of the former. Acetonitrile bonds to the tocopherols by π-electron donation and should make substantially different anisotropy contributions to the methyl groups occupying the 5 and 7 positions because of the linear geometry of the molecule and the one methyl group bonded to the C=N group. This is the only donor of those listed in Table IV which can be expected to make a significantly different anisotropy contribution to each of the aromatic methyls at the 5 and 7 positions when these are jointly occupied.

The pyridine and CCl_4 systems can be used exclusive of the other systems, or supplemented by one or more of the other systems, for the structural assignment of unknown tocopherols. The pyridine systems produce very large, distinctive, as well as systematic aromatic methyl chemical shifts and the CCl_4 solutions provide standard reference spectra. Particularly useful supplemental systems are the trideuterioacetonitrile complexes, which make distinctive anisotropy contributions to the 5 and 7 positions. The pyridine, carbon tetrachloride, and acetonitrile systems all have small average deviations for mean chemical shifts assigned to ring positions, as noted in Table IV.

Five tocopherols were obtained which, as reported in the Experimental Section, required a definitive characterization of their structure. The nmr spectra of these materials were taken as the pyridine and acetonitrile complexes. Significant bands and the relevant assignments are noted in Table V.

It is clear from Table V that the assignments of the structures of the five tocopherols leave little margin for error and that the method is eminently suitable for the assignment of the large number of remaining tocopherols which have thus far eluded successful identification. Other solvent effects owing to the excess of donor molecules in the systems appear to introduce no difficulty in the assignments. There is no reason why this method cannot be extended to permit the structural assignment of the many other important types of phenolic systems as well as perhaps aromatic mercaptans and aromatic amines capable of the role of electron-acceptor substrate. Of particular importance might be related synthetic and naturally occurring

isoprenoid quinones that can be converted to chromanols or chromenols, such as members of the coenzyme Q group and variously substituted analogs.[3,12]

Registry No.—I·Acetonitrile-d_3 complex, 13169-30-7; I·pyridine-d_5 complex, 13127-55-4; 8-methyltocol·acetonitrile-d_3 complex, 13136-70-4; 8-methyltocol·pyridine-d_5 complex, 13136-71-5; 5-methyltocol·acetonitrile-d_3 complex, 13136-72-6; 5-methyltocol·pyridine-d_5 complex, 13136-73-7; 5,8-dimethyltocotrienol·acetonitrile-d_3 complex, 13136-74-8; 5,8-dimethyltocotrienol·pyridine-d_5 complex, 13136-75-9; 7-methyltocol·acetonitrile-d_3 complex, 13136-76-0; 7-methyltocol·pyridine-d_5 complex, 13136-77-1; 5,7,8-trimethyltocol, 59-02-9; 5,7,8-trimethyltocol·pyridine-d_5, 13136-78-2; 5,7,8-trimethyltocol·benzene-d_6, 13136-79-3; 5,7,8-trimethyltocol·chlorobenzene, 13136-80-6; 5,7,8-trimethyltocol·furan, 13136-81-7; 5,7,8-trimethyltocol·acetonitrile-d_3, 13136-82-8; 5,8-dimethyltocol, 148-03-8; 5,8-dimethyltocol·pyridine-d_5, 13136-84-0; 5,8-dimethyltocol·benzene-d_6, 13136-85-1; 5,8-dimethyltocol·chlorobenzene, 13136-86-2; 5,8-dimethyltocol·furan, 13136-87-3; 5,8-dimethyltocol·acetonitrile-d_3, 13136-88-4; 7,8-dimethyltocol, 119-11-9; 7,8-dimethyltocol·pyridine-d_5, 13136-90-8; 7,8-dimethyltocol·benzene-d_6, 13233-10-8; 7,8-dimethyltocol·chlorobenzene, 13136-91-9; 7,8-dimethyltocol·furan, 13136-92-0; 7,8-dimethyltocol·acetonitrile-d_3, 13136-93-1; 5,7-dimethyltocol, 493-35-6; 5,7-dimethyltocol·pyridine-d_5, 13136-95-3; 5,7-dimethyltocol·benzene-d_6, 13136-96-4; 5,7-dimethyltocol·chlorobenzene, 13136-97-5; 5,7-dimethyltocol·furan, 13136-98-6; 5,7-dimethyltocol·acetonitrile-d_3, 13136-99-7.

(12) Commercial designations have been included in the text of this article for the purpose of adequately describing experimental procedure; they are not be be construed as an endorsement by the Department of Agriculture of one particular product over that of competitive products.

Senecio Alkaloids. V. The Synthesis of Trichodesmic Acid[1]

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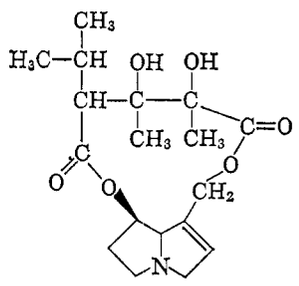
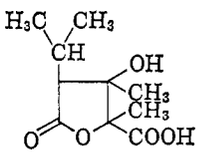
Received March 9, 1967

Trichodesmic acid, the necic acid derived from the alkaloid trichodesmine, has been synthesized from 2,3-dimethyl-4-isopropyl-2-cyclopentenone. The stereospecific hydroxylation step in the synthesis eliminates all but one racemic structure for this acid.

The alkaloid trichodesmine, $C_{18}H_{27}NO_6$, has been obtained from *Trichodesma incanum*,[3] *Crotalaria juncea*,[4] *Heliotropium arguzioides*,[5] and *Crotalaria rubiginosa*.[6] The original degradation studies were inconclusive[3,7] and later work[4,8,9] formulated trichodesmine as I.

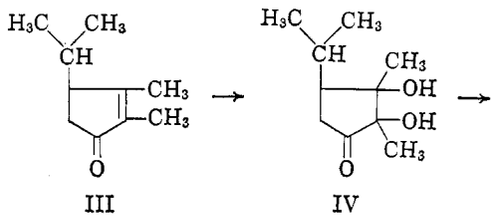


I

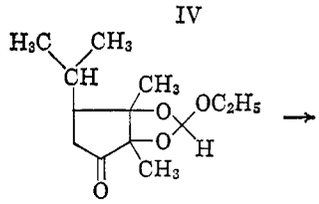


II

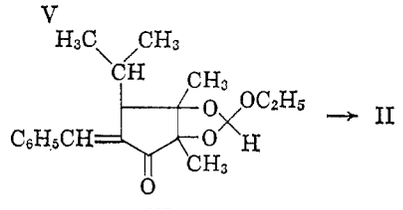
After catalytic reduction of I, acidic hydrolysis gave trichodesmic acid, $C_{10}H_{16}O_5$, for which the structure 2,3-dihydroxy-3,5-dimethylhexane-2,4-dicarboxylic acid 2(γ)-lactone (II) was proposed. Four racemic modifications are possible for II.



III IV



V



VI

Trichodesmic acid has been synthesized from (±)-2,3-dimethyl-4-isopropyl-2-cyclopentenone (III).[10] This compound, on *cis* hydroxylation with osmium tetroxide, gave in 75–80% yield a crystalline glycol racemate (IV). To our knowledge, this is the simplest

(1) This is the fifth paper in this series and the first to be numbered. The previous articles in sequence are J. D. Edwards, Jr., T. Hase, and N. Ichikawa, *Chem. Commun.*, 364 (1965); J. D. Edwards, Jr., T. Hase, C. Hignite, and T. Matsumoto, *J. Org. Chem.*, **31**, 2282 (1966); J. D. Edwards, Jr., T. Matsumoto, and T. Hase, *ibid*, **32**, 244 (1967); J. D. Edwards, Jr., and T. Matsumoto, *ibid*, **32**, 1837 (1967).

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(3) G. P. Menshikov and M. Rubinstein, *Ber.*, **68**, 2039 (1935).

(4) R. Adams and M. Gianturco, *J. Am. Chem. Soc.*, **78**, 1922 (1956).

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(6) C. K. Atal, R. K. Sharma, C. C. J. Culvenor, and L. W. Smith, *Australian J. Chem.*, **19**, 2189 (1966).

(7) N. J. Leonard in "The Alkaloids," Vol. I, R. H. F. Manske and H. L. Holmes, Ed., Academic Press Inc., New York, N. Y., 1950, pp 118, 160; Vol. VI, R. H. F. Manske, Ed., 1960, p 100.

(8) S. Yu. Yunusov and N. V. Plekhanova, *J. Gen. Chem. USSR*, **29**, 670 (1959).

(9) Structures proposed in these studies[4,8] differ only in the configuration assigned to the glycol grouping, *erythro* and *threo*.

(10) R. H. Eastman and A. V. Winn, *J. Am. Chem. Soc.*, **82**, 5908 (1960).