measured. The reaction mixture was then stirred at room temperature for a length of time and after basification with concd. NH_4OH, the organic materials were extracted with $CHCl_3$. The $CHCl_3$ phase was washed well with water, dried and evaporated. The infrared spectrum of the residue then was compared with spectra of known mixtures of starting material and authentic product (XVI) and the yield ascertained by comparison of relevant peaks:

2-Component base, Vb (mmoles)	5.68	0.83
Formaldehyde (mmoles)	12.33	123.3
Time	1 day	8 days
Concentration $\times 10^{-3}$ M	28.40	4.14
pH	4.1	4.5
Yield of XVI	18.9%	60.9%

Mercuric Acetate Oxidation of (XVI).—In a 100 ml. erlenmyer flask, 180 mg. (0.51 mmole) of the 3,4-dimethoxy three component amine (XVI) was dissolved in 11 cc. of 20% acetic acid. To this 540 mg. (1.69 mmoles) of mercuric acetate was added and the solution heated on the steam-bath After 10 minutes colorless platelets began to crystallize out. After the crystals were filtered off and identified as mercurous acetate; wt. 143 mg. (0.275 mmole). The filtrate was heated on the steam-bath for an additional 12 hr. during which time no further precipitation was observed. The solution was cooled, made basic with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ phase was dried over anhydrous $MgSO_4$ and evaporated to a yellow-brown glass which could not be induced to crystallize but contained a new infrared band at 6.0 μ.

Permanganate Oxidations of Vb.—In a 250-ml. erlenmyer flask, 1.20 g. of the 3,4-dimethoxy amine Vb was dissolved in 20 cc. of acetone. About 0.25 g. of KOH was added and then 10.0 g. of $KMnO_4$ in small portions over an hour. An immediate precipitate of MnO_2 was observed. After stirring for 3 hr., the flask was warmed on the steam-bath till almost all the acetone evaporated and 100 cc. of water added. The mixture was heated on the steam-bath for an additional 3 hr. Enough SO_2 gas was bubbled through to dissolve all the solids and the solution made basic with 40% KOH. The flocculent white precipitate was filtered off and washed four times with 20-cc. portions of 10% KOH. The filtrate was made acid and continuously extracted with ether for 24 hr. The ether was dried and evaporated to yield about 30 mg. of a yellowish material which was recrystallized from water to white needles m.p. 180–182°. The mixed m.p. with a sample of 3,4-dimethoxybenzoic acid prepared by oxidation of the aldehyde showed no depression.

The Analogous 2,3-Dimethoxyphenyl Series.—The other compounds prepared were entirely analogous in their methods of preparation, chemical behavior and spectra to the corresponding compounds in the 3,4-dimethoxyphenyl series.

2,3-Dimethoxyphenylacetaldehyde.—Prepared as above and distilled as a colorless oil, infrared (chloroform) 5.81, 7.87, 8.53, 9.22 μ; the last three peaks were typical of the 2,3-dimethoxyphenyl system in almost all of the compounds prepared; yield from the benzaldehyde, 20%.

Preparative Condensation with Oxytryptamine.—2,3-Dimethoxyphenylacetaldehyde (2.33 g., 12.9 mmoles) and 2.33 g. (10.9 mmoles) 3-(β-aminoethyl)-oxindole hydrochloride and 4 g. sodium acetate were condensed as above (procedure B) to afford 3.44 g. (10.1 mmoles) of a pale yellow solid, obtained crystalline from acetone only after extensive purification, white needles, m.p. 166–168°. The N-tosyl derivative (corresponding to Vc) was prepared and recrystallized from methanol, m.p. 199–200°.

Anal. Calcd. for $C_{27}H_{28}O_5N_2S$: C, 65.83; H, 5.73; S, 6.51. Found: C, 65.80; H, 5.74; S, 6.40.

The perchlorate of the free base crystallized from absolute ethanol, m.p. 224–225°.

Cyclization to the Indolenine (Corresponding to XI).—0.959 g. (1.95 mmoles) of N-tosyl derivative above, 0.926 g. polyphosphoric acid, in 7 cc. of phosphorus oxychloride, as before, yielded 0.627 g. (68%) of pale yellow crystals, m.p. 255–256.5°, from methanol.

Anal. Calcd. for $C_{27}H_{26}O_4N_2S$: C, 68.33; H, 5.52; N, 5.90; S, 6.76. Found: C, 68.14; H, 5.57; N, 6.15; S, 6.74.

Reduction with Sodium Borohydride.—Reduced as above, this indolenine afforded 89% yield of fine white crystals, m.p. 162.5–164.0° from methanol, corresponding to XII.

N-Acetyl Derivative of Indoline Corresponding to XII.—The sodium borohydride reduction product above was acetylated directly, 0.23 g. in 2 cc. of pyridine and 1 cc. of acetic anhydride, left overnight at room temperature. The solution was chilled in ice, acidified with cold 10% HCl and the pale yellow precipitate filtered and recrystallized from methylene chloride–methanol to a 75% yield of white crystals, m.p. 274–278°; infrared (chloroform), no N-H peak below 3.3 μ; amide at 6.06 μ.

Anal. Calcd. for $C_{29}H_{30}O_5N_2S$: C, 67.15; H, 5.83; N, 5.40; S, 6.18. Found: C, 67.38; H, 5.96; N, 5.17; S, 6.06.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES, CALIFORNIA]

Stereochemistry of the *Mitragyna* Alkaloids

BY JAMES B. HENDRICKSON

RECEIVED FEBRUARY 27, 1961

Application of conformational analysis to the *Mitragyna* alkaloid structures permits assignment of the stereochemistry of mitraphylline, rhyncophylline, uncarine, and corynoxine.

Structures for the *Mitragyna* alkaloids were first proposed by Loudon in 1955[1] and confirmed in recent years for uncarine A and B and mitraphylline, all represented by I, by the Japanese school of Kondo,[2] and for mitraphylline[3] and rhyncophylline[4] (IIa) by Marion and co-workers in Canada. Some tentative stereochemical assignments have been made[2] but these suffer both from a lack of adequate experimental evidence and insufficient attention to the potential stereochemical and conformational complexity of these structures. Evidence is now available, however, to make rational stereochemical assignments to the *Mitragyna* alkaloids.

The keystone in the evolution of this stereochemistry lies in the widespread existence among the alkaloids and their degradation products of pairs of interconvertible isomers; this was particularly evident in the early degradative studies on the isomers uncarine A and uncarine B.[5] However, it remained for the Canadian group to show that

(1) J. D. Loudon, *Spec. Pub. Chem. Soc. no. 3*, 12 (1955).

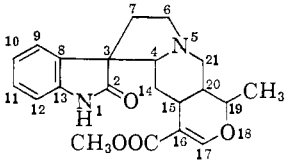
(2) H. Konda and T. Nozoye, *Ann. Rept. Itsuu Lab. (Tokyo)*, **7**, 44 (1956); T. Nozoye, *Chem. Pharm. Bull. (Japan)*, **6**, 300, 306, 309 (1958).

(3) J. C. Seaton, R. Tondeur and Leo Marion, *Can. J. Chem.*, **36**, 1031 (1958).

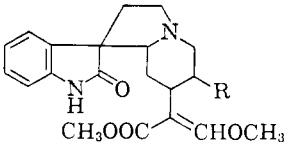
(4) J. C. Seaton and Leo Marion, *ibid.*, **35**, 1102 (1957).

(5) H. Kondo and T. Ikeda, *J. Pharm. Soc. Japan*, **61**, 416, 453 (1941); H. Kondo and T. Nozoye, *Ann. Rept. Itsuu Lab. (Tokyo)*, **1**, 71 (1950).

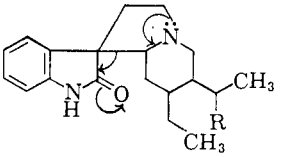
each of the *Mitragyna* alkaloids was in fact one of a pair of stereoisomers interconvertible by refluxing in pyridine or acetic anhydride.[6] Thus either uncarine A or B gave an equilibrium mixture of the two containing 80% A, mitraphylline or isomitraphylline gave a mixture containing 80% isomitraphylline, and rhynocophylline and isorhyncophylline were equilibrated to 70% of the iso-compound. That this involved only the upper portion of the molecule was demonstrated by the identical interconversion in the rhyncophyllane (IIIa) series. The course of this important and ubiquitous isomerization was judged to proceed *via* the reverse Mannich reaction (II, arrows)[7]; such a reaction destroys and reforms the asymmetry at positions 3 and 4. A recent study[8] of this reaction has shown that under the same isomerization conditions the compound IV was mostly recovered unchanged. Since the relative stereochemistry at the two centers in IV was known, it allows the



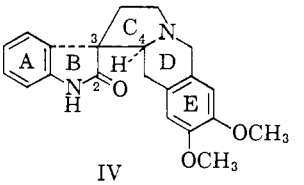
I



IIa, R = C_2H_5
b, R = —CH=CH_2



IIIa, R = H
b, R = OH



IV

conclusion that in these isomerizations the more stable isomer must contain this same relative stereochemistry at C_3 and C_4, *cf.*, the hydrogen on C_4 *trans* to the C_2–C_3 bond, referred to ring C.

Of the natural alkaloid isomer pairs, it was further observed that the preponderant isomer in the equilibrium in each case (the more stable one) is also the less basic of the two[2,6] and (in two pairs) is the only one of the pair which reacts with mercuric acetate.[6] The latter reaction was shown to involve dehydrogenation to the Δ^{4-5} anhydro salt which in one case hydrolyzed to a six-membered D-ring lactam with cleavage of the 3–4 bond. These data are summarized in Table I. The stereochemical implications of the lowered basicity require a close proximity of the basic nitrogen with the electropositive C_2 of the oxindole carbonyl in the less basic isomer; in particular, this isomer cannot possess a conformation in which the hydrogen at C_4 intervenes between these centers. The mercuric acetate oxidation will require a *trans* diaxial geometry[9]

(6) J. C. Seaton, M. D. Nair, O. E. Edwards and Leo Marion, *Can. J. Chem.*, **38**, 1035 (1960).

(7) E. Wenkert, J. H. Udelhofen and N. K. Bhattacharyya, *J. Am. Chem. Soc.*, **81**, 3763 (1959).

(8) J. B. Hendrickson and R. Silva, *ibid.*, **83**, 643 (1961).

(9) N. F. Leonard, A. S. Hay, R. W. Fulmer and V. W. Gash, *ibid.*, **77**, 439 (1955); F. J. Weisenborn and P. A. Diassi, *ibid.*, **78**, 2022 (1956).

TABLE I
COMPARISON OF THE MITRAGYNA ISOMERS

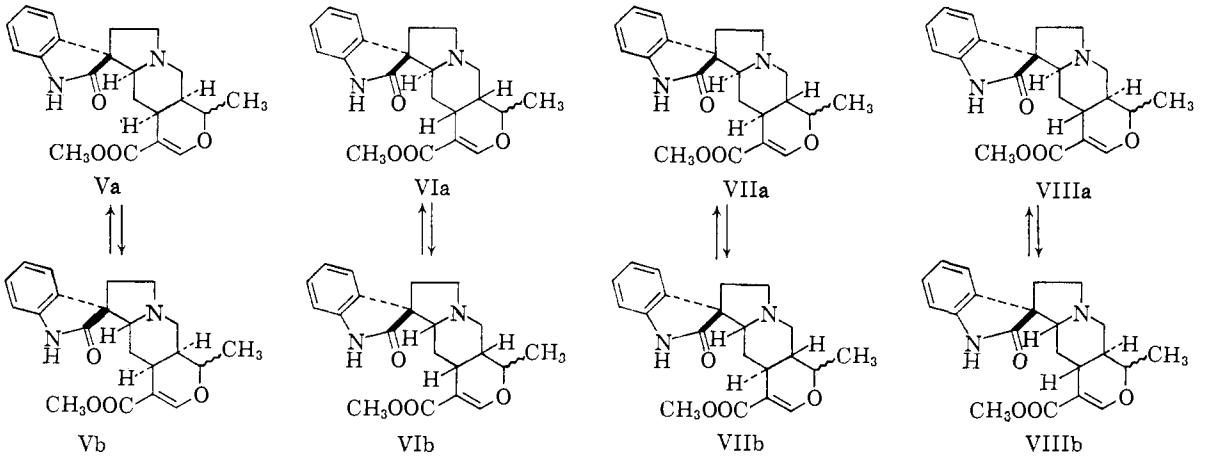
	pK_a[a]	At equilibrium, %	Hg-(OAc)$_2$[b]	Solubility in ether[b]
Uncarine B	5.5	20	[c]	Sl. sol.[a]
Uncarine A	4.2	80	[c]	Very sol.[a]
Mitraphylline	5.3	20	—	Sl. sol.
Isomitraphylline	Weaker base[b]	80	+	Very sol.
Rhyncophylline	6.3	30	—	Sl. sol.
Isorhyncophylline	5.2	70	+	Very sol.

[a] Taken from ref. 2 unless otherwise noted. [b] Taken from ref. 6 unless otherwise noted. [c] No data available.

of C_4-H and the mercury on N_5, hence a favored conformation for the free base such that this hydrogen and the electron-pair on N_5 are also *trans*.

In structures I–III there are five asymmetric centers, hence 32 stereoisomers. If we focus attention on the configurations and conformations about the C–D ring system, there are eight diastereomeric compounds obtainable by varying configurations on the ring system at C_3, C_4, C_{15} and C_{20}; each of these will have two possible positions for the methyl group on C_{19}. If the C_2–C_3 bond be arbitrarily placed in the β-position (steroid convention) as shown, the eight diastereomers may be grouped into four pairs depending on the configuration at C_4. These four pairs are depicted as structures V–VIII; of these, two pairs will have a *cis*-D/E junction and two will have a *trans*-D/E junction. The two compounds in each pair will now be interconvertible by the boiling pyridine isomerization, the more stable of the two being the one with α-C_4–H (*trans* to the C_2–C_3 bond; subscripts "a" in the series V–VIII). This is not the only arrangement capable of explaining the observed isomerization. It is conceivable that *both* the compounds in the pair possess the α-C_4–H shown in the model case to be the stable stereochemistry at this juncture, but that a difference in stability arises in the natural compounds from an opposite placement of ring E. Such a case can arise since *both* C_3 and C_4 are isomerized in the reaction and so may yield a different compound with the same relative, but opposite absolute, configurations at C_3 and C_4; this can occur in the natural compounds with asymmetry at the D/E junction but not in the model case with its aromatic ring E. For example, compound Va may isomerize to the enantiomer of VIa or VIIa to the enantiomer of VIIIa. The possibility of this type of isomerization is considered with the others in arriving at the conclusions below.

It is now necessary to consider the conformational possibilities of each of the eight diastereomers. Focusing on the conformational possibilities of the D-ring, we must consider both the conformational flip from one chair to the other, inverting each substituent from axial to equatorial or the reverse, and the inversion of the basic nitrogen (N_5), which changes the effective geometry of the C/D ring junction from a situation in which the nitrogen electron-pair is *cis* to one in which it is *trans* to the C_4 hydrogen. This has the conformational effect of changing the C/D junction from *cis* to *trans* and also dictates the geometry of the mercuri-acetate group and the proximity of the



basic nitrogen electron-pair to the base-inhibiting oxindole carbonyl. In all, then, *each* of the eight diastereomers can theoretically take up four conformations for each of its isomers at C_{18}, yielding a total of 64 forms to be considered. However, many of these cases are only sterically allowed with the D-ring forced into the boat conformation and, furthermore, a number in the more rigid D/E-*trans* cases are sterically impossible, requiring ring E to bridge two vicinal axial positions.

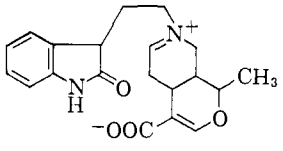
When these various conformations are considered with the aid of models it is possible to come to an unambiguous conclusion as to the most stable form for each of the eight stereoisomers. Only in one pair of compounds (VIIa–VIIb) does the entire set of conditions correspond to the preferred conformations, *i.e.*, one compound of the pair (VIIa) is the more stable with C_4–H *cis* to the C_2–C_3 bond and exhibits, in its preferred conformation, the basic electrons adjacent to the oxindole carbonyl (low basicity) and a *trans* diaxial orientation of those electrons to C_4–H ($Hg(OAc)_2$ reaction), while the other compound (VIIb) is the opposite in all respects. This pair of compounds accordingly is assigned to mitraphylline (VIIb) and isomitraphylline (VIIa). It is gratifying that in conformational terms they differ in stability by one axial substituent, which should account for 1–1.5 kcal./mole difference in their energy; calculation from $\Delta F = -RT\ln K$ (for boiling pyridine and $K = 4$) affords an observed energy difference of 1.1 kcal./mole. The stereochemistry of the methyl group at C_{19} remains unsettled but is not important to the decisions above, being in any event necessarily the same in each compound of an isomerizable pair. Since the same criteria also apply to rhyncophylline and isorhyncophylline, they must be represented by the same stereochemistry, *i.e.*, VIIb and VIIa, respectively. Proof of this contention should be obtainable by conversion of mitraphyllane (IIIb) to rhyncophyllane (IIIa).

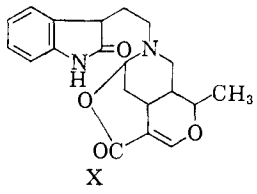
The remaining pair, uncarine A and B, cannot be the other D/E-*trans* pair (VIII) since both compounds in that pair have relatively high basicity and essentially the same in each. (As with mitraphylline, the C_{19}-methyl is unimportant to a decision with the pair VIII.) Hence, the uncarines must have a D/E-*cis* ring junction. This conclusion is strengthened by the report[5] that both uncarines on hot alkali treatment yield the same C_{20} lactone, m.p. 288°, which affords a single active hydrogen (Zerewitinoff). In view of the ready opening of ring C on heating (*vide supra*), it is likely that the product, IX, is attacked by the saponified carboxylate to yield in either case the lactone, X, which requires a *cis*-D/E junction for its formation. It may be noted here that a previous conclusion of a *trans*-D/E junction[2] rested on the inability of the tosylate of the lithium aluminum hydride reduction product, XI, to quaternize at N_5, by analogy with reserpol.[10] However, while the ring-E double bond permits formation of the lactone X, it renders the quaternization at N_5 in XI impossible even with a *cis*-D/E junction. Some evidence is available which suggests that the ester group is close to the oxindole NH in uncarine B, for the only significant difference in the Nujol infrared spectra of A and B[2] is that the NH peak is at longer wave length (3.1 μ) in uncarine B, suggesting H-bonding to the carbomethoxy; uncarine A, like normal oxindoles,[11] shows this absorption at 3.0 μ. Also, uncarine B and its methiodide are both insoluble in alkali, whereas the corresponding compounds in the decarboxy-B series (loss of $COOCH_3$ by hot acid) are soluble, in accord with the normal behavior of oxindoles.[2]

A choice of stereostructures for the uncarines is not so simply made as with mitraphylline, for all of the choices in the D/E-*cis* set (V, VI) are of about equal stability if the C_{19}-methyl is *not* considered; on the other hand, in this set the configuration of that methyl is of crucial importance to a decision on relative stabilities of the different conformers of each compound. This is to say that in any one of the four C/D-*cis* possibilities, a different conformer is preferred depending on the configuration of the C_{19}-methyl. Since the mercuric acetate oxidation has not been applied in this series, that criterion is of no avail, and we are forced to consider the criterion of proximity of the oxindole NH with $COOCH_3$. Here, however, we find one form and one only which fits this requirement, for in Va the most stable conformer appears to be XII

(10) C. F. Huebner and E. Wenkert, *J. Am. Chem. Soc.*, **77**, 4180 (1955); E. E. van Tamelen and P. D. Hance, *ibid.*, **77**, 4692 (1955); P. P. Diassi, C. M. Dylion, F. L. Weisenborn and O. Wintersteiner, *ibid.*, **77**, 4687 (1955).

(11) R. Silva, unpublished observations on Nujol spectra.


IX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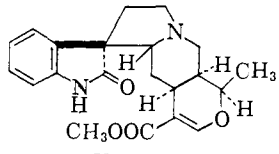
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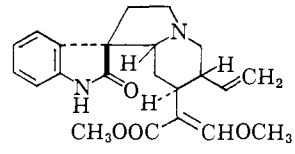
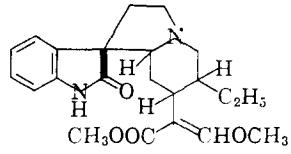

XIV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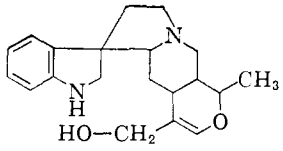
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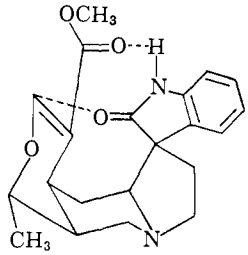
XII

if we grant the C_{19}-methyl a β-configuration. In this conformation the alignment of the oxindole with the carboxyl for H-bonding and shielding is remarkable. Since this represents the less stable (uncarine B = Va with 19-β-CH_3) of the two compounds and has the more stable configuration at C_3–C_4, it follows that the more stable uncarine A must also possess the same relative configuration at C_3–C_4 and hence can only be represented as XIII, the enantiomer of VIa. Again, the energy difference of about 1.1 kcal./mole is not unreasonable for these two isomers, favoring XIII.

Recently, corynoxeine and corynoxine were isolated from the same plant (*Pseudocinchona africana*) that produces corynantheine and several yohimbine isomers.[12] Dihydrocorynoxeine is identical with rhyncophylline, so that corynoxeine is XIV. Corynoxine, however, is a stereoisomer of rhyncophylline; it is convertible to the parent corynoxinane (IIIa), m.p. 70°, $[\alpha]_D$ −25°, which must therefore be the enantiomer of (iso)rhyncophyllane,[6] m.p. 70°, $[\alpha]_D$+24°.[11] This requires that centers C_{15} and C_{20} be epimeric in corynoxine from those in rhyncophylline and isorhyncophylline, but since these parent compounds are produced by conditions (Wolff–Kishner reduction) which probably are capable of isomerizing the C_3–C_4 linkage, there are four orientations at these centers possible for corynoxine itself. Of these, two represent enantiomers of rhyncophylline and isorhyncophylline, which are not consistent with the physical data,[13] so that corynoxine may be represented by XV or its (less stable) epimer at C_4; a slight preference for XV is discernible from the changes in optical rotation on conversion to the reduced parent compounds, wherein corynoxine parallels the optical behavior of isorhyncophylline rather than rhyncophylline.

It is not possible at present to consider the absolute stereochemistry of these alkaloids except to note the interesting circumstance that nature provides both dextro- and levo-rotatory mitraphylline,[14] thus requiring the opposite configuration at each of *five* asymmetric centers. Furthermore, although in the yohimbinoid indole alkaloids, the absolute configuration at C_{15} is apparently invariant,[15] in the oxindole analogs discussed here, this center must have the opposite configuration to the others at least in one of the enantiomeric mitraphyllines as well as in corynoxine as opposed to rhyncophylline.

Further studies aimed at elucidating the stereochemistry of these interesting alkaloids are in progress.

(12) N. AnCu, R. Goutarel and M.-M. Janot, *Bull. soc. chim. France*, [5], **24**, 1292 (1957).

(13) Corynoxine, m.p. 166–168°, $[\alpha]_D$ −14 ± 3°[11]; rhyncophylline, m.p. 210°, $[\alpha]_D$ −17 ± 2°[11]; isorhyncophylline, amorphous, $[\alpha]_D$ +8.1° (T. Nozoe, *Chem. Pharm. Bull. (Japan)*, **6**, 309 (1958)).

(14) T. Nozoe, *ibid.*, **6**, 306 (1958); G. M. Badger, J. W. Cook and P. A. Ongley, *J. Chem. Soc.*, 867 (1959); see also ref. 3.

(15) E Wenkert and N. V. Bringi, *J. Am. Chem. Soc.*, **81**, 1474 (1959).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT LOS ANGELES, LOS ANGELES 24, CALIF.]

The β-Sulfoacrylic Acids: Configuration and Diels–Alder Reactions

BY JAMES B. HENDRICKSON

RECEIVED MARCH 20, 1961

Preparation of the *cis*- and *trans*-β-sulfoacrylic acids has been reexamined and the geometric assignments of previous workers are reversed on grounds of acidity and other physical properties, stereochemistry of their modes of formation, and their reactions as dienophiles with furan and cyclopentadiene. The cyclic β-sulfoacrylic anhydride, corresponding to maleic anhydride, is prepared as well and the various diene adducts characterized with respect to configuration. The *cis*- and *trans*-acids both yield the same *trans*-adducts in a Diels–Alder reaction.

The monosulfonic acid analogs of maleic and fumaric acids and their derivatives appeared to have been little studied when certain related synthetic interests focused our attention on their potential as dienophiles in the Diels–Alder reaction. These two β-sulfoacrylic acids (I and II) were pre-