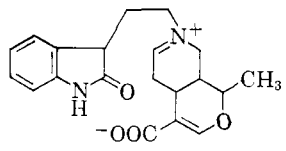
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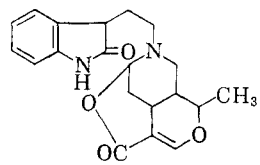
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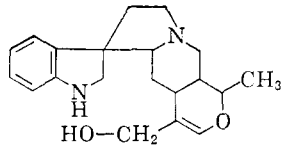
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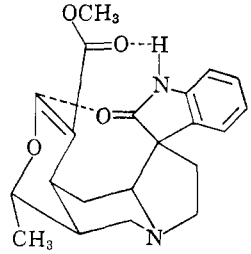
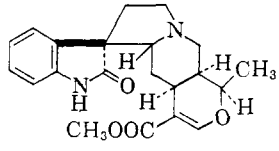

XII

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

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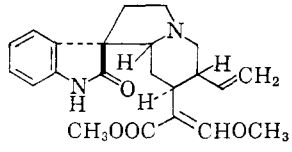
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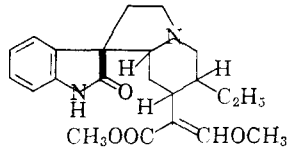
XV

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.

(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

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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-

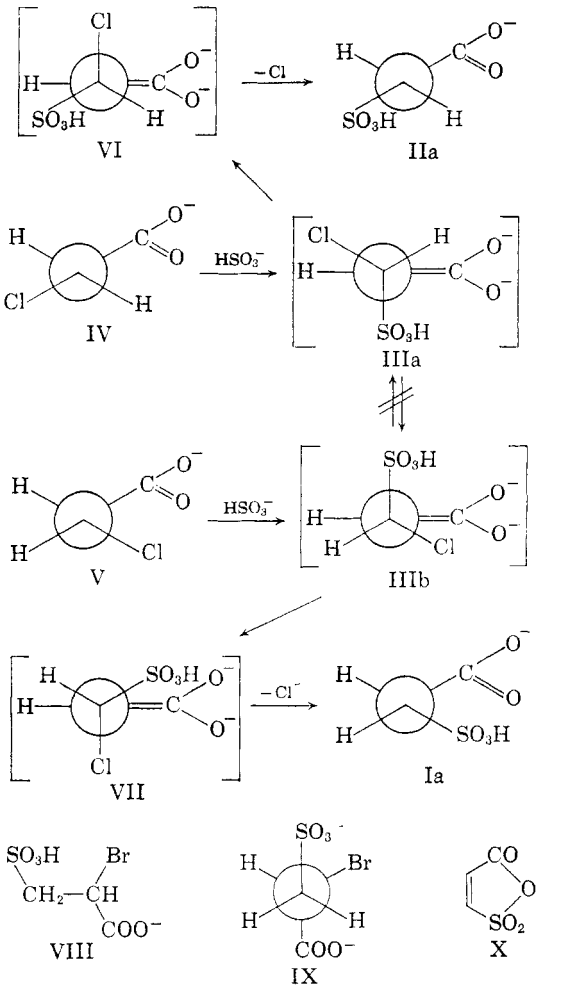
pared by Backer and Beute[1] in several ways and characterized as their barium salts. Acid A, stable hygroscopic crystals, m.p. 87–88°, was the stronger acid (pK 3.3) and formed a barium salt moderately soluble in hot water (15 g./100 cc.), from which it is recrystallized. Acid B, however, was an unstable hygroscopic sirup of pK 3.6 which formed a stable barium salt equally insoluble in hot or cold water (2 g./100 cc). On this basis A was assigned the *cis*-configuration I and B the *trans* configuration II. The assignments of Backer and Beute seemed at best tenuous and in fact their own results led us to the opposite assignments on the following grounds.

(1) Whereas it is true that maleic is a stronger acid than fumaric on ionization of the first proton, the reverse is true for ionization of the second (pK_1: maleic 1.82, fumaric 3.00; pK_2: maleic 5.89, fumaric 4.52).[2] Since it is generally true of sulfonic acids that they show pK values lower than unity, the measured pK's of the sulfoacrylic acids of Backer and Beute must have reference to ionization of the carboxyl groups and thus be comparable to the pK_2 values given above for maleic and fumaric. Therefore, the stronger acid A should by analogy have the *trans* configuration, not the *cis*.

(2) The greater stability and higher melting point of A also suggested the *trans* configuration, while the solubility data are of little value since the solubilities reverse themselves with temperature, B being more soluble than A at room temperature, but less soluble at 100°.

(3) Analysis of the mode of formation of the two acids provides a very compelling basis for assignment of geometry. Thus, acid B is the sole product of the spontaneous Michael addition of bisulfite ion to ammonium propiolate so that its assignment as the *cis* isomer follows directly from *trans* addition of the elements of sulfurous acid to the triple bond. Furthermore, the ammonium salt of *trans*-β-chloroacrylic acid (IV) reacts with bisulfite ion to produce only A while that of *cis*-β-chloroacrylic acid (V) yields only B. If a single Michael addition intermediate, III, were formed in each case as might be expected, then the same mixture of A and B should be produced from each by elimination of chloride ion from III. Accordingly, some more stringent stereoelectronic control must be operative that different products should emerge from these reactions. Thus, attack of the bisulfite ion must proceed in the plane of the π-electrons, *i.e.*, perpendicular to the molecular plane, giving rise to the products IIIa and IIIb[3] from IV and V, respectively. If the lifetime of IIIa or IIIb is very short or if there is a substantial barrier to rotation about the central C–C single bond, very little interconversion of IIIa and IIIb will be able to occur; then, each will take the more favorable path of least (60°) rotation to VI and VII, respectively, so as to be stereoelectronically oriented for elimination of chloride ion in the π-electron plane, analogous to the original bisulfite ion addition. The latter route can give only the single products IIa and Ia, respectively, so that the *trans*-β-chloroacrylic acid yields only the *trans*-β-sulfoacrylic acid. This allows assignment of the *cis* configuration to acid B and the *trans* configuration to (A).

Finally, acid A is produced in good yield on addition of bisulfite ion to the ammonium salt of α-bromoacrylic acid. The first step is again a Michael addition which can only yield the intermediate VIII since no direct, or semi-concerted elimination of bromide is possible here as it was in the previous example. This intermediate now has the leisure to ionize the sulfonic group and take up the preferred *trans* orientation IX of the two negative charges



before *trans* elimination of HBr, which must then result in the *trans*-β-sulfoacrylic acid. Thus this stereoelectronic reasoning in each of the three cases predicts consistently that A should be the *trans*-acid and B the *cis*-acid; this is also in harmony with the preceding deductions and in contradiction to the assignments of Backer and Beute. These authors also prepared the bis-acid chloride from acid A and found that it reverted smoothly in moist air to the stable monochloride (presumably sulfonyl); this fact also supports the *trans* formulation of A since the monochloride of the *cis*-acid would presumably cyclize spontaneously to the anhydride. Thus in the case of *o*-sulfobenzoic acid,

(1) H. J. Backer and A. E. Beute, *Rec. trav. chim.*, **54**, 200, 523 (1935).

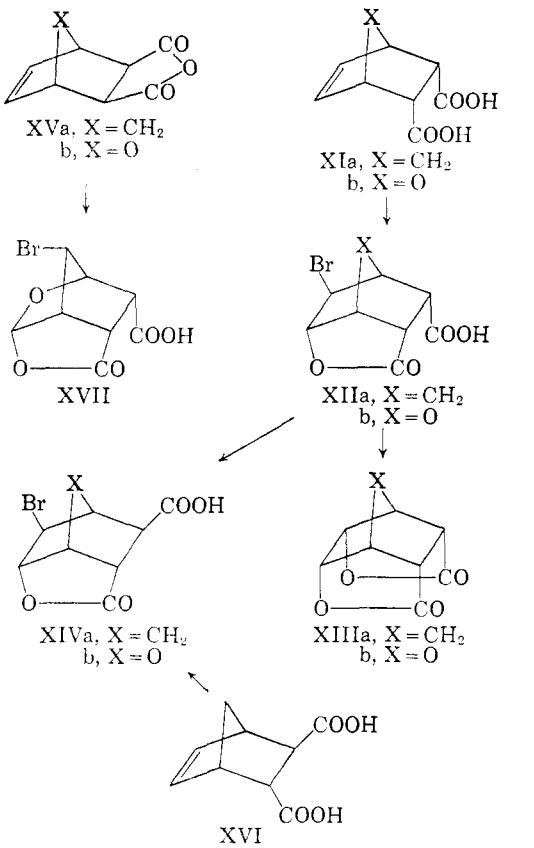
(2) "Handbook of Chemistry and Physics," 39th ed., ed. C. D. Hodgman, Chemical Rubber Publ. Co., Cleveland, Ohio, 1957.

(3) Addition of HSO_3^- from the other side of the molecular plane in each case will yield the mirror image of IIIa or of IIIb but this does not alter the argument.

acid-chloride-forming reagents (CH_3COCl, PCl_5, etc.) invariably produce only the anhydride.[4]

Sublimation of either acid with phosphorus pentoxide afforded good yields of the previously unknown β-sulfoacrylic anhydride X, the analog of maleic anhydride. This material provides the basis for experimental differentiation of the *cis*- and *trans*-acids. Thus, whereas both free acids yield X on heating with phosphorus pentoxide, only with B did the barium salt produce X on heating *in vacuo* with phosphorus pentoxide, the barium salt of A affording virtually no distilled material and charring slowly at 300°. This observation presumably supports assignment of the *trans* configuration to A; the matter should be most clearly solved, of course, by conversion of X to B by hydrolysis, but success in this approach was thwarted by lack of a successful means of either purifying or characterizing acid B. Thus, the invariant solubilities of the barium salt precluded recrystallization, whereas the acid itself was an oil which clearly decomposed slowly on standing. The S-benzylthiouronium salt of A crystallized cleanly from water (as did the barium salt) but that of B could not be obtained crystalline. Nevertheless, the crystalline S-benzylthiouronium salt from the anhydride after solution in water was different from that of acid A. Further attempts to characterize the rather unstable B have not been made, but it may be safely concluded that the present geometric assignments are correct.

Diels–Alder reactions in the maleic–fumaric series with cyclopentadiene and with furan have an extensive history[5–10] and the orientations of the various products are well understood. The more common *endo* adduction is illustrated in the reaction of maleic anhydride with cyclopentadiene, which affords the anhydride of the *endo-cis*-di-acid XIa[5]; the configuration of the acid is revealed by its ready bromination to the bromolactonic acid XIIa. Isomerization of the carboxyl group occurs on heating[5] or on standing with acetic anhydride and pyridine to yield the *exo*-acid XIVa, and the carboxyl configurations of the two can be established to be correct as shown by pyrolysis of the sodium salts, which in the case of XIIa yields the symmetrical cage dilactone XIIIa, whereas with XIVa, no reaction occurs. The other anhydride XVa, from the *exo-cis* acid, is prepared only indirectly,[5] from the *endo-cis*-di-acid, and gives a normal dibromo derivative rather than a bromolactone on hydrolysis and bromination. The *trans*-di-acid adduct XVI is more stable than either *cis*-acid, presumably due to crowding in the *cis*-acids, and is obtained from either of them by isomerization.[5] It is common behavior in these various series of adduct acids for the *cis*-acids to isomerize to the *trans* isomers, which appear generally to be more stable.[6–8] The *trans*-di-acid XVI may also be obtained directly by the addition of cyclopentadiene to fumaryl chloride and hydrolysis.[9] Bromination of the *trans*-acid XVI yields the bromolactone acid XIVa, identical with the one obtained by isomerizing XIIa.[5]



The corresponding series with furan is largely parallel in behavior,[6–10] but does show several interesting features of difference from those above. The acid adduct XIb from maleic acid and furan cannot be isolated,[7] but direct bromination of its aqueous solutions yields the *endo*-acid XIIb, as in the cyclopentadiene series. The dilactone XIIIb[10] is similarly produced by pyrolysis of the sodium salt,[11] and acetic anhydride in pyridine causes isomerization to the more stable *exo*-acid XIVb. When the Diels–Alder reaction is carried out with maleic anhydride instead of the acid, a reversal of steric course occurs and the *exo*-anhydride XVb is produced.[7] When this material is hydrolyzed and brominated the molecule achieves lactonization by

(4) C. Fahlberg and R. Barge, *Ber.*, **22**, 757 (1889); H. T. Clarke and E. E. Dreger, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 2nd ed., 1941, p. 495; Cobb, *Am. Chem. J.*, **35**, 502 (1906); E. C. White and S. F. Acree, *J. Am. Chem. Soc.*, **41**, 1197 (1919).

(5) O. Diels and K. Alder, *Ann.*, **460**, 98, 111 (1928); K. Alder and G. Stein, *ibid.*, **504**, 216 (1933); **514**, 1 (1934).

(6) K. Alder and K. H. Backendorf, *ibid.*, **535**, 101, 113 (1938).

(7) R. B. Woodward and H. Baer, *J. Am. Chem. Soc.*, **70**, 1161 (1948).

(8) H. Kwart and I. Berchuk, *ibid.*, **74**, 3394 (1952).

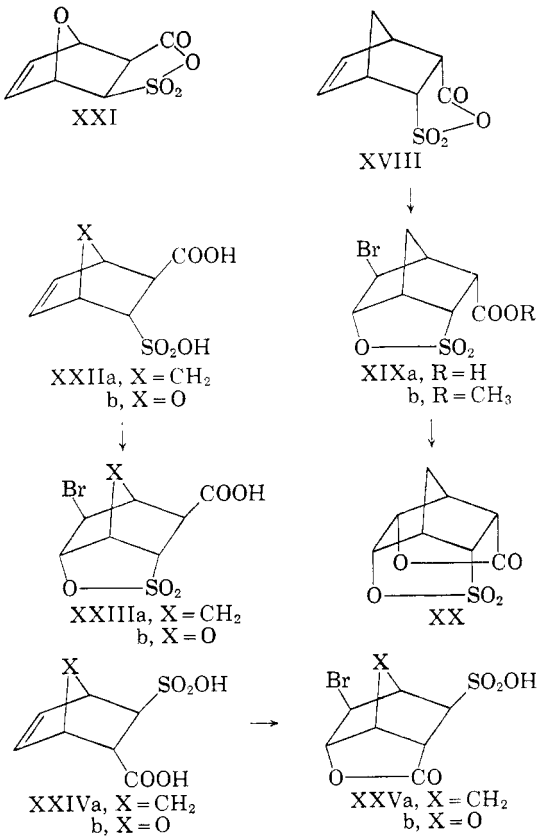
(9) K. Alder and G. Stein, *Ann.*, **514**, 197 (1934).

(10) J. Berson and R. Swidler, *J. Am. Chem. Soc.*, **75**, 1721 (1953).

(11) A new preparative method was developed which yields this curious molecule in good yield: if the bromolactone acid is heated with one equivalent of aqueous alkali or with three or more equivalents the yields are poor, but boiling for an hour with two equivalents and subsequent neutralization provides a 90% yield of the dilactone. This would seem to suggest that the closed lactone affords more hindrance to the requisite S_N2 displacement of bromide by carboxylate than a second, adjacent carboxylate anion does and that an excess of alkali promotes other reactions such as base-catalyzed β-elimination of the oxide bridge with ultimate formation of hydroxyphthalic acids. In this connection, positive ferric chloride tests were occasionally observed with the crude products of excess base reaction. The symmetry of the dilactone XIIIb is signally demonstrated in its boiling point (283°) which is only ten degrees higher than the melting point (273°).

means of a skeletal rearrangement, affording the rather unstable acid XVII. This material, as a masked aldehyde, differs markedly from the other bromolactonic acids in reacting with permanganate and Tollens reagent, but not with silver nitrate.[7]

Against this background, the reactions of the β-sulfoacrylic acids and the anhydride X were examined for dienophilic properties. When an equivalent of cyclopentadiene was added to a dioxane solution of β-sulfoacrylic anhydride (X) an exothermic reaction provided the *endo*-anhydride XVIII, the configuration of which is established by analogy with the maleic series above as well as by formation of the bromosultonic *endo*-acid XIXa by aqueous bromination. The ester XIXb was produced by dissolving the anhydride in methanol and brominating as well as by the action of diazomethane on XIXa. Pyrolysis of the potassium salt of the



endo-acid XIXa under vacuum caused sublimation of the cage sultonelactone XX, by analogy with the formation of the dilactones above However, no crystalline products could be obtained on attempted room-temperature isomerization of the *endo*-acid XIXa with acetic anhydride–pyridine. Since the sultone group, unlike the lactone of XII, is readily displaceable by nucleophiles this failure need not be regarded as significant. The reaction of the anhydride X with furan in dioxane yielded a crystalline adduct in 15 hours. Unlike XVIII, however, bromination of aqueous or methanolic solutions afforded only unstable oils which unlike XIX or its mother liquors decolorized permanganate solutions and precipitated silver from Tollens reagents, but did not yield a precipitate with silver nitrate. Although repeated attempts afforded no crystalline material, the anhydride is assigned the *exo* configuration XXI since its behavior mirrors that of the corresponding anhydride XVb.

It may be noted here that the asymmetry of the sulfoacrylic adducts provides an opportunity in every aqueous bromination for two products instead of one as in the maleic series, for it is always possible to obtain both a bromolactonic sulfonic acid and a bromosultonic carboxylic acid. When anhydride adducts such as XVIII and XXI were to be brominated, primary methanolysis often was employed so that the anhydride might open exclusively to a carboxylic ester, affording only a sulfonate anion for displacement of the bromonium ion in bromination. In the case of XVIII this regimen should lead to the single product XIXb, but consideration of the mechanism of bromination of XVb[7] leads to several possible products for an analogous reaction with XXI, all of which are internal acetals and several are strong sulfonic acids as well, so that the failure to isolate pure products is not surprising. In general, attempts to isolate sulfonic acid by-products in any of these various reactions. after obtaining the carboxylic acid products, led only to darkening and decomposition.

The *trans*-acid II in aqueous solution, after stirring overnight with an equivalent of cyclopentadiene, absorbed 35% of the theoretical aqueous bromine and deposited, in 14% yield, a crystalline acid with an analysis corresponding to XXIIIa. The two possible adducts for *trans*-β-sulfoacrylic acid are XXIIa and XXIVa and bromination yields XXIIIa and XXVa, respectively. The uptake of bromine suggests that both are in fact formed, but that XXVa stays in solution as an ionized strong acid and only XXIIIa precipitates. The acid XXIIIa and its methyl ester bear a strong resemblance to the isomeric XIXa and XIXb in spectra and properties, but they are not identical. In an entirely analogous manner, when excess furan was stirred three days with an aqueous solution of II and brominated, 55% of the theoretical bromine was consumed and a 16% yield of the bromosulfonic acid XXIIIb crystallized out. By analogy with XIVb, it was stable to Tollens reagent and permanganate and its sodium salt yielded no sublimate on pyrolysis.

These reactions appear to allow definition of the structural assignments shown and thus also serve to confirm the *trans* geometry of the β-sulfoacrylic acid (acid A, above). In the light of these results, then, it was especially surprising to find that *the other sulfoacrylic acid yielded, with both cyclopentadiene and furan, the identical bromosultonic acids that were produced by the trans acid!*

It is therefore important to inquire into the stage of the process which conceals the *cis–trans* isomerization. That the barium salt of the *cis*-acid I contains as much as half of the *trans* form (as the yields imply if this is the source of the *exo*-acid XXIII in the *cis* case) is ruled out by the solubility behavior and infrared spectrum of the *cis*-salt. Thus the large solubility of the *trans*-salt in hot water and ready crystallization on cooling contrasts with the low and temperature-invariant solubility

of the *cis*-salt; when the *cis*-salt is heated with small volumes of water and filtered hot, no crystallization occurs on cooling the filtrate, nor are any crystals of the well-defined *trans*-S-benzylthiouronium salt formed on concentrating and adding the reagent. Furthermore, the infrared spectrum of the *trans*-salt shows a major band at 7.9 μ which is not present in the other salt. Hence we may conclude that little if any *trans*-salt (and certainly not over 50% as required by the Diels–Alder evidence) is present in the *cis* samples.

The isomerization of *cis* to *trans*, then, must *a priori* occur either in the sulfoacrylic form in solution before Diels–Alder adduction, on the *cis* adduct after it has been formed, or at an intermediate stage of a two-step adduction reaction. The possibility that the isomerization occurs during the lifetime of such an intermediate is important for its bearing on the mechanism of the Diels–Alder reaction[12] and so was examined at some length. That the free *cis*-β-sulfoacrylic acid does not isomerize in aqueous solution is shown by the recovery, from a solution of the anhydride X in water allowed to stand for three days, of the identical leaflets of the S-benzyl-thiouronium salt formed directly after this anhydride is hydrolyzed, and different from the corresponding salt of the *trans*-acid II. The *endo-cis*-diacid which is the expected product from the *cis*-acid I and cyclopentadiene can be made by hydrolysis of the *endo-cis*-anhydride adduct XVIII; this compound does not isomerize to the more stable *trans*-acids XXIIa or XXIVa on standing in aqueous solution several days (the conditions of the Diels–Alder reaction), as shown by formation of the same bromosultonic *endo*-acid XIXa as that formed directly from hydrolysis of the anhydride, and different from the more stable *exo*-acid XXIIIa formed on bromination of the Diels–Alder adduct from the two sulfoacrylic acids.

The evidence cited above implies that essentially no *trans*-acid salt is present in samples of the *cis*-acid salt, that the *cis*-acid I (at least as formed by hydrolysis of the anhydride) is stable in water several days at room temperature, that the *endo-cis* diacid, its presumed adduct with cyclopentadiene, is also stable, and yet that this *cis*-acid I nonetheless yields the *trans*-acid XXIIa on adduction with cyclopentadiene. Thus the evidence would appear to point to an isomerization during the adduction reaction, *i.e.*, by formation of one adduct bond followed by rotation around the central bond of the sulfoacrylic moiety *before* formation of the second bond. Unfortunately, however, a variety of experiments designed more clearly to demonstrate this have foundered on the apparent instability and contamination of the *cis*-acid as made from its barium salt, and in particular the fact that hydrolysis of the anhydride followed by shaking with cyclopentadiene or furan under the Diels–Alder conditions failed to produce any crystalline products even on bromination. Thus it cannot yet be said with certainty at what stage the isomerization occurs, but the relevance to the mechanism of the Diels–Alder reaction is of sufficient importance to merit a more detailed examination of other derivatives of these sulfoacrylic acids.

(12) For a recent discussion of this mechanism, see R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

Experimental[13]

Improved Preparation of Barium *trans*-β-Sulfoacrylate.—To a solution of 60 g. of potassium hydroxide in 250 ml. of water was added, dropwise with stirring, 100 g. (0.405 mole) of ethyl α,β-dibromoacrylate; addition required 2–3 hours at room temperature. The resultant clear solution was neutralized with concentrated hydrochloric acid to *p*H 7 and 120 ml. of a 3.3 *M* solution of ammonium sulfite was added (this solution, made by passing sulfur dioxide into concentrated aqueous ammonia, should be freshly titrated before use). The clear solution was allowed to stand 24 hours, then a solution of 100 g. of barium chloride dihydrate in 300 ml. of water was added and the resultant suspension heated to boiling and filtered hot through Celite. On cooling to 0° overnight, the barium salt crystallized out. Recrystallized from 100–150 ml. of hot water, it formed heavy white crystals, dried over phosphorus pentoxide *in vacuo* at room temperature to 28.1 g. (23%); infrared spectrum (KBr): 6.16, 6.33, 7.14, 7.9, 8.6, 9.5, 10.5, 11.9 μ.

Anal. Calcd. for $C_3H_2SO_5Ba$: Ba, 47.78. For $C_3H_2SO_5Ba \cdot {}^1/_2 H_2O$: Ba, 46.33. Found: Ba, 46.57.

***trans*-β-Sulfoacrylic Acid (A).**—The barium salt was dissolved in a minimum of hot water and the calculated amount of 1 *M* sulfuric acid added, the resultant barium sulfate filtered through Celite and the solution evaporated under vacuum to an oil which largely turned crystalline after several days drying in vacuum over phosphorus pentoxide. The S-benzylthiouronium salt was best prepared from the barium salt by adding an equimolar quantity of S-benzylthiouronium sulfate in water to a hot aqueous solution of the barium salt, filtering the barium sulfate, and concentrating the filtrate to obtain large colorless needles, m.p. 172°, after recrystallizing from water.

Anal. Calcd. for $C_3H_2SO_5(C_8H_{11}N_2S)_2$: C, 47.09; H, 4.99; N, 11.57. Found: C, 47.09; H, 4.91; N, 11.47.

***cis*-β-Sulfoacrylic Acid (B).**—The barium salt was prepared from freshly distilled propiolic acid according to Backer and Beute,[1] but obtained in lower yields (14%).

Anal. Calcd. for $C_3H_2SO_5Ba \cdot {}^1/_2H_2O$: Ba, 46.33. Found: Ba, 46.60.

Various attempts to make the S-benzylthiouronium salt produced only oils. Preparation of the free acid as above for the *trans*-acid produced thick sirups which darkened on standing in vacuum.

β-Sulfoacrylic Anhydride (X).—Ether *cis*- or *trans*-acids, mixed intimately with about thrice the amount of phosphorus pentoxide and heated an hour at or over 140° and 0.1 mm. pressure sublimed out the anhydride as clean colorless blocks, m.p. 90–92°, in yields of 50–60% depending on the quality of the starting acid. Mixed with twice its weight in phosphorus pentoxide, the dry barium salt of the *trans*-acid II produced no distillate at 310° (0.01 mm.) in 12 hours while the dry barium salt of the *cis*-acid I produced the anhydride in fair yields under the same conditions in less than 1 hour. The anhydride was only slightly soluble in methylene chloride and ether but dissolved exothermically in water or alcohols. Very hygroscopic, it was sublimed for analysis; infrared spectrum (dioxane): 5.49 μ.

Anal. Calcd. for $C_3H_2SO_4$: C, 26.87; H, 1.50. Found: C, 26.84; H, 1.78.

The anhydride (207 mg.) was dissolved in 2 ml. of water and the solution divided in half. One half was neutralized to phenolphthalein and an aqueous solution of 0.3 g. of S-benzylthiouronium sulfate added, the resultant slurry filtered, and the filtrate concentrated to crystallize the salt, which was recrystallized twice from water to fine colorless leaflets, m.p. 164°, mixture m.p. with the salt from acid II, 158–162°.

Anal. Calcd. for $C_3H_2SO_5$ $(C_8H_{11}N_2S_2)$: C, 47.09; H, 4.99. Found: C, 47.03; H, 5.09.

The second half of the dissolved anhydride solution was allowed to stand at room temperature for 3 days, then

(13) All melting points are corrected. Microanalyses were performed by Miss Heather King of this department. Infrared spectra were obtained on a Perkin–Elmer model 21 spectrophotometer using chloroform or methylene chloride as solvents unless otherwise noted.

treated as above to yield the identical S-benzylthiouronium salt, m.p. and mixed m.p. 164°.

Preparation of the Dilactone XIIIa.—The bromolactonic *endo*-acid XIIa, m.p. 159–161°, was prepared according to Alder and Stein (lit.[5] m.p. 157°), neutralized in aqueous solution with 2 *N* potassium hydroxide and evaporated to dryness. The salt so obtained was pyrolyzed at 200° (0.01 mm.) to yield fine blocks of the white dilactone, m.p. 276–277°, identical with a sample prepared according to the German authors.[5] Both the reported m.p. of 266°[5] and the present value are probably unreliable owing to the rapidity with which the compound sublimes; the present m.p. was observed on a hot-stage by placing the compound on the heat above 240° and heating relatively rapidly; infrared spectrum (KBr), 5.60 μ.

Preparation of the Dilactone XIIIb. (1) **Mole Ratio 1:1.**—To 522 mg. of the *endo*-bromolactonic acid XIIb (1.98 mmoles) was added 2.3 ml. of 0.86 *M* sodium hydroxide (1.98 mmoles). The mixture was diluted to 25 ml. with water and refluxed for 1 hour, then cooled and passed through a cation-exchange resin (H^+) column. The eluate was evaporated to a small volume and 81 mg. of crystals of m.p. 190–202° filtered (infrared spectrum identical to starting material, m.p. 210°, which did not depress the melting point.) On standing, the further concentrated filtrate produced 294 mg. of off-white crystals, m.p. 216–255°, with the spectrum of the dilactone.

(2) **Mole Ratio 2:1.**—To 513 mg. of the acid XIIb (1.95 mmoles) was added 4.4 ml. of 0.86 *M* sodium hydroxide (3.78 mmoles) and the above procedure followed, resulting in no starting material and 319 mg. (90%) of hard white blocks, m.p. 272–273° (lit.[10] 269.5°), b.p. 283°; infrared spectrum (KBr), 5.60 μ.

Anal. Calcd. for $C_8H_6O_5$: C, 52.76; H, 3.31. Found: C, 52.80; H, 3.36.

(3) **Mole Ratio 3:1.**—With 551 mg. of the acid XIIb (2.09 mmoles) and 7.3 ml. of 0.86 *M* sodium hydroxide (6.27 mmoles) in the above procedure, a 34% yield of tan crystals, identical with the dilactone above, were produced.

(4) **Pyrolysis of the Sodium Salt of XIIb.**—The salt was prepared in aqueous solution from equivalent amounts of the acid XIIb and sodium bicarbonate and the solution evaporated. Pyrolysis of the salt at 140° (0.002 mm.) caused sublimation of white blocks of the anhydride, m.p. and mixed m.p. 270–272°.

Isomerization of the Bromolactonic Acids XII.—Either acid (200 mg.) dissolved in 1 ml. of acetic anhydride and 2 ml. of pyridine and left to stand overnight, with later evaporation under vacuum and extraction from cold 3 *N* hydrochloric acid with methylene chloride, produced, on drying, evaporating, and recrystallizing from water, the *exo*-acids: XIIIa, 63 mg., m.p. 184–187° (lit.[5] 187°); and XIIIb, 131 mg., m.p. 229°–233° (lit.[14] 232°).

Diels–Alder Reaction of Cyclopentadiene with β-Sulfoacrylic Anhydride (X).—Freshly sublimed anhydride X (262 mg.) was dissolved in 2 ml. of dry dioxane and chilled and 0.2 ml. of freshly distilled cyclopentadiene added. The exothermic reaction gave a clear colorless solution which was evaporated *in vacuo* to a gray oil and crystallized with an ether–methylene chloride mixture to hygroscopic crystals, m.p. 118–120°; infrared spectrum (KBr), 5.51 μ.

Anal. Calcd. for $C_9H_8SO_4$: C, 48.01; H, 4.03. Found: C, 47.77; H, 4.20.

Bromination of the Anhydride XVIII.—To the 2 ml. of chilled dioxane solution from 0.77 g. (5.7 mmoles) of anhydride X and 0.47 ml. of cyclopentadiene, after 5 minutes, was slowly added 10 ml. of water and let stand half an hour. The slightly murky solution was filtered through Celite and made up to 20.0 ml. with water; 15.0 ml. was brominated with 0.22 *M* aqueous bromine solution until excess bromine remained (required 15.0 ml., 3.3 mmoles, or 77%). The slightly milky solution was extracted 3 times with methylene chloride and the extracts dried and evaporated to a residue which afforded 95 mg. (7.4%) of crystals from methanol, m.p. 215–220° (bubbles); recrystallized from methanol to white blocks, m.p. 221–224° (bubbles).

Anal. Calcd. for $C_8H_9SO_5Br$: C, 32.34; H, 3.06. Found: C, 32.56; H, 2.92.

The aqueous mother liquors from bromination and extraction were neutralized with potassium hydroxide, evaporated to dryness and pyrolyzed at 0.05 mm. and up to 280° with only a few mg. of a dark brown film subliming.

The remaining 5.0 ml. of aqueous solution from the above was allowed to stand for 5 days before brominating, whereupon bromination as before (requiring 5 ml. of bromine water) yielded 30 mg. of the identical crystalline acid, m.p. and mixed m.p. 216–221° (bubbles).

The Sultone-lactone XX.—The *endo*-acid XIXa (52 mg., 0.17 mmole) and 18 mg. (0.18 mmole) of potassium bicarbonate were dissolved in 0.5 ml. of water and evaporated to a white salt, which, on pyrolysis at 220° and 0.03 mm. for several hours, produced a small amount of a white crystalline sublimate, m.p. 272–275°(much sublimation).

Anal. Calcd. for $C_8H_8SO_5$: C, 44.45; H, 3.73. Found: C, 44.72; H, 3.92.

The Methyl Ester XIXb of the Bromosultonic *endo*-Acid.—The anhydride XVIII (219 mg., 1.09 mmoles) was dissolved by warming briefly in 3 ml. of methanol, than 0.22 *M* aqueous bromine solution was added until its color remained, which required 3.8 ml. (0.84 mmole). Colorless needles (32 mg., 10%) crystallized from solution, m.p. 138°.

Anal. Calcd. for $C_9H_{11}SO_5Br$: C, 34.95; H, 3.48. Found: C, 35.34; H, 3.54.

Treatment of the acid above of m.p. 215–220° with ethereal diazomethane likewise afforded this ester, m.p. and mixed m.p. 138°.

Diels–Alder Reaction of Furan with β-Sulfoacrylic Anhydride (X).—The freshly sublimed anhydride X was dissolved in 3 ml. of dry dioxane and 101 mg. (1.48 mmoles) of furan added (201 mg., 1.50 mmoles). The ultraviolet spectrum showed virtually complete disappearance of absorption at 250 mμ in 15 hours, at which time disturbance of the solution caused crystallization of 130 mg. (44%) of silvery, hygroscopic needles, darkening at 120°. m.p. 135° dec., recrystallized from ether; infrared spectrum (KBr), 5.5 μ.

Anal. Calcd. for $C_7H_6SO_5$: C, 41.59; H, 2.99. Found: C, 41.32; H, 3.18.

Reactions of the Anhydride XXI.—The anhydride XII (8.5 mg., 0.042 mmole) dissolved in 0.5 ml. of warm water and its solution rapidly decolorized just 0.20 ml. of 0.21 *M* aqueous bromine solution (0.042 mmole), giving a clear, colorless solution which yielded no precipitate on standing. Evaporation at room temperature under vacuum yielded a dark red residue which afforded no sublimate on pyrolysis at 210° and 0.03 mm. Similarly, 53 mg. of XXI (0.26 mmole) dissolved in 2 ml. of methanol on warming, and decolorized just 1.3 ml. of 0.21 *M* aqueous bromine (0.26 mmole) rapidly; a slight excess of bromine remained unchanged for half an hour and was decolorized by a grain of sodium bisulfite. To the clear colorless solution then was added 2.6 ml. of 0.10 *N* sodium hydroxide (0.26 mmole), yielding a neutral solution which was evaporated to a reddish solid. Acetone was added and the red solution filtered from a gray solid (sodium bromide), soluble in water and precipitating with silver nitrate. Evaporation of the red acetone solution yielded a red semi-solid which did not precipitate with cold, alcoholic silver nitrate but did rapidly decolorize 1% potassium permanganate and gave a black precipitate with Tollens reagent.

Diels–Alder Reactions of the β-Sulfoacrylic Acids. (1) **Cyclopentadiene.**—Barium *trans*-β-sulfoacrylate (1.31 g., 4.4. mmoles) was warmed into 5 ml. of water and acidified with 4.80 ml. of 0.91 *M* sulfuric acid, the barium sulfate precipitate filtered off on Celite and the clear filtrate stirred 24 hours with 0.36 ml. (4.4 mmoles) of freshly distilled cyclopentadiene. The mixture was made basic and washed with ether, then reacidified and 0.22 *M* aqueous bromine added until it failed to be immediately decolorized; 7.0 ml. (1.54 mmoles, 35%) was required. In a few minutes fine colorless needles appeared in the solution; filtered and dried they weighed 184 mg. (14%), m.p. 265°, recrystallized from methanol to m.p. 265–266°.

Anal. Calcd. for $C_8H_9SO_5Br$: C, 32.34; H, 3.06. Calcd. for $C_8H_9SO_5Br \cdot {}^1/_2\ CH_3OH$: C, 32.60; H, 3.51. Found: C, 32.89, 33.11; H, 3.21, 3.22.

The methyl ester was obtained from treatment with ethereal diazomethane; m.p. 158–160°, recrystallized from methanol. Mixed with the *endo*-ester XIXb of m.p. 138° this showed m.p. 115°.

(14) O. Diels and K. Alder, *Ann.*, **490**, 243 (1931).

Anal. Calcd. for $C_9H_{11}SO_6Br$: C, 34.74; H, 3.54; Br, 25.69. Found: C, 34.95; H, 3.48; Br, 25.37.

The identical conditions with the other barium salt produced 5.4% yield of the identical acid, m.p. 263°, mixed m.p. 261–263°, as the sole product in the above reaction.

(2) **Furan.**—Barium *trans*-β-sulfoacrylate (1.04 g., 3.46 mmoles) was warmed into about 2 ml. of water, neutralized as above with 3.85 ml. of 0.91 *M* sulfuric acid, and the clear filtrate, made up to 10 ml., was shaken with 1.0 g. (15 mmoles) of furan for 36 hours. The aqueous layer was separated and brominated with 0.22 *M* aqueous bromine solution until it was no longer rapidly decolorized and the fine colorless needles which crystallized from solution filtered and dried. The identical experiment was performed on 1.04 g. of the other barium salt and a control on furan and water alone with the results as tabulated.

The mixed m.p. of the products was 224–228°. The product was recrystallized from water to long fine needles, m.p. 224–229°.

Barium β-sulfoacrylate	Bromine required[a] Ml.	%	Cryst. prod. Mg.	%	M.p., °C.
trans	8.8	55	174	16	226–230
cis	6.0	38	105	10	225–229

[a] Minus the control experiment quantity (2.4 ml.).

Anal. Calcd. for $C_7H_7SO_6Br$: C, 28.11; H, 2.33; Br, 26.72. Found: C, 27.90; H, 2.61; Br, 26.21.

When the reaction mixture was half-neutralized first to remove the strong acid of the sulfonic group or the time increased to 10 days or the amount of furan varied, the results were substantially the same. The methyl ester of the acid was obtained from ethereal diazomethane as brilliant needles, recrystallized from methanol, m.p. 184°.

Anal. Calcd. for $C_8H_9SO_6Br$: C, 30.68; H, 2.88; Br, 25.55. Found: C, 30.75; H, 3.07; Br, 25.55.

[CONTRIBUTION FROM THE CLAYTON FOUNDATION BIOCHEMICAL INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS, AUSTIN, TEXAS]

Synthesis and Properties of 2-Acetyl-3,4-dimethylthiazolium Iodide[1]

BY KOJI DAIGO[2] AND LESTER J. REED

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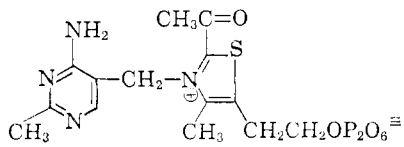
2-Acetyl-3,4-dimethylthiazolium iodide (II) was synthesized by reaction of 2-acetyl-4-methylthiazole with methyl iodide. Evidence is presented that compound II undergoes nucleophilic attack by water to give acetic acid, by hydroxylamine to give acethydroxamic acid and by mercaptide ions to give thiolacetates. These data point up the kinetic and thermodynamic instability of the 2-acetylthiazolium salt and provide support for the mechanism previously proposed for thiamine pyrophosphate action in the oxidative decarboxylation of α-keto acids.

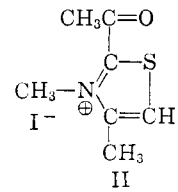
Implicit in the mechanism of thiamine action proposed by Breslow is the requirement that 2-acetylthiamine contain an "active" acetyl group.[3–5] Breslow and McNelis[5] reported in a preliminary communication the preparation in crude form of 2-acetyl-3,4-dimethylthiazolium nitrate and presented evidence that this compound is easily deacylated in the presence of water or methanol. White and Ingraham[6] reported similar observations indicating kinetic instability of a crude preparation of 2-benzoyl-3,4-dimethylthiazolium iodide.

Breslow has suggested[4] that 2-acetylthiamine

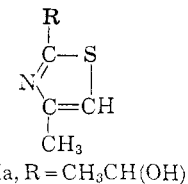


I

pyrophosphate (I) is an intermediate in the phosphoketolase catalyzed reactions. In a recent publication from this Laboratory[7] evidence was presented that an energy-rich acetyl compound, presumably compound I, is an intermediate in the ferricyanide-linked oxidation of pyruvate catalyzed by the pyruvic carboxylase component of the *Escherichia coli* pyruvate dehydrogenation complex. Compound I also was considered to be a possible intermediate in enzymatic oxidations of pyruvate involving electron acceptors other than ferricyanide, *e.g.*, protein-bound lipoic acid. Similar suggestions were made independently by Holzer and Crawford[8] and by Krampitz.[9] In view of the possible significance of 2-acetylthiamine pyrophosphate in these enzyme catalyzed reactions, it appeared highly desirable to obtain a pure sample of a 2-acetylthiazolium salt for model studies. This paper reports the synthesis of 2-acetyl-3,4-dimethylthiazolium iodide (II) and evidence indicating its kinetic and thermodynamic instability.



II



IIIa, R = $CH_3CH(OH)$
b, R = CH_3CO

2-(α-Hydroxyethyl)-4-methylthiazole (IIIa)[10] was oxidized with dichromic acid to obtain 2-acetyl-4-methylthiazole (IIIb). Quaternization of the latter compound was found to be rather difficult in agreement with the findings of Breslow and McNelis.[5] Some quaternization was accomplished

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(2) Rosalie B. Hite Postdoctoral Fellow, 1959–1961.

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(9) Paper presented at the 45th Annual Meeting of the Federation of American Societies for Experimental Biology, Atlantic City, N. J., April, 1961.

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