TABLE I

ASSIGNMENTS OF CHARACTERISTIC BANDS IN THE INFRARED ABSORPTION SPECTRA OF MYOSMINE AND ITS TWO HYDROCHLORIDES

Compound	Ammonium bands of Δ^1-Pyrroline	Ammonium bands of Δ^1-Pyridine	Immonium bands of Δ^1-Pyrroline	Immonium bands of Δ^1-Pyridine	Azomethine group of Δ^1-Pyrroline	Azomethine group of Δ^1-Pyridine
Myosmine[a]	[4.07][b]		...	...	6.15[c]	6.26[d]
Myosmine monohydrochloride[e]	3.94[f]	...	5.30[g]	...	6.00[h]	6.31
Myosmine dihydrochloride[i]	3.99	4.30[k]	5.30	4.79[l] 5.04	6.00	6.12[m]

[a] A sample of this base, m.p. 45°, was kindly placed at my disposal by Dr. A. Eisner through the courtesy of Dr. B. A. Brice. [b] This slight but distinct band in the ammonium region is lacking in the spectrum of myosmine in carbon tetrachloride solution (C. R. Eddy and A. Eisner, *Anal. Chem.*, in press); it may be due to traces of HCl present in the solvent rather than to a possible zwitterionic form of Δ^2-myosmine. [c] As has been pointed out by Eddy and Eisner, ref. 5, this strong and characteristic >C=N— band, together with the absence of bands in the NH region, clearly prove that myosmine is derived from a Δ^1- rather than Δ^2-pyrroline. [d] *Cf.* B. Witkop, *Experientia*, **10**, Oct. (1954), footnote 5. [e] The monohydrochloride was prepared by adding somewhat less than one equivalent of standardized ethereal hydrogen chloride solution to a solution of myosmine in ether; very hygroscopic microcrystalline colorless powder, subliming around 100° to glistening rods, m.p. 155–158° (clear melt). *Anal.* Calcd. for $C_9H_{10}N_2 \cdot HCl \cdot {}^2/_3H_2O$: C, 55.55; H, 6.38; N, 14.38; Cl, 18.28. Found: C, 55.58; H, 6.42; N, 14.81; Cl, 18.70. [f] The hydrochlorides of ethyl iminoacetate and cyclohexylidene aniline show ammonium bands at 4.97 and 4.90; 5.05 (B. Witkop, THIS JOURNAL, **76**, Unpubl. (1954); conjugation with aromatic rings, such as in indolenines, moves this band to 4.0–4.36. [g] Immonium bands at 5.30 and higher are only shown by the hydrochlorides of pyridines bearing substituents in the 4-position, *e.g.*, 8-picoline, 4-ethyl-, 4-isopropyl-, 4-*t*-butyl-, 4-benzylpyridine, etc. (B. Witkop, *Anal. Chem.*, in preparation). [h] The hypsochromic shift of this band produced by salt formation is highly characteristic of a conjugated or isolated $<C{=}\overset{\oplus}{N}H-$ group, *cf.* ref. *d*. [i] Prepared by adding an ethereal solution of myosmine to a solution of excess HCl in ether; microcrystalline colorless powder, subliming to stubby needles at 100° and higher, melting unsharply between 150 and 175°. *Anal.* Calcd. for $C_9H_{10}N_2 \cdot 2HCl$: C, 49.36; H, 5.52; N, 12.79. Found: C, 49.90; H, 5.39; N, 12.62. Both di- and monohydrochlorides are insoluble in chloroform. [k] No pyridine has been found so far whose hydrochloride shows a band below 4.0 in the ammonium band region. [l] These two bands are immonium bands of the pyridine ring as the comparison with the identical doublet in nicotine dihydrochloride (ref. *d*), at 4.77 and 5.04 μ shows (Fig. 1B). [m] The hypsochromic shift and the position of this band are very characteristic of a protonated pyridine (ref. *d*).

ketone (267 → 264 mμ) and dissimilar to the bathochromic shift of 3-vinylpyridine (278 → 287). With or without hydrolysis, this behavior is well explained by structure I. The name N-methylmyosmine for dihydronicotyrine[3] should be expunged from the literature.

The extension of the application of the immonium band method to the study of tautomeric pyrrolines and piperideines (anabaseine, anatabine, etc.) is being contemplated.

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[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH]

Chemistry of Dihydroxyfumaric Acid[1]

BY SIDNEY GOODWIN AND BERNHARD WITKOP

RECEIVED APRIL 5, 1954

Infrared data on derivatives of dihydroxyfumaric acid are presented and discussed. Infrared evidence suggests that both dimethyl as well as diethyl ester A are derived from dihydroxyfumaric acid. The methanolysis and subsequent diazomethane esterification of diacetoxy- (II) and dibenzoyloxymaleic anhydride (XI) did not lead to isomers of dimethyl diacetoxy- (VII) and dibenzoyloxyfumarate (IX) but to trimethoxy derivatives (presumably VIII and XII). The colorless addition product (XV, dimethyl α-keto-α'-hydroperoxysuccinate) of ethereal hydrogen peroxide to dimethyl diketosuccinate (XIV) could not replace dihydroxyfumaric or ascorbic acid–hydrogen peroxide in the modified Wieland system.

The so-called dihydroxymaleic acid is in reality dihydroxyfumaric acid (I).[2–4] Interest in the mechanism of oxidation and isomerization of *cis*- and *trans*-enediols prompted us, some time ago, to attempt the preparation of *cis–trans* isomers in this series.[5] Table I summarizes reactions some of which have been described by Fenton[6] and recently repeated and reinterpreted by Hartree.[3]

The infrared data (Table I) add important material to the discussion of the complex picture of esterification of dihydroxyfumaric acid which itself shows the strong shifts (OH at 3.10, CO at 6.08)[7] expected from the strongly internally hydrogen-bonded structure I. The centrosymmetrical nature of the *trans*-structure I according to the rules of selection would not be expected to show any band for the >C=C< element.[8] Compounds III, VIII, XII displaying bands in the >C=C< region (5.9–6.1 μ) are apparently not centrosymmetrical, or, like VII, may need further investigation.

Fenton's ethyl ester A, obtained as one isomer in

(1) Oxidation Mechanisms. XII. Preceding paper in this series: S. M. Goodwin, N. M. Johnson and B. Witkop, THIS JOURNAL, **75**, 4273 (1953). This paper was presented as part of a more comprehensive lecture on enediols at the Sixth Summer Seminar in the Chemistry of Natural Products at the University of New Brunswick, Fredericton, N.B., August 17–21, 1954.

(2) W. Franke and G. Brathuhn, *Ann.*, **487**, 1 (1931).

(3) E. F. Hartree, THIS JOURNAL, **75**, 6244 (1953).

(4) M. P. Gupta, *ibid.*, **75**, 6312 (1953).

(5) Examples of enediol derivatives which seem to have been isolated in *cis* and *trans* forms are 1,2-dimesitylacetylene glycol [R. C. Fuson, C. H. McKeever and J. Corse, *ibid.*, **62**, 600 (1940)] and triose reductone [H. v. Euler and H. Hasselquist, *Arkiv Kemi*, **3**, 405 (1951)].

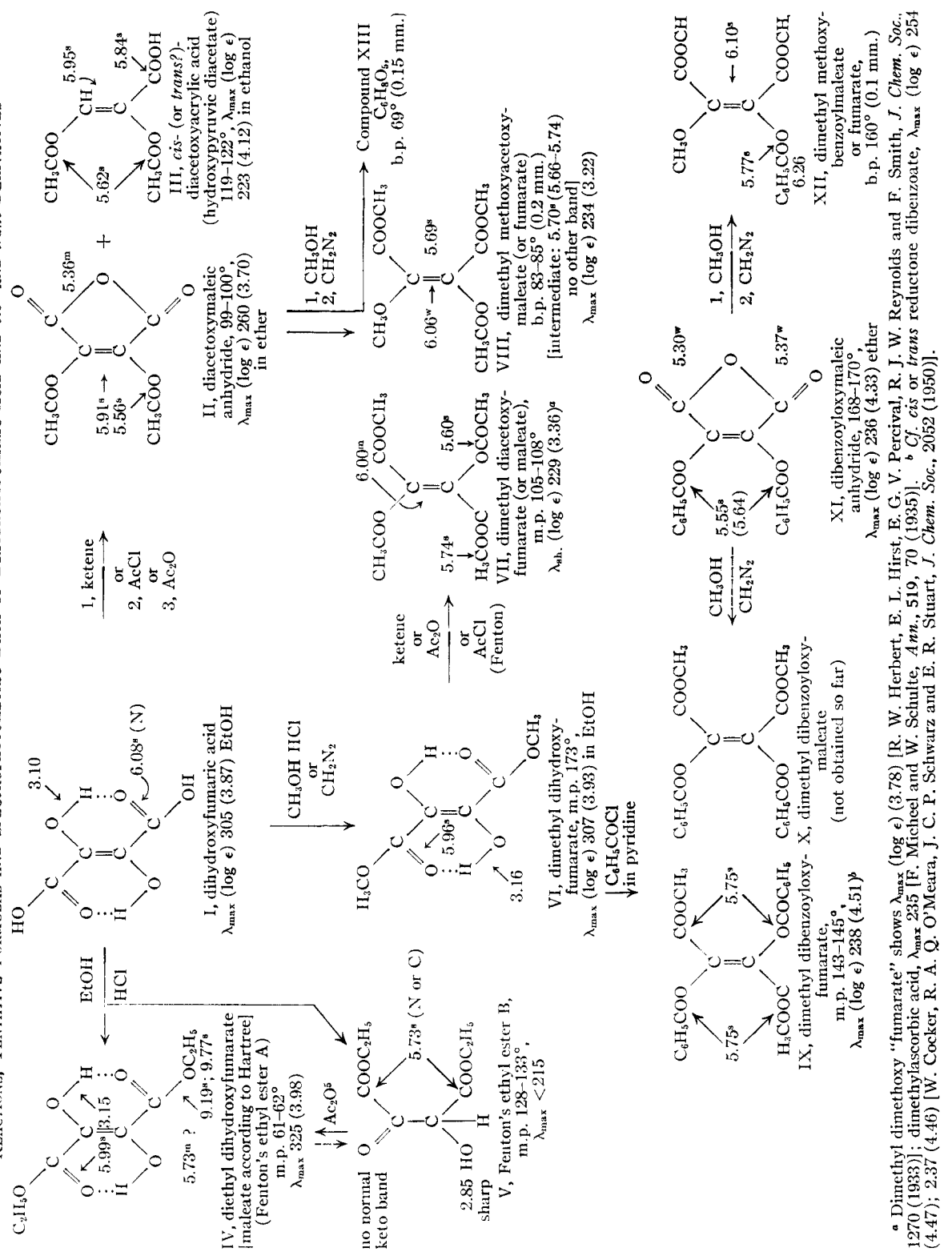
(6) H. J. H. Fenton, *J. Chem. Soc.*, **65**, 899 (1894); **69**, 546 (1896); **73**, 78 (1898); **101**, 1570 (1912).

(7) The shift due to *external* hydrogen bonding of the usually dimeric carboxylic acids (measured as solid films) is smaller: maleic acid (dimerization sterically hindered to some degree) shows CO at 5.87 μ, fumaric acid at 5.95 [M. S. C. Flett, *J. Chem. Soc.*, 962 (1951)]. *Cf.* J. T. Harris, Jr., and M. E. Hobbs, THIS JOURNAL, **76**, 1419 (1954).

(8) See H. Gilman, "Organic Chemistry," J. Wiley and Sons, Inc., New York, 1953, p. 153; *cf.* the absence of the >C=C< band in the similarly constituted molecule of α-pyridoine: W. Lüttke and H. Marsen, *Z. Elektrochem.* **57**, 680 (1953).

TABLE I

REACTIONS, TENTATIVE FORMULAS AND SPECTROPHOTOMETRIC DATA OF DIHYDROXYFUMARIC ACID AND *cis*- AND *trans*-DERIVATIVES



[a] Dimethyl dimethoxy "fumarate" shows λmax (log ε) (3.78) [R. W. Herbert, E. L. Hirst, E. G. V. Percival, R. J. W. Reynolds and F. Smith, *J. Chem. Soc.*, 1270 (1933)]; dimethylascorbic acid, λmax 235 [F. Micheel and W. Schulte, *Ann.*, 519, 70 (1935)]. [b] *Cf. cis* or *trans* reductone dibenzoate, λmax (log ε) 254 (4.47); 2.37 (4.46) [W. Cocker, R. A. Q. O'Meara, J. C. P. Schwarz and E. R. Stuart, *J. Chem. Soc.*, 2052 (1950)].

the normal esterification of dihydroxyfumaric acid, or as the sole product in the reduction of diethyl diketosuccinate with sodium hydrosulfite[9] has an infrared spectrum very similar to the methyl ester VI. The shift of the ester band (normally at 5.76–5.82 μ for esters of aromatic and unsaturated acids,[10,11]) to 5.96 μ in VI and 5.99 μ in IV (*cf.* alkyl salicylate >C=O at 5.97 μ, OH at 3.14 μ[11]),

(9) H. H. Fox, *J. Org. Chem.*, **12**, 535 (1947).

(10) J. F. Grove and H. A. Wallis, *J. Chem. Soc.*, 877 (1951).

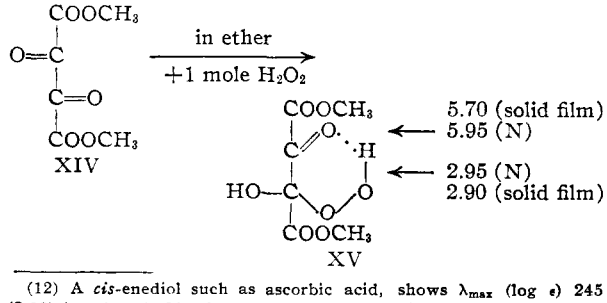
(11) R. S. Rasmussen and R. R. Brattain, THIS JOURNAL, **71**, 1073 (1949).

the broad hydroxyl bands at 3.16 μ (3.15) and the absence of >C=C< bands[8] suggest that *both dimethyl VI as well as diethyl ester A (IV) are derived from dihydroxyfumaric acid (I)*. The 5.73^{m} band in VI is much weaker than the very strong 5.99 band and might theoretically be caused by the presence of some non-bonded ester B (see below). Benzoylation of VI in pyridine leads to dimethyl dibenzoyloxyfumarate (IX) which, as the centrosymmetrical structure requires, shows no band for the >C=C< group and only one very strong band at 5.75 μ for both benzoyl and carbomethoxy groups. In the analogous diacetyl ester VII these ester bands are separated: the two carbomethoxy groups, conjugated through the >C=C< element show, as in IX, peaks at 5.74 μ, the acetoxy groups at 5.60 μ. The distinct band at 6.00 μ raises the question whether VII is centrosymmetrical or derived from, or possibly contaminated by, the *cis*-isomer. Further study would be required to answer these questions unequivocally.

Ester A is, according to Fenton,[6] not altered by mild treatment with acetic anhydride—a fact illustrative of the strong participation of the hydroxyl groups in the six-membered chelated rings IV.

Fenton's ethyl ester B, formulated as the keto-maleate by Hartree,[3] has *one* very strong carbonyl band at 5.73 μ. The lacking ultraviolet absorption rules out the structure of diethyl dihydroxy-maleate.[12] The lack of a normal carbonyl (5.81–5.86 μ), the failure to obtain this ester in the reduction of diethyl diketosuccinate[9] and the stability of the ester toward acetic anhydride and permanganate seem to militate against the ketomaleate structure V.

The molecular weight in molten camphor (~160°) is in good agreement with the monomer. Determinations by the method of Signer in chloroform (but not in acetone) at 37° gave slightly higher values and do not rigidly exclude an equilibrium between monomer and a possible dimer (or trimer). The analogous carbonyl in dimethyl α-keto-α'-hydroperoxysuccinate (XV) obtained from dimethyl diketosuccinate (XIV)[9] by addition of one mole of hydrogen peroxide in absolute ether showed (in Nujol) a broad band at 5.95 and a bonded –O–OH at 2.95 μ.[13] However, the hydroperoxy compound XV is not comparable to the hydroxy compound V because of the enhanced opportunities for hydrogen bonding in the former.



(12) A *cis*-enediol such as ascorbic acid, shows λ_{max} (log ϵ) 245 (3.98) in ethanol (H. Mohler and H. Lohr, *Helv. Chim. Acta*, **21**, 485 (1938)].

(13) The normal position of the –O–OH band is 2.85 μ: O. D. Shreve, M. R. Heether, H. B. Knight and D. Swern, *Anal. Chem.*, **23**, 282 (1951).

Accepting structure V for Fenton's ester A one may possibly ascribe the lack of normal carbonyl absorption in the 5.81–5.86 μ region to the location of the keto carbonyl adjacent to an ester carbonyl grouping. It is possible that the $>\overset{\oplus}{C}—\overset{\ominus}{O}$ polarization in this type of compound would be inhibited, giving the C=O less double bond character, and bringing its absorption into the 5.73 μ region.[14]

Compound XV was synthesized in order to obtain a model of the reactive intermediate labile oxidation product of ascorbic acid which in the modified system of Wieland,[15] *i.e.*, ascorbic acid, hydrogen peroxide, ferric ion and ethylenediamine tetraacetate (Versene), effectively hydroxylates aromatic compounds.[16] As Udenfriend, *et al.*, found, the hydroperoxide XV could not replace ascorbic acid–hydrogen peroxide or dihydroxy-fumaric acid–hydrogen peroxide in this system. Alloxan hydroperoxide[17] was prepared by the same method. The labile intermediate in reactions where ascorbic acid functions as a catalyst of oxidation is not likely to be a labile hydroperoxide[14] but according to more recent views[18–19] a monodehydroascorbic acid of the radical semiquinone type. Attempts to obtain such an intermediate by using highly aromatic enediols are in progress.

The dimethyl ester VI with ketene yielded the diacetoxy ester VII previously obtained by Fenton by the use of acetyl chloride.[6] The low absorption of the acetate carbonyls, 5.60 μ (instead of 5.65 μ for vinyl esters) is a combination of two effects: (i) enol acetates of β-diketone derivatives absorb at shorter wave lengths than normal unconjugated esters; (ii) compounds with two ester oxygen functions at the same carbon (*e.g.*, 1,1-diacetoxypropane CO at 5.68 μ) exhibit ester CO bands at shorter wave lengths than normal.[11] In VII similar inductive effects apparently are operative. The band at 6.00^{m} (>C=C<) would not be expected from a pure centrosymmetrical *trans* structure and puts the formulation VII on a tentative basis. The new dibenzoyl ester IX, exhibiting only one single ester CO for two pairs of different esters, shows no absorption in the >C=C< region.

(14) Likewise, the infrared spectrum of the deoxy-analog, *i.e.*, the largely enolic diethyl oxalacetate exhibits no normal keto band between 5.80 and 5.84 μ and shows the following bands (measured in carbon tetrachloride): 2.87 (bonded enolic hydroxyl); 5.74^{vs} (unconjugated ester carbonyl); 6.02^{s} (conjugated ester carbonyl); 6.12^{w} (conjugated >C=C<). The presence of the unconjugated ester band shows that the absence of a normal keto band cannot be due to complete enolization as in the related diethyl cyclohexanone-2,6-dicarboxylate [N. J. Leonard, H. S. Gutowsky, W. J. Middleton and E. M. Petersen, THIS JOURNAL, **74**, 4070 (1952)]. Normal keto bands are displayed by ethyl cyclohexanone-2-carboxylate (5.83^{s}), cyclopentanone-2-carboxylate (5.80^{vs}) and ketoglutarate (5.82^{s}).

(15) H. Wieland, "On the Mechanism of Oxidation," Silliman Memorial Lectures, Volume XXII, Yale University Press, New Haven, Conn., 1932, p. 86.

(16) S. Udenfriend, C. T. Clark, J. Axelrod and B. B. Brodie, *J. Biol. Chem.*, in press.

(17) B. Witkop, S. Goodwin and T. W. Beiler, THIS JOURNAL, **76**, 5813 (1954).

(18) J. E. LuValle, *ibid.*, **70**, 2234 (1948); *cf.* D. M. H. Kern, *ibid.*, **76**, 1011 (1954).

(19) (a) A. Nason, W. D. Wosilait and A. J. Terrell, *Arch. Biochem. Biophys.*, **48**, 233 (1954); (b) M. Kern and E. Racker, *ibid.*, **48**, 235 (1954).

Whereas the absorption of the conjugated >C=C< group is normally found at 6.00 μ or higher (*cf.* structures VII and VIII), a hypsochromic shift to 5.91 μ is observed on ring closure to the five-membered anhydride II. The same observation has been made on α,β-unsaturated five-membered lactones.[20] The two anhydrides II[6] and XI exhibit the respective ester carbonyls at unusual positions as a consequence of the 5-membered anhydride ring. As a by-product in the preparation of II, the more ether-soluble compound III was obtained; it is probably *cis*-diacetoxyacrylic acid. If in the acetylation of I decarboxylation occurred prior to anhydridization III may have the *trans* configuration.

Our hope to obtain from the anhydrides II and XI the isomers of VII and IX, respectively, has not been fulfilled. Probably on methanolysis of the anhydride, rather than in the further esterification with diazomethane,[20a] one acetoxy or benzoyloxy group is replaced by methoxy and compounds which are tentatively formulated as VIII and XII are isolated.

Experimental[21]

Dimethyl Dihydroxyfumarate (VI).—A solution of 5.9 g. of dihydroxymaleic acid in 50 ml. of methanol was treated with an ethereal solution of diazomethane prepared from 20 g. of N-methyl-N-nitrosonitroguanidine. After standing for one hour 3.6 g. (53%) of colorless crystals were collected, m.p. 165–173° (reported 157–165°,[6] 178–180°[3] and 174–175°[9]).

Infrared spectrum (a) mulled in Nujol: 3.18 (bonded OH), 5.98^s 6.94^s, 7.29, 8.03^s, 9.82^s, 11.41 μ; (b) in chloroform: 3.16; 5.74^w, 5.96^s.

Dimethyl Diacetoxyfumarate (or Maleate?) (VII): A. By the Action of Ketene.—A solution of 0.5 g. of the unrecrystallized methyl ester (VI) in 30 ml. of acetone was treated with a large excess of ketene and allowed to stand overnight. The amber oil remaining after evaporation of the solvent was taken up in ether and washed well with sodium bicarbonate solution. The dried ether extract left a small crop of colorless needles, m.p. 100–110° (reported m.p. 93° from ether, 101.5° from water[6]).

Infrared spectrum in chloroform: no OH band, 5.60^s, 5.74^s, 6.00^m, 6.96^s, 7.30^s, 7.67^s, 8.50^s, 9.64^s, 9.96^m, 10.38^w, 10.64^w.

B. By the Action of Acetic Anhydride in Pyridine.—One gram of the methyl ester dissolved in a mixture of 10 ml. of acetic anhydride and 5 ml. of pyridine was warmed on the steam-bath for one hour. After evaporation to dryness *in vacuo* the solid residue, after two recrystallizations from methanol, yielded 0.37 g. of well-formed, colorless needles, m.p. 105–108°, identical (mixed m.p., infrared spectra) with that obtained by the action of ketene.

Dimethyl Dibenzoyloxyfumarate (or Maleate?) (IX).—A mixture of 0.2 g. of the methyl ester VI, 0.5 g. of benzoyl chloride and 5 ml. of pyridine was warmed on the steam-bath for one hour. After evaporation *in vacuo* the crude reaction product (m.p. 132–143°) was recrystallized twice from benzene and formed colorless short rods, m.p. 143–145°.

Anal. Calcd. for $C_{20}H_{16}O_8$: C, 62.50; H, 4.20. Found: C, 62.55; H, 4.24.

Infrared spectrum in chloroform: 5.75^s, 6.24^w, 6.90^w, 6.98^w, 7.45^w, 8.63^s, 9.16^s, 9.42^s μ.

The Reaction of Dihydroxyfumaric Acid with Hydrogen Chloride in Ethanol. Fenton's Ethyl Ester B.—Following the procedure of Fenton[6] there was obtained from 5.9 g. of dihydroxyfumaric acid (I), 2.5 g. of colorless rods, m.p. 128–133° (reported 126–128°[6]) soluble in ethanol and benzene, sparingly soluble in ether. The compound gave the correct analysis for $C_8H_{12}O_6$.

Infrared spectrum: (a) in Nujol: 2.94 (strong, sharp and narrow band, non-bonded OH), 5.72^s (shoulder at 5.68^s), 6.90^m, 7.31^m, 7.55^m, 7.70^s, 8.09^s, 8.56^s, 9.06^s, 9.35^s, 9.90^s, 9.15^w, 11.25^w, 11.55^w, 11.70^w, 11.90^m, 12.11^m, 13.65^m μ. (b) in chloroform: 2.85 (sharp and narrow), 5.73^s, 6.81^w, 6.93^w, 7.30^s, 7.49^w, 7.69^s, 8.53^s, 9.10^s, 9.37^s, 9.88^s, 11.73^m, 12.0^m μ.

The melting point of Fenton's ethyl ester B depends largely on the rate of heating. Taking melting points under strictly comparable conditions two more preparations of markedly different melting range (110–122°, 145–148°) were obtained from mother liquors or by recrystallization. None of these fractions showed more than end absorption in the ultraviolet (λ_{max} below 215 mμ).

Molecular Weight.—By the method of Rast a sample (m.p. 120–124°) gave a molecular weight of 206 (calcd. for $C_8H_{12}O_6$: mol. wt., 204.18). Another sample (m.p. 137–141°) in chloroform at 37° (method of Signer) gave 250, not changed after standing for two months at 37°; in acetone 207.

Fenton's Ethyl Ester A.—On concentration of the mother liquor of Ester A a thick yellow oil was obtained which partly crystallized in long thin needles. Recrystallization from ether, chilled in a Dry Ice–acetone bath, yielded colorless needles, which could be sublimed *in vacuo*, m.p. 61–62° (reported 58–60°,[3] 71–73°[9] and 72–73°[6]). These needles liquefied in the desiccator. In other runs it was found that the addition of water to the yellow sirup (after removal of Ester B) caused an immediate precipitation of crystalline needles. However, the material became discolored and deliquescent on attempted collection.

Infrared spectrum in chloroform: 3.15 (broad band indicative of bonded OH), 5.73^m, 5.98^s, 6.81^m, 6.93^m, 7.03^m, 7.20^w, 7.30^s, 9.19^s, 9.77^s, 11.70^m μ.

Diacetoxymaleic Anhydride (II).—A suspension of 5 g. of dihydroxymaleic acid in 50 ml. of acetone was treated with a stream of ketene for one hour. The brown solution was filtered to remove some iron salts (0.21 g.) and concentrated to about 25 ml. On standing large colorless prisms, m.p. 60–70°, formed in the brown solution (6.0 g., 82%). The material was recrystallized from benzene–pentane or ether–pentane. The best purification was found to be sublimation *in vacuo* which yielded snow-white crystalline material, m.p. 99–100° (reported m.p. 97–98°[6]).

The compound gave the correct analysis and no depression on admixture with a sample of the anhydride prepared in 78% yield following the method of Fenton[6] (refluxing dihydroxyfumaric acid with excess acetyl chloride).

Infrared spectrum in chloroform: 5.36^m, 5.56^s, 5.91^s, 7.03^w, 7.30^s, 7.47^s, 7.82^m, 8.50^m, 8.85^s, 9.15^s, 9.10^w, 9.95^m, 10.60^s, 11.75^m μ.

***cis* (or *trans*)-Diacetoxyacrylic Acid (III).**—This compound was found in the mother liquor of the crude product resulting from the action of ketene on dihydroxyfumaric acid. The addition of pentane to the ethereal mother liquor caused the separation of an oil mixed with needles, which after careful washing with benzene, showed m.p. 110–120°. After recrystallization from ether–pentane or ether–benzene colorless rods were obtained, m.p. 119–122°.

Anal. Calcd. for $C_7H_8O_6$: C, 44.69; H, 4.28. Found: C, 44.67; H, 4.45.

Infrared spectrum in chloroform: shoulder at 2.84, 3.21, 5.62^s, 5.84^s, 5.95^s, 6.96^m, 7.30^s, 7.83^m, 8.50^s, 9.61^m, 9.88^m, 10.52^m, 11.48^m, 12.05^m μ.

Dimethyl Acetoxymethoxymaleate (Presumably VIII).—A solution of 0.3 g. of diacetoxymaleic anhydride (II) in a small volume of methanol was evaporated to a colorless oil which gave the following analysis: C, 40.42; H, 5.57; molecular weight based on the neutralization equivalent assuming one carboxyl group, 158.7. Methyl methoxyacetoxymaleate, $C_8H_{10}O_7 \cdot H_2O$ requires: C, 40.71; H, 5.12; mol. wt., 236.2. The infrared spectrum in chloroform showed no OH, 5.70^{vs}, 6.96^m, 7.29^s, 9.25^s. The oily reaction product of the anhydride with methanol was taken up in ether and treated with an excess of diazomethane. After standing overnight the solvent was evaporated and the yellow oily residue distilled *in vacuo*. The sample for analysis was collected at 83–85° (0.2 mm.).

(20) C. Djerassi, P. Sengupta, J. Herran and F. Walls, THIS JOURNAL, **76**, 2966 (1954).

(20a) *Cf.* J. Davoll, *J. Chem. Soc.*, 3802 (1953).

(21) The melting points are corrected, all boiling points are uncorrected. The analyses were performed by Dr. W. C. Alford and associates, Analytical Service Laboratory, National Institutes of Health.

Anal. Calcd. for $C_9H_{12}O_7$: C, 46.55; H, 5.21; OCH_3, 40.14 (three methoxyls); C-CH_3,[22] 6.45; CH_3CO, 18.54. Found: C, 46.33; H, 5.99; OCH_3, 39.34; C-CH_3, 6.57; CH_3CO, 18.82.

Infrared spectrum in chloroform: 2.86 (weak; partly bonded OH), 5.69^s, 6.06^w, 6.95^s, 7.29^s, 7.65^s, 7.93^s, 9.02^s, 9.25^s, 9.78^w, 10.30^w μ.

Compound $C_6H_8O_5$ (XIII).—In a larger scale run, using 6.6 g. of diacetoxymaleic anhydride, diazomethane in large excess was immediately used on the freshly prepared solution of the anhydride in a mixture of methanol–ether. The oily product, obtained after evaporation of the solvents, distilled *in vacuo* over a wide range. A fraction of colorless distillate (bands at 5.64 and 5.75 μ) collected at 69° (0.15 mm.), was analyzed.

Anal. Calcd. for $C_6H_8O_5$: C, 45.00; H, 5.04; OCH_3, mol. wt., 160.2. Found: C, 44.89; H, 4.85; OCH_3, 17.64; mol. wt., 176 (calcd. from methoxyl value).

Dibenzoyloxymaleic Anhydride (XI).—Following Fenton's procedure[6] the compound was prepared in 40% yield, crystallizing from cyclohexane or benzene, silky white needles, m.p. 168–170° (reported 167–168°).

Infrared spectrum in chloroform: no OH, no aliphatic CH, weak duplet at 5.30^w, 5.37^w μ; very strong duplet at 5.55^s, 5.64^s μ; shoulder at 5.84^w, 5.90^w; 6.22^m, 6.87^m, 7.40^m, 7.97^s, 8.50^s, 8.83^s, 9.11^s, 9.63^m, 9.95^s, 10.26^s, 10.72^m μ.

Dimethyl Methoxybenzoyloxymaleate (Presumably XII).—A suspension of dibenzoyloxymaleic anhydride in a small volume of methanol was warmed slightly to effect solution. After cooling an excess of diazomethane in ether solution was added and the reaction mixture allowed to stand overnight. The oily residue obtained after evaporation of the solvents, had a peppermint odor; it was distilled *in vacuo*. A fraction of distillate, b.p. 160° (0.1 mm.), was analyzed.

Anal. Calcd. for $C_{14}H_{14}O_7$: C, 57.14; H, 4.80. Found: C, 56.43; H, 4.67.

Infrared spectrum in chloroform: 2.78^w, 5.70–5.80^{vs}, 6.23^s, 6.30^m, 6.70^m, 6.88^s, 6.94^s, 9.03^s, 9.37^s, 9.77^s μ.

Dimethyl Diketosuccinate (XIV).—Prepared according to the directions of Anschütz[23] the yellow oily compound was obtained by vacuum distillation, b.p. 102–104° (14 mm.) (reported 102–110° (12–13 mm.)[9]).

The infrared spectrum of several different fractions measured in chloroform still showed OH at 2.85 μ and one single ester CO at 5.70 μ. The very hygroscopic diketosuccinate apparently became hydrated in the process of transfer and solution.

Dimethyl α-Keto-α'-hydroperoxysuccinate (XV).—A solution of 360 mg. (2 mm.) of dimethyl diketosuccinate (XIV) in 1 ml. of dry ether was treated with 0.4 ml. of 4.55 *M* hydrogen peroxide (1.8 mm.) in absolute ether. The initially *yellow* solution became *colorless* immediately after addition of the hydrogen peroxide. Evaporation *in vacuo* yielded a colorless viscous residue, giving a strong peroxide test (iodide–starch paper, lead tetraacetate.)[24] On standing this compound solidified to a new compound[25] which no longer gave peroxide reactions.

Infrared spectrum in Nujol: broad and strong band at 2.95 (bonded O–OH and/or OH); very broad C=O at 5.95–6.00 μ. The viscous material was difficult to mull and gave a poorly resolved spectrum.

(22) The C-methyl determination was carried out, since C-methylation of a related (quinoid) system by diazomethane has been observed by L. F. Fieser and J. Hartwell, THIS JOURNAL, **57**, 1479 (1935). The finding of only one C-methyl group (from the acetoxy group) eliminates the possibility of C-methylation.

(23) R. Anschütz and O. Parlato, *Ber.*, **25**, 1975 (1892).

(24) R. Criegee, H. Pilz and M. Flygare, *ibid.*, **72**, 1799 (1939).

(25) *Cf.* J. E. Leffler, *J. Org. Chem.*, **16**, 1785 (1951).

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[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH]

Aspidospermine. II

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The reactions and infrared data of the mono-(VI) and diacetyl (VIII) derivatives of aspidosine (VII) support the same 7-position for the oxygen function in aspidospermine as in vomicine and strychnospermine. The reactions of deacetylaspidospermine (II) with benzoyl chloride, methyl and ethyl iodide are clarified (Chart I). Hypothetical working structures (XVI, XVII) are discussed for aspidospermine.

In continuation of our studies on aspidospermine (I), a new type of dihydroindole alkaloid,[1] it was necessary to establish the position of the methoxy group in the benzene ring. On the basis of spectral comparison Openshaw and Smith[2] favored the position *meta* to N^a (harmine position). We have now found new evidence which allocates the 7-position (*peri* to the (acet)imino group) to the methoxy group (Chart I).

The aluminum chloride-catalyzed ether cleavage of aspidospermine led to phenolic demethylaspidospermine (VI, N-acetylaspidosine) also obtainable from aspidosine (VII) by acetylation or from N,O-diacetylaspidosine (VIII) by treatment with acid or base. The ultraviolet spectrum of demethylaspidospermine is closely related to that of another N-acetyl-*peri*-hydroxydihydroindole, *viz.*, vomicine (Chart I, ref. *d*). Like vomicine, the analogous compound VI shows no band in the OH or NH region as a consequence of strong hydrogen bonding of the cryptophenolic hydroxyl. The same effect is operative in shifting the carbonyl band of the amide group to 6.12 μ (6.12 μ in vomicine) compared with 6.01 μ in the non-bonded diacetyl compound VIII.[3] The acetylation of aspidosine and the failure to obtain O-acetylaspidosine from diacetylaspidosine are reactions which have been encountered similarly in the homologous system, 8-hydroxy-1,2,3,4-tetrahydroquinoline.[4] Table I shows that in a tricyclic system, such as vomicine, the phenolic hydroxyl group is more strongly hydrogen-bonded than in bicyclic or monocyclic systems.

(1) B. Witkop, THIS JOURNAL, **70**, 3712 (1948). ADDED IN PROOF.—A referee directed our attention to an abstract of a recent paper by H. T. Openshaw, G. F. Smith and J. R. Chalmers, presented at the XIIIth International Congress of Pure and Applied Chemistry, Stockholm and Uppsala, 1953, Abstracts p. 223, in which these authors arrive at similar conclusions with regard to the position of the methoxy group on the basis of comparison with the ultraviolet spectra of suitable model compounds.

(2) H. T. Openshaw and G. F. Smith, *Experientia*, **4**, 428 (1948).

(3) The CO amide band in the diacetyl derivative of diaboline, a dihydroindole alkaloid, is at 6.02 μ (F. E. Bader, E. Schlittler and H. Schwarz, *Helv. Chim. Acta*, **36**, 1257 (1953)), the CO of O-acetyl at 5.73 μ (unconjugated ester, *cf.* J. F. Grove and H. A. Willis, *J. Chem. Soc.*, 877 (1951)); the position of this ester band does not support a cryptophenolic hydroxyl. Diacetylyohimbine shows bands at 5.76 (strong narrow band, no separate band for the carbomethoxy group) and 5.90 (CO of N-acetylindole).

(4) C. J. Cavallito and T. H. Haskell, THIS JOURNAL, **66**, 1166 (1944); *cf.* A. Ek and B. Witkop, *ibid.*, **76**, 5579 (1954).