had been absorbed. The cooled reaction mixture was removed from the bomb, filtered, and distilled to give 25 g. (54%) of *p*-(α-hydroxyethyl)-phenylmethylcarbinol acetate, b.p. 116–117° (0.5 mm.), $n^{25}D$ 1.5120.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.2; H, 7.6; acetyl, 21.3. Found: C, 69.3; H, 7.6; acetyl, 20.8.

1,4-Bis-(α-hydroxyethyl)-benzene Diacetate (VIII). Method A.—A mixture of 13.5 g. (0.065 mole) of *p*-(α-hydroxyethyl)-phenylmethylcarbinol acetate, 20 g. (0.2 mole) of acetic anhydride, and 5 drops of pyridine was heated on the steam-cone for 16 hours. Distillation of the reaction mixture yielded 21.0 g. (80%) of the diacetate, b.p. 104° (0.2 mm.), $n^{25}D$ 1.4955.

Method B.—1,4-Bis-(α-hydroxyethyl)-benzene was also prepared from *p*-diacetylbenzene. A mixture of 16.2 g. (0.1 mole) of *p*-diacetylbenzene, 8.1 g. of W-7 Raney nickel, and 200 cc. of methanol was hydrogenated in a Parr low-pressure apparatus at 50 p.s.i. The pressure drop was 13 p.s.i.; calcd., 12.8 p.s.i. After the catalyst had been filtered off, the methanol was evaporated to yield 12 g. of 1,4-bis-(α-hydroxyethyl)-benzene. A mixture of 9.0 g. (0.055 mole) of 1,4-bis-(α-hydroxyethyl)-benzene, 1.25 g. of acetic anhydride and 1 cc. of pyridine was heated on the steam-cone for 16 hours. Distillation of the reaction mixture gave 10.5 g. of 1,4-bis-(α-acetoxyethyl)-benzene, b.p. 110–112° (0.25 mm.), $n^{25}D$ 1.4932.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.2; H, 7.3. Found: C, 67.9; H, 7.4.

***p*-Divinylbenzene (VI).**—A solution of 21.0 g. (0.084 mole) of 1,4-bis-(α-hydroxyethyl)-benzene diacetate in 25.0 cc. of benzene was passed dropwise during the course of 1.5 hours through a 25-mm. o.d. Pyrex tube, packed for a distance of 30 inches with glass beads, and heated to 525–535° by means of an electrically controlled furnace. The reaction products were swept into a Dry Ice trap by a slow stream of nitrogen. The reaction products were melted, washed with water, and dried over anhydrous magnesium sulfate. Distillation yielded 7.7 g. (70% of the theoretical) of *p*-divinylbenzene, b.p. 34° (0.2 mm.). Titration of 0.52 g. of this material with $^1/_{12}$ *M* bromide–bromate solution required 30.2 cc., corresponding to a purity of 97.6%.

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Degradation of Veratramine to Benzene-1,2,3,4-tetracarboxylic Acid

BY O. WINTERSTEINER, M. MOORE AND N. HOSANSKY

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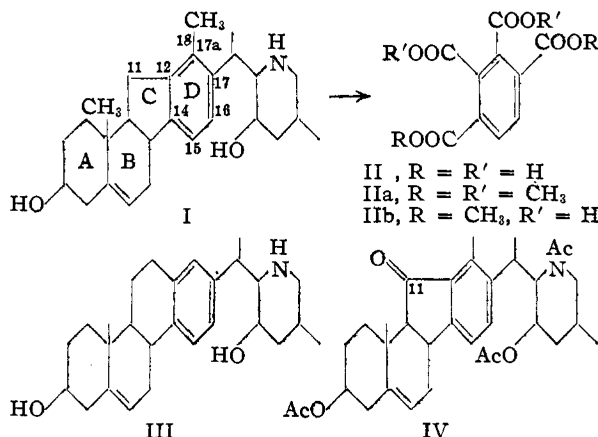
The structure I proposed by Tamm and Wintersteiner[1] for the secondary base veratramine from *Veratrum viride* Aiton requires that oxidative degradation of the alkaloid should result in the formation of II, benzene-1,2,3,4-tetracarboxylic acid (prehnitic acid[2]). This was indeed found to be the case. When veratramine was oxidized with hot alkaline permanganate and the mixture was worked up by the procedure described by Read and Purves[3] for the separation of the benzene polycarboxylic acids derived from coal and lignin, there was obtained a crystalline acid, m.p. 238–241°, $C_{10}H_6O_8$, identified as benzene-1,2,3,4-tetracarboxylic acid by analysis and comparison with an authentic sample.[4] The melting point of the tetramethyl ester (m.p. 128–130°) and of the (apparently slightly impure) 1,4-diester (160–167°, lit.[3] 171–172°) served to confirm this conclusion,[4] as did the identity of the infrared spectrum of the tetramethyl ester with that of an authentic specimen.



This result places the methyl group representing carbon atom 18 in the normal steroid skeleton into position 17a of ring D as visualized in formula I, and in conjunction with other facts[5,6] rules out the perhydrochrysene structure III proposed by Jacobs and Sato,[7] in which this carbon atom is incorporated in the ring system proper. Since there is ample evidence to show that rings A and B in veratramine are constituted as in normal steroids,[1,7] and that it is ring D which is aromatic,[1,5,7] it follows that ring C must be five-membered as postulated. These conclusions also apply to the related secondary alkaloid jervine, which has been correlated with veratramine[5] through one of its acetolysis products, the indanone IV.[6]

Experimental

The melting points were taken in capillaries and are corrected for stem exposure. The ultraviolet spectra were determined with a Cary self-recording spectrophotometer model 11-M. The infrared measurements were carried out with a Perkin–Elmer spectrophotometer model 12-B. The analytical samples were dried over phosphorus pentoxide at 110° (2 mm.).

Oxidation of Veratramine with Permanganate.—A suspension of veratramine (free base, 5 g.) in 500 cc. of water containing 8.0 g. of potassium hydroxide was brought to boiling in a vessel fitted with a reflux condenser, a separatory funnel and an air inlet tube extending to the bottom of the flask. Aqueous 3.5% potassium permanganate was added to the boiling mixture in 50-cc. portions at intervals governed by the consumption of the most of the reagent from the preceding addition. A stream of air admitted through the inlet tube served to prevent excessive bumping. When the last 50-cc. portion of a total of 1550 cc. added had remained unreduced for 5 hours (aggregate reaction time 30 hours), the contents of the flask were cooled and the excess permanganate destroyed by the addition of ethanol. The manganese dioxide was filtered off and washed thoroughly with hot water. The combined filtrate and washings were acidified to *p*H 2 with hydrochloric acid, filtered through a bed of Super-Cel, and concentrated *in vacuo* to about 200 cc. The solution was then brought to *p*H 10 by

(1) Ch. Tamm and O. Wintersteiner, THIS JOURNAL, **74**, 3842 (1952).

(2) As pointed out by L. I. Smith and E. J. Carlson, *ibid.*, **61**, 288 (1939), the still widespread use in the contemporary literature of the trivial name mellophanic acid for this instead of for the 1,2,4,5-isomer is incorrect. We are following in this paper the suggestion of Read and Purves (ref. 3) to use the rational terms only.

(3) D. E. Read and C. B. Purves, *ibid.*, **74**, 116, 120 (1952).

(4) We wish to express our sincere thanks to Prof. C. B. Purves for making available to us samples of this acid and of its tetra and dimethyl esters.

(5) O. Wintersteiner and N. Hosansky, THIS JOURNAL, **74**, 4474 (1952).

(6) J. Fried, O. Wintersteiner, A. Klingsberg, M. Moore and B. M. Iselin, *ibid.*, **73**, 2970 (1951); O. Wintersteiner, B. M. Iselin and M. Moore, Abstracts, XIIth Internat. Congress of Chemistry, New York, N. Y., September 10–13, 1951, Medicinal Chemistry, p. 292.

(7) W. A. Jacobs and Y. Sato, *J. Biol. Chem.*, **191**, 71 (1951).

the addition of 2 *N* potassium hydroxide. After removal of a small amount of an amorphous precipitate by filtration, 10% barium chloride solution (147 cc.) was added, and the resulting suspension of precipitated barium salts was heated on the steam-bath for 30 minutes. The precipitate was collected after cooling to room temperature, washed with water, and dried (9.67 g., 56.9% Ba).

The barium salts were dissolved in hot 3 *N* hydrochloric acid (100 cc.) and decomposed by the addition of the calculated amount of 3 *N* sulfuric acid (27.8 cc.). The filtrate and hot water washings from the barium sulfate were concentrated to 50 cc. and placed in the refrigerator. The oxalic acid crystals which were deposited overnight were removed by filtration (3.57 g.). The filtrate, after reduction of its volume to 10 cc., was again placed in the refrigerator. The resulting mixture of large oxalic acid crystals and very small short rods was separated by aspirating the latter together with the mother liquor with a rubber-capped pipet. The fine crystals were collected by centrifugation (180 mg.). The mother liquor was brought to dryness (418 mg.), and the residue triturated with absolute ethanol. The insoluble portion, consisting of inorganic material, was removed by filtration, and the filtrate brought to dryness. The semicrystalline residue (375 mg.), as well as the original crop of fine rods, was treated separately with boiling concentrated nitric acid (3 cc.) under reflux till the evolution of brown nitrous gases ceased (*ca.* 1 hour). The solutions were concentrated on a hot-plate till crystallization commenced. Since the two batches of crystalline material collected after chilling did not differ materially in melting point and appearance, they were combined (185 mg.) and recrystallized again from boiling concentrated nitric acid, from which it formed small, clear-cut prisms melting with effervescence at 241–245° after softening beginning at 224°. The product did not depress the melting point of the reference specimen (244–248°, soft 224°) obtained from Professor Purves.[4] For analysis the compound was recrystallized from acetone–hexane (m.p. 235–238.5°, soft, 231°).

Anal. Calcd. for $C_{10}H_6O_8$ (254.1): C, 47.25; H, 2.38; neut. equiv., 63.5. Found: C, 47.43; H, 2.49; neut. equiv., 63.1.

The tetramethyl ester IIa was prepared in the usual manner by adding excess ethereal diazomethane to a solution of the acid in dry methanol. After recrystallization from acetone–hexane it melted at 127–130°, alone or in mixture with an authentic preparation of the same melting point.[4]

Anal. Calcd. for $C_{14}H_{14}O_8$ (310.3): C, 54.20; H, 4.55; OCH_3, 40.0. Found: C, 54.40; H, 4.77; OCH_3, 39.6.

The infrared spectrum (Nujol mull) of the ester was identical with that of the reference preparation[4]; 3.45 d, 3.87 ss, 5.76 d, 6.05 s, 6.27 ss, 6.36 ss, 10.48 ss, 10.56 m, 11.13 s, 11.54 m, 11.65 s, 12.79 s, 13.22 md, 13.62 sm, 14.30 s (d = deep, m = medium, s = small, ss = very small).

The 1,4-dimethyl ester IIb was prepared by refluxing a solution of the acid (48 mg.) in 3% methanolic hydrogen chloride (3 cc.) for 6 hours.[3] The esterified material was separated into acidic and neutral fractions in the usual manner. The acidic fraction (47.3 mg.) was recrystallized from acetone–hexane, from which it formed rosettes of platelets melting at 160–167.5°. Further recrystallization failed to raise or sharpen the melting point. In mixture with the reference specimen[4] (m.p. 171–175°) the preparation melted at 167–173°.

Anal. Calcd. for $C_{10}H_{10}O_8$ (282.2): OCH_3, 22.0; neut. equiv., 141. Found: OCH_3, 21.9; neut. equiv., 138.

Ultraviolet Absorption Spectra of Acid II and its Esters.—The ultraviolet absorption spectra of the acid II and its esters IIa and IIb in ethanol are practically identical. They are characterized by a single maximum at 288 mμ (II, IIa) or 290 mμ (IIb), with ε 1260–1300, a shallow minimum at 279 mμ (II) or 275 mμ (IIa, IIb), with ε 1130–1250, and end absorption with an inflection at about 240 mμ, ε 8000–8300, which probably corresponds to the high band at 226 mμ in the spectrum of phthalic acid (butyl phthalate, λ_{max}^{alc} 226 mμ (9500), 272 mμ (1500)). The spectrum of the isomeric ester, tetramethyl benzene-1,2,4,5-tetracarboxylate[8] in ethanol shows the same general pattern (maximum at 291 mμ (2370), minimum at 275 mμ (1780), end absorption with inflection at 240 mμ (9050)). It would thus appear that these features are associated with the number of carboxyl functions (and hence of possible resonance structures) rather than with their distribution over the benzene ring. On the other hand, the segregation in the isomeric ester of the carbomethoxy groups into two pairs insulated from each other by unsubstituted ring carbon atoms seems to impart on each of these groupings something like the character of a separate chromophore, if the nearly twice as high extinction of the maximum over that of the corresponding band of the 1,2,3,4-substituted ester IIa can be so interpreted.

The authors are indebted to Mr. Joseph A. Alicino and his associates for the microanalyses, and to Dr. Nettie Coy for the ultraviolet and infrared measurements.

(8) We are greatly indebted to Prof. R. T. Arnold of the University of Minnesota for making available to us a sample of this ester.

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COMMUNICATIONS TO THE EDITOR

N-PANTOTHENYLCYSTEINE AS A PRECURSOR FOR PANTETHEINE AND COENZYME A

Sir:

Pantetheine is readily converted *in vivo* to coenzyme A (CoA), and the intermediate reactions involved are now known.[1] In contrast, nothing is known of the mechanisms by which pantetheine arises from pantothenic acid. A study of this transformation revealed that in the presence of adenosine triphosphate and cysteine, extracts of acetone-dried cells of *Proteus morganii* transform pantothenate to a compound (I) essentially inactive in replacing pantothenate for *Saccharomyces carlsbergensis*, *Lactobacillus arabinosus* and *Lactobacillus casei*.[2] Pantethine was not formed.[2] However, the product (I) formed was considerably more active in promoting growth of *Acetobacter suboxydans*[2] than an amount of pantothenate equal to that inactivated by the enzyme preparation.

Since cysteine could not be replaced by β-mercaptoethylamine in the inactivation reaction with *P. morganii*, it appeared that I might be N-pantothenylcysteine (II). The corresponding disulfide,

(1) G. D. Novelli and M. H. Hoagland, Abstract 26C, 123rd Meeting, Am. Chem. Soc., Los Angeles, March, 1953; G. D. Novelli, *Fed. Proc.*, in press.

(2) Free pantothenate was determined by assay with *S. carlsbergensis*; pantethine was determined with *Lactobacillus helveticus* 80 (J. Craig and E. E. Snell, *J. Bact.*, **61**, 283 (1951)) before and after digestion with intestinal phosphatase. Assays for pantothenate activity with *A. suboxidans* were conducted in the medium of L. A. Underkofler, A. C. Banz and W. H. Peterson (*J. Bact.*, **45**, 183 (1943)).