tilled water and passed through a column containing 100 ml. of Dowex-2[18] which had been regenerated with carbonate-free sodium hydroxide. The effluent was freeze-dried and suitable precautions were taken to minimize contact with carbon dioxide from the air. The yield was 3.8 g. of a white amorphous solid having the following properties: residue on ignition, 0.38%; carbonate, none; sulfate, none; chloride, trace; loss on drying at 50° in high vacuum, 6.88%; water (Karl Fischer), 7.3%; water (Karl Fischer) on sample dried at 50° in high vacuum, 0.64%.

Neomycin B Hydrochloride.—Neomycin B base was dissolved in a slight excess of dilute hydrochloric acid and the solution was freeze-dried to give a white amorphous solid.

Neomycin C Base.—It was prepared from the chromatographed neomycin C sulfate by the same process that was used for neomycin B base and was found to have the following properties: carbonate, none; sulfate, none; chloride, trace; loss on drying at 50° in high vacuum, 5.34%; water (Karl Fischer), 5.7; water (Karl Fischer) on sample dried at 50° in high vacuum, 0.51%.

Neomycin C Hydrochloride.—Neomycin C base was dissolved in a slight excess of dilute hydrochloric acid and freeze-dried to give an amorphous solid.

Effect of Concentration on Specific Rotation.—A preparation of neomycin B sulfate was found to have a specific rotation of +53.2 ± 0.3° (average deviation) when measured at concentrations from 10 mg./ml. to 100 mg./ml. in water at 22°. The data showed no trend with concentration.

Potentiometric Titrations.—The aqueous titrations were run under oxygen-free nitrogen with a Precision-Dow Recordomatic Titrator and the maximum probable error in a specific *p*H reading is ±0.1 *p*H unit. The titrations in glacial acetic acid were made with 200–400 mcg./ml. solutions of the base *vs.* 0.1 *N* perchloric acid using a Beckman Model G *p*H meter equipped with glass (Beckman No. 1190-42) and silver–silver chloride (Beckman No. 1264) electrodes. End-points were determined from a plot of relative millivolts *vs.* acid volume, using second derivatives for greater accuracy.

Methanolysis of Neomycin B and C.—A mixture of 1.0 g. of neomycin B sulfate ($[\alpha]^{25}D$ +54°; residue on ignition, 3.8%) and 120 ml. of anhydrous methanol 0.38 *N* in dry hydrogen chloride was refluxed for 2.5 hours. Complete solution occurred after one hour. The colorless solution was chilled in an ice-bath and was diluted with 40 ml. of anhydrous ether. The flocculent, white precipitate of neamine hydrochloride which formed was removed by filtration on a tared sintered glass funnel, washed with 5 ml. of anhydrous ether, and dried *in vacuo* over phosphorus pentoxide to yield 476 mg. of material. The filtrate was evaporated *in vacuo* to a volume of 10 ml., chilled in an ice-bath, and diluted with 100 ml. of anhydrous ether. The flocculent precipitate of methyl neobiosaminide B hydrochloride which formed was removed by filtration on a tared sintered glass funnel, washed with 10 ml. of anhydrous ether, and dried *in vacuo* over phosphorus pentoxide to yield 343 mg. of material.

The above procedure was exactly repeated using 1.0 g. of neomycin C sulfate ($[\alpha]^{25}D$ +78°; residue on ignition, 3.4%). The yield of neamine hydrochloride was 495 mg.; the yield of methyl neobiosaminide C hydrochloride was 361 mg.

Vigorous Acid Hydrolysis of the Neomycins.—Solutions of 50 mg. of neamine, 100 mg. of neomycin B sulfate ($[\alpha]^{25}D$ +54°; residue on ignition, 3.8%), and 100 mg. of neomycin C sulfate ($[\alpha]^{25}D$ +78°; residue on ignition, 3.4%) in 5 ml. of 48% hydrobromic acid were refluxed for 10 hours. Each hydrolysate rapidly became dark maroon in color. Each hydrolysate was concentrated to dryness by distillation *in vacuo* and two 5-ml. portions of distilled water were distilled *in vacuo* from the hydrolysis residues. Dilutions for ultraviolet[19] spectral analysis of the respective hydrolysates were made such as to contain 63 mcg. (0.20 micromole) of parent neamine per ml., 115 mcg. (0.19 micromole) of parent neomycin B per ml., and 115 mcg. (0.19 micromole) of parent neomycin C per ml.

Acknowledgments.—We wish to express our thanks to Dr. A. D. Cooper for the potentiometric titrations in glacial acetic acid, to Mr. W. A. Struck and associates for the microanalyses, to Mrs. Jean W. Snyder and associates for the microbiological assays, and to Dr. O. K. Sebek for the microbiological estimation of the neomycin B content of our neomycin C.

(18) A strongly basic anion-exchange resin obtained from the Dow Chemical Co.

(19) The ultraviolet spectra were measured on a Beckman Spectrophotometer, model D.

KALAMAZOO, MICHIGAN
URBANA, ILLINOIS

[CONTRIBUTION FROM COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Nuclear Substituted Analogs of Norepinephrine, Dihydroxyphenylalanine and Adrenochrome

BY EDWIN D. HORNBAKER[1] AND ALFRED BURGER

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Syntheses of 2-methylnorepinephrine, (±)4-methylnoradrenochrome, 1-(2-chloro-3,4-dimethoxyphenyl)-2-aminoethanol, β-(2-methyl-3,4-dihydroxyphenyl)-α-alanine and β-(2-chloro-3,4-dihydroxyphenyl)-α-alanine are described.

As part of a program designed to investigate the pharmacological effects of nuclear substitution in epinephrine precursors, the study of certain nuclear substituted derivatives of 3,4-dihydroxyphenylalanine (DOPA) and norepinephrine appeared desirable since DOPA and norepinephrine may play a role in the biosynthesis of epinephrine.[2] Structural analogs of DOPA produced by side chain alterations have been shown to cause inhibition of mammalian DOPA decarboxylase,[3] and modifications of the side chain in norepinephrine are known to produce valuable pharmacodynamic properties.[4] The effects of nuclear substitution of epinephrine have been studied only for the (±)6-methyl homolog.[5] Hydroxy[6] and amino[7] derivatives of 3,4-dihydroxyphenylethanolamine have been described but their biological properties have not been divulged. Likewise, syntheses of 2-methyl-,[8] 5-

(1) National Science Foundation Fellow, 1953–1955.

(2) K. H. Beyer, "Chemical Factors in Hypertension," A.C.S. Advances in Chemistry Series, No. 2, 1950, p. 37.

(3) T. L. Sourkes, *Arch. Biochim. Biophys.*, **51**, 444 (1954); G. A. Stein, H. A. Bronner and K. Pfister, 3rd, THIS JOURNAL, **77**, 700 (1955); G. J. Martin, R. Brendel and J. M. Beiler, *Exper. Med. & Surg.*, **8**, 5 (1950).

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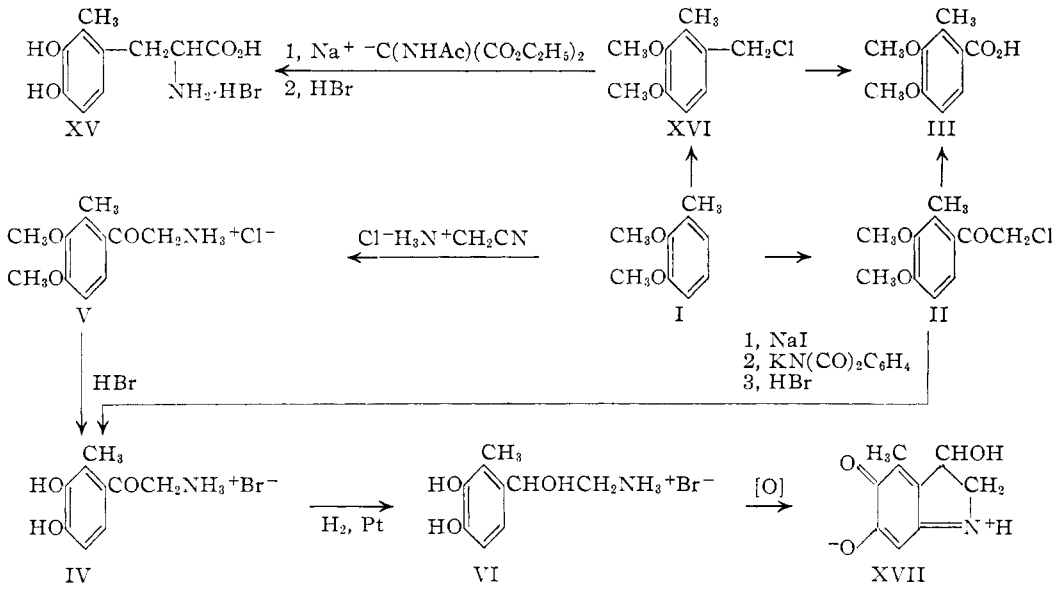
(5) R. S. Grewal, *Brit. J. Pharmacol.*, **7**, 338 (1952).

(6) O. Hinsberg, *Ber.*, **56**, 852 (1923); A. Dornow and G. Petsch, *Arch. Pharm.*, **284**, 160 (1951).

(7) C. Mannich and G. Berger, *ibid.*, **277**, 117 (1939).

(8) R. I. T. Croumartie and J. Harley-Mason, *J. Chem. Soc.*, 1052 (1952).



methyl-,[8] 6-methyl-,[9] 5-*n*-propyl-3,4-dihydroxyphenylalanine,[10] and of 2,3,4- and 3,4,5-trihydroxyphenylalanine[11] have been reported. In extending these series we hope to obtain information regarding the effect of nuclear substitution on biological properties of such compounds and to make available new analogs of adrenochrome which has shown interesting hemostatic,[12] depressor[13] and hallucinogenic effects.[14]

The first analog of norepinephrine to be described here is 2-methyl-3,4-dihydroxyphenylethanolamine (VI). Its synthesis started from 2,3-dimethoxybenzaldehyde which was reduced to 2,3-dimethoxytoluene (I) by the Huang-Minlon modification of the Wolff–Kishner method.[15] Two routes to 2-methyl-5,4-dihydroxy-α-aminoacetophenone were explored. Condensation of 2,3-dimethoxytoluene with chloroacetyl chloride under the conditions of the Friedel–Crafts reaction furnished 2-methyl-3,4-dimethoxyphenacyl chloride (II); its structure was proved by Kröhnke degradation to 2-methyl-3,4-dimethoxybenzoic acid (III) which was compared with an authentic sample.[16] Treatment of II with sodium iodide in acetone solution followed by a Gabriel reaction led to 2-methyl-3,4-dimethoxy-α-phthalimidoacetophenone and this, on boiling with hydrobromic acid, gave 2-methyl-3,4-dihydroxy-α-aminoacetophenone hydrobromide (IV). The second shorter route to IV followed the Asscher[17] extension of the Houben–Hoesch synthesis using 2,3-dimethoxytoluene and aminoacetonitrile. The resulting 2-methyl-3,4-dimethoxy-α-aminoacetophenone could be demethylated to IV. This amino ketone was then hydrogenated to VI. Our next objective, the preparation of 2-chloro-3,4-dihydroxyphenylethanolamine, has not been attained although its dimethyl ether could be synthesized after considerable experimentation. Starting with 3-aminoveratrole (VII)[18] 3-chloroveratrole (VIII) was prepared by a Sandmeyer reaction. Attempts to chloroacetylate this compound under a variety of conditions and to prepare an aminoacetyl derivative by the Houben–Hoesch method were unsuccessful. Chloromethylation of 3-chloroveratrole appeared as a promising alternative, and when chloromethyl ether was used, an excellent yield of 2-chloro-3,4-dimethoxybenzyl chloride (IX) was obtained. The structure of this derivative follows from its oxidation to 2-chloro-3,4-dimethoxybenzoic acid (X) which was identical with an authentic sample.[19] 2-Chloro-3,4-dimethoxybenzaldehyde (XI) was formed readily from IX by the Sommelet method and condensed with nitromethane in ethanolic potassium hydroxide solution. The resulting nitro alcohol XII was reduced best with lithium aluminum hydride, but suitable conditions for the demethylation of 2-chloro-3,4-dimethoxyphenylethanolamine (XIII) could not be elaborated.

With the hope of obtaining 2-chloro-3,4-dihydroxybenzaldehyde for the synthesis of 2-chloro-3,4-dihydroxyphenylethanolamine, the dimethoxyaldehyde XI was heated briefly with hydrobromic acid but only one methoxyl group was cleaved in this process. Longer heating gave mainly intractable black solids, and such materials also were formed in the treatment of XI with aluminum chloride or with pyridinium chloride.

For the synthesis of a chloro derivative of DOPA, 2-chloro-3,4-dimethoxybenzyl chloride (IX) was condensed with diethyl sodium acetamidomalonate,

(9) R. I. T. Croumartie and J. Harley-Mason, *Chemistry & Industry*, 972 (1953).

(10) G. Clemo and F. K. Duxbury, *J. Chem. Soc.*, 3844 (1952).

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(12) G. Derouaux, *Compt. rend. soc. biol.*, **131**, 830 (1949); J. Roskam and G. Derouaux, *Arch. internat. pharm. ther.*, **69**, 348 (1944).

(13) K. A. Oster and H. Sobotka, *J. Pharmacol. Exp. Therap.*, **78**, 100 (1943).

(14) A. Hoffer, H. Osmond and J. Smythies, *J. Ment. Sci.*, **100**, 29 (1954); H. Bakwin, *J. Pediatrics*, **46**, 133 (1955).

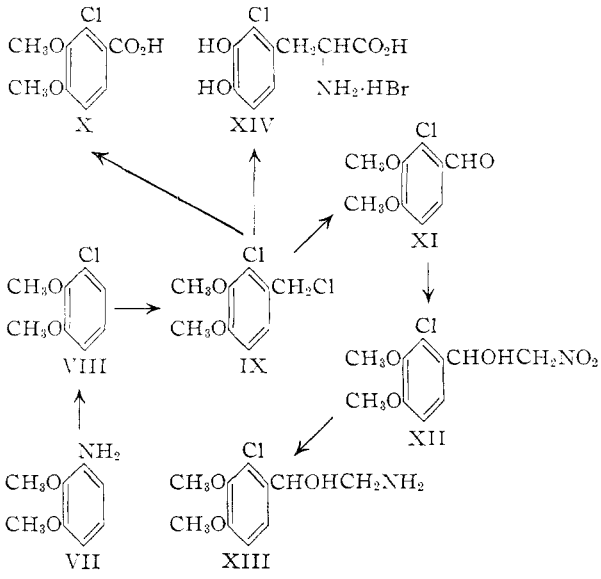
(15) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

(16) F. Bruchhausen, *Arch. Pharm.*, **263**, 570 (1925) (p. 595).

(17) M. Asscher, *Rec. trav. chim.*, **68**, 960 (1949); H. D. Moed, M. Asscher, P. J. A. Van Draanen and H. Niewind, *ibid.*, **71**, 933 (1952).

(18) F. Mauthner, *J. prakt. Chem.*, **149**, 328 (1937); H. S. Mason, THIS JOURNAL, **69**, 2241 (1947).

(19) L. C. Raiford and D. E. Floyd, *J. Org. Chem.*, **8**, 358 (1943). We are indebted to Professor Stanley Wawzonek for procuring this sample from the collection of the late L. Chas. Raiford.



and the product, ethyl 2-acetamido-2-carbethoxy-3-(2-chloro-3,4-dimethoxyphenyl)-propionate, was hydrolyzed, demethylated and decarboxylated with hydrobromic acid to β-(2-chloro-3,4-dihydroxyphenyl)-α-alanine hydrobromide (XIV).

β-(2-Methyl-3,4-dihydroxyphenyl)-α-alanine (XV) had been synthesized by Croumartie and Harley-Mason[8] by the azlactone route from 2-methyl-3,4-dimethoxybenzaldehyde, prepared from 2,3-dimethoxytoluene and hydrogen cyanide. We found it more convenient to chloromethylate 2,3-dimethoxytoluene with chloromethyl ether and to follow the same synthetic path as described for the chloro analog above. The position of the entering group in 2-methyl-3,4-dimethoxybenzyl chloride (XVI) was ascertained by oxidation to 2-methyl-3,4-dimethoxybenzoic acid (III).

When the chloromethylation of I was carried out with formaldehyde and hydrochloric acid, only small amounts of a bis-chloromethyl derivative, or of a compound which may be regarded as 1,5-dimethyl-2,3,6,7-tetramethoxy-9,10-dihydroanthracene were formed depending on the reaction conditions.

2-Methyl-3,4-dihydroxyphenylethanolamine could be oxidized under carefully controlled conditions to (±)4-methylnoradrenochrome (XVII) which was isolated and purified as the semicarbazone.

The amino acid XV showed no activity against Sarcoma 180 when tested in standard doses by Dr. C. C. Stock of the Sloan-Kettering Institute. It was relatively non-toxic to rats (tests by Smith, Kline and French Laboratories). The norepinephrine homolog VI exhibited low pressor activity in the cat in preliminary tests.

Experimental[20]

2-Methyl-3,4-dimethoxyphenacyl Chloride (II).—Anhydrous aluminum chloride (200 g.) was added in portions to a stirred and cooled solution of 100 g. of 3-methylveratrole (I)[21] and 80 g. of chloroacetyl chloride in 300 ml. of dry carbon disulfide. The mixture was stirred for another 1.5 hours, the solvent was decanted, and the brown complex decomposed with 1500 ml. of ice-cold 2.5% hydrochloric acid. The solid was filtered, dissolved in *ca.* 3 l. of ether and washed with 2.5% sodium hydroxide solution and with water. Evaporation of the dried ether solution gave 75 g. of crude chloro ketone which after one recrystallization from benzene afforded 63.8 g. (42.5%) of colorless leaflets, m.p. 101–102°.

Anal. Calcd. for $C_{11}H_{13}ClO_3$: C, 57.77; H, 5.73. Found: C, 57.67; H, 5.59.

In order to prove the position of the chloroacetyl group, a mixture of 0.4 g. of 2-methyl-3,4-dimethoxyphenacyl chloride and 2 ml. of pyridine was heated at 60–80° for five minutes, ether was added, and the supernatant liquid was decanted from the precipitated pyridinium salt. A solution of this salt in 10 ml. of ethanol was refluxed with 10 ml. of a 10% sodium hydroxide solution for five minutes, cooled, and acidified. The precipitated solid was recrystallized from dilute acetic acid, m.p. 182.5–184.5°. It did not depress the melting point of an authentic sample[16] of 3-methylveratric acid.

2-Methyl-3,4-dimethoxyphenacyl Iodide.—A solution of 25 g. of 2-methyl-3,4-dimethoxyphenacyl chloride and 16.5 g. of sodium iodide in 350 ml. of acetone was allowed to stand for one-half hour, filtered, and the filtrate evaporated under reduced pressure. The colorless reaction product crystallized from benzene–petroleum ether, m.p. 99–101°. The yield was 29.6 g. (84%).

Anal. Calcd. for $C_{11}H_{13}IO_3$: C, 41.27; H, 4.09. Found: C, 41.21; H, 4.38.

2-Methyl-3,4-dimethoxy-α-phthalimidoacetophenone.—A mixture of 10 g. of 2-methyl-3,4-dimethoxyphenacyl iodide, 100 ml. of ethanol and 10 g. of potassium phthalimide was refluxed for three hours, cooled to 0°, filtered, and the filtrate was extracted exhaustively with boiling acetone. Concentration of the acetone extracts gave 5.3 g. (50%) of colorless needles which after recrystallization from acetone melted at 194–195.5°.

Anal. Calcd. for $C_{19}H_{17}NO_5$: C, 67.24; H, 5.05. Found: C, 67.10; H, 4.95.

2-Methyl-3,4-dimethoxy-α-aminoacetophenone Hydrochloride (V).—Aminoacetonitrile[22] dissolved in methanol was treated with ethereal hydrogen chloride, and 40 g. of the resulting salt was added at 30°, with stirring and cooling, to a solution of 128 g. of anhydrous aluminum chloride in 258 g. of nitrobenzene. To this mixture 65.6 g. of 3-methylveratrole was added, and hydrogen chloride was passed into the vigorously stirred solution at 30° for eight hours. After standing overnight, the mixture was poured into 400 ml. of ice-water, and the solid reaction product was filtered, washed with ether and recrystallized from methanol–ether. The colorless crystals, m.p. 180–181° dec., weighed 55 g. (53%).

Anal. Calcd. for $C_{11}H_{16}ClNO_3$: C, 53.77; H, 6.56. Found: C, 53.86; H, 6.62.

2-Methyl-3,4-dihydroxy-α-aminoacetophenone Hydrobromide (IV).—A solution of 46 g. of 2-methyl-3,4-dimethoxy-α-aminoacetophenone hydrochloride (V) in 470 ml. of 48% hydrobromic acid and 470 ml. of glacial acetic acid was refluxed for 30 hours and then concentrated to 440 ml. On cooling, 39 g. of crude hydrobromide IV precipitated out from which, by recrystallization from methanol—ether, 15.6 g. (32%) of pure material, m.p. 265–266° dec., and 17 g. of less pure product was elaborated.

The same hydrobromide salt was obtained in 52% yield when 2-methyl-3,4-dimethoxy-α-phthalimidoacetophenone was refluxed with 48% hydrobromic acid for ten hours.

Anal. Calcd. for $C_9H_{12}BrNO_3$: C, 41.24; H, 4.62. Found: C, 41.39; H, 4.64.

1-(2-Methyl-3,4-dihydroxyphenyl)-2-aminoethanol Hydrobromide (VI).—A solution of 7.0 g. of 2-methyl-3,4-di-

(20) All melting points are corrected. Microanalyses by Miss Patricia L. Paynter and Miss May Lai.

(21) Prepared by modified Wolff–Kishner reduction[15] of 2,3-dimethoxybenzaldehyde in 77% yield, b.p. 205° (758 mm.) (*cf.* R. Majima and Y. Okazaki, *Ber.*, **49**, 1482 (1916)) and characterized by demethylation to 3-methylcatechol, m.p. 65–68° (*cf.* Fahlberg, List and Co., German Patent 256,345 (1913)), and conversion to **3-methylcatechol diacetate** m.p. 68–69° (*Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.35; H, 5.99).

(22) S. Nishigaki, *J. Pharm. Soc. Japan*, **71**, 1248 (1951); *C. A.*, **46**, 8092[a] (1952).

hydroxy-α-aminoacetophenone hydrobromide in 110 ml. of ethanol absorbed the required amount of hydrogen under atmospheric pressure in the presence of 0.2 g. of Adams platinum catalyst. The catalyst was filtered, the solution concentrated to about 50 ml. and treated with ether under a blanket of nitrogen. The precipitated colorless crystals weighed 6.2 g. (88%) and melted at 155.5–156.5° dec.

Anal. Calcd. for $C_9H_{14}BrNO_3$: C, 40.92; H, 5.34. Found: C, 41.01; H, 5.24.

(±)4-Methylnoradrenochrome (XVII).—A solution of 1 g. of 1-(2-methyl-3,4-dihydroxyphenyl)-2-aminoethanol hydrobromide in 11 ml. of water was treated, in portions, with a solution of 4.95 g. of potassium ferricyanide and 1.62 g. of sodium bicarbonate in 25 ml. of water. After five minutes a solution of 0.5 g. of semicarbazide hydrochloride and 0.75 g. of sodium acetate in 6 ml. of water was added, the mixture was cooled overnight, the dark red precipitate was filtered and washed with a little cold water. **The semicarbazone** was dissolved in boiling water, adsorbed on carbon, and the carbon was extracted with hot acetone. Evaporation of the solvent and repeated recrystallization from water gave *ca.* 30 mg. of orange crystals, m.p. 197–198° dec.

Anal. Calcd. for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12. Found: C, 50.21; H, 5.29.

3-Methyl-4-chloromethylveratrole (XVI).—A solution of 76.1 g. (0.5 mole) of 3-methylveratrole and 80.5 g. (1.0 mole) of monochloromethyl ether[23] in 80 g. of glacial acetic acid was stirred for six hours at 30°, poured with stirring into 500 ml. of ice-water and filtered. The semi-crystalline product was freed from oil by pressing between filter paper, and recrystallized from petroleum ether. The resulting colorless crystals, m.p. 69–70.5°, weighed 42 g. (42%).

Anal. Calcd. for $C_{10}H_{13}ClO_2$: C, 59.85; H, 6.53. Found: C, 59.89; H, 6.24.

To prove its structure, a solution of 3 g. of XVI and 3.17 g. of potassium permanganate in 150 ml. of water was heated with 3 g. of sodium carbonate monohydrate at 80° for 24 hours, the manganese dioxide was filtered, and the filtrate decolorized with dilute hydrogen peroxide. Acidification, filtration and recrystallization from dilute acetic acid gave colorless crystals, m.p. 185–186°, which did not depress the melting point of authentic[16] 3-methylveratric acid.

Chloromethylation of 3-Methylveratrole with Formaldehyde and Hydrochloric acid.—(a) Hydrogen chloride was passed into a vigorously stirred mixture of 10 g. of 3-methylveratrole, 50 ml. of 38% aqueous formaldehyde solution and 60 ml. of 37% hydrochloric acid at 60° for two hours, and at 70–75° for another six hours. Neutralization with sodium bicarbonate, extraction with ether, and distillation of the residual oil at 3 mm. pressure gave a distillate which crystallized slowly by itself, or on treatment with ethanol. Recrystallization from petroleum ether furnished colorless needles of a bis-(chloromethyl)-3-methylveratrole, m.p. 71–72.5°.

Anal. Calcd. for $C_{11}H_{14}Cl_2O_2$: C, 53.18; H, 5.71. Found: C, 53.02; H, 5.66.

(b) When 10 g. (0.066 mole) of 3-methylveratrole, 5.2 g. (0.066 mole) of 38% formaldehyde solution and 60 ml. of 37% hydrochloric acid was treated with hydrogen chloride at 65–75° for six hours, and the reaction mixture was poured into ice-water, a gummy material was formed. Crystallization from ethanol yielded *ca.* 0.5 g. of colorless crystals, m.p. 176–177.5°. Their analysis suggests that the product might be impure 1,5-dimethyl-2,3,6,7-tetramethoxy-9,10-dihydroanthracene formed by dimerization of 3-methyl-4-chloromethylveratrole.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 71.75; H, 7.16.

Ethyl 2-Acetamido-2-carbethoxy-3-(2-methyl-3,4-dimethoxyphenyl)-propionate.—To a solution of 4.56 g. of sodium in 400 ml. of absolute ethanol was added 43.2 g. of ethyl acetamidomalonate and 40 g. of 3-methyl-4-chloromethylveratrole, and the solution was refluxed for five hours. Filtration from sodium chloride and evaporation of the filtrate under reduced pressure gave an oil which crystallized on standing. Oily portions were removed by pressing between filter paper for several days, the dry material (42.6 g., 56%) was washed with hot petroleum ether and recrystallized from dilute ethanol. The colorless crystals (28 g., 37%) melted at 101–102°.

Anal. Calcd. for $C_{19}H_{27}NO_7$: C, 59.83; H, 7.17. Found: C, 59.89; H, 6.84.

β-(2-Methyl-3,4-dihydroxyphenyl)-α-alanine Hydrobromide (XV).—A mixture of 28 g. of ethyl 2-acetamido-2-carbethoxy-3-(2-methyl-3,4-dimethoxyphenyl)-propionate and 50 ml. of 48% hydrobromic acid was refluxed for seven hours. A Dean–Stark water removal trap was attached, 50 ml. of toluene was added, and the aqueous layer distilled off azeotropically. The toluene was decanted from the solid cake which formed, and the solid was triturated with acetone in a mortar and filtered. It weighed 15.0 g. (70%), m.p. 237–239.5°. The colorless material showed, after recrystallization from ethanol–ether, m.p. 236–238° depending on the rate of heating.

Anal. Calcd. for $C_{10}H_{14}BrNO_4$: C, 41.11; H, 4.83. Found: C, 41.14; H, 4.94.

3-Chloroveratrole (VIII).—A suspension of 110 g. of 3-aminoveratrole[18] in 500 ml. of ice-cold 20% hydrochloric acid was diazotized with 245 g. of a 22% sodium nitrite solution and added in a thin stream to a solution of 74 g. of cuprous chloride in 1500 ml. of 20% hydrochloric acid through which steam was passed. When all the chloroveratrole had been steam distilled, the distillate was saturated with sodium chloride and extracted with ether. After washing with three 150-ml. portions of a 5% sodium hydroxide solution followed by 100 ml. of water and drying, the ether extract was fractionated. The colorless oily product weighed 107 g. (86%) and had b.p. 95–99° (3 mm.); the purest sample boiled at 98° (3 mm.).

Anal. Calcd. for $C_8H_9ClO_2$: C, 55.66; H, 5.25. Found: C, 55.77; H, 5.46.

In order to characterize the oil further, it was converted to 3-chlorocatechol and its dibenzoate which had been prepared previously by a different route.[24] **3-Chlorocatechol** was obtained by boiling 3-chloroveratrole with 48% hydrobromic acid. It melted at 48–50°. The reported melting point[24] is 46–48°.

3-Chlorocatechol dibenzoate melted at 110–111°. The literature[24] records m.p. 108–109°.

3-Chloro-4-chloromethylveratrole (IX).—A solution of 100 g. of 3-chloroveratrole and 93 g. of monochloromethyl ether[23] in 400 g. of glacial acetic acid was stirred at 60° for 24 hours, poured into 1 l. of ice-water, and filtered from 118 g. (92%) of precipitate, m.p. 50–55°. Recrystallization from petroleum ether and from ethanol gave 107 g. (84%) of colorless crystals, m.p. 56–58°.

Anal. Calcd. for $C_9H_{10}Cl_2O_2$: C, 48.89; H, 4.56. Found: C, 48.63; H, 4.55.

The position of the chloromethyl group was proved by oxidation of IX with potassium permanganate as described for the methyl analog XVI above. A yield of 50% of colorless crystals, m.p. 201–203°, was obtained. This compound did not depress the melting point of an authentic sample of 2-chloroveratric acid (X).[19]

Ethyl 2-Acetamido-2-carbethoxy-3-(2-chloro-3,4-dimethoxyphenyl)-propionate.—A solution containing 1.04 g. of sodium in 100 ml. of absolute ethanol, as well as 9.83 g. of ethyl acetamidomalonate and 10 g. of 3-chloro-4-chloromethylveratrole was refluxed with stirring for eight hours, filtered, and the filtrate evaporated under reduced pressure. The residual oil crystallized very slowly. It was washed with hexane and recrystallized from dilute ethanol. The colorless crystals, m.p. 86–87.5°, weighed 10.5 g. (58%).

Anal. Calcd. for $C_{18}H_{24}ClNO_7$: C, 53.80; H, 6.02. Found: C, 53.85; H, 5.80.

β-(2-Chloro-3,4-dihydroxyphenyl)-α-alanine Hydrobromide (XIV).—A solution of 10.5 g. of ethyl 2-acetamido-2-carbethoxy-3-(2-chloro-3,4-dimethoxyphenyl)-propionate in 60 ml. of 48% hydrobromic acid was refluxed for seven hours and worked up as described for XV above. The crude material was washed with a little butanone and recrystallized from ethanol–ether. The colorless crystals weighed 4.4 g. (54%) and melted at 220–221° dec.

(23) C. S. Marvel and P. K. Porter, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 337.

(24) R. Willstätter and H. E. Müller, *Ber.*, **44**, 2182 (1911).

Anal. Calcd. for $C_9H_{11}BrClNO_4$: C, 34.58; H, 3.55. Found: C, 34.82; H, 3.52.

2-Chloroveratraldehyde (XI).—A solution of 83 g. of 3-chloro-4-chloromethylveratrole and 60 g. of hexamethylenetetramine in 400 ml. of chloroform was refluxed for three hours, cooled, and the precipitated colorless salt (127 g., 93%) filtered and washed with chloroform. It then was refluxed with 400 ml. of 50% acetic acid for seven hours, the solution was stirred into 800 ml. of ice-water, the aldehyde was filtered and washed with water. The dried material weighed 48 g. (64%). Recrystallization from petroleum ether gave colorless needles, m.p. 70.5–72°.

Anal. Calcd. for $C_9H_9ClO_3$: C, 53.88; H, 4.52. Found: C, 53.83; H, 4.50.

1-(2-Chloro-3,4-dimethoxyphenyl)-2-nitroethanol (XII).—A stirred solution of 10 g. of 2-chloroveratraldehyde and 3.5 g. of nitromethane in 90 ml. of ethanol was cooled to 0°, and a solution of 2.8 g. of potassium hydroxide in 4 ml. of water and 7 ml. of ethanol was added dropwise to the resulting suspension at 0°. The suspension cleared as the first drops of base were added, but the sodium salt of the nitro alcohol soon precipitated. It was filtered after 30 minutes, washed with ethanol and ether, dissolved in 75 ml. of water and, at 0°, added dropwise and with stirring to 45 ml. of 50% acetic acid. The nitro alcohol was precipitated with 170 ml. of water, dried and recrystallized from benzene–petroleum ether. The pale yellow needles, m.p. 111–113°, weighed 7.6 g. (58%).

Anal. Calcd. for $C_{10}H_{12}ClNO_5$: C, 45.89; H, 4.62. Found: C, 46.06; H, 4.56.

1-(2-Chloro-3,4-dimethoxyphenyl)-2-aminoethanol (XIII).—(a) A stirred solution of 3 g. of 1-(2-chloro-3,4-dimethoxyphenyl)-2-nitroethanol in 190 ml. of ether was reduced with 3.6 g. of lithium aluminum hydride under reflux for 30 hours. Water was added dropwise until a granular precipitate had formed, the ether layer was decanted, dried, and treated with hydrogen chloride. Filtration of the precipitate gave 1.8 g. (59%) of hydrochloride as colorless leaflets which were recrystallized from ethanol–ether, m.p. 220–221° dec.

Anal. Calcd. for $C_{10}H_{15}Cl_2NO_3$: C, 44.79; H, 5.64. Found: C, 44.87; H, 5.50.

(b) A mixture of 2 g. of the nitro alcohol, 2.3 g. of 30-mesh zinc dust, 15 ml. of ethanol and 25 ml. of 30% sulfuric acid was stirred at 50–60° for four hours. The clear solution was extracted with ether, made strongly alkaline with sodium hydroxide, and the supernatant liquid was decanted from the inorganic precipitate. Both this solid and the alkaline solution were extracted repeatedly with ether, the combined ether extracts were dried, and the hydrochloride of the amino alcohol precipitated with hydrogen chloride. It weighed 0.8 g. (39%) and after recrystallization from ethanol–ether did not depress the melting point of a sample prepared by method (a).

Anal. Found: C, 44.79; H, 5.52.

Demethylation of 2-Chloroveratraldehyde.—A mixture of 3 g. of 2-chloroveratraldehyde and 20 ml. of 48% hydrobromic acid was refluxed for 20 minutes, cooled and filtered. Recrystallization of the product from ethanol with the aid of carbon gave 1.5 g. (54%) of colorless needles, m.p. 208–209°.

Anal. Calcd. for $C_8H_7ClO_3$: C, 51.49; H, 3.78. Found: C, 51.26; H, 3.83.

The product was soluble in 5% sodium hydroxide solution and essentially insoluble in water and in 5% sodium bicarbonate solution. It gave the Schiff aldehyde test, and a green color with ferric chloride.

CHARLOTTESVILLE, VIRGINIA

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Jervine. VIII. Δ^{13}-Jervine, a New Double Bond Isomer of Jervine

BY B. M. ISELIN[1] AND O. WINTERSTEINER

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Jervine (I) is transformed by prolonged treatment with hydrogen and palladium black in aqueous acetic acid into a double bond isomer, Δ^{13}-jervine (II). Δ^{13}-Jervine is far more stable toward acidic reagents than jervine, but, in contradistinction to the latter, is attacked by strong alkali with the formation of yet another isomer to which the dienone structure V is ascribed. This assignment rests mainly on the fact that the diketone XII obtained by Oppenauer oxidation of the N-acetate of V shows the same ultraviolet absorption spectrum as V, while the spectrum of the corresponding diketone XI from Δ^{13}-jervine N-acetate reveals the presence of a new α,β-unsaturated ketone chromophore. Various observations indicate that the formation of XI is accompanied by inversion of the configuration of carbon atom 8.

In early attempts to improve on existing methods for the preparation of tetrahydrojervine[2,3] we essayed the catalytic reduction of jervine (later assigned structure I[4–6]) in 10% aqueous acetic acid solution with palladium black as the catalyst. The reaction proceeded rather sluggishly and came to a standstill after several days of shaking with an uptake of only 1.3 to 1.5 moles of hydrogen. The crude product still exhibited jervine-like ultraviolet absorption, but it was noted that the main maximum at 250 mμ had shifted to a somewhat lower wave length (around 245 mμ). The entity responsible for this absorption, isolated from the mixture in about 20% yield, had the composition $C_{27}H_{39}O_3N$, *i.e.*, that of jervine, but markedly differed from the native alkaloid in its physical properties (m.p. 269–271°, $[\alpha]^{22}D$ −50°, λ_{max}^{alc} 245 mμ (8,300) and 320 mμ (37)). The change in the α,β-unsaturated ketone chromophore was also evident in the infrared spectrum, the C=O and C=C bands in the double bond stretching vibration region appearing at 5.94 and 6.12 μ, respectively, rather than at the positions characteristic for jervine (5.88, 6.16). It is interesting that these are also the positions occupied by these bands in the spectrum of *isojervine* (m.p. 114–116°), an isomer of an as yet undetermined structure which Jacobs and Craig[7] had obtained by treatment of jervine with methanolic hydrogen chloride.

The new isomer, like jervine, formed an O,N-diacetate (m.p. 189–192°, $[\alpha]^{23}D$ −18°), which on mild alkaline hydrolysis yielded the N-acetate (m.p. 240–242°, $[\alpha]^{24}D$ −41°), also obtainable directly from the free base by selective N-acetylation. Hydrogenation in acetic acid yielded a difficultly separable and ill-reproducible mixture of tetrahy-

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