reagent of Overell and Petrow[12] was fairly effective. There was some indication that more vigorous conditions were required for the 2,5-series than the 3,4-series. The polymers prepared by this method of deacetylation analyzed poorly for carbon, hydrogen and nitrogen. A summary of results is given in Table I.

Acknowledgments.—We are indebted to Drs. Alfred M. Holtzer and E. Peter Geiduschek for furnishing the apparatus and solvents used in the viscosity studies and for helpful suggestions.

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF VIRGINIA]

2-Substituted Derivatives of 3,4-Dihydroxyphenylalanine

BY CARL KAISER[1] AND ALFRED BURGER

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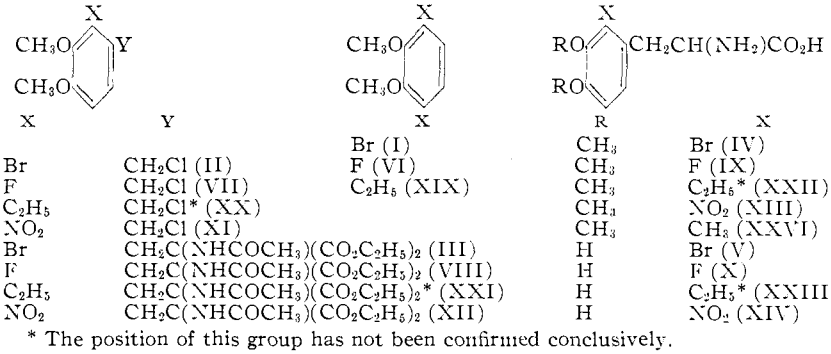
Because 2-methyl- and 2-chloro-3,4-dihydroxyphenylalanine inhibited the multiplication of influenza virus in the allantoic fluid of the chick embryo, the following additional 2-substituted derivatives of DOPA and their dimethyl ethers have been synthesized for biological screening: 2-bromo-, 2-fluoro-, 2-ethyl- and 2-nitro-DOPA. In addition, the synthesis of β-(2-methyl-3,4-dihydroxyphenyl)-N-methyl-α-alanine and β-(2-chloro-3,4-dihydroxyphenyl)-β-alanine has been performed.

3,4-Dihydroxyphenylalanine (DOPA) is the substrate of several enzyme systems such as dopa oxidase and dopa decarboxylase which convert it to melanins[2] and to 3,4-dihydroxyphenethylamine and norepinephrine.[3,4] These reactions play an important role in animal and plant metabolism and have been studied extensively *in vitro* and *in vivo*. Interference with these reactions should prevent the accumulation of the respective reaction products in certain pathogenic conditions and for this purpose inhibitors for dopa decarboxylase have been sought repeatedly.[5-10] When 2-methyl-3,4-dihydroxyphenylalanine[11,12] became available, it was included in a series of some two hundred compounds in tests for dopa decarboxylase inhibition *in vitro*, and the same substance and its 2-chloro analog[11] were screened for anti-phenylalanine behavior in various biological systems. Since several analogs of amino acids had been found to possess antiviral activity,[13,14] it seemed desirable to test the effect of both compounds against influenza virus. In the course of these experiments it was observed that both compounds inhibited the multiplication of the PR-8 strain of influenza virus in the allantoic fluid of the chick embryo.[15] Although in rats infected with the virus these two compounds were inactive, additional 2-substituted derivatives of 3,4-dihydroxyphenylalanine were prepared with the hope of overcoming this obstacle.



X	Y	X	R	X
		Br (I)	CH_3	Br (IV)
Br	CH_2Cl (II)	F (VI)	CH_3	F (IX)
F	CH_2Cl (VII)	C_2H_5 (XIX)	CH_3	C_2H_5* (XXII)
C_2H_5	CH_2Cl* (XX)		CH_3	NO_2 (XIII)
NO_2	CH_2Cl (XI)		CH_3	CH_3 (XXVI)
Br	$CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ (III)		H	Br (V)
F	$CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ (VIII)		H	F (X)
C_2H_5	$CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$* (XXI)		H	C_2H_5* (XXIII)
NO_2	$CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$ (XII)		H	NO_2 (XIV)

* The position of this group has not been confirmed conclusively.

Fig. 1.

For the synthesis of 2-bromo-3,4-dihydroxyphenylalanine, 3-bromoveratrole (I)[16] was chloromethylated to 2-bromoveratryl chloride (II); this was condensed with diethyl acetamidomalonate to give III which was hydrolyzed to β-(2-bromo-3,4-dimethoxyphenyl)-α-alanine (IV) with hydrochloric acid. β-(2-Bromo-3,4-dihydroxyphenyl)-α-alanine (V) was obtained by ether cleavage with 47% hydriodic acid. By an analogous sequence (VI → VII → VIII → X) 3-fluoroveratrole (VI)[17] was transformed into β-(2-fluoro-3,4-dihydroxy-

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TABLE I

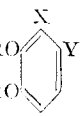
INFRARED SPECTRA OF DIMETHOXY-SUBSTITUTED BENZOIC ACIDS[a]

Dimethoxybenzoic acid derivative	Wave length, microns																	
2(?)-Ethyl-3,4-	9.13	9.33	9.48	9.78	10.16		10.84		11.67	11.95	12.10	12.61	12.75	13.06	13.26		14.35	
2-Methyl-3,4-	9.23		9.54		9.96	10.56	10.90		11.74	11.93	12.16		12.75	13.02	13.33		14.35	
2-Fluoro-3,4-	9.14			9.72		10.43	10.79	11.25			12.16		12.80	13.06		13.51	14.19	15.09
2-Bromo-3,4-				9.72			10.94			11.97	12.27		12.80	13.06				15.07
5-Methyl-3,4-	9.11		9.50		10.04		10.79	11.35	11.65				12.84	13.03	13.34		14.03	
2,3-	9.18		9.50		9.97	10.30	10.68	11.15			12.20	12.42		13.19		13.68		15.45

[a] Perkin–Elmer model 21 infrared spectrophotometer, potassium bromide pellets.

TABLE II

DESCRIPTIVE AND ANALYTICAL DATA



Compound	R	X	Y	Yield, %	M.p., °C.	Solvent of crystn.	Composition	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
2-Bromoveratryl chloride	CH_3	Br	CH_2Cl[a]	78	37.5–39	EtOH	$C_9H_{10}BrClO_2$	40.71	3.79	40.82	4.09
2-Fluoroveratryl chloride	CH_3	F	CH_2Cl	68	50.5–51.5	MeOH	$C_9H_{10}ClFO_2$	52.82	4.93	53.37	4.74
2-Ethylveratryl chloride	CH_3	C_2H_5	CH_2Cl	16	36–37.5	Ligroin	$C_{11}H_{15}ClO_2$	61.54	7.04	61.93	7.04
Diethyl acetamido-(2-bromo-3,4-dimethoxybenzyl)-malonate	CH_3	Br	$CH_2C(NHAc)(CO_2C_2H_5)_2$	86	139.5–141	$(i\text{-Pr})_2O$[b]	$C_{18}H_{24}BrNO_7$	48.44	5.42	48.31	5.25
Diethyl acetamido-(2-fluoro-3,4-dimethoxybenzyl)-malonate	CH_3	F	$CH_2C(NHAc)(CO_2C_2H_5)_2$	75	93–95	EtOH–H_2O	$C_{18}H_{24}FNO_7$	56.10	6.27	56.40	6.22
Diethyl acetamido-(2-ethyl-3,4-dimethoxybenzyl)-malonate	CH_3	C_2H_5	$CH_2C(NHAc)(CO_2C_2H_5)_2$	40	86–88	EtOH–H_2O	$C_{20}H_{27}NO_7$	60.74	7.39	60.45	7.22
Diethyl acetamido-(2-nitro-3,4-dimethoxybenzyl)-malonate	CH_3	NO_2	$CH_2C(NHAc)(CO_2C_2H_5)_2$[c]	64	144–146	EtOH	$C_{18}H_{24}N_2O_9$	52.42	5.87	52.61	5.68
β-(2-Bromo-3,4-dimethoxyphenyl)-α-alanine·HCl	CH_3	Br	$CH_2CH(NH_2)CO_2H$		237.5–239 d.	[d]	$C_{11}H_{14}BrNO_4$	43.44	4.64	43.31	4.68
β-(2-Fluoro-3,4-dimethoxyphenyl)-α-alanine·HCl	CH_3	Br	$CH_2CH(NH_2)CO_2H$·HCl	73	258–259 d.	EtOH–Et_2O	$C_{11}H_{15}BrClNO_4$	38.79	4.44	38.76	4.58
β-(2-Ethyl-3,4-dimethoxyphenyl)-α-alanine·HCl	CH_3	F	$CH_2CH(NH_2)CO_2H$		219 d.	[d]	$C_{11}H_{13}FNO_4$	54.32	5.80	54.39	6.16
β-(2-Nitro-3,4-dimethoxyphenyl)-α-alanine	CH_3	C_2H_5	$CH_2CH(NH_2)CO_2H$·HCl	69	209–211 d.	EtOH–Et_2O	$C_{11}H_{15}ClFNO_4$	47.23	5.41	47.31	5.19
β-(2-Methyl-3,4-dimethoxyphenyl)-α-alanine·HCl	CH_3	C_2H_5	$CH_2CH(NH_2)CO_2H$	50	255.5–256.5 d.	[d]	$C_{13}H_{19}NO_4$	61.64	7.56	61.04	7.69
β-(2-Ethyl-3,4-dihydroxyphenyl)-α-alanine·HBr	CH_3	NO_2	$CH_2CH(NH_2)CO_2H$[e]	81	218 d.	[d]	$C_{11}H_{14}N_2O_6$	48.89	5.22	48.58	4.96
β-(2-Fluoro-3,4-dihydroxyphenyl)-α-alanine	H	F	$CH_2CH(NH_2)CO_2H$		282–283 d.	H_2O[f]	$C_9H_{10}FNO_4$	50.23	4.68	49.97	4.60
β-(2-Bromo-3,4-dihydroxyphenyl)-α-alanine	H	Br	$CH_2CH(NH_2)CO_2H$·HBr	93	187–190 d.	$(i\text{-Pr})_2O$–i-PrOH	$C_9H_{11}BrFNO_4$	36.50	3.75	36.69	4.15
β-(2-Ethyl-3,4-dihydroxyphenyl)-α-alanine	H	Br	$CH_2CH(NH_2)CO_2H$	39	205 d.	H_2O[f]	$C_9H_{10}BrNO_4$	39.15	3.65	39.56	4.19
	H	C_2H_5	$CH_2CH(NH_2)CO_2H$	26	196–198 d.	H_2O[f]	$C_{11}H_{15}NO_4$	58.66	6.71	57.79	6.92

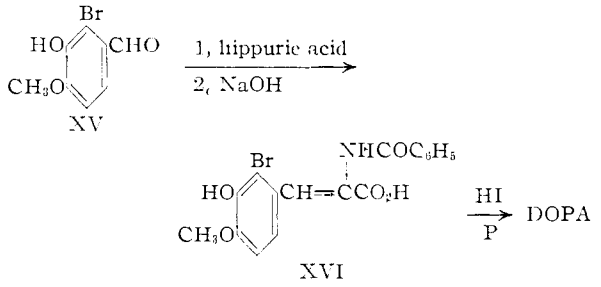
β-(2-Nitro-3,4-dihydroxyphenyl)-α-alanine	H	NO_2	$CH_2CH(NH_2)CO_2H$[e]	67	182–185 d.	H_2O[f]	$C_9H_{10}N_2O_6 \cdot H_2O$	41.54	4.65	41.46	4.49
2-Ethylveratric acid	CH_3	C_2H_5	CO_2H		152–154	EtOH–H_2O	$C_{11}H_{14}O_4$	62.84	6.71	62.57	6.55
2-Fluoroveratric acid	CH_3	F	CO_2H	74	188–190	MeOH–H_2O	$C_9H_9FO_4$	54.01	4.53	53.94	4.36
2,3-Dimethoxy-6-carbomethoxybenzenediazonium fluoborate	CH_3	N_2BF_4	CO_2CH_3[e]	78	167.5–169 d.	Me_2CO–Et_2O	$C_{10}H_{11}BF_4N_2O_4$	38.74	3.58	38.30	3.60
Methyl 2-fluoroveratrate	CH_3	F	CO_2CH_3	9	80–81.5	EtOH–H_2O	$C_{10}H_{11}FO_4$	56.07	5.17	55.99	5.18
2-Ethylveratraldehyde semicarbazone	CH_3	C_2H_5	$CH{=}NNHCONH_2$		191–193	EtOH	$C_{12}H_{17}N_3O_3$	57.35	6.82	57.26	6.37
2-Ethylveratraldoxime	CH_3	C_2H_5	CH=NOH		89–90	EtOH–H_2O	$C_{11}H_{15}NO_3$	63.14	7.23	62.94	6.72
4-(2-Ethyl-3,4-dimethoxybenzal)-2-phenyl-5-oxazolone	CH_3	C_2H_5	Azl[g,h]	41	157.5–158.5	EtOH	$C_{20}H_{18}NO_4$	71.20	5.68	71.40	5.84
4-(2-Nitro-3,4-dimethoxybenzal)-2-phenyl-5-oxazolone	CH_3	NO_2	Azl[g,h]	37	168.5–170	AcOH	$C_{18}H_{14}N_2O_6$	61.01	3.98	61.32	4.26
4-(2-Bromo-3-acetoxy-4-methoxybenzal)-2-phenyl-5-oxazolone	3-CH_3CO 4-CH_3	Br	Azl[g,h]	67	178–179	C_6H_6	$C_{19}H_{14}BrNO_5$	54.82	3.39	54.85	3.13
α-Benzamido-2-ethyl-3,4-dimethoxycinnamic acid	CH_3	C_2H_5	CH=C(NHBz)CO_2H	95	162–163.5	EtOH–H_2O	$C_{20}H_{21}NO_5$	67.59	5.95	67.79	6.03
α-Benzamido-2-nitro-3,4-dimethoxycinnamic acid	CH_3	NO_2	CH=C(NHBz)CO_2H[i]	91	212–213.5	EtOH–H_2O	$C_{18}H_{16}N_2O_7$	58.06	4.33	58.25	3.97
α-Benzamido-2-bromo-3-hydroxy-4-methoxycinnamic acid	3-H 4-CH_3	Br	CH=C(NHBz)CO_2H	83	119–121	EtOH–H_2O	$C_{17}H_{14}BrNO_5$	52.06	3.60	52.17	3.71
α-Benzamido-2-ethyl-3,4-dimethoxyphenylpropionic acid	CH_3	C_2H_5	$CH_2CH(NHBz)CO_2H$	98	75–76	EtOH–H_2O	$C_{20}H_{23}NO_5 \cdot C_2H_6O$	65.49	7.25	65.58	7.63
2-Chloro-3,4-dimethoxycinnamic acid	CH_3	Cl	CH=$CHCO_2H$	65	220–222	EtOH	$C_{11}H_{11}ClO_4$	54.44	4.57	54.76	4.62
β-(2-Chloro-3,4-dimethoxyphenyl)-β-alanine	CH_3	Cl	$CH(NH_2)CH_2CO_2H$	37	240–241 d.	[d]	$C_{11}H_{14}ClNO_4$	50.87	5.43	50.44	5.19
β-(2-Chloro-3,4-dihydroxyphenyl)-β-alanine	H	Cl	$CH(NH_2)CH_2CO_2H$	90	163–164 d.[j]	[d]	$C_9H_{10}ClNO_4 \cdot H_2O$	43.29	4.85	43.16	5.08
Methyl β-(2-methyl-3,4-dimethoxyphenyl)-α-aminopropionate hydrochloride	CH_3	CH_3	$CH_2CH(NH_2)CO_2CH_3 \cdot HCl$[k]	95	176–177	EtOH–Et_2O	$C_{13}H_{20}ClNO_4$	53.89	6.95	53.55	6.81
β-(2-Methyl-3,4-dimethoxyphenyl)-N-*p*-tosyl-α-alanine	CH_3	CH_3	$CH_2CH(NH\text{-}p\text{-}Ts)CO_2H$[l,m]	91	171–172.5	EtOH–H_2O	$C_{19}H_{23}NO_6S$	58.00	5.89	58.15	5.89
β-(2-Methyl-3,4-dimethoxyphenyl)-N-*p*-tosyl-N-methyl-α-alanine	CH_3	CH_3	$CH_2CH[N(CH_3)(p\text{-}Ts)]CO_2H$	63	154–155.5	AcOEt–Ligroin	$C_{20}H_{25}NO_6S$	58.95	6.18	59.02	6.17
β-(2-Methyl-3,4-dihydroxyphenyl)-N-methyl-α-alanine	H	CH_3	$CH_2CH(NHCH_3)CO_2H$	27	303–304 d.	[d]	$C_{11}H_{15}NO_4$	58.65	6.71	58.39	6.65

[a] All compounds are colorless crystalline solids unless otherwise noted. [b] Also crystallized from aqueous ethanol producing a dimorph, m.p. 90–91°. Found: C, 48.18; H, 5.24. [c] Turned pink on standing. [d] Purified by reprecipitation from 10% hydrochloric acid. [e] Bright yellow prisms. [f] Containing a small amount of sulfur dioxide. [g] Fine yellow needles. [h] The 4-methylidene-2-phenyl-5-oxazolone group, —CH=C(—N=C(C_6H_6)—O)—C=O, has been abbreviated as Azl. [i] Pale yellow crystals. [j] After drying over phosphorus pentoxide for two days. [k] Prepared by Fischer esterification from the amino acid. [l] Tan crystals. [m] *p*-Ts represents the *p*-toluenesulfonyl group.

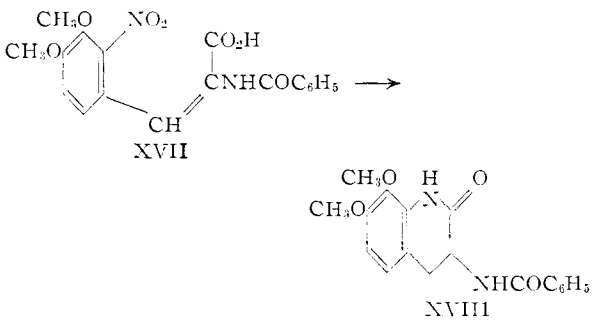
phenyl)-α-alanine (X); here, isolation of the intermediate dimethoxy derivative IX was possible but not necessary. This held also for the similar series of steps from 2-nitroveratryl chloride (XI)[18] to β-(2-nitro-3,4-dihydroxyphenyl)-α-alanine (XIV).

The position of the chloromethyl group in II was proved by oxidation to 2-bromoveratric acid.[18] In an analogous manner, 2-fluoroveratryl chloride (VII) was oxidized to 2-fluoroveratric acid. The identity of this acid was established by a Schiemann synthesis from methyl 2-aminoveratrate.[19]

An attempt was made to synthesize β-(2-bromo-3,4-dihydroxyphenyl)-α-alanine (IV) by a shorter route starting from the readily accessible 2-bromoisovanillin (XV).[20] The acetoxy-azlactone from this aldehyde was hydrolyzed to α-benzamido-2-bromo-3-hydroxy-4-methoxycinnamic acid (XVI) but this compound was debrominated to DOPA on heating with hydriodic acid and phosphorus.



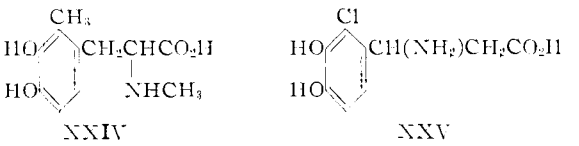
α-Benzamido-2-nitro-3,4-dimethoxycinnamic acid (XVII) was prepared from 2-nitroveratraldehyde[21] in a similar way and was hydrogenated in the presence of Adams catalyst in the hope of securing the corresponding saturated 2-amino derivative. While this compound was undoubtedly formed, it lactamized spontaneously to 3-benzamido-7,8-dimethoxy-3,4-dihydro-2-quinolone (XVIII).



The yields in the preparation of the ethyl substituted malonate ester XXI from 3-ethylveratrole (XIX) were so low that a different route to β-(ethyldihydroxyphenyl)-α-alanine (XXIII) was chosen. 3-Ethylveratrole,[22] obtained by the Huang-Minlon modification of the Wolff–Kishner method[23] from 2,3-dimethoxyacetophenone, was subjected to a Gattermann aldehyde synthesis with hydrogen cyanide; the position of the formyl group in the resulting ethyldimethoxybenzaldehyde could not be proved conclusively since oxidation with potassium permanganate or chromic acid only led to an ethyldimethoxybenzoic acid which decomposed on continued oxidation. The same acid was obtained from the oxidation of the chloromethylation product of 3-ethylveratrole. Since the chloromethylation of 3-methyl-, 3-chloro-, 3-bromo- and 3-fluoroveratrole introduced the chloromethyl group *ortho* to the 3-substituent, a similar orientation could be expected for the chloromethylation of 3-ethylveratrole. In support of this assumption the infrared spectra of pertinent dimethoxybenzoic acids are listed in Table I. It may be significant that 2-methylveratric acid and our ethyldimethoxybenzoic acid differ from 5-methylveratric acid in their absorption characteristics at 11.0–12.3 μ. The aldehyde and chloromethyl derivatives obtained from 3-ethylveratrole are tentatively assigned the structures 2-ethylveratraldehyde and 2-ethylveratryl chloride (XX), respectively.

2-Ethylveratraldehyde gave β-(2-ethyl-3,4-dimethoxyphenyl)-α-alanine (XXII) by an azlactone synthesis followed by hydrolysis, saturation of the side chain and removal of the benzoyl group. The ether groups of XXII were cleaved with hydriodic acid (XXIII).

In order to study the effect of various structural alterations in the amino group of antiviral 2-substituted derivatives of 3,4-dihydroxyphenylalanine, β-(2-methyl-3,4-dihydroxyphenyl)-N-methyl-α-alanine (XXIV) and β-(2-chloro-3,4-dihydroxyphenyl)-β-alanine (XXV) have been synthesized. Diethyl acetamido-(2-methyl-3,4-dimethoxybenzyl)-malonate[11] was hydrolyzed and decarboxylated, the amino acid XXVI was tosylated and the N-tosyl derivative treated with dimethyl sulfate. Scission of the methoxyl groups and the N-tosyl linkage furnished XXIV. The chloro derivative XXV was prepared by subjecting 2-chloroveratraldehyde[11] to a Perkin reaction, treating the resulting 2-chloro-3,4-dimethoxycinnamic acid with hydroxylamine and cleaving the methoxyl groups.



β-(2-Fluoro-3,4-dihydroxyphenyl)-α-alanine had activity against influenza virus similar to β-(2-methyl-3,4-dihydroxyphenyl)-α-alanine. 2-Bromo-, 2-fluoro-, 2-ethyl- and 2-nitro-DOPA and their dimethyl ethers were screened for bacteriostatic, antifungal and antiviral activity. In chick embryo protection tests, using the PR-8 strain of the influenza virus, XXII and XXVI possessed slight activity. β-(2-Chloro-3,4-dihydroxyphenyl)-β-alanine (XXV), in concentrations of 1:500, inhibited the growth of *Histoplasma capsulatum* and *Micrococcus pyogenes*, as well as *Diplococcus pneumoniae*, and provided slight protection in mice infected with this organism.[15]

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Experimental[24]

General Directions. (a) **Chloromethylation of Veratrole Derivatives (II, VII, XX).**—A solution of 0.25 mole of the 3-substituted veratrole derivative and 0.50 mole of monochloromethyl ether in 175 ml. of glacial acetic acid was stirred and warmed. Reaction times and temperatures were as follows: for 3-bromoveratrole,[16] 24 hr., 50–55°; for 3-ethylveratrole,[22] 8 hr., 30°; and for 3-fluoroveratrole,[17] 24 hr., 60°. The mixture was poured into 750 ml. of ice-water and the colorless solid recrystallized.

(b) (1) **Structural Proof of Chloromethylveratrole Derivatives.**—A solution of 1.5 g. of the chloromethyl derivative and 3.0 g. of potassium permanganate in 50 ml. of water and 1.0 ml. of 25% sodium hydroxide solution was refluxed for 1 hr., filtered from manganese dioxide and acidified. The precipitated benzoic acid derivatives were recrystallized. 2-Bromo-[16] and 2 fluoroveratric acid were identified by mixture melting points with samples prepared by unequivocal routes.

(2) **2-Fluoroveratric Acid.**—An ice-cold stirred suspension of 23.7 g. of methyl 2-aminoveratrate[19] and fluoboric acid, prepared by saturating 60 ml. of 48% hydrofluoric acid with boric acid at 10°, was diazotized with 30 ml. of a 33% aqueous solution of sodium nitrite. The yellow diazonium fluoborate was filtered and recrystallized. For data, see Table II. Thirteen grams of the salt was decomposed by heating at 170° for 2 hr., the black tarry residue was distilled under reduced pressure and recrystallized.

A mixture melting point of the resulting methyl 2-fluoroveratrate with a sample obtained by diazomethane methylation of 2-fluoroveratric acid from the oxidation of 2-fluoroveratryl chloride showed no depression.

Saponification of 0.1 g. of methyl 2-fluoroveratrate with 0.5 ml. of a hot 10% sodium hydroxide solution yielded, upon acidification, 70 mg. (74.5%) of 2-fluoroveratric acid, m.p. 188–190°. A mixture melting point of this substance and of the acid procured by oxidation of 2-fluoroveratryl chloride remained undepressed.

(c) **Diethyl Arylacetamidomalonates (III, VIII, XII, XXI).**—To 250 ml. of an absolute ethanolic solution of 0.13 mole of sodium ethoxide were added 0.13 mole of diethyl acetamidomalonate and 0.13 mole of the 2-substituted chloromethylveratrole, and the mixture was stirred and refluxed for 8 hr. The precipitated sodium chloride was filtered, the filtrate concentrated under reduced pressure and the residue recrystallized.

(d) **β-(2-Substituted-dimethoxyphenyl)-α-alanine Derivatives (IV, IX, XIII, XXII, XXVI).**—To a solution of 2.0 g. of the respective diethyl arylacetamidomalonate in 5 ml. of glacial acetic acid was added 8 ml. of 37% hydrochloric acid, and the mixture was heated at 95° for 6 hr. The solvents were distilled under reduced pressure, the crystalline hydrochloride was triturated with dry acetone and recrystallized.

The free phenylalanine derivatives were prepared by buffering the aqueous solutions of the hydrochlorides with potassium carbonate to *p*H 5–6 and purifying by reprecipitation from dilute hydrochloric acid solution with the same reagent.

(e) **Nuclear 2-Substituted Derivatives of DOPA.**—(1) A solution of 8.5 g. of the diethyl malonate derivatives (VIII, XII) in 40 ml. of redistilled 47% hydrobromic acid was refluxed for 7 hr. while hydrogen was bubbled through, concentrated under reduced pressure at 90° and the residual hydrobromide was recrystallized. The amino acid was liberated by adjusting the concentrated aqueous solution of the pure salt to *p*H 5–6 with sodium acetate with the help of a trace of sodium hydrosulfite. The material crystallized on cooling.

(2) Solutions of 6.4 g. of the dimethoxyphenylalanine derivatives (IV, XXII) in 60 ml. of 47% hydriodic acid were refluxed for 7 hr., concentrated as above, and the amorphous residue was adjusted to *p*H 5–6 with a saturated solution of sodium acetate. The amino acids crystallized on prolonged standing.

(f) **Azlactones.**—Starting with 2-bromoisovanillin,[20] 2-nitroveratraldehyde[21] and 2-ethylveratraldehyde, respectively, a mixture of 0.08 mole of the aldehyde, 0.09 mole of hippuric acid and 0.09 mole of anhydrous sodium acetate and 35 ml. of acetic anhydride was heated at 95° for 3 hr. The mixture solidified; it was diluted with 100 ml. of absolute ethanol, cooled to 0° and the crystalline deposit was filtered and washed with water.

(g) **Hydrolysis of Azlactones.**—The azlactones were refluxed with 30 volumes of a 1% sodium hydroxide solution in 50% aqueous ethanol for 10 minutes, the mixture was filtered and the filtrate acidified with 10% hydrochloric acid. The precipitated oils crystallized on standing.

Reductive Cleavage of α-Benzamido-2-bromo-3-hydroxy-4-methoxycinnamic Acid.—To an ice-cold mixture of 35 ml. of acetic anhydride and 35 ml. of 57% hydriodic acid was added 3.5 g. of red phosphorus and 6.5 g. of the acid XVI, and the mixture was refluxed for 3 hr. After filtering from phosphorus and extraction with ether, the solution was evaporated to dryness under reduced pressure, the residue was taken up in 10 ml. of water and buffered to *p*H 5–6 with sodium acetate. After standing for several days, 2.5 g. (77%) of crystals deposited which were recrystallized from water, m.p. 280° dec. The compound contained no halogen and did not depress the melting point of β-(3,4-dihydroxyphenyl)-α-alanine.

2-Ethylveratraldehyde.—3-Ethylveratrole[22] (30 g.) was dropped with stirring into a suspension of 29.8 g. of powdered aluminum chloride in 21 ml. of benzene at 0°, and then an anhydrous solution of 18.6 g. of hydrogen cyanide in 25 ml. of benzene was added. A slow stream of anhydrous hydrogen chloride was passed through at 28–30° for 8 hr., and the dark red mixture was poured onto a mixture of 106 ml. of 37% hydrochloric acid and 250 g. of crushed ice. Excess hydrogen cyanide was boiled out, the cooled mixture was extracted with ether, the ether extract was dried and distilled. The aldehyde was a straw-colored oil, b.p. 145–148° (5 mm.), yield 24.8 g. (70.5%). It was converted to the **oxime** and **semicarbazone** (Table II).

Oxidation of the aldehyde with alkaline potassium permanganate or chromic acid yielded the same ethyldimethoxybenzoic acid, m.p. 152–154°, which also resulted from the oxidation of ethyldimethoxybenzyl chloride (XX).

α-Benzamido-2-ethyl-3,4-dimethoxyphenylpropionic Acid.—A solution of 1.0 g. of α-benzamido-2-ethyl-3,4-dimethoxycinnamic acid in 50 ml. of absolute ethanol containing 0.1 g. of Adams catalyst was hydrogenated under 3 atm. of pressure at 25° for 48 hr. and worked up as usual. The oily residue of the evaporated solution crystallized on standing. The yield was quantitative.

The benzamido group was hydrolyzed with a 5:8 mixture of glacial acetic acid and 37% hydrochloric acid as described under the general directions (d) above.

3-Benzamido-7,8-dimethoxy-3,4-dihydro-2-quinolone (XVIII).—A solution of 13.0 g. of α-benzamido-2-nitro-3,4-dimethoxycinnamic acid in 100 ml. of absolute ethanol was hydrogenated in the presence of 0.25 g. of platinum oxide at a pressure of 3 atmospheres for 24 hr. and worked up. The filtered solution deposited 4.5 g. (39%) of a colorless product on cooling, m.p. 223.5–226° after recrystallization from ethanol. The substance was insoluble in dilute acid and base.

Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56. Found: C, 66.42; H, 6.23.

2-Chloro-3,4-dimethoxycinnamic Acid.—A mixture of 20.6 g. of 2-chloroveratraldehyde,[11] 10 g. of anhydrous sodium acetate and 20 ml. of acetic anhydride was heated at 170–180° for 8 hr., allowed to cool and diluted with 100 ml. of water. The solid precipitate was filtered and recrystallized.

β-(2-Chloro-3,4-dimethoxyphenyl)-β-alanine.—To a hot solution of 6.8 g. of sodium ethoxide in 80 ml. of ethanol was added a hot solution of 6.95 g. of hydroxylamine hydrochloride in 5 ml. of water. The mixture was cooled rapidly and the precipitated sodium chloride was filtered. To the filtrate was added 12.1 g. of 2-chloro-3,4-dimethoxycinnamic acid and the mixture heated on a steam-bath for 24 hr. After cooling, the crystalline product was filtered.

β-(2-Chloro-3,4-dihydroxyphenyl)-β-alanine (XXV).—A mixture of 1 g. of β-(2-chloro-3,4-dimethoxyphenyl)-β-alanine and 10 ml. of 57% hydriodic acid was refluxed for 5 hr., evaporated to dryness under reduced pressure and the residue was taken up in 5 ml. of water. Colorless crystals formed when the *p*H was adjusted to 6 with sodium acetate. They were filtered, washed with water, acetone and ether.

β-(2-Methyl-3,4-dimethoxyphenyl)-N-*p*-tosyl-α-alanine.—A mixture of 17 g. of β-(2-methyl-3,4-dimethoxyphenyl)-

(24) All melting points are corrected. Microanalyses by Miss Barbara J. Williamson.

α-alanine (XXVI), 17 g. of *p*-toluenesulfonyl chloride and 170 ml. of 4% sodium hydroxide solution was shaken for 24 hr. The reddish-black solution was filtered and acidified with 10% hydrochloric acid. The gummy precipitate solidified when the mixture was heated on a steam-bath for 30 minutes and was filtered.

β-(2-Methyl-3,4-dimethoxyphenyl)-N-methyl-N-*p*-tosyl-α-alanine.—To a stirred solution of 19.6 g. of β-(2-methyl-3,4-dimethoxyphenyl)-N-*p*-tosyl-α-alanine in 100 ml. of 10% sodium hydroxide solution was added 20 ml. of dimethyl sulfate, at room temperature. After 10 minutes, the mixture was made alkaline by adding 10% sodium hydroxide solution, diluted with 2 l. of water and heated on a steam-bath until solution was complete. After treatment with Darco the solution was acidified with dilute hydrochloric acid. The gummy solid became crystalline after standing for several hours.

β-(2-Methyl-3,4-dihydroxyphenyl)-N-methyl-α-alanine (XXIV).—A mixture of 2 g. of β-(2-methyl-3,4-dimethoxyphenyl)-N-methyl-N-*p*-tosyl-α-alanine and 17 ml. of 57% hydriodic acid was heated under reflux for 4 hr. The dark brown reaction mixture was concentrated under reduced pressure, the residue suspended in 20 ml. of water and extracted continuously with ether for 5 days. The clear aqueous layer was separated and concentrated to dryness under reduced pressure. When the residue was dissolved in 4 ml. of water and adjusted to *p*H 5–6, colorless crystals appeared.

5-Methylveratric Acid.—5-Methylvanillin[25] was methylated with dimethyl sulfate and 10% sodium hydroxide solution, as described for an analogous case,[26] and the crude oily 5-methylveratraldehyde was oxidized with alkaline potassium permanganate solution under the conditions used in the oxidation of 2-methylveratryl chloride.[11] Recrystallization from 50% aqueous ethanol gave colorless needles, m.p. 146–148°.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 60.87; H, 5.91.

(25) J. Koetschet and P. Koetschet, *Helv. Chim. Acta*, **13**, 476 (1930).

(26) H. Decker and O. Koch, *Ber.*, **40**, 4794 (1907).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

The $BF_3 \cdot N_2O_3$ Complex. Its Use in Diazotization and Nitration[1]

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Boron trifluoride reacts with nitrogen trioxide to form a stable, white, solid complex, $BF_3 \cdot N_2O_3$. Physical and chemical properties suggest that the structure is best represented as $(F_3B \leftarrow NO_2)^-(NO)^+$. The complex is a weak nitrating agent but a powerful diazotizing agent in the aromatic series.

It was reported recently that boron trifluoride forms a 1:1 addition complex with dinitrogen tetroxide[2] which is an excellent nitrating agent. It has now been found that boron trifluoride also forms a similar complex with dinitrogen trioxide. The combining ratio was determined gravimetrically to be 1:1. The complex is a white, stable solid, insoluble in all solvents with which it does not react, including alkanes, nitroalkanes and polychlorinated alkanes. It sublimes at room temperatures and does not melt in a sealed tube below 300°. Above this temperature, the very dark color of the dissociation products (especially NO_2) prevents observation of the remaining solid. These properties suggest that the complex is ionic in character and is formed as illustrated in equation 1 or 2

$$F_3B + ON|{:}NO_2 \longrightarrow \underset{A}{(F_3B \leftarrow NO_2)^-(NO)^+} \quad (1)$$

$$F_3B + O_2N|{:}NO \longrightarrow \underset{B}{(F_3B \leftarrow NO)^-(NO_2)^+} \quad (2)$$

That the preferred one of the above two formulations is A is probable on the basis of the chemical properties described below.

The $BF_3 \cdot N_2O_3$ complex reacts rapidly with substances with which BF_3 and N_2O_3 react separately, including water, alcohols, ethers, ketones, carboxylic acids, amines and pyridine. However, under rather vigorous conditions it will introduce an NO_2 group into aromatic nuclei. If benzene is refluxed over the complex in a glass fiber thimble in a Soxhlet extractor for 42 hr., a 5–6% yield of nitrobenzene is obtained. Under the same conditions, toluene yields a red-black tar, but in the solvent nitroethane at 60–65° for 3 days, toluene gives a 56% yield of *o*-nitrotoluene. Other nitration results are shown in Table I. It will be noted that the complex produces a different ratio of isomers than is reported for nitric acid nitrations of toluene, 1-nitronaphthalene and chlorobenzene. This apparently is the result of its mild nitrating action since the isomer distribution obtained represents increased amounts of the principal isomer produced in nitric acid nitrations. Powerful reagents favor a more nearly statistical distribution of isomers in aromatic substitution.

The nitrating action of the complex suggests structure B but does not preclude structure A since it has been shown by Ingold[3] that primary attack by a nitrosonium ion is probably a factor in the nitration of *p*-nitrophenol and *p*-chloroanisole. Furthermore it has been shown that nitrogen trioxide produces nitrosonium cations in the presence of another strong acid, namely, sulfuric acid.[4,5] In addition there remains the possibility that oxidation by air occurs during the nitration and converts the nitroso product to a nitro product or converts the complex $BF_3 \cdot N_2O_3$ to $BF_3 \cdot N_2O_4$ a known nitrating agent.[2] To test this, naphthalene was nitrated at 25° in three different ways: under air, under nitrogen, and with oxygen bubbling through the mixture. The second of these produced a low yield (14%) of 1-nitronaphthalene and

(1) From the M.S. Thesis of Takeo Hokama, Purdue University, January, 1956.

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(3) C. K. Ingold, C. A. Bunton, E. D. Hughes, D. I. H. Jacobs, M. H. Jones, G. J. Minkoff and R. I. Reed, *J. Chem. Soc.*, 2628 (1950).

(4) C. K. Ingold and E. D. Hughes, *et al.*, *ibid.*, 2504 (1950).

(5) J. D. S. Goulden and D. J. Millen, *ibid.*, 2620 (1950).