a portion of V while it was on a filter; it was then left standing overnight.

Anal. Found, VI: C, 19.56; H, 2.00; Ag, 49.25.

Preparation VII. A portion of the pure 1:2 complex (III) was recrystallized from a mixture of ethanol (90%) and norbornane (10%).

Anal. Found, VII: C, 19.47; H, 2.19; Ag, 50.44.

Infrared spectra were obtained for Nujol mulls of III and V. There was apparently no reaction between the silver salts and the sodium chloride cell windows.

Vapor pressure measurements. Solid 1:2 complex (0.1–0.5 g.) was placed in a small apparatus designed for vapor pressure measurements. The tube (A) containing complex was equipped with a differential manometer and two stopcocks. One stopcock opened to a vacuum pump and one to a tube (B) containing either norbornadiene or norbornane. The two tubes were frozen in Dry Ice–acetone, the stopcocks were opened, and the entire system was evacuated. The stopcocks were closed, and the apparatus was permitted to warm to room temperature. Vapor was admitted from B until the pressure in A was 50–90 mm. The stopcock was closed and the pressure in A was recorded from time to time during several hours. With norbornadiene vapor and powdered complex,[13] the pressure dropped rapidly (up to 65-mm. decrease with 0.5 g. of complex), but with norbornane vapor, the pressure did not change during 19 hr.

To insure that the drop in norbornadiene vapor pressure was not a result of simply replacing diene which had been removed from the 1:2 complex during evacuation, the complex which had been equilibrated with diene was refrozen, and the apparatus was again evacuated. After the apparatus had warmed to room temperature, the complex failed to absorb more diene vapor admitted from B. When the tube containing equilibrated complex was evacuated without freezing, fresh norbornadiene vapor was again absorbed rapidly.

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COATES CHEMICAL LABORATORIES
LOUISIANA STATE UNIVERSITY
BATON ROUGE 3, LA.

(13) Absorption of olefin seems to be related to the amount of surface available; the pressure decrease was greater with powdered complex than with larger sized crystals.

Substituted Phenylalanines and Phenylethylamines[1]

L. V. FENNOY[2]

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The general synthesis of α-amino acids as employed by Erlenmeyer[3] has been used by many other workers. The initial step, the preparation of an azlactone, in almost all cases proceeds smoothly and in good yields. Carter[4] gives an excellent review of azlactone synthesis.

Methods of converting azlactones to the final α-amino acids have offered some difficulties. The azlactone or its hydrolytic product, an acylaminoacrylic acid, can be converted to an α-amino acid by reduction and hydrolysis.[4]

It has been found that some azlactones could be reduced and deacetylated in one step with Raney nickel and hydrogen in a mildly alkaline suspension. The resulting benzoylamino acids upon hydrolysis with hydrochloric acid yielded the corresponding phenylalanine hydrochlorides (Table I). In the case of Ic, its benzoylamino acid was not isolated (because of its instability under alkaline conditions); the reduction solution was hydrolyzed directly to IIIc.

Ramirez and Burger[5] have shown that nitrostyrenes (IV) can be reduced with lithium aluminum hydride to the corresponding β-phenylethylamines (V). This method was used successfully here.

The nitrostyrenes were prepared by the method of Crowder, Grundon and Lewis[6] (Table II).

EXPERIMENTAL

The following directions will serve as a general description of the preparative method for the compounds in Table I and Table II.

2-Phenyl-4-(3-methoxy-4,5-diacetoxybenzal)-5-oxazolone (Ic). A mixture of 5-hydroxyvanillin[10] (17 g., 0.1 mole), hippuric acid (18 g., 0.1 mole), freshly fused sodium acetate (15 g.) and acetic anhydride (35 ml.) was heated on a water bath for 15 min. and then allowed to stand at room temperature for 1 hr. The yellow solid was triturated with 250 ml. of ice water and then collected on a filter; yield 25 g. (65%), m.p. 184–185°. After two recrystallizations from glacial acetic acid, the m.p. was 189°.

3-Methoxy-4,5-dihydroxyphenylalaninehydrochloride (IIIc). A suspension of Ic (10 g., 0.025 mole), sodium hydroxide (8 g.) and Raney nickel (4 g.) in 200 ml. of water was hydrogenated at 5 atm. and 60° for 4 hr. The slightly reddish clear solution was filtered into 500 ml. of concd. hydrochloric acid. This mixture was then refluxed for 3 hr. When the mixture was cooled some benzoic acid crystallized. It was removed by filtration. The filtrate was extracted with three 150- ml. portions of ether to remove the remaining benzoic acid. The water fraction was evaporated on a steam bath under vacuum to dryness. The light tan solid (2.6 g., 50% yield) was recrystallized once from ethanol-ether; it melted at 229–230° dec.

3-Methoxy-4-hydroxy-α-aminobenzoylhydrocinnamic acid (IIa). A suspension of vanillin azlactone (16.8 g., 0.05 mole), 8 g. of sodium hydroxide and 4 g. of Raney nickel in 250 ml. of water was hydrogenated at 4 atm. and 60° for 4 hr. When the required amount of hydrogen had been absorbed,

(1) This investigation was carried out during the tenuer of a Postdoctoral Fellowship from the National Institute of Neurological Diseases and Blindness, U. S. Public Health Service.

(2) Present address: Lab. di Chim. Terap., Instituto Superiore di Sanità, Rome, Italy.

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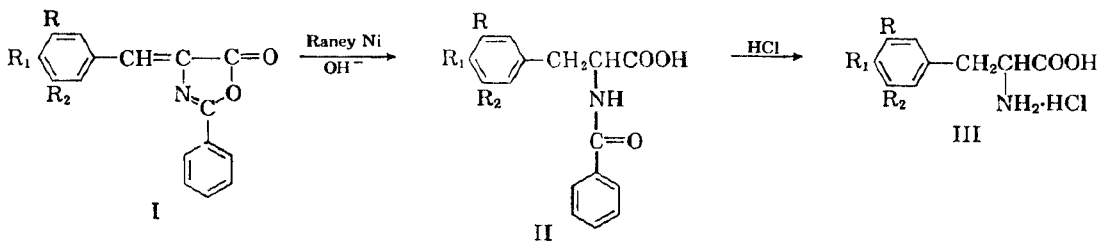
TABLE I

REDUCTION AND HYDROLYSIS OF THE AZLACTONES

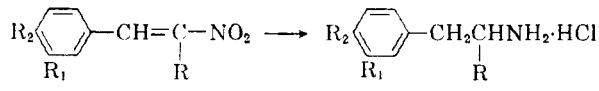


I II III

	R	R_1	R_2	Formula	M.P.[a]	Recryst.[b] Solvent	Yield, % (g.)	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Ia	H	CH_3CO	CH_3O	$C_{19}H_{18}NO_5$	198–199[b]	A	51 (17)	67.65	4.68	4.15	67.42	4.35	4.27
Ib	H	CH_3CO	CH_3CO	$C_{19}H_{15}NO_5$	137–139[c]	A	73 (24)		—			—	
Ic	CH_3CO	CH_3CO	CH_3O	$C_{21}H_{17}NO_7$	189	A	65 (25)	63.79	4.33	3.54	63.99	4.49	3.54
IIa	H	HO	CH_3O	$C_{17}H_{17}NO_5$	169–170[d]	B–D	80 (13)	64.75	5.43	4.44	64.66	5.41	4.45
IIb	H	CH_3O	HO	$C_{17}H_{17}NO_5$	184–185[e]	D	70 (11)		—		64.64	5.68	4.43
IIIa	H	HO	CH_3O	$C_{10}H_{13}NO_4$·HCl	210[f]	B–C	80 (8)	48.53	5.70	5.65	48.36	5.81	5.60
IIIb	H	CH_3O	HO	$C_{10}H_{13}NO_4$·HCl	225–226[g]	B–C	90 (9)		—		48.37	5.73	5.73
IIIc	HO	HO	CH_3O	$C_{10}H_{13}NO_5$·HCl	229–230 dec.	B–C	50 (2.6)	45.54	5.35	5.32	45.00	5.55	5.13

[a] All melting points are uncorrected. [b] Reported[7] m.p. 194–195°. [c] Reported[8] m.p. 139°. [d] Reported[7] m.p. 164°. [e] Reported[8] m.p. 180°. [f] Reported[9] free acid m.p. 228–229°. [g] Reported[8] free acid m.p. 272°. [h] A = glacial acetic acid, B = ethanol, C = ether, D = water.

TABLE II. REDUCTION OF NITROSTYRENES



IV V

	R	R_1	R_2	Formula	M.P.[a]	Recryst.[f] Solvent	Yield, % (G.)	Calcd., % C	Calcd., % H	Found, % C	Found, % H
IVa	H	OH	CH_3O	$C_9H_9NO_4$	162–164[b]	A	87 (17)	55.38	4.65	55.53	4.65
IVb	H	CH_3O	HO	$C_9H_9NO_4$	169[c]	A	83 (16.5)	—	—	55.43	4.20
IVc	CH_3	CH_3O	HO	$C_{10}H_{11}NO_4$	101–103	A	70 (14.5)	57.41	5.30	57.38	5.28
Va	H	HO	CH_3O	$C_9H_{13}NO_2$·HCl	206–207[d]	B	80 (6.8)	53.19	6.93	52.80	6.64
Vb	H	CH_3O	HO	$C_9H_{13}NO_2$·HCl	213–214[e]	B	80 (6.8)	—	—	53.08	6.93
Vc	CH_3	CH_3O	HO	$C_{10}H_{15}NO_2$·HCl	262–263	B	50 (5)	55.17	7.41	55.10	7.24

[a] All melting points are uncorrected. [b] Reported[5] m.p. 161–162°. [c] 166–168°, [d] 206–207°, [e] 213–214°. [f] A = ethanol, B = methanol–ethyl acetate.

a colorless solution resulted. This solution was filtered to remove catalyst, the catalyst was washed with 100 ml. of hot water, and this added to the filtrate. To this clear solution, concentrated hydrochloric acid was added until the *p*H was 6.5; then it was heated on a water bath to 70° and more acid added to *p*H 3. The white precipitate was allowed to cool to room temperature. The white solid IIa was collected on a filter; 13 g. (80% yield), m.p. 164–166°. It was recrystallized once from dilute ethanol, m.p. 169–170°.

3-Methoxy-4-hydroxyphenylalanine hydrochloride (IIIa). To 300 ml. of dilute hydrochloric acid (1:3) was added 10 g. of IIa and this mixture was refluxed for 3 hr. (after 1 hr. solution was complete). When the mixture was cooled 3.1 g. of benzoic acid crystallized. It was removed by filtration. The clear filtrate was treated as in IIIc, yielding 8 g. (80% yield), m.p. 200° dec. The product was recrystallized once from ethanol-ether, m.p. 210° dec.

α-Methyl-3-methoxy-4-hydroxy-α-nitrostyrene (IVc). A mixture of vanillin (15.2 g., 0.1 mole), ammonium acetate (8 g.), nitroethane (25 g., 0.33 mole) and 80 ml. of glacial acetic acid was refluxed for 2 hr. The mixture was then poured into 1 l. of ice cold water. After cooling overnight gave a yellow crystalline product. It was collected on a filter and recrystallized from 50 ml. of ethanol, m.p. 101–103.° The yield was 14.5 g. (70%).

α-Methyl-β-(3-methoxy-4-hydroxyphenyl)ethylamine hydrochloride (Vc). In a Sohxlet thimble was placed 10.5 g. (0.05 mole) of IVc which was extracted into a well-stirred suspension of 5 g. of lithium aluminum hydride in 500 ml. of dry ether. When the reaction was complete (72 hr.), there was slowly added 600 ml. of ice cold 1.5*N* sulfuric acid. The aqueous layer was separated and the *p*H adjusted to 6 with solid lithium carbonate, and the mixture was then filtered. The clear filtrate was heated to 70° and a hot solution of 14 g. of picric acid in the minimum amount of ethanol was added. The mixture was cooled, whereupon the crystals which separated were collected and dissolved in 200 ml. of boiling water. To this hot solution was added 40 ml. of concd. hydrochloric acid. Cooling the solution gave picric acid which was collected. Then the filtrate was extracted three times with 100-ml. portions of nitrobenzene and twice with 100-ml. portions of ether. The aqueous portion was concentrated under vacuum until crystals formed. Recrystallization from methanol-ethyl acetate yielded 5 g. (50% yield) of white plates, m.p. 262–263°.

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PHARMACOLOGY DEPARTMENT
UNIVERSITY OF EDINBURGH
EDINBURGH, SCOTLAND

N-Acylation of D-Ribosylamine[1]

R. STUART TIPSON[2] AND BEVERLY A. PAWSON[3]

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In a previous article,[4] the *N*-acetylation of D-ribosylamine (in water) with acetic anhydride was described. Two other acylation procedures have now been studied. In the first, an aqueous solution of D-ribosylamine (RNH_2) was treated with an acyl chloride in the presence of excess magnesium oxide, according to Equation 1.

$$RNH_2 + R_1COCl + 0.5\ MgO \longrightarrow RNHCOR_1 + 0.5\ MgCl_2 + 0.5\ H_2O \quad (1)$$

I. $R_1 = OC_2H_5$

II. $R_1 = CH_2Cl$

III. $R_1 = CHCl_2$

In the second procedure, an *N*-substituted amino acid (prepared according to Equations 2 or Equation 3) was converted to a mixed anhydride (by Equations 4), and this anhydride was condensed with D-ribosylamine (Equation 5) in water:

$$HCO_2H + (CH_3CO)_2O \longrightarrow HCO{-}O{-}COCH_3 + CH_3CO_2H \quad (2a)$$

$$HCO{-}O{-}COCH_3 + H_2NCHR_2CO_2H \longrightarrow HCONHCHR_2CO_2H + CH_3CO_2H \quad (2b)$$

IV. $R_2 = H$

V. $R_2 = CH_3$ (L form)

$$C_6H_5CH_2OCOCl + HN(R_3)CH_2CO_2H \longrightarrow C_6H_5CH_2OCON(R_3)CH_2CO_2H + HCl \quad (3)$$

VI. $R_3 = H$

VII. $R_3 = CH_3$

$$R_4CO_2H + (C_4H_9)_3N \longrightarrow R_4COO^-(C_4H_9)_3NH^+ \quad (4a)$$

(1) The work described herein was completed prior to June 21, 1957.

(2) Present address: Division of Physical Chemistry, National Bureau of Standards, Washington 25, D. C.

(3) Present address: Esso Research and Engineering Co., Linden, N. J.

(4) R. S. Tipson, *J. Org. Chem.*, 26, 2462 (1961).