Although I is soluble in water to only about 1%, it dissolves in acetone to the extent of about 30 g. per 100 ml. of acetone.

The infrared spectrum showed broad OH at 3310, CH_2–N at 2865 (medium), CH–OH at 1050, and C–Cl at 700 cm.$^{-1}$. The n.m.r. spectrum (in DMSO-d_6) had peaks at 4.89 (OH, doublet), near 6.2 (HC≤), 6.32 (CH_2Cl), and 7.42 τ (NCH_2, doublet).

One ammonia–epichlorohydrin reaction mixture, prepared as described for I, deposited a very small yield of a different solid which melted at 66–76°. This material has not been analyzed or identified; its infrared spectrum (mineral oil mull) was different from that of I, but showed OH at 3200, CH–OH at 1087 and 1067, and C–Cl at 730 and 695 cm.$^{-1}$.

Tris(2,3-epoxypropyl)amine (VI).—The reaction mixture from one mole of ammonia with three of epichlorohydrin, prepared as described for I, was cooled to 20°. A solution of 140 g. of sodium hydroxide (3.5 moles) in 200 ml. of water was added over a 7-min. period with stirring and cooling to maintain the mixture at 20–25°. After stirring for 50 min. at 20–25°, the layers were separated. The aqueous layer was extracted with ether, with addition of just enough water to dissolve the inorganic salt which had separated, and the combined ether and organic layers were dried with three successive portions of potassium hydroxide pellets and evaporated *in vacuo* from a bath at 45°.

The orange sirup partly crystallized when stored in a refrigerator. Extraction with several portions of boiling hexane gave several crops of a colorless solid (total, 18%) which melted in the vicinity of 45°.

The product was purified by recrystallization from methylcyclohexane (heated to 70°) and melted at 45–46°.

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56; oxirane oxygen, 25.9; mol. wt., 185.22. Found: C, 58.73; H, 7.95; N, 7.0; oxirane oxygen, 24.2; Cl, <0.5; mol. wt., 169.0.

Although the analytical figures are not ideal, they show the chemical identity of the product with the liquids previously reported.[3,6]

The infrared spectrum showed NCH_2 at 2800 and epoxide group at 3600, 3000, and 857 cm.$^{-1}$.

1,1-Diethyl-3-hydroxyazetidinium Chloride (VII).—To a solution of 14.6 g. (0.2 mole) of diethylamine and 0.6 g. of water was added 18.5 g. (0.2 mole) of epichlorohydrin over a period of 10 min. The solution was then maintained at 28–30° with stirring for 6 hr.

The solution crystallized partly upon standing at room temperature or in a refrigerator. The solid was recrystallized from a mixture of acetonitrile (in which it is very soluble) and acetone and had m.p. 154–155°.

Anal. Calcd. for $C_7H_{16}ClNO$: Cl, 21.40; mol. wt., 165.67. Found: ionic chlorine, 21.4; apparent mol. wt., 76 (in water), 162 (in acetonitrile).

The infrared spectrum (mineral oil mull) showed OH absorption at 3200 cm.$^{-1}$ (in addition to that attributed to a small amount of water).

The proton n.m.r. spectrum in DMSO-d_6 showed two ethyl groups whose methylene groups gave two overlapping quartets at 6.4 τ. The remaining spectrum consisted of a five-proton group of complicated multiplets centered at 5.5, and a one-proton doublet (OH) at 2.94 τ, splitting equal to 6.0 c.p.s. The doublet was easily exchanged upon the addition of deuterium oxide, and almost disappeared with sufficient deuterium oxide.

1,1-Diethyl-3-hydroxyazetidinium Picrate (VIII).—A crude diethylamine–epichlorohydrin product was treated with alcoholic picric acid in the hope of stabilizing the chlorohydrin intermediate as a picrate salt. Instead, an azetidinium picrate crystallized slowly from the solution, m.p. 223–226°.

Anal. Calcd. for $C_{13}H_{18}N_4O_4$: C, 43.57; H, 5.06; N, 15.64; Cl, 0.00. Found: C, 43.97; H, 5.07; N, 15.47; Cl (total), none.

Treatment of VII with picric acid gave VIII which melted at 223–227°.

Anal. Found: C, 44.07; H, 5.01; N, 16.12; Beilstein test, negative.

The proton n.m.r. spectrum (DMSO-d_6) was virtually identical with that of the chloride (except, of course, for picrate protons); the OH proton was shifted to ~3.8 τ.

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A New Synthesis of β,β-Diarylethylamines[1]

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A number of new β,β-diarylethylamines have been prepared by the reaction between β-phenylethanolamines and aromatic nucleophiles in acid solution. The amines included β-phenylethanolamine, *o*-, *m*-, and *p*-octopamine, *p*-sympatol, norepinephrine, and normetanephrine. The nucleophiles included phenol, catechol, guaiacol, resorcinol, phloroglucinol, β-naphthol, anisole, 4-hydroxycoumarin, and indole.

In the course of work on the biochemistry of octopamine [norsympatol, norsynephrine, α-(amino methyl)-4-hydroxybenzyl alcohol], it was desirable to seek a synthesis that might allow a convenient laboratory preparation of larger amounts than are practical with the usual methods. Hinsberg[2] had reported a synthesis which involved the Baeyer reaction of phenol and an amino acetal. With 1 mole of acetal for each mole of phenol he claimed that octopamine was formed, (eq. 1), and with 2 moles of phenol, β,β-bis(4-hydroxyphenyl)ethylamine (eq. 2).

$$C_6H_5OH + H_2NCH_2CH(OC_2H_5)_2 + HCl + H_2O \longrightarrow 4\text{-}HOC_6H_4CHOHCH_2NH_3^+ Cl^- + 2C_2H_5OH \quad (1)$$

$$2C_6H_5OH + H_2NCH_2CH(OC_2H_5)_2 + HCl \longrightarrow (4\text{-}HOC_6H_4)_2CHCH_2NH_3^+ Cl^- + 2C_2H_5OH \quad (2)$$

Repetition of these reactions in the manner described gave a product which had the reported properties but which was found to contain no octopamine when subjected to analysis by paper chromatography. Furthermore, when authentic octopamine was treated with hydrochloric acid under the conditions used by Hinsberg, it was completely destroyed. The condensation between 2 moles of phenol and 1 mole of amino acetal did yield a product with the properties of the bis(hydroxyphenyl)ethylamine described by Hinsberg. However, paper chromatographic examination of the compound showed that it contained at least three major byproducts which could not be removed completely by recrystallization.

Despite the lack of success in preparing pure β,β-bis(4-hydroxyphenyl)ethylamine from amino acetal and phenol it seemed possible that condensation of octop-

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(2) O. Hinsberg, German Patent 373,286 (March 5, 1923); *Friedländers Fortschr. Teerfarben fabr.*, **14**, 1278 (1923); *Ber.*, **56**, 852 (1923).

amine and phenol might provide this amine, since the Baeyer reaction is usually considered to proceed *via* the corresponding alcohol as intermediate. If successful, such a procedure would provide a route to symmetrical diarylethylamines, and also could be extended to the preparation of unsymmetrical derivatives that would be difficult to make by other syntheses.[3] The condensation of octopamine and phenol was tried, and was found to proceed smoothly in 2 *N* hydrochloric acid at steam bath temperature to give a 94% yield of the expected product in 2 hr.

$$4\text{-}HOC_6H_4CHOHCH_2NH_2 + C_6H_5OH \xrightarrow{H_3O^+} (4\text{-}HOC_6H_4)_2CHCH_2NH_2 \quad (3)$$

The generality of this reaction (eq. 3) was tested with several β-phenylethanolamines and several phenolic compounds. The amines included the *ortho* and *meta* isomers of octopamine, norepinephrine [arterenol, α-(aminomethyl)-3,4-dihydroxybenzyl alcohol], normetanephrine [α-(aminomethyl)-4-hydroxy-3-methoxybenzyl alcohol], *p*-sympatol [synephrine, α-(methylaminomethyl)-4-hydroxybenzyl alcohol], and β-phenylethanolamine itself. The phenolic compounds tested were catechol, guaiacol, resorcinol, phloroglucinol, β-naphthol, anisole, and 4-hydroxycoumarin in addition to phenol; indole also could be used for the condensation.

The reaction took place with the formation of a minimum amount of side products when an excess (3–5 equiv.) of the phenolic compound was used, the acid was not stronger than 2 *N*, and the total reaction volume was kept relatively small (method A). The excess of phenolic compound could be recovered easily by steam distillation or by extraction from the acid reaction mixture with an organic solvent.

Another successful procedure involved the condensation of the amines with phenols in glacial acetic acid in the presence of *p*-toluenesulfonic acid (method B). The latter method had an advantage in some cases because most of the diarylethylamine toluenesulfonates could be recrystallized readily from water. In general, the toluenesulfonates of the primary amines could be recrystallized more easily than those of secondary amines, while the hydrochlorides of the secondary amines crystallized better than those of the primary amines. Furthermore, method B was more effective when the phenolic compound was less reactive or was insoluble in hot 2 *N* hydrochloric acid, as was the case with anisole or 4-hydroxycoumarin.

The yields, melting points, and analyses for the diarylethylamines which were prepared are summarized in Table I. Excellent yields of products were obtained with all the β-phenylethanolamines tested except *m*-octopamine and β-phenylethanolamine itself. When these two compounds were treated according to method A or B, only traces of the expected diarylethylamines could be detected in the reaction mixture. However, when either *m*-octopamine or β-phenylethanolamine was refluxed for 24 hr. with an excess of phenol in 6 *N* hydrochloric acid, a 65% yield of β-(3-hydroxyphenyl)-β-(4-hydroxyphenyl)ethylamine and a 22% yield of β-(4-hydroxyphenyl)-β-phenylethylamine (β-phenyltyramine), respectively, were obtained. It was interesting and somewhat disturbing that β-phenyltyramine had the same melting point as the previously known α-phenyltyramine.[4] In formulating a reaction path for the formation of the β,β-diarylethylamines, the possibility had been considered that a cyclammonium rearrangement[5] might occur, and that the product might be the α,β-disubstituted ethylamine. The possibility of this rearrangement could be excluded for the more reactive 4-hydroxyphenylethanolamines because the same product (compound 2 in Table I) was obtained by the condensation of octopamine with catechol or by the condensation of norepinephrine with phenol, and the same substance (compound 3 in Table I) was obtained from octopamine and guaiacol as from normetanephrine and phenol. The physical properties of the β-phenyltyramine obtained, however, made it necessary to compare it with an authentic compound prepared by an unambiguous synthesis. Thus, α-phenyltyramine was prepared by the lithium aluminum hydride reduction of 1-(4-hydroxyphenyl)-2-nitro-2-phenylethylene, which was obtained by the condensation of 4-hydroxybenzaldehyde and α-nitrotoluene. In addition to having the same melting point, α- and β-phenyltyramine had nearly identical ultraviolet absorption spectra and showed the same R_f values in several solvent systems. However, the color and speed of development of color of the two compounds with ninhydrin was distinctly different and the mixture melting point of the compounds was markedly depressed; so the product obtained from the condensation reaction must be the β-phenyl derivative.

The failure of *m*-octopamine to form diarylethylamines with the usual reaction conditions occurred because of a self-condensation which took place when it was heated in acid solution. Both *m*-octopamine and its N-methyl derivative, phenylephrine, yielded materials which appeared to be of high molecular weight when they were subjected to these conditions.

Some of these new diarylethylamines might have interesting physiological or pharmacological properties. Hinsberg noted that β,β-bis(3,4,5-trimethoxyphenyl)-ethylamine has a strong action on the surviving uterus. 4-Hydroxycoumarin had already been condensed with primary or secondary benzyl alcohols[6] in chloroform or tetrachloroethane in the presence of hydrogen chloride gas or phosphorus oxychloride, but not with β-phenylethanolamines.

Experimental[7]

Method A. β,β-Bis(4-hydroxyphenyl)ethylmethylamine.—A mixture of 2.04 g. (0.01 mole) of *p*-sympatol hydrochloride [α-(methylaminomethyl)-4-hydroxybenzyl alcohol], 2.8 g. (0.03 mole) of phenol, and 5 ml. of 2 *N* hydrochloric acid was heated for 2 hr. at 100°. The reaction mixture was diluted with 150 ml. of water, extracted with three 100-ml. portions of ether, and then evaporated to dryness *in vacuo*. The residual oil crystallized when it was digested with absolute ether. Recrystallization of the product from 10 ml. of 95% ethanol yielded 2.6 g. of β,β-bis(4-hydroxyphenyl)ethylmethylamine hydrochloride monohydrate, m.p. 136–140°. Addition of 50 ml. of absolute ether to the mother liquor yielded another 0.2 g., total yield 95%.

(3) G. Ehrhart, *Arch. Pharm.*, **295**, 198 (1962).

(4) B. Reichert, and W. Hoffman, *ibid.*, **274**, 153 (1936); J. Tular and L. Lespagnol, *Bull. sci. pharmacol.*, **46**, 305 (1939).

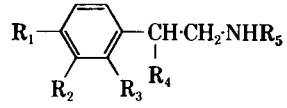
(5) H. Henecka, U. Hörlein, and K. H. Risse, *Angew. Chem.*, **72**, 960 (1960).

(6) E. Ziegler and U. Rossmann, *Monatsh. Chem.*, **88**, 22 (1957); E. Ziegler, U. Rossmann, and F. Litvan, *ibid.*, **88**, 587 (1957).

(7) All melting points were made in open capillary tubes and are corrected.

TABLE I

β,β-DIARYLETHYLAMINES



No.	R_1	R_2	R_3	R_4	R_5	Starting materials: β-(Aryl)-ethanolamine	Starting materials: Phenol	Method[a]	Yield %	M.p., °C.	Formula	Nitrogen: Calcd.	Nitrogen: Found	Salt[b]	M.p., °C.	Nitrogen: Calcd.	Nitrogen: Found
1	OH	H	H	4-Hydroxyphenyl	H	4-Hydroxyphenyl	Phenol	A	94	206–209	$C_{14}H_{15}NO_2$	6.11	5.89	Ts	224–226	3.49	3.42
								B	93								
2	OH	H	H	3,4-Dihydroxyphenyl	H	4-Hydroxyphenyl	Catechol	B	95	160–165[c,d]	$C_{14}H_{15}NO_3$	5.70	5.66	Ts	218–220	3.35	3.27
						3,4-Dihydroxyphenyl	Phenol	B	94						218–220		3.31
3	OH	H	H	4-Hydroxy-3-methoxyphenyl	H	4-Hydroxyphenyl	Guaiacol	B	80	205–209	$C_{15}H_{17}NO_3$	5.40	5.38	Ts	172–175	3.25	3.23
						4-Hydroxy-3-methoxyphenyl	Phenol	B	87						173–176		3.21
4	OH	H	H	2-Hydroxynaphthyl-1	H	4-Hydroxyphenyl	β-Naphthol	B	71	214–218	$C_{18}H_{17}NO_2$	5.02	5.18	Ts	209–211	3.11	3.00
5	OH	H	H	2,4,6-Trihydroxyphenyl	H	4-Hydroxyphenyl	Phloroglucinol	B	88		$C_{14}H_{15}NO_4$			Ts	139–143	3.23	3.14
6	OH	H	H	4-Hydroxyphenyl	CH_3	N-Methyl-4-hydroxyphenyl	Phenol	A	95	233–236	$C_{15}H_{17}NO_2$	5.76	5.63	HCl	186–189[e,f]	5.00	4.99
7	OH	H	H	3,4-Dihydroxyphenyl	CH_3	N-Methyl-4-hydroxyphenyl	Catechol	A	90		$C_{15}H_{17}NO_3$			HCl	126–128	4.73	4.70
8	OH	H	H	4-Hydroxy-3-methoxyphenyl	CH_3	N-Methyl-4-hydroxyphenyl	Guaiacol	A	81	197–198	$C_{16}H_{19}NO_3$	5.12	5.14	HCl	246–249	4.52	4.30
								B	76					Ts	211–215	3.14	3.09
9	OH	H	H	2,4-Dihydroxyphenyl	CH_3	N-Methyl-4-hydroxyphenyl	Resorcinol	A	92	142–144[d]	$C_{15}H_{17}NO_3$	5.40	5.23	HCl	116–118	4.73	4.72
10	OH	H	H	2-Hydroxynaphthyl-1	CH_3	N-Methyl-4-hydroxyphenyl	β-Naphthol	A	92	195–198	$C_{19}H_{19}NO_2$	4.77	4.65	HCl	223–224	4.25	4.19
11	OH	OCH_3	H	3,4-Dihydroxyphenyl	H	4-Hydroxy-3-methoxyphenyl	Catechol	B	79		$C_{15}H_{17}NO_4$			Ts	190–192	3.14	3.05
12	OH	OCH_3	H	4-Hydroxy-3-methoxyphenyl	H	4-Hydroxy-3-methoxyphenyl	Guaiacol	B	73		$C_{16}H_{19}NO_4$			Ts	174–179	3.04	2.97
13	OH	OH	H	3,4-Dihydroxyphenyl	H	3,4-Dihydroxyphenyl	Catechol	A	97					HCl	229–231	4.71	4.68
								B	92		$C_{14}H_{15}NO_4$			Ts	222–225	3.23	3.19
14	OH	H	H	4-Methoxyphenyl	H	4-Hydroxyphenyl	Anisole	B	56	165–166	$C_{15}H_{17}NO_2$	5.75	5.58	Ts	191–193	3.37	3.27
15	OH	H	H	4-Methoxyphenyl	CH_3	N-Methyl-4-hydroxyphenyl	Anisole	B	61	187–188	$C_{16}H_{19}NO_2$	5.44	5.33	Ts	63–65	3.26	3.09
16	H	H	OH	4-Hydroxyphenyl	H	2-Hydroxyphenyl	Phenol	B	98	205–206	$C_{14}H_{15}NO_2$	6.11	6.09	Ts	239–242	3.49	3.46
17	H	OH	H	4-Hydroxyphenyl	H	3-Hydroxyphenyl	Phenol	*e*	65	95–105[f]	$C_{14}H_{15}NO_2$	6.11	6.00				
18	OH	H	H	4-Hydroxycoumarinyl-(3)	H	4-Hydroxyphenyl	4-Hydroxycoumarin	B[e]	39	155–160	$C_{17}H_{15}NO_4$	4.71	4.64	Ts	230–233[d]	2.98	2.99
19	H	H	H	4-Hydroxyphenyl	H	Phenyl	Phenol	*e*	22	160–162	$C_{14}H_{15}NO$	6.56	6.54				
20	OH	H	H	Indolyl-3	H	4-Hydroxyphenyl	Indole	B[e]	56	188–194	$C_{16}H_{16}N_2O$	11.10	11.25				

[a] For the preparation of the compounds the same molar quantities and reaction conditions were used as described in the Experimental section of the paper. Different amounts of solvents were required for the recrystallization of the different products. [b] Ts is *p*-toluenesulfonate. [c] See ref. 8. [d] Melts with decomposition. [e] See Experimental. [f] See ref. 9.

Anal. Calcd. for $C_{15}H_{17}NO_2 \cdot HCl \cdot H_2O$: N, 4.70. Found: N, 4.61.

The compound lost 6.0% by weight when dried for 1 day at 100° (2 mm.) over phosphorus pentoxide (calcd.: 6.05%). The anhydrous compound melted at 130–135°, solidified between 150–170°, and remelted at 186–189°.

Anal. Calcd. for $C_{15}H_{17}NO_2 \cdot HCl$: N, 5.76. Found: N, 5.63.

Method B. β,β-Bis(4-hydroxyphenyl)ethylamine.—A mixture of 1.53 g. (0.01 mole) of octopamine [α-(aminomethyl)-4-hydroxybenzyl alcohol], 2.8 g. (0.03 mole) of phenol, 2.3 g. (0.012 mole) of *p*-toluenesulfonic acid monohydrate, and 4 ml. of glacial acetic acid was heated for 1.5 hr. at 100°. The acetic acid was removed *in vacuo*, the residue was diluted with 200 ml. of water, and the excess of phenol was extracted with three 100-ml. portions of ether. When the aqueous solution was concentrated to about 50 ml. and kept in a refrigerator for 2 hr., 3.4 g. of β,β-bis(4-hydroxyphenyl)ethylamine *p*-toluenesulfonate, m.p. 224–226°, separated; 0.35 g. of less pure product, m.p. 210–220°, was obtained from the mother liquor.

The free amine was precipitated from an aqueous solution of the salt by the addition of dilute ammonium hydroxide.[8] It contains 1 to 2 moles of water if it is dried in a vacuum desiccator at room temperature (12 mm.) and melts at 100–110°. However, the water can be removed completely by drying over phosphorus pentoxide at 100° (2 mm.). The amine obtained in this manner sintered at 125–130° and melted at 206–209°.[9]

β-(3-Hydroxyphenyl)-β-(4-hydroxyphenyl)ethylamine.—A mixture of 5 g. (0.0264 mole) of *m*-octopamine hydrochloride [α-(aminomethyl)-3-hydroxybenzyl alcohol], 25 g. (0.266 mole) of phenol, and 100 ml. of 6 *N* hydrochloric acid was refluxed for 24 hr. The reaction mixture was diluted with 100 ml. of water and the excess of phenol was extracted with four 100-ml. portions of ether. The aqueous solution was concentrated to a volume of about 50 ml. and dilute ammonium hydroxide was added. When a precipitate first appeared, charcoal was added and the solution was filtered. More dilute ammonium hydroxide was then added to the filtrate until no further precipitate formed. The resulting β-(3-hydroxyphenyl)-β-(4-hydroxyphenyl)ethylamine (compound 17 in Table I) was collected, recrystallized from ethanol–water, and dried at 80° (2 mm.). The yield was 3.9 g. (64.5%) and the melting point was 95–105°. Several attempts to obtain a product with a higher melting point were unsuccessful, and even when the compound was kept for 24 hr. at 120–130° it did not resolidify (see ref. 9). Chromatographic examination of the heated amine showed that it had not undergone alteration or decomposition.

β-Phenyltyramine.—A solution of 12 g. (0.069 mole) of β-phenylethanolamine hydrochloride and 7 g. (0.0745 mole) of phenol in 50 ml. of 6 *N* hydrochloric acid was refluxed for 24 hr. The mixture was cooled, diluted with 80 ml. of water, and extracted with four 100-ml. portions of ether. The aqueous solution was made alkaline (pH 12) by the addition of 50% sodium hydroxide solution (some ammonia was liberated), and the remaining β-phenylethanolamine (less than 1 g.) was extracted with two 100-ml. portions of ether. The aqueous layer was neutralized to pH 8.5 by the addition of hydrochloric acid and β-phenyltyramine was extracted with five 100-ml. portions of ether. The solvent was evaporated *in vacuo* and the crystalline residue was digested with a little dry benzene. The yield was 3.2 g. (22%), m.p. 158–160.5°. One recrystallization of this material from aqueous ethanol yielded a product melting at 160–162°; λ_{max}^{MeOH} 279 mμ (ε 1850), 233 (6900).

1-(4′-Hydroxyphenyl)-2-nitro-2-phenylethylene.—A mixture of 9.5 g. (0.07 mole) of α-nitrotoluene, 10 g. (0.082 mole) of 4-hydroxybenzaldehyde, 4 g. (0.052 mole) of ammonium acetate, and 50 ml. of glacial acetic acid was refluxed for 2 hr. and then poured into 500 ml. of cold water. The resulting oil, which crystallized slowly, was separated, dried, washed with petroleum ether (b.p. 30–60°), and dissolved in 50 ml. of absolute ether. A small amount of insoluble material was removed by filtration, the ethereal solution was evaporated to dryness, and the residue was recrystallized from ethanol–water; 2.9 g. (17%) of yellow prisms, m.p. 147–149°, was obtained.

Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.80; H, 4.60; N, 5.80. Found: C, 69.93; H, 4.83; N, 5.47.

α-Phenyltyramine.—A solution of 2 g. (0.0083 mole) of 1-(4′-hydroxyphenyl)-2-nitro-2-phenylethylene in 100 ml. of absolute ether was added to the refluxing ether of a well-stirred and boiling mixture of 2 g. (0.064 mole) of lithium aluminum hydride and 250 ml. of absolute ether during a period of about 1 hr. Stirring and refluxing was continued for another 4 hr. The excess of lithium aluminum hydride was decomposed by the addition of 400 ml. of water, and concentrated hydrochloric acid was added until all inorganic material had dissolved. The aqueous layer was then separated and passed through a 7 × 10 cm. column of Amberlite CG-120 (H^+) (100–200 mesh). α-Phenyltyramine was eluted from the resin with a mixture of concentrated ammonium hydroxide and ethanol (1:2). The first 350 ml. of alkaline eluate was collected and evaporated to dryness *in vacuo*. The residue was recrystallized from ethanol–water to yield 1.1 g. (63%) of α-phenyltyramine, m.p. 157–159°. After two more recrystallizations from 95% ethanol the product melted at 160–162°, lit.[4] m.p. 159°. A mixture with β-phenyltyramine softened at 143° and melted at 146–148°; λ_{max}^{MeOH} 279 mμ (ε 1750), 231 (6300).

β-(4-Hydroxycoumarinyl-3)-*p*-tyramine.—A mixture of 1.53 g. (0.01 mole) of octopamine [α-(aminomethyl)-4-hydroxybenzyl alcohol], 1.70 g. (0.0105 mole) of 4-hydroxycoumarin, 2.3 g. (0.012 mole) of *p*-toluenesulfonic acid monohydrate, and 6 ml. of glacial acetic acid was heated at 100° for 2 hr. The acetic acid was removed at 70° (12 mm.), the residue was digested two times with a mixture of 8 ml. of ethanol, and 12 ml. of benzene, and was then recrystallized from methanol. The yield[10] was 1.94 g. (39%) of the *p*-toluenesulfonate, m.p. 230–233° dec.

β-(Indolyl-3)-*p*-tyramine.—A mixture of 1.53 g. (0.01 mole) of octopamine, [α-(aminomethyl)-4-hydroxybenzyl alcohol], 4 g. (0.034 mole) of indole, 3.8 g. (0.02 mole) of *p*-toluenesulfonic acid monohydrate, and 5 ml. of glacial acetic acid was heated on a boiling water bath for 4 hr. The acetic acid was removed *in vacuo* and the remaining brown oil was taken up into 200 ml. of methanol and passed through a 4 × 4 cm. column of Amberlite CG-120 (H^+). The column was washed with 1 l. of methanol to remove most of the colored impurity. β-(Indolyl-3)-*p*-tyramine was eluted from the column with a mixture of one part of concentrated ammonium hydroxide with two parts of methanol. The first 1.2 l. of alkaline eluate was collected and evaporated to dryness. The residue was washed with 25 ml. of ether and was recrystallized from ethanol to yield 1.4 g. (56%) of product, m.p. 188–194°.

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.22; H, 6.41; N, 11.10. Found: C, 76.20; H, 6.81; N, 11.25.

Acknowledgment.—Mrs. Kerin N. Yates performed the nitrogen analyses of these compounds. The other analyses were made by the Weiler and Strauss Microanalytical Laboratory, Oxford, England.

(8) All the free amines listed in Table I were obtained in this manner. They were usually insoluble in water (except for the phloroglucinol derivative) and could be recrystallized from dilute ethanol. However, in solution the catechol derivatives were quite unstable in the presence of oxygen, and even in the solid state they darkened within a few weeks; hence, only one free catecholamine (compound 2 in Table I) was prepared.

(9) Hinsberg (see ref. 2) first reported a melting point of 95°, and then later 105°, but did not give an analysis; this melting point probably is for the hydrate. However, the anhydrous form also melted at about 100–120° if it was quickly heated, and then solidified and melted again at 206–209°. Even if it was heated very slowly a sintering could be observed at about 125–130°. This phenomenon occurred with many of the compounds listed in Table I, and also with some of the hydrochlorides (compounds 6, 7, and 9 in Table I). The phenomenon could be observed especially well with the condensation product of octopamine and β-naphthol (compound 4 in Table I) which melted at 95–105° to a glass-like substance even when it was heated very slowly, crystallized at 120–130°, and melted again at 214–218°. The melting and resolidifying was not connected with a structural change, since compound 1 was recovered unchanged after it had been heated at 200° for 10 min. A possible explanation for this behavior is that the anhydrous compounds might have retained the crystal structure of the hydrates after the water had been removed.

(10) Only one run was made with equal amounts of *p*-sympatol and of 4-hydroxycoumarin. The yield might well be improved by a variation of the reaction conditions, in particular by the use of an excess of 4-hydroxycoumarin.