leads to no racemization upon conversion to the Grignard reagent.[9]

Experimental[10]

3-α-Cholesteryl Carbinol (III).—To 10.0 g. (24 millimoles) of 3-α-cholesterylcarboxylic acid dissolved in 500 ml. of boiling butyl ether was added at one time 10 g. (260 millimoles) of powdered lithium aluminum hydride. After 10 minutes hydrogen was no longer evolved and the suspension was allowed to cool. The mixture was decomposed with 20% potassium hydroxide during 12 hours. Extraction with five 200-ml. portions of ether and then crystallization from a mixture of Skellysolves B and F (petroleum ether, b.p. 60–70° and 30–60°, respectively) afforded 8.2 g., 85%, of white plates, m.p. 127–128°; $[\alpha]^{29}D$ −34° (*c* 2.6 in chloroform).

Anal. Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 84.44; H, 11.74.

3-α-Cholesteryl Carbinyl Tosylate (IV).—One gram (2.5 millimoles) of the powdered carbinol was mixed with 0.8 g. (4.2 millimoles) of *p*-toluenesulfonyl chloride and dissolved in the minimum quantity of pyridine. The solution was warmed momentarily to 50° and allowed to stand for two hours when crystals had formed. This tosylate was removed by filtration and was crystallized from absolute ethanol; yield 1.3 g., 95%; m.p. 148–149°; $[\alpha]^{29}D$ −13° (*c* 0.8 in chloroform).

Anal. Calcd. for $C_{35}H_{54}O_3S$: C, 75.76; H, 9.81. Found: C, 76.12; H, 10.00.

3-α-Cholesterylmethyl Iodide (V).—To 5.8 g. (10 millimoles) of the tosylate in 500 ml. of dry acetone was added 15 g. (100 millimoles) of sodium iodide. The solution was refluxed for 12 hours and the sodium *p*-toluenesulfonate was removed by filtration. Evaporation of the filtrate and separation from the excess sodium iodide by ether extraction gave a solution from which there was obtained colorless prisms. These were crystallized from methyl ethyl ketone to give 4.6 g. of iodide which could not be brought to analytical purity; m.p. 104.5–105°; $[\alpha]^{29}D$ −23° (*c* 3.7 in chloroform).

Anal. Calcd. for $C_{28}H_{47}I$: C, 65.86; H, 9.28. Found: C, 68.27; H, 9.92.

Repeated attempts to improve the purification and analytical techniques failed to produce better values than these.

3-α-Cholesterylacetic Acid (VI).—To 1.0 g. (40 millimoles) of powdered magnesium which had been previously baked under nitrogen was added 100 ml. of an ether solution containing 5 g. (10 millimoles) of 3-α-cholesterylmethyl iodide and a drop of methyl iodide. The mixture was stirred and refluxed under nitrogen for six hours during which time there was added dropwise an ether solution containing 0.6 ml. (10 millimoles) of methyl iodide. After an additional 18 hours of refluxing dry carbon dioxide was bubbled through the cloudy Grignard solution for five hours. The mixture was decomposed with 6 *N* hydrochloric acid and extracted with ether, 600 ml. The ether phase was extracted alternately with 300-ml. portions of water and 5% potassium hydroxide solution until 2 l. of extract had accumulated. The cholesterylacetic acid was precipitated by acidification with hydrochloric acid to the congo red end-point. It was crystallized from acetone to yield 2.8 g., 67%, m.p. 170–175°; $[\alpha]^{29}D$ −31° (*c* 1.9 in chloroform). The mixture m.p. with Dr. Kaiser's acid, m.p. 204–220°, reported 212–213°, was 163–166°.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.27; H, 11.27; neut. equiv., 429. Found: C, 81.71; H, 11.32; neut. equiv., 444, 452.

Methyl 3-α-Cholesterylacetate.—A solution of 0.7 g. (1.6 millimoles) of the acid in 100 ml. of dry methanol was treated with two drops of concd. sulfuric acid and refluxed for four hours. The product crystallized upon cooling, and it was recrystallized from methanol to yield 0.7 g. (97%), m.p. 79–79.5°; $[\alpha]^{29}D$ −32° (*c* 2.6 in chloroform).

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.39. Found: C, 81.21; H, 11.12.

EVANSTON, ILLINOIS RECEIVED FEBRUARY 12, 1951

(9) F. C. Whitmore and J. H. Olewine, THIS JOURNAL, **60**, 2570 (1938).

(10) Microanalyses by Misses M. Hines and J. Sorensen. Melting points are uncorrected.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, SYRACUSE UNIVERSITY]

A New Synthesis of Hordenine and Other *p*-Dialkylaminoethylphenols and Some of Their Derivatives

BY CHAO-SHING CHENG, CLAUS FERBER, RAYMOND I. BASHFORD, JR., AND GERALD F. GRILLOT[1]

A series of *p*-dialkylaminoethylphenols including hordenine has been prepared by a new synthesis that includes the following steps: *p*-(β-hydroxyethyl)-anisole, *p*-(β-iodoethyl)-phenol and *p*-(β-dialkylaminoethyl)-phenol. The *p*-nitro- and the *p*-aminobenzoate esters of these dialkylaminoethylphenols have also been prepared and described. *p*-(β-Iodoethyl)-phenol has been converted to tyrosol and to the *p*-nitrobenzoate ester. The hydrochloride of the *p*-nitrobenzoate ester of di-*n*-butylaminoethylphenol is unusually low melting and appears to form a solvate with one molecule of benzene and toluene.

We have undertaken the preparation and study of a number of β-dialkylaminoethylphenols. The most important of these is *p*-(β-dimethylaminoethyl)-phenol called hordenine or anhaline which occurs in barley germs and in the cactus "Anhalonium fissuratum." Léger[2] isolated it from the former source and established its structure, which was independently confirmed by Gaebel.[3]

Syntheses of hordenine were developed by Barger,[4] Rosenmund,[5] Voswinkel,[6] Spaeth and Sobel,[7] and Kindler.[8] The yields of hordenine in these syntheses were usually poor but they did serve to confirm the structure assigned to this alkaloid.

In 1938 Buck, Baltzly and Ide[9] reported a synthesis of this compound starting with *p*-anisaldehyde and which proceeded through the following steps: aldehyde, azlactone, phenylpyruvic acid, pyruvic acid oxime, phenylacetonitrile, followed by the preparation of the methoxyphenylethyldimethylamine by catalytic reduction in the presence of an excess of diethylamine. The final step involved O-dealkylation with hydrochloric acid.

The synthesis that we have employed, not only for the *p*-dimethylamino-, but also for the diethylamino-, the di-*n*-butylamino-, the piperidino- and the morpholinoethylphenols, is theoretically more

(1) To whom all communications concerning this article should be addressed.

(2) Léger, *Compt. rend.*, **142**, 108 (1906); **143**, 916, 234 (1906); **144**, 488 (1907); *Bull. soc. chim.*, [3] **35**, 868 (1906); [4] **1**, 148 (1907).

(3) Gaebel, *Arch. Pharm.*, **244**, 441 (1906); *C. A.*, **1**, 437 (1907).

(4) Barger, *J. Chem. Soc.*, **95**, 2193 (1909).

(5) Rosenmund, *Ber.*, **42**, 4778 (1909); **43**, 306 (1910).

(6) Voswinkel, German Patent 248,385 (1911); *C. A.*, **6**, 3165 (1912).

(7) Spaeth and Sobel, *Monatsh*, **41**, 77 (1920).

(8) Kindler, *Arch. Pharm.*, **265**, 389 (1927); *C. A.*, **21**, 2668 (1927).

(9) Buck, Baltzly and Ide, THIS JOURNAL, **60**, 1789 (1938).

direct and should be adaptable as a preparative method. It consists of the following steps: *p*-(β-hydroxyethyl)-anisole, *p*-(β-iodoethyl)-phenol and *p*-(β-dialkylaminoethyl)-phenol.

p-(β-Hydroxyethyl)-anisole was demethylated and converted to the iodide in one step. Twelve volumes of 57% hydriodic acid gave *p*-iodoethylphenol in a yield of 67%, however, the procedure described in this communication involves the use of five volumes of the 47% acid and gave a yield of 53%. This yield was gratifying as we expected reduction in part to a substituted phenylethane and were warned that large amounts of a substituted styrene might form.

Reaction of *p*-(β-iodoethyl)-phenol with the appropriate amines produce the dialkylaminoethylphenols. The *p*-nitrobenzoate esters of the dimethyl-, diethyl- and the di-*n*-butylamino compounds were prepared by treating a benzene solution of the phenolic compound with a benzene solution of *p*-nitrobenzoyl chloride to produce a precipitate that is the hydrochloride of the ester. The morpholino- and piperidino- compounds were prepared by a modified Schotten–Baumann reaction and the resulting esters were then converted to their hydrochlorides. All of the *p*-nitrobenzoate esters were reduced to the corresponding *p*-aminobenzoate esters by hydrogenation at about three atmospheres pressure in the presence of a platinum catalyst.

The *p*-aminobenzoate ester of hordenine has previously been prepared by von Braun[10] by the reduction of the *p*-nitrobenzoate ester with stannous chloride. The piperidine analog of hordenine was prepared by Kindler[8] by the reduction of N-(*p*-methoxyphenylthioacetyl)-piperidine followed by O-demethylation.

The preparation of the *p*-nitrobenzoate ester of *p*-(β-iodoethyl)-phenol in a yield of 82% is described. An attempt to convert this ester to the dialkylaminoethylphenols by reaction with the appropriate amines resulted in the isolation of a small amount of the dialkylaminoethylphenols.

Because of the similarity in structure between procaine and the *p*-aminobenzoate esters of the dialkylaminoethylphenols, these latter compounds may be expected to possess some local anesthetic action. J. von Braun[10] has already reported that the dihydrochloride of the *p*-aminobenzoate ester of hordenine possesses excellent anesthetic action but is quite toxic.

Since the dialkylaminoethylphenols resemble epinephrine and similar sympathomimetic drugs in structure, they and their derivatives may possess pressor action. Sexton[11] mentions that hordenine does exert some sympathomimetic action. Hartung[12] states that dialkylation or conversion (of phenylethylamines) into tertiary amines decreases the pressor activity and the larger the alkyl group the greater the decrease, while the toxicity usually increases. He further states that when the alkyl group is large enough, the molecule will take on anesthetic properties and will lose most of its hypertensive properties.

(10) von Braun, *Ber.*, **47**, 504 (1914).

(11) Sexton, "Chemical Constitution and Biological Activity," E. and F. N. Spon, Ltd., London, 1949, p. 228.

(12) Hartung, *Ind. Eng. Chem.*, **37**, 126 (1945).

Many of these compounds are now being submitted to the Sterling–Winthrop Research Institute at Rennselaer, N. Y., for evaluation of their anesthetic and pressor action.

Experimental

p-(β-**Iodoethyl**)-**phenol**.—In a one-liter flask were placed 98 g. of *p*-(β-hydroxyethyl)-anisole[13] and 5 volumes (460 ml.) of 47% hydriodic acid. The water and methyl iodide formed in the reaction were removed by passing carbon dioxide over the reaction mixture. The reaction was maintained at a temperature of about 135° for 1.5 hours and was continuously stirred. A yellow oil separated as the reaction proceeded.

At the end of the reaction, the reaction mixture was poured into two volumes of ice-water and the crude product separated as white needles. These were recrystallized from a minimum amount of hot ethyl alcohol and were further purified by recrystallization from chloroform. The final product was a white powder and was obtained in a yield of 86 g. or 53%. It melted at 113°.

Anal. Calcd. for C_6H_9OI: I, 51.2. Found: I, 51.17, 51.31.

Tyrosol or *p*-(β-**Hydroxyethyl**)-**phenol**.—Some of the *p*-(β-iodoethyl)-phenol was boiled with an aqueous suspension of silver oxide, most of the water was evaporated and the residue was extracted with chloroform. On cooling, crystals, that melted at 92°, formed.[14] These crystals gave the characteristic reactions of tyrosol. Among these was the conversion of the surface of a freshly cut potato to a pink color.

p-(β-**Iodoethyl**)-**phenyl** *p*-**Nitrobenzoate**.—A mixture of 24.8 g. (0.1 mole) of *p*-(β-iodoethyl)-phenol, 20.4 g. (0.11 mole) of *p*-nitrobenzoyl chloride, 21.2 g. of anhydrous sodium carbonate and 100 ml. of benzene was refluxed over a steam-bath for one hour. When the reaction was complete, 200 ml. of benzene, previously warmed, was added and then sufficient hot water to dissolve any solid sodium carbonate and sodium chloride. After separation from the aqueous layer a part of the benzene was removed by distillation. Upon cooling, a large crop of crystals formed. These were purified by dispersing them in 100 ml. of hot alcohol followed by washing them with additional alcohol. A yellowish powder was obtained, which after thorough drying melted at 152–153°. The yield was 32.5 g. or 82%.

Anal. Calcd. for $C_{15}H_{12}O_4NI$: I, 31.96. Found: I, 31.84, 31.86.

p-(β-**Dimethylaminoethyl**)-**phenol** (Hordenine).—In a Pyrex tube was placed 40 ml. of toluene and 12.4 g. (0.05 mole) of *p*-(β-iodoethyl)-phenol. This mixture was then cooled in a Dry Ice–acetone mixture. To this cooled solution was added 7.4 ml. (0.11 mole) of anhydrous dimethylamine (Eastman Kodak Co.) previously cooled in a Dry Ice–acetone mixture. The contents of the tube were then shaken until all the solid dissolved. After sealing the tube, it was heated for five hours in an iron tube at 100°. After cooling and opening the tube, the contents were heated to boiling and the precipitated dimethylamine hydroiodide was removed by filtration. On cooling the resulting filtrate, a white precipitate formed. Upon recrystallizing this product from toluene a colorless powder melting at 116–117° was obtained. Barger[4] gave a melting point of 117° for hordenine. The yield of product amounted to 5.2 g. or 63%.

p-(β-**Diethylaminoethyl**)-**phenol Hydrochloride**.—In a manner similar to the preparation of hordenine described above, a mixture of 24.8 g. (0.1 mole) of *p*-(β-iodoethyl)-phenol, 24 ml. (0.22 mole), of diethylamine and 50 ml. of benzene reacted in a sealed tube. After separation of the precipitated diethylamine hydroiodide, 50 ml. of benzene was added to the filtrate and the resulting solution was washed with 100 ml. of 2% sodium carbonate solution and 100 ml. of water. After removal of the benzene, a fraction distilling between 88 and 144° at 6 mm. of pressure was collected and amounted to 12.1 g. On standing it solidified and after washing with ligroin it melted at 91–93°.

The hydrochloride salt of this product melted at 172–173° and gave the following analyses.

(13) J. Altwegg, U. S. Patent 1,315,619, Sept. 9, 1919; *C. A.*, **13**, 2883 (1919).

(14) Ferber, *Ber.*, **62**, 190 (1929).

TABLE I

HYDROCHLORIDE SALTS OF THE *p*-NITROBENZOATE ESTER OF DIALKYLAMINOETHYLPHENOLS $R_2NCH_2CH_2C_6H_4OH$

	Yield, %	Formula	M.p. or dec. p., °C.	Method of prepn.	Chlorine, % Calcd.	Found
Dimethylamino-	76	$C_{17}H_{19}O_4N_2Cl$	227–229[a]	A	10.11	.....
Diethylamino-	43	$C_{19}H_{23}O_4N_2Cl$	203–208	A	9.36	9.28 9.41
Di-*n*-butylamino-	30	$C_{23}H_{31}O_4N_2Cl$	81–85	A	8.15	8.10 8.15
Piperidino-	55	$C_{20}H_{23}O_4N_2Cl$	245–246	B	9.07	9.14
Morpholino-	58	$C_{19}H_{21}O_5N_2Cl$	256	B	9.03	9.08 8.95

[a] J. von Braun[10] gives a melting point of 228° for this compound.

TABLE II

HYDROCHLORIDE SALTS OF THE *p*-AMINOBENZOATE ESTERS OF THE DIALKYLAMINOETHYLPHENOLS $R_2NCH_2CH_2C_6H_4OH$

R_2N	Yield, %	Recryst. solv.	M.p., °C.	Formula	Chlorine, % Calcd.	Found
Dimethylamino-	76	Methyl alc.	[a]	$C_{17}H_{21}O_2N_2Cl$	11.05	10.88 10.86
Diethylamino-	57	Methyl alc.	201–204	$C_{19}H_{25}O_2N_2Cl$	10.16	10.15 10.19
Di-*n*-butylamino-	67	Ethyl alc. (ab.)	198–200	$C_{23}H_{33}O_2N_2Cl$	8.76	8.84 8.86
Piperidino-	78	[b]	256–257	$C_{20}H_{25}O_2N_2Cl$	9.83	9.65 9.74
Morpholino-[c]	75	[d]	237–238	$C_{19}H_{23}O_3N_2Cl$	9.77	9.62 9.78

[a] Turns blood red at 190° and begins to char at 265°. [b] Crude product was boiled with dry benzene, filtered and dried. [c] A solution of four parts of methyl alcohol and one part water was used as the solvent for hydrogenation. [d] For recrystallization this was dissolved in hot glacial acetic acid and was precipitated by the addition of anhydrous isopropyl ether.

Anal. Calcd. for $C_{12}H_{20}ONCl$: Cl, 15.43. Found: Cl, 15.42, 15.40.

p-(β-**Di-*n*-butylaminoethyl)-phenol Hydrochloride.**—The free base was prepared in the same fashion as the *p*-(β-diethylaminoethyl)-phenol except that the reaction was performed in a flask instead of a sealed tube. After removal of the solvent, a fraction amounting to 13.3 g. and boiling between 65 and 165° at 3 mm. pressure was collected. This was mostly *p*-(β-di-*n*-butylaminoethyl)-phenol. Its hydrochloride melts at 152–154° and gave the following analyses.

Anal. Calcd. for $C_{16}H_{28}ONCl$: Cl, 12.41. Found: Cl, 12.48, 12.33.

p-(β-**Piperidinoethyl)-phenol.**—To 8 ml. (0.05+ mole) of piperidine was added 6.2 g. (0.025 mole) of *p*-(β-iodoethyl)-phenol. The resulting spontaneous reaction removed the excess piperidine by evaporation. Upon cooling the reaction mixture, it solidified. To this was added 40 ml. of hot water with stirring. After cooling, the yellow solid that remained was separated and washed with 100 ml. of cold water. After drying, the solid was dissolved in 50 ml. of dioxane and to this was added 10 ml. of acetone. After cooling, and standing for one-half hour, the crystals were separated and washed with 20 ml. of acetone. After drying at 100°, they melted at 165–166°. The yield amounted to 3.9 g. or 76%. Upon a second recrystallization, a product melting at 167–168° was obtained. Kindler[8] reported a melting point of 163° for this compound.

p-(β-**Morpholinoethyl)-phenol.**—The same general method using 11 ml. (0.084+ mole) of morpholine and 10.4 g. (0.042 mole) of *p*-(β-iodoethyl)-phenol was employed as for the preparation of *p*-(β-piperidinoethyl)-phenol. The crude product was obtained as a yellow fluffy powder. After washing with water and drying, it was recrystallized using 300 ml. of boiling toluene. Upon drying the recrystallized product at 100°, it melted at 169–170°. The yield amounted to 6.8 g. or 78%.

Anal. Calcd. for $C_{12}H_{17}O_2N$: N, 6.78. Found: N, 7.02.

p-**Nitrobenzoate Esters of the Dialkylaminoethylphenol Hydrochlorides. Method A.**—A solution of about 0.05–0.06 mole of the dialkylaminoethylphenol in 300 ml. of benzene was added to a filtered solution of an equivalent amount of *p*-nitrobenzoyl chloride also dissolved in 300 ml. of benzene. A precipitate began to form at once. The reaction mixture was heated for one-half to one hour and after cooling, the precipitate was separated and washed with benzene and ether. After drying at 90°, it was warmed with about 100 ml. of chloroform (for the di-*n*-butylamino- compound acetone was used) until no more of the solid dissolved. The residue that remained was removed by filtration and it was probably the aminoethylphenol hydrochloride. Most of the chloroform (or acetone) was now removed by evaporation and 200 ml. of toluene was added. Pale yellow solids were obtained.

In place of solution in chloroform or acetone, the dimethyl derivative was precipitated with 200 ml. of ether after evaporating to a volume of 50 ml. Then after filtration and drying, it was dissolved in 100 ml. of isopropyl alcohol and 15 ml. of *n*-propyl alcohol. Upon cooling, 100 ml. of *t*-butyl alcohol was added, whereupon crystallization occurred.

Method B.—In 30 ml. of water was dissolved 0.015 to 0.020 mole of sodium hydroxide and an equivalent quantity of the dialkylaminoethylphenol. A solution of a slight excess of *p*-nitrobenzoyl chloride in 20 ml. of dioxane was then poured into this solution. A yellow precipitate formed at once. The reaction mixture was stirred for a half-hour and 50–100 ml. of water added. The residue was separated and dried at 100°.

The hydrochlorides of these esters were obtained as nearly colorless powders.

The yields, melting points and analyses for the hydrochloride salts of the *p*-nitrobenzoate esters are summarized in Table I.

p-**Aminobenzoate Esters of the *p*-Dialkylaminoethylphenol Hydrochlorides.**—In 250 ml. of absolute methyl alcohol was dissolved 0.01 mole of the hydrochloride salt of the *p*-nitrobenzoate ester of the *p*-dialkylaminoethylphenol. To this was added about 0.2 g. of Adams platinum catalyst,[15] and hydrogen gas was introduced into this solution at a pressure of about three atmospheres and at room temperature while shaking. When 0.03 mole of hydrogen was absorbed, which usually took about 20 minutes, the reduction was complete.

The catalyst was removed by filtration and the solvent was removed from the filtrate by distillation under a somewhat reduced pressure until its volume was about 15 ml. (for the dimethyl compound, about 60 ml.). On cooling a precipitate formed which was usually colored buff or pink. It was recrystallized using the solvent indicated in Table II. The melting points, yields and analyses of these *p*-aminobenzoate esters are also summarized in Table II.

The Dihydrochloride of *p*-(β-**Dimethylaminoethyl)-phenyl** *p*-**Aminobenzoate.**—In 20 ml. of boiling glacial acetic acid was dissolved 1.5 g. (0.005 mole) of the monohydrochloride salt. This was cooled and hydrogen chloride gas was passed into the solution until no more heat was evolved. To the resulting solution 20 ml. of isopropyl ether was added. The resulting yellowish precipitate was filtered and washed with fresh portions of ether. Following a washing with 30 ml. of acetone, the precipitate was dissolved in 20 ml. of hot methyl alcohol and the resulting solution was decolorized with activated charcoal. The filtrate was then evaporated to 15 ml. and 20 ml. of the isopropyl ether was added. The above treatment was repeated if the resulting precipitate was still contaminated with colored material.

(15) Adams, Vorhees and Shriner, "Organic Syntheses," second edition, Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 463.

A light buff powder was obtained that began to darken at 210° and charred at 295°. J. von Braun[10] states that this salt does not melt below 240°. The yield was 1.2 g. or 72%.

Anal. Calcd. for $C_{17}H_{22}O_2N_2Cl_2$: Cl, 19.85. Found: Cl, 19.51.

The Solvates of the *p*-Nitrobenzoate Ester of *p*-(β-Di-*n*-butylaminoethyl)-phenol Hydrochloride with Benzene and Toluene.—The hydrochloride of *p*-(β-di-*n*-butylaminoethyl)-phenyl *p*-nitrobenzoate exhibits a rather high solubility in hot benzene and if such a solution was cooled slowly overnight pale yellow transparent prismatic crystals 3–4 mm. long were formed. A sample of 0.7801 g. of these crystals lost 0.1080 g. or 15.11% of their weight upon drying for 14 hours at 45°. This corresponds closely to a benzene solvation compound with a molecular ratio of 1:1, which should theoretically have a benzene content of 15.21%. The crystals slowly lose their transparency and the molecule of benzene of solvation at room temperature.

This compound forms a similar addition product when crystallized from hot toluene. The resulting solvation compound crystallizes as pale yellow needles that are 10–15 mm. long. A sample of 0.3016 g. lost 0.0447 g. or 14.82% of its weight after drying at about 75° for 12 hours and 0.0522 g. or 17.32% for 18 hours. The last figure corresponds closely to a toluene solvation compound with a molecular ratio of 1:1 which should have a toluene content of 17.45%. These crystals lost their transparency and the molecule of solvation more slowly at room temperature than the corresponding benzene solvate.

The Attempted Preparation of the *p*-Nitrobenzoate Ester of *p*-(β-Diethylaminoethyl)-phenol Hydrochloride by Reaction of Diethylamine with *p*-Nitrobenzoate Ester of *p*-(β-Iodoethyl)-phenol.—A mixture of 4 g. (0.01 mole) of the *p*-nitrobenzoate ester of *p*-(β-iodoethyl)-phenol, 2.3 ml. (0.022 mole) of diethylamine and 12 ml. of benzene was heated in a sealed tube for five hours at 100°. After filtration the benzene was removed by evaporation and the residue was distilled at 4 mm. Extensive decomposition took place and only a few drops of distillate boiling in the range 135–178° were obtained. The hydrochloride of the distillate melted at 169–172° and gave no depression when mixed with *p*-(β-diethylaminoethyl)-phenol hydrochloride (m.p. 172–173°).

Attempts were also made to isolate the desired product without distillation by using ethyl and methyl alcohol as solvents. Ethyl and methyl *p*-nitrobenzoate, respectively, were obtained indicating that transesterification had taken place.

Similar results were obtained when attempts to prepare the corresponding derivative of *p*-(β-di-*n*-butylaminoethyl)-phenol were made by this method.

Acknowledgment.—We want to express our appreciation to Mr. K. C. Li, Chairman of Board, Wah Chang Corporation, New York, and Dr. Ralph Montonna, former director of the Syracuse University Institute of Industrial Research, whose support made much of this study possible.

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[CONTRIBUTION FROM THE WEIZMANN INSTITUTE OF SCIENCE]

Poly-L-aspartic Acid

BY ARIEH BERGER AND EPHRAIM KATCHALSKI

The preparation of optically pure poly-L-aspartic acid is described. The synthesized poly-α-amino acid yields quantitatively on acid hydrolysis L-aspartic acid. The potentiometric titration curve and the dependence of viscosity on degree of ionization are employed to demonstrate the behavior of poly-L-aspartic acid as a polyelectrolyte. The infrared absorption spectrum of poly-L-aspartic acid is compared with that of synthetic poly-L-glutamic acid.

The synthesis of poly-aspartic acid from L-aspartic acid has been reported by Frankel and Berger.[1] A polymer obtained by the published procedure yielded on acid hydrolysis an extensively racemized aspartic acid. Since an optically pure poly-L-aspartic acid was required in the course of our enzymatic and biological studies of water-soluble polyamino acids,[2] the synthesis was reinvestigated and a procedure for the preparation of an optically pure poly-L-aspartic acid worked out.

The course of synthesis of poly-L-aspartic acid is represented in the scheme.

The optical purity of the various intermediates was checked by their conversion into aspartic acid (by reduction or acid hydrolysis) and determination of the specific rotation of the latter. The use of benzyl esters (II, III, IV and V), originally suggested by Frankel and Berger,[1] was found advantageous, as the regeneration of free carboxyl groups by reduction with phosphonium iodide,[3] was found to cause no change in steric configuration. N-Carbobenzoxy-L-aspartic acid[4] (I) was converted to the dibenzyl ester II, with benzyl alcohol in toluene, using *p*-toluenesulfonic acid as catalyst. This procedure was found more convenient and gave higher yields than the esterification by the reaction of the disilver salt of I with benzyl iodide.[1] The removal of catalyst with magnesium oxide permitted isolation of the optically active compound, whereas aqueous potassium carbonate caused partial racemization. II yielded on treatment with an equimolar amount of sodium hydroxide in aqueous dioxane a monobenzyl ester to which formula III was attributed. The constitution of the monoester was proved by its conversion into N-carbobenzoxy-L-asparagine (VII) by means of liquid ammonia. Admixture of the latter with an authentic specimen[4] showed no depression in melting point. The monoester differed from α-benzyl N-carbobenzoxy-L-aspartate[5] in its melting point and dissociation constant. The lower pK value of the β-benzyl ester may be explained by the proximity of the carbobenzoxy group to the free carboxyl group in this compound. The preferential hydrolysis of the α-ester group of II is in accord with the findings of Pauly and Weir[6] for the hydrolysis of dimethyl N-benzoylaspartate. The alkaline hydrolysis of II in benzyl alcohol[1] leads to considerable racemization.

β-Benzyl N-carbobenzoxy-L-aspartate (III)

(1) M. Frankel and A. Berger, *Nature*, **163**, 213 (1949).

(2) E. Katchalski, *Advances in Protein Chem.*, **6**, in press; A. de Vries, A. Schwager and E. Katchalski, *Biochem. J.*, in press.

(3) C. R. Harington and T. H. Mead, *ibid.*, **29**, 1603 (1935).

(4) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

(5) M. Bergmann, L. Zervas and L. Salzmann, *ibid.*, **66**, 1288 (1933).

(6) H. Pauly and J. Weir, *ibid.*, **43**, 661 (1910).