If desired, the intermediate, 2-phthalimidoethanol (I), could be isolated by cooling the benzene solution (above); yield 190 g. (99%), m.p. 126–127° (lit.,[5] m.p. 126–127°).

Poly(vinylamine perchlorate) (VI). Following Hanford and Stevenson,[4] the 2-phthalimidoethyl acetate was passed through a packed tube heated at 570°. The *N*-vinyl-phthalimide (III) obtained, m.p. 85.5–86.5° (lit.,[4] m.p. 85–86°), in 75% yield was polymerized with dibenzoyl peroxide in methanol-1,2-dichloroethane (15/85, v/v) following the method of Reynolds and Kenyon.[3] The nearly quantitative yields of white, finely divided poly(*N*-vinylphthalimide) (IV) were treated with hydrazine following the method of Reynolds and Kenyon.[3] Thus, the polymer (120 g., 0.69 mole) was added in portions to 180 ml. of hydrazine hydrate (85%) stirred at 100° under nitrogen. After 24 hr., the solution was cooled, diluted with an equal volume of water, and steam-distilled until no additional hydrazine could be detected[6] in the distillate. After acidification to *p*H 4 with perchloric acid, the mixture was filtered and dialyzed against water. The dialyzate was concentrated under reduced pressure to 200 ml. and treated successively with three 100-ml. portions of Amberlite IRA-400 (OH^-) resin. The solution was adjusted to *p*H 3.0 with dilute perchloric acid. The solid product obtained on lyophilization contained less chlorine than calculated for the desired product. The denciency was determined by the analysis, and after dissolving the polymer in water, the required amount of perchloric acid (about 5% of the total) was added and the product was again recovered by lyophilization; yield 48 g. (49%) of light-brown, hygroscopic poly(vinylamine perchlorate) (VI); analytical sample dried under reduced pressure over sodium hydroxide.

Anal. Calcd. for $C_2H_5N \cdot HClO_4$: C, 16.74; H, 4.21; N, 9.76; Cl, 24.70. Found: C, 16.83; H, 4.29; N, 9.70; Cl, 24.95.

Properties of poly(vinylamine perchlorate). The molecular weight was determined by Dr. Quentin Van Winkle of the Department of Chemistry of The Ohio State University employing a B-S Light Scattering Photometer (Phoenix Precision Instrument Co., Philadelphia). From measurements in 0.1*M* sodium chloride a value of 90,000 was obtained. This molecular weight resulted from calculations employing the value of C/τ at infinite dilution as determined by the linear extrapolation of the data obtained at finite concentrations.

Poly(vinylamine perchlorate) is very soluble in water and ethanol, dissolves very slowly in acetone but not in ethyl acetate, benzene, or ether. On heating in a test tube, the salt melts and then explodes with a small flash of light leaving a small carbonaceous residue. The polymer also can be detonated by a firm hammer blow on a steel anvil but has been pulverized (caution) in small amounts with a mortar and pestle.

Bis(2-phthalimidoethyl) o-phthalate (IX). 2-Phthalimidoethanol (206 g., 1.08 mole), which had been purified by three wasteful recrystallizations from ethanol (95%), was dissolved in 1.5 l. of refluxing benzene containing 2 ml. of 95% sulfuric acid. Phthalic anhydride (80 g., 0.54 mole) was added in portions to the refluxing solution and the water formed (10 ml.) was removed with a phase-separating head during 20 hr. On cooling and diluting with an equal volume of absolute ethanol, crystals formed which were filtered, washed with water, and dried (110°); yield 220 g. (80%), m.p. 161–162°. The analytical sample (m.p. 164–165°) was obtained by a single crystallization from acetone-ethanol.

Anal. Calcd. for $C_{28}H_{20}N_2O_8$: C, 65.62; H, 3.93; N, 5.47; mol. wt., 512. Found: C, 65.68; H, 3.82; N, 5.43; mol. wt., 511 (Rast).

2-Phthalimidoethylpyridinium p-toluenesulfonate (VIII). 2-Phthalimidoethyl *p*-toluenesulfonate (VII) was prepared following the procedure of Peacock and Dutta[7] in 90% yield (m.p. 142–143°). This sulfonate (30 g.) was refluxed for 5 hr. with 150 ml. of dry pyridine and the solution on cooling deposited crystals (VIII) which were washed with ether and dried; yield 36.5 g. (99%), m.p. 205–206°.

Anal. Calcd. for $C_{22}H_{20}N_2O_5S$: C, 62.25; H, 4.75; N, 6.60; S, 7.55; neut. equiv., 424. Found: C, 62.31; H, 4.70; N, 6.64; S, 7.57; neut. equiv., 427.

The pyridinium compound (VIII) was originally isolated as the major product during an attempt to prepare the tosylate (VII) employing a mixture of pyridine and *p*-toluenesulfonyl chloride.

If the 2-phthalimidoethanol employed for the synthesis of the sulfonate derivatives was contaminated with phthalic anhydride, small amounts of the bis(2-phthalimidoethyl) *o*-phthalate could be isolated by pouring the crude pyridinium compound into water which left the phthalate as an insoluble residue. The phthalate derivative could also be recovered under similar circumstances from the mother liquors formed during the crystallization of the 2-phthalimidoethyl *p*-toluenesulfonate. The only way found to avoid the appearance of this contaminant in the sulfonate derivatives was to effect the condensation of the phthalic anhydride with a slight excess of the 2-aminoethanol.

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Glycyliminodiacetic Acid

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The literature contains few examples of peptides of an imino acid other than those derived from proline. Attempts in this laboratory to prepare β-alanyliminodipropionic acid[2] and α-alanyliminodiacetic acid[3] were unsuccessful, but the simplest member of the series, glycyliminodiacetic acid, $NH_2CH_2CON(CH_2COOH)_2$, has now been obtained.

The conversion of carbobenzoxyglycinehydrazide[4] to the azide and the coupling of the latter with the dimethyl ester of iminodiacetic acid[5] gave a syrup, which was saponified to the crystalline carbobenzoxyglycyliminodiacetic acid. Hydrogenolysis produced glycyliminodiacetic acid.

Possible by-products of the azide coupling are derivatives of the isocyanate resulting from a Curtius rearrangement of the azide. For example, Nyman and Herbst,[6] in attempting to condense the azide of carbobenzoxy-L-valine hydrazide with L-valine ethyl ester, obtained the substituted urea, formed by interaction of the isocyanate with the valine ester. A similar substituted urea was ap-

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parently obtained by Majewski[3] in the attempted reaction of the azide from carbobenzoxy-α-alaninehydrazide with the dimethyl ester of iminodiacetic acid. In the current work the coupling of the azide from carbobenzoxyglycinehydrazide with the same imino ester gave small amounts of a presumed isocyanate polymer, $(C_6H_5CH_2OCONHCH_2NCO)_x$.

The carbodiimide method of coupling was investigated because of its prior use[7] in a notable case of imino coupling in the penicillin synthesis. In the present work, a simple model, the reaction of carbobenzoxyglycine[8] with di-*n*-propylamine in the presence of dicyclohexylcarbodiimide[9] gave crystalline carbobenzoxyglycine-di-*n*-propylamide. When carbobenzoxyglycine was treated with iminodiacetic acid dimethyl ester in the presence of a quaternized carbodiimide,[10] a syrup was obtained having similar properties to that from the azide coupling.

With phthalyl as the protective group on the glycine, crystalline coupling products could be obtained in good yields. Phthalylglycine[11] and iminodiacetic acid dimethyl ester reacted in the presence of either dicyclohexylcarbodiimide or a quaternized carbodiimide to give crystalline phthalylglycyliminodiacetic acid dimethyl ester. The same ester (or free acid) was formed from the reaction of phthalylglycylchloride[12] with the imino ester (or acid). However, the use of phthalyl compounds had the disadvantage that removal of the phthalyl group from phthalylglycyliminodiacetic acid caused dehydration of the peptide with the formation of 1-carboxymethyl-2,5-diketopiperazine. A dehydration on hydrazinolysis of other glycyl peptides was observed by Emerson.[13]

EXPERIMENTAL

Carbobenzoxyglycyliminodiacetic acid dimethyl ester. To a solution of 8.0 g. (0.036 mole) of carbobenzoxyglycinehydrazide[4] in 42 ml. of glacial acetic acid were added 200 ml. of water, 18 ml. of 5*N* hydrochloric acid and 200 ml. of ether, then dropwise with stirring at 0° a concentrated aqueous solution of 2.52 g. (0.037 mole) of sodium nitrite. The azide was purified and coupled with 0.036 mole of the dimethyl ester of iminodiacetic acid[5] by the general procedures outlined by Erlanger and Brand.[14] The product was 7.12 g. (56% yield, based on the hydrazide) of a syrup which could not be crystallized nor further purified by chromatography. It was eluted as one band from silica with varying proportions of chloroform and carbon tetrachloride.

Anal. Calcd. for $C_{16}H_{20}N_2O_7$: N, 7.95; OCH_3, 17.62. Found: N, 8.22; OCH_3, 16.90.

A syrup of similar properties resulted in 55% yield from the reaction of carbobenzoxyglycine[8] (0.01 mole) with iminodiacetic acid dimethyl ester hydrochloride (0.01 mole) in acetonitrile in the presence of triethylamine (0.01 mole) and 1-cyclohexyl-3-(2-morpholinyl-(4)-ethyl)carbodiimide metho-*p*-toluenesulfonate.[10]

During the azide coupling described above, a precipitate (1.43 g.) separated from the ether layer while the azide was being washed. This substance, which decomposed at 247–252°, was soluble only in dimethylformamide. The analysis and lack of solubility suggested that it was an impure polymer of the isocyanate formed from the rearrangement of the azide.

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: N, 13.58. Found: N, 13.16.

Carbobenzoxyglycyliminodiacetic acid. An ethanol solution of 6.08 g. of the dimethyl ester was saponified in the usual way.[15] The yield of acid, m.p. 155–159° dec., was 75%. It was recrystallized from water to constant melting point (159–160° dec.).

Anal. Calcd. for $C_{14}H_{16}N_2O_7$: C, 51.84; H, 4.97; N, 8.64; neut. equiv., 162. Found: C, 52.03; H, 5.29; N, 8.65; neut. equiv., 162.

Glycyliminodiacetic acid. The hydrogenolysis of a solution of 1.0 g. (0.003 mole) of carbobenzoxyglycine[8] in 10 ml. of methanol containing 4 drops of glacial acetic acid was conducted as usual[14] with a total of 0.05 g. of palladium on charcoal as catalyst. After recrystallization from water-methanol (6:5), 0.48 g. (69% yield) of product, m.p. 153–155° was obtained. It separated as a hydrate.

Anal. Calcd. for $C_6H_{10}N_2O_6.H_2O$: C, 34.61; H, 5.81; N, 13.46; neut. equiv., 208. Found: C, 34.44; H, 6.09; N, 13.43; neut. equiv., 207.

Phthalylglycyliminodiacetic acid. To a mixture of 17.59 g. (0.0787 mole) of phthalylglycyl chloride[12] and 21.99 g. (0.165 mole) of finely ground dried iminodiacetic acid (prepared from the disodium salt) in a pressure bottle containing a magnetic stirrer was added 50 ml. of dry dioxane. The bottle was sealed, evacuated, filled with nitrogen (at 5 p.s.i.) and heated slowly with stirring to 50°, kept at this temperature for 3 hr., then heated slowly to 90° for 20 hr. After addition of 200 ml. of hot water and cooling, 18.16 g. (72% yield) of the product, m.p. 215.5–216.5°, separated. When recrystallized from water, it melted at 216–217° with effervescence.

Anal. Calcd. for $C_{14}H_{12}N_2O_7$: C, 52.50; H, 3.78; N, 8.75. Found: C, 52.54; H, 4.01; N, 8.73.

Phthalylglycyliminodiacetic acid dimethyl ester. By the reaction of 0.99 g. (0.005 mole) of iminodiacetic acid dimethyl ester hydrochloride[5] in 10 ml. of pyridine with 1.12 g. (0.005 mole) of phthalyl glycyl chloride[12] in an ice bath for 2 hr. during stirring followed by shaking at room temperature overnight, a 90% yield of crude product was obtained, m.p. 191–192.5°. After recrystallization from dimethylformamide, it melted at 193–193.5°.

Anal. Calcd. for $C_{16}H_{16}N_2O_7$: OCH_3, 17.8. Found: OCH_3, 17.7.

The same ester was obtained by three other methods in the yields (crude) indicated: (a) from phthalylglycine[11] and iminodiacetic dimethyl ester in tetrahydrofuran with dicyclohexylcarbodiimide as condensing agent, 80%; (b) from the same reactants as in (a) with 1-cyclohexyl-3-(2-morpholinyl-(4)-ethyl)carbodiimide metho-*p*-toluene sulfonate,[10] 60%; (c) from phthalylglycylchloride[12] in tetrahydrofuran with 2 equivalents of iminodiacetic acid dimethyl ester, 96%.

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N-Carboxymethyldiketopiperazine. Hydrazinolysis under standard conditions[12] was not successful, but could be accomplished in the following way. A mixture of 2.303 g. (0.01 mole) of phthalylglycyliminodiacetic acid, 10 ml. of ethanol, 10 ml. of 1*N* piperidine in ethanol (0.01 mole), and 10 ml. of 1*N* hydrazine hydrate in ethanol was heated in a pressure tube at 100° for 40 min. with occasional shaking. After the removal of the solvent, the residue was treated with 18.81 ml. of 0.5315*N* hydrochloric acid (0.01 mole) and 50 ml. of water. The phthalhydrazide was filtered, the filtrate evaporated *in vacuo* and the residue crystallized from water, giving 1.326 g. (70% yield) of product, m.p. 165–171°. After four recrystallizations from water the melting point was 174.5–175.5° dec.

Anal. Calcd. for $C_6H_8N_2O_4$: C, 41.86; H, 4.68; N, 16.27. Found: C, 41.96; H, 4.79; N, 16.34.

Carbobenzoxyglycine di-n-propylamide. A mixture of 2.02 g. (0.02 mole) of di-*n*-propylamine, 2.09 g. (0.01 mole) of carbobenzoxyglycine,[8] 2.04 g. (0.01 mole) of dicyclohexylcarbodiimide,[9] and 5.7 ml. of acetonitrile was shaken for 36 hr. After removal of the precipitate, the filtrate was evaporated, taken up in ethyl acetate and washed with acid, water, bicarbonate, and water. The yield of product from the organic layer was 1.46 g. (50%). After recrystallization from ethyl acetate the substance melted at 146–147°.

Anal. Calcd. for $C_{16}H_{24}N_2O_3$: N, 10.42. Found: N, 10.13.

Phthalylglycine di-n-propylamide. The reaction of phthalylglycylchloride and di-*n*-propylamine in pyridine gave a 71% yield of product melting at 104–105° after recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.61; H, 7.04; N, 9.88.

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Pyridylethylated *d*-α-Methylphenethylamines

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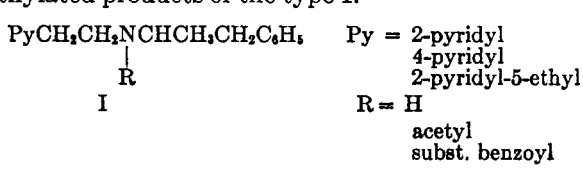
Our explorations[1,2] of derivatives of *d*-α-methylphenethylamine are herein extended to pyridylethylated products of the type I.



Other work[3,4] has shown that the pyridylethyl substituent, particularly the 4-pyridylethyl group, promotes central nervous system depression. It was therefore of interest to assess the effect of this radical on the analeptic activity of *d*-α-methylphenethylamine. Conversion of this amine to a secondary amine (*N*-methyl)[5] or to a tertiary amine (*N*-methyl, *N*-benzyl)[6] has been associated with significant retention of analeptic properties.

The examination of I as acyl- and arylamides[1] was suggested by "reverse" chelidamic acid[7] structures.

Pyridylethylation of *d*-α-methylphenethylamine[8] proceeded readily[9] in acetic acid following the method of Levine,[10] to give compounds 1, 7, and 9.[11] In the preparation of compound 9, some *N*-*d*-α-methylphenethylacetamide was obtained as a side product.

The amino nitrogen of I R = H, although hindered to a large degree, was readily acylated or arylated. In an effort to obtain the corresponding *N*-methylpiperidylethyl analogs of I, preliminary trials of hydrogenation of compound 3 failed. This work, however, is being pursued further.

Pharmacology. Using the reduction of motor activity as an indicator of effect on the central nervous system,[12] the analeptic activity of the *d*-α-methylphenethylamine was retained with compound 1, and depressant effects were observed with compounds 7 and 9. Compounds 4 and 5 also gave depressant effects. Other significant activity was 3+ hypotension[13] and anesthesia (ED_{50} = 9.7 mg./ml.)[14] with compound 4, and potentiation of adrenalin[14] with compounds 3 and 7.

EXPERIMENTAL[15]

N-d-α-Methylphenethyl-2-(5-ethyl-2-pyridyl)ethylamine (Compound 9). A mixture of one-third mole each of *d*-α-methylphenethylamine, 2-vinyl-5-ethylpyridine, and acetic acid in 80 ml. of methanol was heated under reflux for 8 hr. and distilled. After removal of low boiling fractions, a forerun was collected at 128–140° (0.3 mm.), and the product

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(13) For method of testing, see S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 2743 (1958).

(14) For method of testing, see S. L. Shapiro, H. Soloway, E. Chodos, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 203 (1959).

(15) Descriptive data shown in the table are not herein reproduced.