In preliminary experiments it was found that the carbon dioxide which evolved during the polymerization amounted to 97% of the theoretical.

Various preparations of polyproline obtained as above were found to contain no free imino groups, as determined by titration with 0.1 *N* perchloric acid in glacial acetic acid, using crystal violet as indicator.[18] Proline required one equivalent of perchloric acid under similar conditions. The amount of free carboxyl groups in the various preparations of III, obtained by bulk polymerization, was determined by titration with 0.1 *N* sodium methoxide using thymol blue as indicator.[14] Values of 0.030 to 0.015 carboxyl groups per one proline residue were obtained. These values correspond to an average chain length $n = 67$ to 133, assuming the presence of two terminal carboxyl groups per each peptide chain.

A polyproline preparation with an average degree of polymerization $n = 67$ showed an optical rotation of $[\alpha]^{20}D$ −372° (*c* 2.0 in glacial acetic acid), $[\alpha]^{20}D$ −483° (*c* 1.5 in formic acid) and $[\alpha]^{20}D$ −353° (*c* 2.0 in water).

The various preparations of poly-L-proline (*n* 67 to 133) dissolved readily in formic acid, glacial acetic acid and phenol. They dissolved partially in methanol and ethanol and were practically insoluble in dioxane, petroleum ether, acetone, ether and nitrobenzene. The solubility of polyproline in water was found to depend on the way in which the solutions were prepared. When 200 mg. of polyproline (*n* 80) was stirred with 10 ml. of water for 48 hours at room temperature, only 100 mg. went into solution. The material, obtained from the aqueous solution on drying, dissolved readily in water. Complete dissolution in water of the original polymer was achieved when it was dissolved in a minimal amount of hot formic acid, or glacial acetic acid, and diluted with water to the required concentration. No precipitate formed on neutralization with sodium hydroxide. When the polyproline was dissolved in cold formic acid or acetic acid, a slight precipitate formed on the addition of water. An excess of water precipitated the polymer from its solution in phenol, either hot or cold. Polyproline may be precipitated from its aqueous solution with trichloroacetic acid or with a concentrated sodium chloride solution. From its solution in glacial acetic acid it may be precipitated by ether, acetone or perchloric acid (at a final concentration of about 0.1%).

(b) By Polymerization in Solution.—A solution of N-carboxy-L-proline anhydride (0.30 g.) and diethylamine (0.003 g.) in anhydrous dioxane (7.0 ml.) was heated under reflux to 80° for 12 hours. The reaction mixture was protected from moisture by means of a calcium chloride tube. The polymer which separated out was filtered, washed with dioxane and dried *in vacuo* over concentrated sulfuric acid, yield 0.2 g.

The elementary analysis of the polyamino acid obtained agreed closely with that given for the poly-L-proline obtained by bulk polymerization.

Various preparations of polyproline obtained by polymerization in solution, contained no free imino groups. The free carboxyl groups were determined as described previously. From the values obtained (0.029 to 0.024 carboxyl group per one proline residue), average degrees of polymerization of $n = 35$ to 42 were calculated on the assumption that there is one free carboxyl group per each peptide chain.

Hydrolysis of Poly-L-proline.—Poly-L-proline (*n* 67, 16.6 mg.) was dissolved in 2 ml. of 6 *N* hydrochloric acid and hydrolyzed in a sealed tube at 110° for 24 hours. The hydrolyzate was concentrated in a vacuum desiccator over solid sodium hydroxide and concentrated sulfuric acid, and the dry residue dissolved in water (50 ml.). A chromatographic analysis of the hydrolyzate on paper using *n*-butyl alcohol–acetic acid–water (4:1:5) as the mobile phase, yielded with ninhydrin one spot with R_f 0.22 identical with that of an authentic sample of L-proline. The amount of proline in the aqueous solution was determined colorimetrically.[19]

Anal. Calcd. for hydrolyzate of 100 mg. of poly-L-proline $(C_5H_7ON)_n$: proline, 118 mg. Found: proline, 120 mg.

From the optical rotation of the total hydrolyzate of poly-L-proline, $[\alpha]^{20}D$ −51.5 (*c* 5.75 in 0.5 *N* hydrochloric acid), was calculated for the proline liberated. An authentic sample of proline showed under identical conditions $[\alpha]^{20}D$ −52.6°.

N-Benzoyl-α-methylaminoisobutyryl-N,N-dimethylamide.—N-Benzoyl-α-methylaminoisobutyryl chloride[20] was added to an excess of dimethylamine in anhydrous ether and left at room temperature overnight. The dimethylamine hydrochloride formed was filtered off and the ethereal solution extracted with water. The residue after the removal of the ether was crystallized from dibutyl ether; m.p. 127°, yield 75%.

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.6; H, 8.1; N, 11.2. Found: C, 67.1; H, 7.7; N, 11.2.

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The Conversion of Primary Amines to Carbonyl Compounds by a Chloromine Degradation[1]

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The oxidation of a primary amine to the corresponding aldehyde or ketone can be a useful conversion, particularly for degradative purposes. This change has been effected by chlorination of an amine with hypochlorous acid to an N-chloramine, followed by dehydrochlorination to an imine, and hydrolysis of the latter to a carbonyl compound.[4] One adaptation of this method which has been described qualitatively[5] is the conversion of the primary steroidal amine, 3β-acetoxy-20-amino-5-pregnene to 5-pregnenolone.

We have found that *t*-butyl hypochlorite, a fairly stable and readily obtainable material, is a much more convenient reagent for the N-chlorination of amines than is hypochlorous acid itself. A series of five different primary amines has been treated with *t*-butyl hypochlorite. The N-chloramines were converted directly to the imines by reaction with sodium ethoxide, and hydrolysis with dilute mineral acid gave the carbonyl compound, which was isolated either directly or as its 2,4-dinitrophenylhydrazone.

Experimental

5-Pregnenolone.—To a suspension of 621 mg. of 3β-acetoxy-20-amino-5-pregnene acetate[6] (m.p. 200–204°) in 10 ml. of dry ether at 0° was added 120 mg. of sodium bicarbonate, followed by a solution of 165 mg. of *t*-butyl hypochlorite in 10 ml. of dry ether. After allowing the mixture to stand in the cold for 20 minutes, 5 ml. of ethanol was added, followed by a cold solution of sodium ethoxide made by dissolving 350 mg. of sodium in 15 ml. of ethanol. The mixture was heated without reflux on a steam-bath and boiled until a drop of the solution no longer gave a positive reaction with acidified starch-iodide paper. Water was added until the precipitated sodium chloride just dissolved,

(1) Abstracted in part from the Ph.D. dissertation of Michael P. Cava, University of Michigan, 1951.

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TABLE I

Amine	Ketone or aldehyde	Yield crude, %	M.p. crude, °C.	(Recryst.), m.p.
9-Aminofluorene	Fluorenone	98	82–83	83–84
3β-Acetoxy-20-amino-5-pregnene acetate	5-Pregnenolone	71	181–185	185–188
Benzylamine	Benzaldehyde	80[a]	236–237[a]	237[a]
Cyclohexylamine	Cyclohexanone	73[a]	157–160[a]	160–161[a]
β-Phenylethylamine	Phenylacetaldehyde	39[a]	70–105[a]	118–120[a]

[a] 2,4-Dinitrophenylhydrazone.

and the solution was made strongly acid with 10% sulfuric acid. After boiling the solution for 30 minutes, an excess of cold water was added, and the resulting white suspension was extracted with ether. The ethereal solution was washed with water, dried over sodium sulfate and evaporated to dryness, leaving crude 5-pregnenolone as a yellowish crystalline powder, m.p. 181–185°; yield 340 mg. (71%). Recrystallization from aqueous methanol gave colorless needles, m.p. 185–188°. The mixed melting point with an authentic sample, m.p. 188–190°, was 186–189°. During the course of this reaction the 3-acetoxy group was hydrolyzed.

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Synthesis of 4-Hydroxy- and 4-Ethoxy-3,5-dimethoxy-β-phenethylamines[1]

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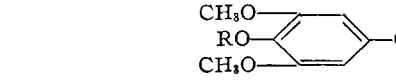
Some of the physiological properties of both 4-hydroxy-3,5-dimethoxy-β-phenethylamine (I) and 4-ethoxy-3,5-dimethoxy-β-phenethylamine (II) have been reported by Noteboom[4]; although a synthesis of the latter compound from 4-hydroxy-3,5-dimethoxybenzyl alcohol is given in the patent literature,[5] the synthesis and chemical and physical properties of compounds I and III do not appear



I, R = R′ = H
II, R = C_2H_5; R′ = H
III, R = H; R′ = CH_3

to have been described. We have found that the synthesis of these phenethylamines from syringaldehyde proceeds readily and in good yield.

Syringaldehyde, which was obtained from 2,6-dimethoxyphenol by the method of Pearl,[6] was condensed with nitromethane in the presence of methylamine to give 4-hydroxy-3,5-dimethoxy-β-nitrostyrene. Subsequent reduction with lithium aluminum hydride[7] afforded 4-hydroxy-3,5-dimethoxy-β-phenethylamine (I). Similarly, condensation of syringaldehyde with nitroethane gave 1-(4-hydroxy-3,5-dimethoxyphenyl)-2-nitropropene which was reduced to *dl*-1-(4-hydroxy-3,5-dimethoxyphenyl)-2-aminopropane (III) with lithium aluminum hydride.

4-Ethoxy-3,5-dimethoxybenzaldehyde was prepared by the action of diethyl sulfate and sodium hydroxide on syringaldehyde. Condensation of 4-ethoxy-3,5-dimethoxybenzaldehyde with nitromethane in the presence of methylamine failed to give 4-ethoxy-3,5-dimethoxy-β-nitrostyrene; however, this intermediate was obtained readily when the condensation was carried out in acetic acid solution in the presence of ammonium acetate.[8] An attempted condensation of syringaldehyde with nitromethane by the acetic acid–ammonium acetate method gave only tarry decomposition products. In the case of 3,4,5-trimethoxybenzaldehyde, which can be obtained readily by either methylation of syringaldehyde with methyl sulfate and sodium hydroxide or from trimethylgallic acid,[9] the methylamine-catalyzed reaction gave a high-melting polymeric product instead of the desired 3,4,5-trimethoxy-β-nitrostyrene, while catalysis with ammonium acetate gave the desired product in good yield. The amine-catalyzed condensation of these benzaldehydes with nitromethane is preferred when a free phenolic hydroxyl is present; the acetic acid–ammonium acetate method is superior for condensation of 3,4,5-trialkoxybenzaldehydes with nitromethane.

In distinct contrast to results obtained with tyramine hydrochloride and 4-hydroxy-3-methoxy-β-phenethylamine hydrochloride, 4-hydroxy-3,5-dimethoxy-β-phenethylamine hydrochloride, in ethanol solution, failed to undergo ring hydrogenation in the presence of Adams catalyst. In this respect, its behavior is more like the completely alkylated trihydroxyphenethylamines. Alternate methods for hydrogenating this class of compounds are currently being examined.

Experimental[10]

4-Ethoxy-3,5-dimethoxybenzaldehyde.—Syringaldehyde was obtained in 50% yield from 2,6-dimethoxyphenol by the procedure of Pearl.[6] The action of ethyl iodide and anhydrous potassium carbonate on syringaldehyde, in accordance with the procedure of Head and Robertson,[11] failed to give 4-ethoxy-3,5-dimethoxybenzaldehyde. In an alternate scheme, a mixture of 21.9 g. of syringaldehyde and 45 ml. of water was heated to boiling and 36 ml. of aqueous sodium hydroxide (15 g. of NaOH in 75 ml. of solution) was then added to the boiling suspension. The sodium salt of syringaldehyde which separated redissolved in the mixture on further heating and stirring. Diethyl sulfate (23 g.) was then added to the boiling solution over a period of 10 minutes, and refluxing was continued for an additional hour. The boiling mixture was treated alternately with four 5.0-g. portions of diethyl sulfate and four 6-ml. portions of aqueous alkali. The oily product, which separated on cooling, was extracted with ether. After drying the ether layer over anhydrous magnesium sulfate and decolorizing with Norite, the solvent was removed under diminished pressure. A light yellow, crystalline, crude product remained as a residue; yield 21.8 g. (86%), m.p. 51–52°. Recrystallization from ether gave light yellow plates melting at 52–53°.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.7; H, 6.5. Found: C, 62.9; H, 6.7.

3,4,5-Trimethoxybenzaldehyde.—Syringaldehyde was methylated by means of methyl sulfate and alkali by the procedure of Buck[12]; 21.9 g. of syringaldehyde afforded 21.2 g. of 3,4,5-trimethoxybenzaldehyde, m.p. 72–74° (lit.[9] 75–76°).

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