The Hofmann degradation of the *cis*-methiodide (XIIb, 3.0 g.) was conducted in practically the same way, and the base (XVI, 0.8 g.) was obtained. The ultraviolet and infrared spectra of the product were completely identical with those of the base from the *trans* isomer.

Anal. Calcd. for $C_{15}H_{21}N$: C, 83.66; H, 9.83. Found: C, 83.79; H, 9.68.

The picrate melted at 87–88° (from acetone).

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 56.40; H, 5.26.

Acknowledgment.—The authors are greatly indebted to Professor T. Irie for his continuous encouragement during this work, and to Miss A. Maeda for microanalyses.

Degradation of α-Methyl-3,4-dihydroxyphenylalanine (α-MethylDOPA)

H. L. SLATES, D. TAUB, C. H. KUO, AND N. L. WENDLER

Merck Sharp and Dohme Research Laboratories, Merck and Company, Inc., Rahway, New Jersey

Received December 16, 1963

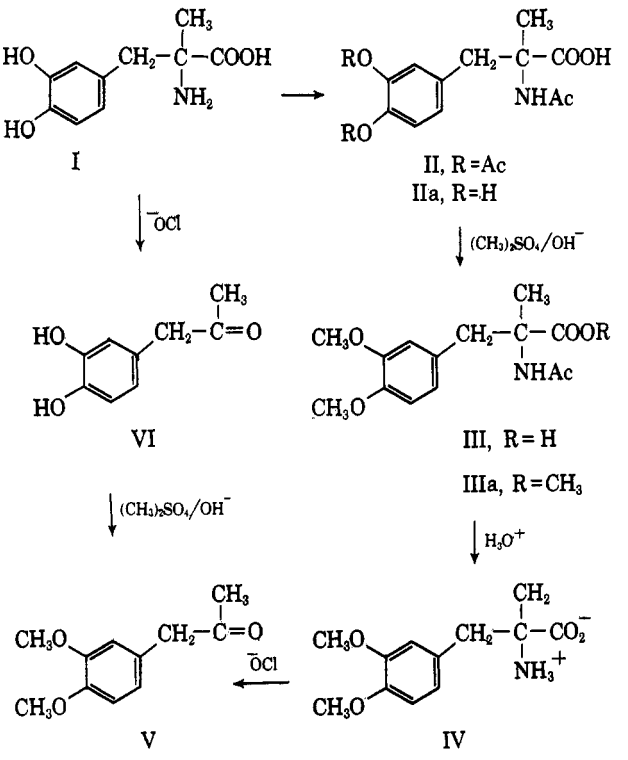
α-MethylDOPA has been degraded in high yield by several pathways to derivatives of 3,4-dihydroxyphenylacetone. These degradations comprise recycle routes for the utilization of D-(+)-α-methylDOPA in the synthesis of L-(−)-α-methylDOPA.

The importance of α-methylDOPA as an antihypertensive agent is well recognized.[1] The synthesis of this substance from 3,4-dimethoxyphenylacetone *via* the Strecker hydantoin sequence[2] requires an optical resolution whereby the biologically inactive D-(+) isomer is made available in equal amount with the active component, L-(−)-α-methylDOPA.[3]

It became of interest to examine possible modes for utilization of the biologically inactive D-(+) isomer for resynthesis of its optical antipode. In view of the character of substitution at the optically active α-position and the consequent inaccessibility of the latter to normal racemization procedures, attention was directed to degradation of the α-methylDOPA system to a precursor, namely, 3,4-dimethoxyphenylacetone. As a result of this investigation, two methods were developed for effecting this degradation in 85–90% conversion and a third method was found effective to the extent of 70–75%.

The great instability to alkali of the catechol system present in α-methylDOPA had long represented a formidable deterrent to procedural undertakings designed to inactivate this portion of the molecule, and, thereby, provide latitude for chemical manipulation of the amino acid segment. It subsequently was discovered that, by scrupulous exclusion of air and by working with solutions previously purged with nitrogen, α-methylDOPA could be handled in alkaline solution without decomposition. A further observation was made as well, namely, that the N-acetyl group of acetylated α-methylDOPA is exceedingly resistant to alkaline saponification and is stable, for example, to 10% sodium hydroxide solution at 150°. Pursuant to these observations, the O,O′,N-triacetate of α-methylDOPA (II),[3] obtained quantitatively from α-methylDOPA, was methylated with dimethyl sulfate and potassium hydroxide, in a typical Schotten–Baumann manner, to give 95% of the N-acetyl dimethyl ether (III), m.p. 187–188°, together with 5% of the corresponding methyl ester (IIIa), m.p. 126–127°. The total methylation product (III + IIIa) was hydrolyzed essentially quantitatively with hydrochloric acid to α-methylDOPA dimethyl ether (IV).[2] Thus, α-methylDOPA could be converted to its dimethyl ether in nearly quantitative over-all conversion. Methylation of α-methylDOPA unprotected by the N-acetyl group resulted in N-methylation products. The N-acetyl derivative of α-methylDOPA, on the other hand, was easily prepared by hydrolysis of the corresponding triacetate and it, in turn, gave results similar to its precursor in the methylation reaction. The transformation of α-methylDOPA dimethyl ether to 3,4-dimethoxyphenylacetone (V) was effected oxidatively with sodium hypochlorite[4] in 90% yield. Thus, the total

CHART I



(1) See, for example: L. Gillespie, Jr., *Ann. N. Y. Acad. Sci.*, **88**, 1011 (1960); H. Smirk, *Brit. Med. J.*, 146 (1963), and references therein.

(2) G. Stein, H. A. Bronner, and K. Pfister, III, *J. Am. Chem. Soc.*, **77**, 700 (1955).

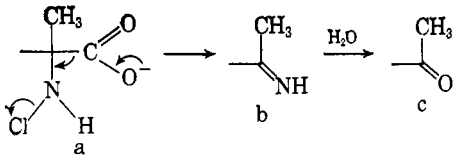
(3) E. W. Tristram, J. ten Broeke, D. F. Reinhold, M. Sletzinger, and D. E. Williams, *J. Org. Chem.*, in press.

(4) For the employment of hypochlorite in the degradation of natural amino acids, see: (a) K. Langheld, *Ber.*, **42**, 392 (1909); (b) H. P. Dakin *Biochem. J.*, **10**, 319 (1916); **11**, 79 (1917); (c) D. D. van Slyke, D. A Mcfayden, and D. Hamilton, *J. Biol. Chem.*, **141**, 627 (1941); (d) I. D. Spenser, J. C. Crowhall, and D. G. Smyth, *Chem. Ind.* (London), 796 (1956).

sequence (Chart I) from α-methylDOPA to 3,4-dimethoxyphenylacetone, consisting of the four steps, acetylation, methylation, hydrolysis, and hypochlorite oxidation, can be effected with a potential over-all yield of 90%.

The direct hypochlorite oxidation of α-methylDOPA itself proceeds in the desired manner to give 3,4-dihydroxyphenylacetone in *ca.* 50% yield. The latter substance is highly water soluble and sensitive as well to manipulation, although it can be methylated to V in reasonable yield. To a large and competitive extent, however, the direct hypochlorite oxidation of α-methylDOPA involves nuclear attack as evidenced by accompanying resinification. The use of *t*-butyl hypochlorite was found to be superior to sodium hypochlorite in this instance and suggests, thereby, that the breakdown reaction to ketone is faster than nuclear involvement. The hypochlorite degradation of the 3-monomethyl ether of α-methylDOPA to 3-methoxy-4-hydroxyphenylacetone also can be accomplished in at least 60–70% yield.

The oxidative degradation IV → V would appear clearly to be initiated by N-chlorination (compare a → b → c) inasmuch as the N-acetate derivative III is unchanged under the conditions of hypochlorite oxidation, whereas the latter (III) is oxidized smoothly by lead tetraacetate (see later text), a reagent known to attack carboxyl functions.[5]



Acetylation of α-methylDOPA (I) or its dimethyl ether (IV) with acetic anhydride in pyridine produces directly the corresponding azlactones VII and VIIa (Chart II) in the absence of a hydrolytic work-up. The former (VII) was obtained as a viscous distillable liquid, whereas VIIa was isolated as a crystalline compound, m.p. 90–91°. Ultraviolet irradiation of the azlactone VIIa in dioxane solution slowly but smoothly converted this substance *via* VIII (or its eneamine tautomer) to 3,4-dimethoxyphenylacetone (V) with liberation of carbon monoxide. The latter was characterized by displacement from dioxane solution and identification by its infrared spectrum. The course of the irradiation could be followed readily by the decrease in optical rotation with time. The irradiation was arbitrarily interrupted after 3 days at a point corresponding to 85% conversion and a commensurate amount of 3,4-dimethoxyphenylacetone was isolated. Irradiation of the corresponding diacetoxy azlactone VII took an indeterminate course. Work-up of the irradiation product, however, did yield a small amount of α-methylDOPA triacetate (II) identical by melting point and infrared spectrum with authentic II but exhibiting a 14% lower optical rotation. This finding suggests that II derived from the irradiation of VII had suffered racemization to a commensurate extent

(5) W. von E. Doering, M. Farber, and A. Sayigh, *J. Am. Chem. Soc.*, **74**, 4370 (1952); C. A. Grob, M. Ohta, E. Renk, and A. Weiss, *Helv. Chim. Acta*, **41**, 1191 (1958); E. J. Corey and J. Casanova, Jr., *J. Am. Chem. Soc.*, **85**, 165 (1963).

CHART II

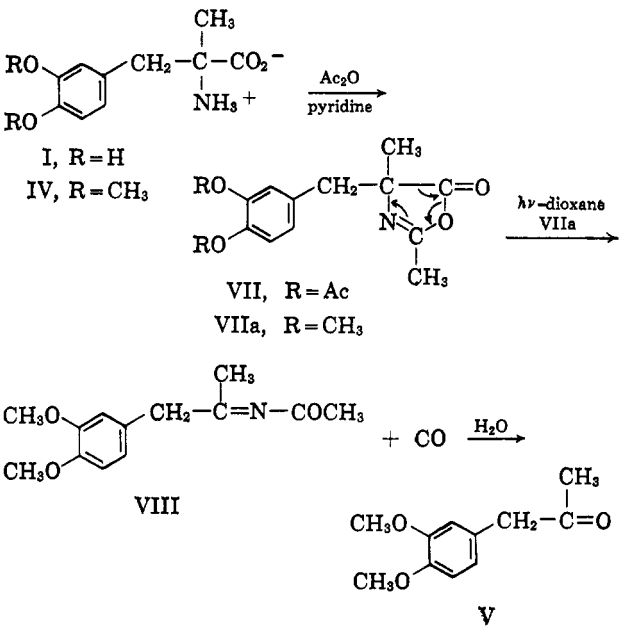
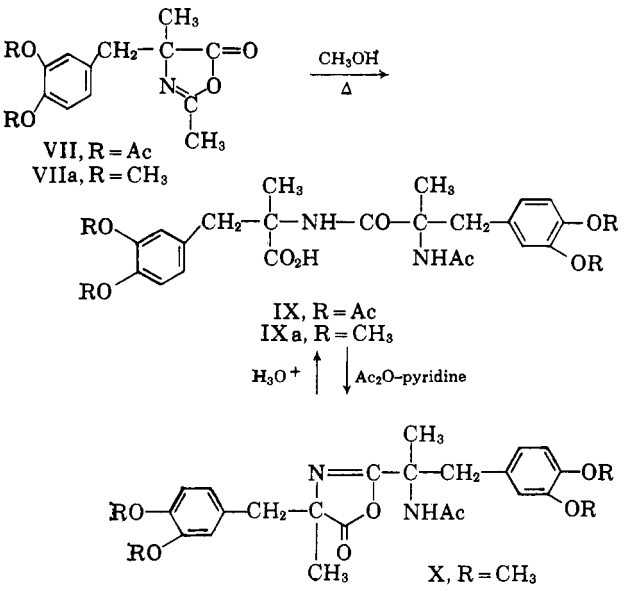


CHART III



and in a manner quite possibly parallel with the light-induced isomerization of estrone to lumiestrone.[6]

Treatment of the azlactone VIIa with anhydrous methyl alcohol, in the anticipation of preparing the corresponding methyl ester of III, produced an unexpected result (Chart III). The dipeptide acid IXa was formed in consequence to this treatment. The latter was subsequently treated with acetic anhydride in pyridine to give the dipeptide azlactone X. The dipeptide acid IXa also was formed from VIIa in hot ethyl alcohol but was recovered when *t*-butyl alcohol was employed. Treatment of VIIa with 2 equiv. of sodium methoxide in methyl alcohol afforded the methyl ester of IV (m.p. 128–129°) but only in 15–20% yield. One might wish to speculate as to the pathway whereby VIIa, under ostensibly anhydrous conditions, is converted to the dipeptide in alcohol solution. If, as an alternative to methanolysis of the lactone ring to

(6) A. Butenandt, A. Wolff, and P. Karlson, *Ber.*, **74**, 1308 (1941).

CHART IV

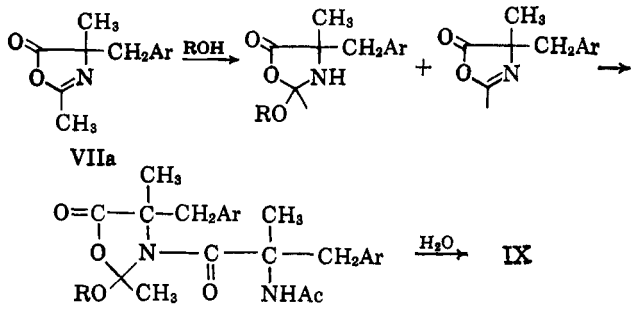


CHART V

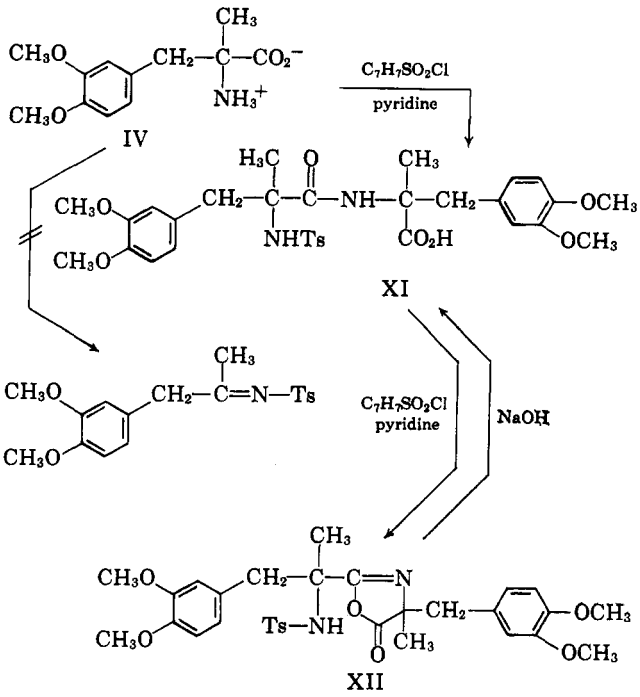
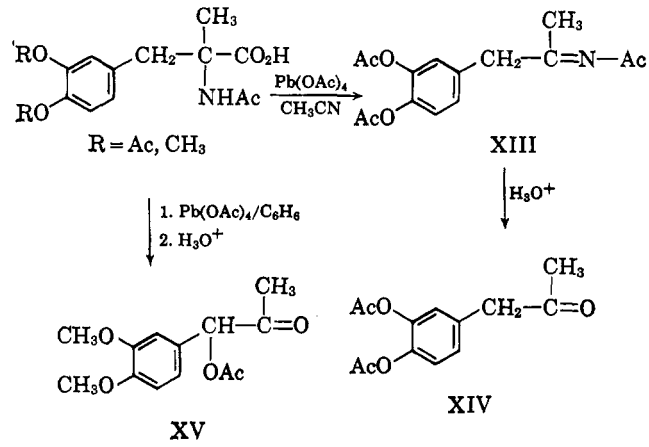


CHART VI



give ester, addition of this reagent were to occur at the azomethine linkage, a donor center would then be created which could function as a coupler with a second azlactone molecule (Chart IV).

Attempts to effect conversion of α-methylDOPA dimethyl ether to 3,4-dimethoxyphenylacetone by means of the mixed-anhydride degradation with *p*-toluenesulfonyl chloride[7] were not successful. Instead of the anticipated reaction, the dipeptide azlactone (XII) was formed (Chart V). The latter was, in turn, readily hydrolyzed to the dipeptide acid (XI). This result parallels in kind the experience observed on methyl alcohol treatment of the azlactone (VIIa). In this instance, it may be surmised that in the tosylation reaction untosylated amino acid reacts with tosylated material to provide the coupled system XI. This suggests that the primary locus of tosylation is the carboxyl group rather than the amine function.

The final degradation conversion of α-methylDOPA to its ketone precursor was effected by means of lead tetraacetate oxidation of α-methylDOPA triacetate in acetonitrile solution (Chart VI). The intermediate ketimine acetate (XIII) (or its enamine tautomer) was hydrolyzed with dilute acid to provide the ketone XIV in 70–75% over-all yield. This method is advantageous in being simple and straightforward[8] and providing a rapid means of executing the desired degradation. If the lead tetraacetate oxidation is effected in benzene solution, there results, in addition to oxidative decarboxylation, acetoxylation at the position α to the aromatic nucleus. The latter consequence was ascertained in the case of III by hydrolysis of the oxidation product to the corresponding ketol acetate XV which exhibited a strong positive tetrazolium test and possessed bands in the infrared at 5.72 and 5.78 μ characteristic of this functional type.[9] The structure of XV was secured by alkaline hydrolysis which led to a mixture of ketols that was cleaved by periodic acid to veratraldehyde and veratric acid.

Experimental

L-(−)-**N-Acetyl-α-methyl-3,4-diacetoxyphenylalanine (II).**[8]—Acetic anhydride, 400 ml. was added portionwise to a stirred slurry of 100 g. of L-(−)-α-methyl-3,4-dihydroxyphenylalanine[10] [L-(−)-α-methylDOPA contained 12.1% water by Karl Fischer titration] in 400 ml. of pyridine. A clear yellow solution was obtained after 0.5 hr., and the reaction mixture was maintained at room temperature for 16 hr. The reaction mixture was concentrated *in vacuo* and flushed three times with toluene, cooled in an ice bath, and acidified with 2.5 *N* hydrochloric acid. The semisolid product was extracted with hot ethyl acetate and the ethyl acetate extract washed with saturated salt solution, dried over magnesium sulfate, and concentrated *in vacuo*. Addition of ether afforded a 134-g. first crop of L-(−)-α-methylDOPA triacetate (II). The latter gave a negative methanolic ferric chloride test and melted at 178–180°. A sample recrystallized from hot acetone melted at 178–180°; $\lambda_{max}^{CH_3OH}$ 268 mμ (ε 372) and 263 (415); $\lambda_{max}^{CHCl_3}$ 2.96, 3–4.2, 5.69, 5.85, 5.99, 6.15, and 6.6 μ; $[\alpha]^{acetone}D$ −45.6°.

Anal. Calcd. for $C_{16}H_{19}NO_7$: C, 56.97; H, 5.68; N, 4.15. Found: C, 57.20; H, 6.17; N, 4.06.

A second crop of 1–2 g. was obtained from the above ether filtrate.

L-(−)-**N-Acetyl-α-methyl-3,4-dimethoxyphenylalanine (III).**—A stream of nitrogen was bubbled through 200 ml. of 4 *N* potassium hydroxide solution for 20 min. and the alkaline solution was cooled to 5–10° prior to the addition of 50.0 g. (0.148 mole) of L-(−)-α-methylDOPA triacetate (nitrogen flow maintained

(7) Compare A. F. Beecham, *J. Am. Chem. Soc.*, **79**, 3257 (1957); E. Wünsch, *Proc. Symp. Methods Peptide Syn.*, 1958; *Collection Czech. Chem. Commun.*, **24**, 60 (1959). See also J. C. Sheehan and J. W. Frankenfeld, *J. Org. Chem.*, **27**, 628 (1962).

(8) Lead tetraacetate has been reported not to react with N-acetyl- and N-benzoyl-α-amino acids [review by R. Criegee, *Angew. Chem.*, **53**, 321 (1940)]. However, cleavage of N-acyl-α-amino acids by this reagent has been described [O. Süss, *Ann.*, **564**, 137 (1949)].

(9) See, for example, R. N. Jones and G. Roberts, *Chem. Ind.* (London), 1269 (1957), and references listed therein.

(10) For reasons of convenience and availability, the L-(−) isomer was employed. Obviously the optical antipode could have been utilized with the same essential consequences.

throughout). The cooling bath was removed and 50 ml. of dimethyl sulfate (0.56 mole) and 100 ml. of 4 *N* potassium hydroxide were then added with occasional use of a cooling bath to maintain the temperature at about 25°. An essentially negative methanolic ferric chloride reaction was obtained after stirring for 30 min. An additional 25 ml. of dimethyl sulfate (0.28 mole) followed by 50 ml. of 4 *N* potassium hydroxide were added and stirring was continued for an additional 30 min.[11] The strongly basic reaction mixture was then extracted with ether.

The ethereal solution was washed to neutrality with water and salt solution, dried over magnesium sulfate, and concentrated *in vacuo* to give 2.5 g. of crystalline O,O-dimethyl-N-acetyl-L-(−)-α-methylDOPA methyl ester (IIIa),[12] m.p. 127–129° after recrystallization from acetone–ether; $\lambda_{max}^{CH_3CN}$ 233 mμ (ε 8850) and 280 (2970); $[\alpha]^{acetone}D$ −45.5°.

Anal. Calcd. for $C_{15}H_{21}O_5N$: C, 61.01; H, 7.17; N, 4.74. Found: C, 61.12; H, 6.83; N, 5.14.

The aqueous solution was chilled and acidified with concentrated hydrochloric acid to yield a heavy precipitate of III. The latter was aged and filtered. This product (m.p. 182–185°) was dissolved in hot ethyl acetate,[13] washed with salt solution, dried over magnesium sulfate, and concentrated under reduced pressure to give 35.10 g. of L-(−)-α-methylDOPA dimethyl ether N-acetate as fine needles, m.p. 186–187°; $\lambda_{max}^{CH_3CN}$ 232 mμ (ε 8960) and 288 (2980); $[\alpha]^{acetone}D$ −21.0°.

Anal. Calcd. for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 60.10; H, 6.77; N, 4.74.

The aqueous filtrate was saturated with salt and extracted with ethyl acetate; the organic phase was washed with salt solution, dried over magnesium sulfate, and concentrated *in vacuo* to afford an additional 4.97 g. of III, m.p. 181–184° (total 96.5%). The combined product, namely, III and its methyl ester, correspond to a 100% yield of utilizable methylation product.

L-(−)-α-Methyl-3,4-dimethoxyphenylalanine Hydrochloride.—The dimethoxy-α-methylDOPA N-acetate (160 g.) in 1800 ml. of 6 *N* hydrochloric acid was magnetically stirred and refluxed for 2 hr. The light brown reaction mixture was concentrated *in vacuo* to dryness and flushed three times with *t*-butyl alcohol, two two times with toluene, and twice with ether to afford 161 g. (97%) of the hydrochloride IV, m.p. 235–238°, with phase change from granular to star-like needles at 192°. Crystallization from aqueous acetone gave the analytical sample, melting point unchanged; $\lambda_{max}^{CH_3OH}$ 231 mμ (ε 8160) and 278 (2680); λ_{max}^{Nujol} 2.86, 2.99, 3.3–3.5, 5.74, 6.17, 6.25, and 6.59 μ.

Anal. Calcd. for $C_{12}H_{18}NO_4Cl \cdot H_2O$: C, 49.08; H, 6.86; N, 4.77; Cl, 12.07; H_2O, 6.1 (Karl Fischer test). Found: C, 48.93; H, 6.75; N, 4.81; Cl, 12.10; H_2O, 5.7 (Karl Fischer test).

α-Methyl-3,4-dimethoxyphenylalanine (IV).—L(−)-α-Methyl-3,4-dimethoxyphenylalanine hydrochloride (518 mg., 1.78 mmoles) in 15 ml. of water was magnetically stirred and 2.00 g. of the basic resin Dowex 1-X8[14] added. A net change of 1.35 pH units from 2.3 to 3.65 was realized within 1 hr. The resin was filtered and washed thoroughly with water. The combined aqueous filtrate was azeotroped to dryness with toluene to afford 450 mg. of crystalline free amino acid monohydrate in quantitative yield exhibiting a negative Beilstein test and a single spot by paper chromatogram (*n*-butyl alcohol–acetic acid–water system, 4:1:1), m.p. 246–249°, with phase change from granular to needles at 215–240°; λ_{max}^{Nujol} 2.7, 2.85, 6.1 (sh), and 6.3 μ; Karl Fischer test, 13.2% (calculated for monohydrate, 14.4%).

The L-(−)-α-methylDOPA dimethyl ether monohydrate was recrystallized from aqueous isopropyl alcohol to afford a first crop of 350.7 mg. of the corresponding anhydrous amino acid; plates, m.p. 250–254°, with phase change at 223–245° from plates to needles; $\lambda_{max}^{CH_3OH}$ 233 mμ (ε 9450) and 280 (3200); λ_{max}^{Nujol} 3.8–4.2, 6.08, 6.33, and 6.61 μ.

Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.23; H, 7.16; N, 5.86. Found: C, 59.92; H, 7.28; N, 5.91.

Dipeptide Azlactone (XII) Derived from α-Methyl-3,4-dimethoxyphenylalanine (IV).—*p*-Toluenesulfonyl chloride (29.96 g., 0.157 mole) was added in portions to a stirred suspension of 9.38 g. (0.039 mole) of L-(−)-α-methylDOPA dimethyl ether (IV) in 80 cc. of dry pyridine at 0° and the reaction mixture was stored at 0° for 16 hr. Pyridine salts were removed by filtration and the filtrate was acidified with 6 *N* hydrochloric acid to give a gummy residue which was extracted into ethyl acetate. The organic phase was washed with water, 5% sodium bicarbonate, and salt solution, dried over magnesium sulfate, and concentrated *in vacuo* to 12.3 g. of yellow foam. The latter crystallized on trituration with ether. The crystalline compound was filtered to afford 6.7 g. of crude dimeric lactone (XII), m.p. 156–168°. The latter was recrystallized from acetone–ether to provide 3.35 g. of product, m.p. 179–184°. Another recrystallization from the same solvent combination furnished the analytical sample, m.p. 184–185°; $\lambda_{max}^{CH_3OH}$ 278 mμ (ε 5600) and 230 (28,300); $\lambda_{max}^{CHCl_3}$ 5.50, 5.95, 6.20, 6.56, and 7.42 μ; n.m.r., in accord with the structure.

Anal. Calcd. for $C_{31}H_{36}O_8N_2S$: C, 62.39; H, 6.08; N, 4.70; S, 5.37; neut. equiv., 596. Found: C, 62.67; H, 5.86; N, 5.16; S, 5.15; neut. equiv., 550.

Hydrolysis of the above azlactone was effected with 1 *N* sodium hydroxide by dissolving hot and precipitating the free acid with hydrochloric acid. The crude dipeptide acid (XI) was obtained in amorphous form from acetone (m.p. 91–95°); $\lambda_{max}^{CH_3OH}$ 279 mμ (ε 5480) and 230 (26,200); $\lambda_{max}^{CHCl_3}$ 2.9, 3.0–4.2, 5.75, 5.94, 6.2, and 6.55 μ.

Anal. Calcd. for $C_{31}H_{38}N_2O_9S$: N, 4.56; S, 5.22. Found: N, 4.94; S, 5.06.

3,4-Dimethoxyphenylacetone (V) from IV.—To a stirred solution (20–25°) of 956 mg. (4.00 mmoles) of α-methyl-3,4-dimethoxyphenylalanine (IV) in 25 ml. of water was added 10 ml. of benzene. Sodium hypochlorite solution (14 ml., 0.3 *N* active chlorine)[15] was added dropwise over 20 min. The reaction was followed by spotting aliquots on starch–iodide paper. After each addition of hypochlorite, a negative test was obtained in about 30 sec. At the reaction's completion, a positive test was obtained 5 min. after addition of the last drop of hypochlorite. The layers were separated and the basic aqueous layer was extracted twice with 50% benzene–ether; the combined organic phase was dried over magnesium sulfate and concentrated to dryness *in vacuo*. The neutral residue (725 mg., 92%) consisted of 3,4-dimethoxyphenylacetone; infrared spectrum was identical with standard; v.p.c. showed it to be 97% pure.

Semicarbazone.—The semicarbazone crystallized from ether–chloroform and had m.p. 171–174°; mixture melting point was undepressed with an authentic sample of m.p. 175–176°.

Anal. Calcd for $C_{12}H_{17}N_3O_3$: C, 57.34; H, 6.82; N, 16.73. Found: C, 57.21; H, 6.67; N, 16.51.

3,4-Dihydroxyphenylacetone (VI). A. Sodium Hypochlorite.—To a stirred solution of 844 mg. (4.00 mmoles) of α-methyl-3,4-dihydroxyphenylalanine (I) in 20 ml. of 0.5 *M* borax buffer (pH 8.5)[16] was added 10 ml. of benzene. Nitrogen was bubbled through the solution and 12.0 ml. of 0.34 *N* sodium hypochlorite solution added dropwise. The red solution was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The latter extract was dried and concentrated to dryness. The residue was triturated with chloroform, the latter suspension filtered, and the filtrate concentrated to dryness *in vacuo* to give 3,4-dihydroxyphenylacetone, 235 mg. (~36%), with additional mate-

(11) The completion of this reaction is marked by a negative ferric chloride test which at this point was essentially secured. The additional quantities of dimethyl sulfate and potassium hydroxide solution added thereafter were, in the pertinent case, precautionary rather than essential.

(12) A separate experiment revealed that the methyl ester is hydrolyzable with 6 *N* hydrochloric acid to afford the same L-(−)-α-methylDOPA dimethyl ether hydrochloride monohydrate as the product of the subsequent step. Thus, the step involving removal of the ester is neither essential nor, in fact, to be recommended.

(13) The precipitated material which may be directly filtered from the acidified aqueous solution is chemically pure in all respects and utilizable as such for the subsequent acid hydrolysis. This step, therefore, is not necessary in a large run.

(14) Basic resin (200–400 mesh), Dowex 1-X8 (Technical Service and Development, Dow Chemical Co., Midland, Mich.), in the chloride form was converted to the corresponding quaternary hydroxide by eluting with five volumes of 5% sodium hydroxide on a chromatographic column followed by washing to near-neutrality with water. Three volumes each of ethyl alcohol and ether were passed through the column to provide the resin in a dry form which was further dried to constant weight in a vacuum desiccator. The base equivalence of the dry resin was determined by slurrying a weighed sample in excess standard hydrochloric acid followed by filtration and back titration of the filtrate with standard sodium hydroxide.

(15) Commercial "5%" sodium hypochlorite was used. A 5.00-ml. aliquot was added to 2 g. of potassium iodide in 30 ml. of 0.5 *N* hydrochloric acid and the iodine formed titrated *vs.* 0.1 *N* sodium thiosulfate; 30.50 ml. of 0.1 *N* sodium thiosulfate was required.

(16) Borax buffer: 3.1 g. of boric acid in 50 ml. of water, 8.5 ml. of 1 *N* sodium hydroxide, and enough water to bring the total to 100 ml.

rial still in the aqueous mother liquors; $\lambda_{max}^{CHCl_3}$ 2.75, 2.90 (O–H), and 5.88 μ (C=O). Acetylation of a probe (pyridine–acetic anhydride, 25°, 18 hr.) gave 3,4-diacetoxyphenylacetone. The latter was identified as the diacetate by comparison with an authentic sample (see diacetoxyphenylacetone section).

B. *t*-Butyl Hypochlorite.—To a stirred suspension of 844 mg. (4.00 mmoles) of α-methyl-3,4-dihydroxyphenylalanine in 10 ml. of water (under nitrogen) was added 340 mg. (4.00 mmoles) of sodium bicarbonate. *t*-Butyl hypochlorite (0.50 g., 4.5 mmoles) in 10 ml. of *t*-butyl alcohol was added dropwise over 30 min. The deep red reaction mixture was acidified with 5 ml. of 2 *N* hydrochloric acid and extracted thoroughly with ethyl acetate. Further work-up as in A led to 335 mg. (50%) of 3,4-dihydroxyphenyl acetone; infrared spectrum was identical with that of an authentic sample.

3,4-Diacetoxyphenylacetone (XIV) from II.—To a stirred solution of 16.85 g. (50 mmoles) of N-acetyl-α-methyl-3,4-diacetoxyphenylalanine (II) in 125 ml. of acetonitrile was added 4.00 ml. (50 mmoles) of pyridine followed by 22.15 g. (50 mmoles) of lead tetraacetate. The mixture was warmed cautiously to reflux temperature at which point lead acetate precipitated rapidly from solution. The mixture was refluxed gently for 30 min., cooled, filtered, and the filtrate concentrated to dryness. The residue, consisting mainly of the intermediate decarboxylated imine triacetate (XIII), was hydrolyzed by heating on the steam bath (90–95°) with 15 ml. of acetic acid and 10 ml. of water for 50 min. The mixture was cooled, water was added, and it was extracted with chloroform. The chloroform extract was washed with dilute potassium bicarbonate solution and salt solution, dried over magnesium sulfate, and concentrated to dryness to give 3,4-diacetoxyphenylacetone (XIV), 9.4 g. (75%); b.p. 145–150° (0.05 mm.); $\lambda_{max}^{CHCl_3}$ 5.80 and 5.84 μ; v.p.c. showed a single peak.

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.05; H, 5.75.

The diacetoxy ketone was converted in good yield by the appropriate processes to the corresponding dimethoxy ketone V and to the dihydroxy hydantoin and α-methylDOPA.

Similar lead tetraacetate treatment of the N-acetyldimethoxyamino acid IIIa in acetonitrile–pyridine led to the dimethoxy ketone V.

α-Acetoxy-3,4-dimethoxyphenylacetone (XV) from IIIa.—To a stirred suspension of 2.81 g. (10 mmoles) of N-acetyl-α-methyl-3,4-dimethoxyphenylalanine (IIIa) in 70 ml. of benzene and 0.80 ml. (10 mmoles) of pyridine was added 4.41 g. (10 mmoles) of lead tetraacetate.

The mixture was refluxed 30 min. and cooled; the precipitated lead acetate was removed by filtration; the filtrate was concentrated to dryness to give an orange oil, 2.32 g. A 1-g. portion of the latter in 20 ml. of 50% aqueous acetic acid was warmed on the steam bath for 1 hr., cooled, and extracted with chloroform. The latter extract was washed with dilute aqueous potassium bicarbonate and saturated sodium chloride solution, dried over magnesium sulfate, and concentrated to dryness to give a yellow oil. By paper chromatography (benzene–cyclohexane (2:1)–formamide), this material contained only a minor amount of 3,4-dimethoxyphenylacetone (V). It consisted mainly of the slightly more mobile substance XV which gave a strong positive tetrazolium test characteristic of α-ketol systems (V gave a negative test); $\lambda_{max}^{CHCl_3}$ 5.72 and 5.78 μ.

Veratraldehyde and Veratric Acid from XV.—A 250-mg. sample of the above dimethoxyphenyl ketol acetate XV was treated with 110 mg. of sodium hydroxide in 5 ml. of methyl alcohol and 2 ml. of water for 30 min., following which, periodic acid dihydrate (700 mg.) in 4 ml. of water was added. After 18 hr. at 25° the methyl alcohol was removed *in vacuo*, water was added, and the mixture was extracted with chloroform. The latter extract was washed with 5% potassium bicarbonate solution, acidification of which led to a precipitate (60 mg.) of veratric acid. Crystallization from aqueous acetone led to 50 mg., m.p. 176–179°, mixture melting point undepressed with an authentic sample of m.p. 180°. The neutral residue (120 mg.) from the original chloroform extract had an infrared spectrum similar to that of veratraldehyde and, on treatment with 2,4-dinitrophenylhydrazine in aqueous methanolic sulfuric acid, the corresponding red 2,4-dinitrophenylhydrazone (m.p. 250–255°, plates from ethyl acetate) was produced. This substance gave an undepressed mixture melting point with authentic veratraldehyde 2,4-dinitrophenylhydrazone of m.p. 254–256°.

L-(−)-2,4-Dimethyl-4-(3,4-dimethoxybenzyl)-2-oxazolin-5-one (VIIa).—L-(−)-N-Acetyl-α-methyl-3,4-dimethoxyphenylalanine-(IV), 4.0 g., was dissolved in 30 ml. of pyridine and 20 ml. of acetic anhydride and the reaction mixture was allowed to stand at room temperature overnight. The solvents were removed *in vacuo* and the residue was crystallized from ether–hexane to give 3.5 g. of L-(−)-2,4-dimethyl-4-(3,4-dimethoxbenzyl)-2-oxazolin-5-one (VIIa), m.p. 91–92°, $[\alpha]^{acetone}D$ −84.2°.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.82; H, 6.21; N, 5.45.

Irradiation of L-(−)-2,4-Dimethyl-4-(3,4-dimethoxybenzyl)-2-oxazolin-5-one (VIIa) to Give 3,4-Dimethoxyphenylacetone (V).—A solution of 1.1 g. of L-(−)-2,4-dimethyl-4-(3,4-dimethoxybenzyl)-2-oxazolin-5-one (VIIa) in 40 ml. of dioxane in a quartz flask was irradiated for 90 hr. with a high pressure mercury arc ultraviolet lamp[17] equipped with a heat filter. At this point, the solution had lost 85% of its optical activity. The reaction mixture was concentrated *in vacuo* and the residue dissolved in 60 ml. of ether. The ether solution was extracted thoroughly with saturated potassium bicarbonate solution, dried over magnesium sulfate, and concentrated *in vacuo* to afford 0.65 g. of esssentially pure 3,4-dimethoxyphenylacetone characterized spectroscopically and by comparison with authentic material.

In a similar experiment, the irradiation was carried out in a quartz flask equipped with a reflux condenser and connected to a nitrometer. After 90 hr., the reaction mixture was refluxed briefly and the gas phase product was collected. The presence of carbon monoxide in the gas phase was shown by strong bands at 4.2 and 4.7 μ in its infrared spectrum.

L(−)-2,4-Dimethyl-4-(3,4-diacetoxybenzyl)-2-oxazolin-5-one (VII).—L-(−)-α-Methyl-3,4-dihydroxyphenylalanine, 10 g., was dissolved in 70 ml. of pyridine and 50 ml. of acetic anhydride and the reaction mixture was held at room temperature overnight. The solvents were removed *in vacuo* and the residue was distilled at 160–170° (0.05 mm.) in a short-path still. There was obtained, as a viscous colorless oil, 9.0 g. of the azlactone, $[\alpha]^{acetone}D$ −66.8°.

Anal. Calcd. for $C_{16}H_{17}O_6N$: C, 60.19; H, 5.36; N, 4.39. Found: C, 59.81; H, 5.22; N, 3.87.

Irradiation of L-(−)-2,4-Dimethyl-4-(3,4-diacetoxybenzyl)-2-oxazolin-5-one (VII).—A solution of 600 mg. of the azlactone (VII) in 20 ml. of dry dioxane in a quartz flask was irradiated with a high pressure mercury arc ultraviolet lamp[17] equipped with a heat filter (transmission cut-off at 220 mμ). The reaction mixture was sampled periodically for measurement of optical rotation. After 6 days, the optical rotation value of the reaction mixture had diminished 24%. The solvent was removed *in vacuo* and the residue was warmed on the steam bath for 1 hr. with aqueous acetone containing a few drops of acetic acid. The hydrolysis mixture was concentrated *in vacuo* to a small volume and allowed to stand at room temperature overnight. There was isolated *ca.* 100 mg. of crystalline material which, after recrystallization from acetone–hexane, afforded 30 mg. of α-methyl-3,4-dihydroxyphenylalanine triacetate, $[\alpha]^{acetone}D$ −39.1°, m.p. 176–179°. The infrared spectrum in chloroform was identical with an authentic specimen. This material exhibits a change of optical rotation attributable to 14% racemization.

Dipeptide Acid IX.—To a solution of 500 mg. of the azlactone (VII) in 10 ml. of methyl alcohol was added a trace of *p*-toluenesulfonic acid.

The mixture was held at room temperature for 18 hr. and then concentrated *in vacuo*. The residual gel was crystallized from aqueous methanol to give 400 mg. of the dipeptide acid IX with m.p. 219–221°. Recrystallization from the same solvents afforded an analytical sample, m.p. 228–230°, $[\alpha]^{acetone}D$ −11.5°.

Anal. Calcd. for $C_{30}H_{34}N_2O_{12}$: C, 58.62; H, 5.58; N, 4.56; neut. equiv., 614. Found: C, 58.72; H, 6.00; N, 4.58; neut. equiv., 581.

The infrared and n.m.r. spectra were in accord with the proposed structure.

Dipeptide Acid IXa. A.—A solution of 500 mg. of the azlactone (VIIa) in 20 ml. of methyl alcohol was refluxed for 18 hr. and then concentrated *in vacuo*.

The residue was treated with 25 ml. of boiling acetone and

(17) Hanovia mercury arc lamp, Utility Model Type 30600.

an insoluble crystalline product, 70 mg., m.p. 255–259°, was isolated by filtration and identified as α-methylDOPA dimethyl ether (IV). From the filtrate there was obtained, after concentration on the steam bath, 230 mg. of the dipeptide acid IXa, m.p. 213–222°. Recrystallization from acetone gave an analytical sample with m.p. 220–221°, $[\alpha]^{pyridine}D$ −37.9.

Anal. Calcd. for $C_{26}H_{34}N_2O_8$: C, 62.13; H, 6.83; N, 5.58; neut. equiv., 502. Found: C, 61.59; H, 6.53; N, 5.88; neut. equiv., 486.

The infrared and n.m.r. spectra were in agreement with the assigned structure.

The filtrate from the isolation of the dipeptide acid IXa was shown by thin-layer chromatography to contain, in addition to IXa, a small amount of the methyl ester of the N-acetyl dimethyl ether IIIa.

Substitution of ethyl for methyl alcohol in the above reaction gave analogous results. However, no reaction was observed with *t*-butyl alcohol.

B.—To a solution of 263 mg. of the dimethoxy azlactone VIIa in 30 ml. of dry pyridine was added 239 mg. of α-methylDOPA dimethyl ether. The amino acid gradually dissolved as the suspension was refluxed gently for 18 hr. The reaction mixture was cooled to room temperature, filtered, and concentrated *in vacuo*. Crystallization of the residue from acetone afforded 150 mg. of the dipeptide acid IXa, m.p. 219–2221°, identical with that described in A preceding.

Dipeptide Azlactone X.—A solution of 100 mg. of dipeptide acid IXa in 2 ml. of pyridine was treated with 2 ml. of acetic anhydride and allowed to stand at room temperature for 18 hr. The reagents were evaporated *in vacuo* and flushed by toluene distillation. The residue was dissolved in ether, filtered, and crystallized from the same solvent to provide 50–60 mg. of X, m.p. 105–108°; $\lambda_{max}^{CHCl_3}$ 2.94 (N–H), 5.46 (azlactone), 5.98 and 6.58 (amide), and 6.2 and 6.25 (aromatic).

Anal. Calcd. for $C_{26}H_{32}N_2O_7$: C, 64.46; H, 6.61; N, 5.78. Found: C, 64.42; H, 6.57; N, 5.83.

The Synthesis of 3,3'-Bipyrrolidines in Both Configurational Series[1a]

PHILIP L. SOUTHWICK, JULIUS A. VIDA, AND DAVID P. MAYER[1b]

Department of Chemistry, Carnegie Institute of Technology, Pittsburgh 13, Pennsylvania

Received December 16, 1963

New compounds in the 3,3'-bipyrrolidine series have been obtained from the aldol condensation product of 1-cyclohexyl-2,3-dioxopyrrolidine, the enol of 1,1'-dicyclohexyl-3-hydroxy-2,4',5'-trioxo-3,3'-bipyrrolidine (I). Sodium borohydride reduction of I yielded a mixture of diastereoisomeric 1,1'-dicyclohexyl-3,4'-dihydroxy-2,5'-dioxo-3,3'-bipyrrolidines (II) from which one of the four possible racemic forms was separated. Lithium aluminum hydride reduction of compounds of structure II yielded 1,1'-dicyclohexyl-3,4'-dihydroxy-3,3'-bipyrrolidines (III); two of the four possible racemic forms were separately characterized. The dehydration product of I, 1,1'-dicyclohexyl-2,4',5'-trioxo-3,3'-bipyrrolidylidene (IV), yielded the enol of 1,1'-dicyclohexyl-2,4',5'-trioxo-3,3'-bipyrrolidine (V) when hydrogenated. Sodium borohydride reduction of V produced a mixture of the four possible racemic forms of 1,1'-dicyclohexyl-4'-hydroxy-2,5'-dioxo-3,3'-bipyrrolidine (VI), all of which were separated. These four compounds were converted to 1,1'-dicyclohexyl-3,3'-bipyrrolidines (VIII); as expected, two of the forms yielded the symmetric (*meso*) structure (VIIIa) and two yielded the racemic form of the dissymmetric structure (VIIIb). Lithium aluminum hydride reduction of the four racemic forms of VI yielded corresponding forms of 1,1'-dicyclohexyl-4-hydroxy-3,3'-bipyrrolidine (IX). Compounds of types III and IX yielded bismethiodides. Stereoisomer IIIb displayed antiinflammatory and hypotensive effects, but also toxicity.

It was pointed out previously[2] that the very facile aldol condensation of those 2,3-pyrrolidinediones which are unsubstituted in the 4-position provides ready synthetic access to compounds in the little-known[3] 3,3'-bipyrrolidine series. The present investigation was undertaken with the objective of developing procedures for preparing other types of 3,3'-bipyrrolidine derivatives from the initial condensation products (I), and thereby permitting examination of the potential physiological activity of compounds in the series. As had been anticipated, the formation of mixtures of stereoisomers constituted the principal difficulty in the synthetic operations which were conducted. The assignment of configurations to the stereoisomers obtained was another desirable objective which presented difficulties but was accomplished in part.

The work to be described here is concerned with a series of compounds having the cyclohexyl substituent on both nitrogen atoms. The pyridine-catalyzed self-condensation of 1-cyclohexyl-2,3-dioxopyrrolidine, which approaches completion within a few minutes at room temperature, was described previously,[2] and it had been observed that product I was enolized. Since the enol I would contain only one asymmetric carbon atom, only one racemic form should exist, and the product did, in fact, behave as a single substance rather than a mixture. Reduction of I with sodium borohydride (see Chart I) reduced the enolic function to yield the 1,1'-dicyclohexyl-3,4'-dihydroxy-2,5'-dioxo-3,3'-bipyrrolidine structure (II) in the form of a mixture of solid diastereoisomers. One racemic form (IIa, m.p. 229.5–231°) crystallized in *ca.* 18% yield after this mixture had been dissolved in an acetone–ethanol solvent mixture. Efforts to induce the separation of other isomers were not successful.

Lithium aluminum hydride reduction of IIa yielded one of the racemic forms of 1,1'-dicyclohexyl-3,4'-dihydroxy-3,3'-bipyrrolidine (IIIa, m.p. 123.5–125°). On the other hand, reduction by the same procedure of the total unseparated mixture of diastereoisomers of structure II yielded a mixture of diastereoisomers of structure III from which a second, higher melting form (IIIb, m.p. 185–186°) was separated by fractional crystallization. Thus two of the four possible racemic forms of III were separately characterized, whereas only one of the four forms of II was so characterized.

(1) (a) This investigation was supported by a research grant (RG-4371) from the National Institutes of Health, Public Health Service. Parts of the work are described in theses submitted by J. A. Vida (1960) and D. P. Mayer (1958) in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Carnegie Institute of Technology; (b) Allied Chemical Corp. Fellow, 1957–1958.

(2) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956).

(3) A few other compounds in the 3,3'-bipyrrolidine series have been described by S. Gabriel [*Ber.*, **47**, 3033 (1914)], E. B. Knott [*J. Chem. Soc.*, 1196 (1947)], and E. Buchta and K. Greiner [*Chem. Ber.*, **94**, 1331 (1961)]. No work on the stereochemistry of these compounds has been reported to this time.