Peyote and Related Alkaloids. XV. *O*-Methylpeyoxylic Acid and *O*-Methylpeyoruvic Acid, the New Cyclic Amino Acid Analogs of Mescaline

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Sir:

Recently we considered the involvement of mescaline (I), the major base of the peyote cactus, in the reductive amination of glyoxylate (II) and pyruvate (III) which could result in the formation of two types of products. Earlier we reported (2) the synthesis and occurrence of mescaloxylic acid (IV) and mescaloruvic acid (V), the noncyclic reductive amination products (Scheme I). The present communication deals with the synthesis of *O*-methylpeyoxylic acid (VI) and *O*-methylpeyoruvic acid (VII), the cyclic reductive amination products and their occurrence as trace constituents of peyote. The identification of peyoxylic acid (VIII) and peyoruvic acid (IX), and their role in the biosynthesis of peyote 1,2,3,4-tetrahydroisoquinoline alkaloids, anhalamine (X) and anhalonidine (XI), have been established (3).

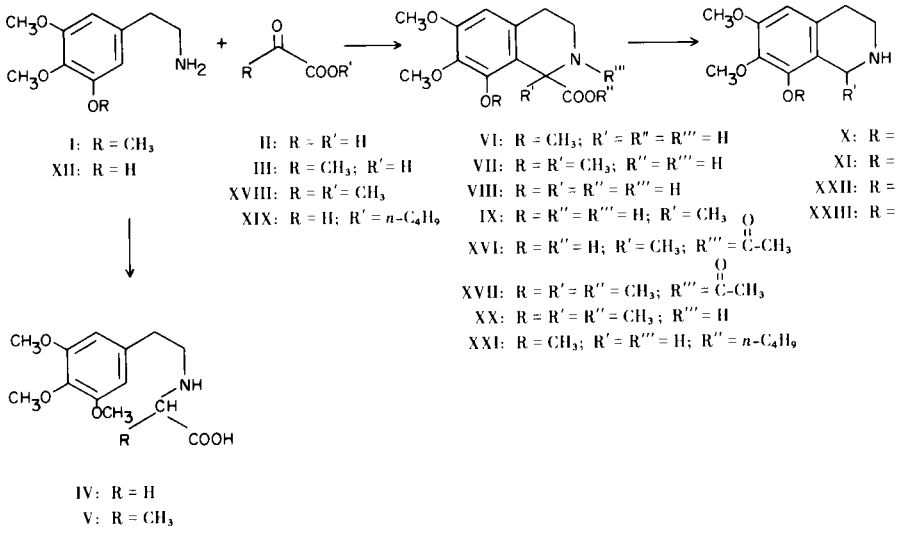
Attempts to synthesize the new amino acids, VI and VII by a single-step procedure involving Pictet-Spengler condensation of mescaline (I) with glyoxylic (II) and pyruvic (III) acids under conditions such as those reported (3) for the facile formation of VIII and IX from 3-demethylmescaline (XII) or under varying and more severe conditions, were unsuccessful. Also, formation of VI and VII could not be realized by diazomethane methylation of the corresponding phenolic amino acids, VIII and IX.

A multistep synthetic procedure that afforded *dl-O*-methylpeyoxylic acid (VI) is outlined in Scheme II. Reaction of mescaline (I) with ethyl oxalyl chloride furnished the amido ester XIII which was cyclodehydrated under Bishler-Napieralski conditions to yield the Schiff's base XIV. Sodium borohydride reduction of XIV afforded the amino ester XV which was hydrolyzed to yield *dl-O*-methylpeyoxylic acid (VI), m.p. 238-240° dec. in 52.3% overall yield (4).

Synthesis of *dl-O*-methylpeyoruvic acid (VII) was accomplished by acetylation of IX to yield *N*-acetylpeyoruvic acid (XVI) which on methylation with dimethylsulfate provided the amido ester XVII. Alkaline hydrolysis of XVII furnished VII, m.p. 245-246° dec., in 18% overall yield (4).

Subsequently, we have obtained VI and VII by a one-step procedure: mescaline (I) hydrochloride was

SCHEME I



I: R = CH_3
XII: R = H

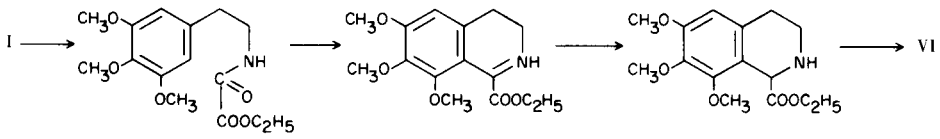
II: R = R′ = H
III: R = CH_3; R′ = H
XVIII: R = R′ = CH_3
XIX: R = H; R′ = n-C_4H_9

VI: R = CH_3; R′ = R″ = R‴ = H
VII: R = R′ = CH_3; R″ = R‴ = H
VIII: R = R′ = R″ = R‴ = H
IX: R = R″ = R‴ = H; R′ = CH_3
XVI: R = R″ = H; R′ = CH_3; R‴ = $C{-}CH_3$ (O)
XVII: R = R′ = R″ = CH_3; R‴ = $C{-}CH_3$ (O)
XX: R = R′ = R″ = CH_3; R‴ = H
XXI: R = CH_3; R′ = R‴ = H; R″ = n-C_4H_9

X: R = R′ = H
XI: R = H; R′ = CH_3
XXII: R = CH_3; R′ = H
XXIII: R = R′ = CH_3

IV: R = H
V: R = CH_3

SCHEME II



XIII XIV XV

separately refluxed with aqueous solutions of methyl pyruvate (XVIII) and *n*-butyl glyoxylate (XIX). The former reaction afforded VII as the major product (yield 51%) along with a small amount (yield 5%) of the methyl ester (XX). In the latter reaction, *dl*-*O*-methylpeyoxylic acid (VI) was obtained as a minor product (yield 10%) along with its *n*-butyl ester (XXI) which was saponified to yield VI (combined yield 45%). Thus, for the successful Pictet-Spengler condensations, free keto acids II and III could be used with 3-demethylmescaline (XII) and their alkyl esters with less activated phenethylamines, such as mescaline (I).

The new synthetic acids VI and VII were characterized by nmr and mass spectrometry. Nmr spectra in deuterium-oxide solvent: VI, δ 2.88-3.10 (m, 2, C_4-H_2), 3.42-3.65 (m, 2, C_3-H_2), 3.82 (s, 3), 3.84 (s, 3) and 3.88 (s, 3) (C_6, C_7, C_8 - tri - OCH_3), 5.01 (s, 1, C_1-H), and 6.70 ppm (s, 1, aromatic C_5-H); VII, δ 1.84 (s, 3, C_1-CH_3), 2.87-3.10 (m, 2, C_4-H_2), 3.20-3.58 (m, 2, C_3-H_2), 3.80 (s, 3), 3.84 (s, 3) and 3.90 (s, 3) (C_6, C_7, C_8 - tri OCH_3), and 6.54 ppm (s, 1, aromatic C_5-H). For mass spectrometry, trimethylsilyl (TMS) derivatives of the two amino acids were prepared by treatment with bis(trimethylsilyl) trifluoroacetamide in acetonitrile. *O*-Methylpeyoxylic acid (VI) gave N, carboxy-diTMS derivative [m/e 411 (M^+), 396 (M-CH_3), 294 (M-COOTMS, base peak)] while *O*-methylpeyoruvic acid (VII) formed monoTMS derivative involving the carboxyl group [m/e 353 (M^+), 338 (M-CH_3), 236 (M-COOTMS, base peak)].

Paper chromatography (PC) of the peyote amino acid fraction (3) indicated the presence of *O*-methylpeyoxylic acid (VI) and *O*-methylpeyoruvic acid (VII). The two amino acids were separated by preparative PC and identified by GC-mass spectrometry (3) of their TMS derivatives (see above).

On the basis of our earlier biosynthetic studies (3), it does not seem unlikely that the new amino acids VI and VII could contribute to the biogenesis of the peyote alkaloids, anhalinine (XXII) and *O*-methylanhalonidine (XXIII), respectively *via* oxidative decarboxylation. Currently we are evaluating the hallucinogenic activity of the new cyclic analogs of mescaline, VI and VII.

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(4) All new compounds gave satisfactory elemental analyses.