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CONCERNING THE STRUCTURE OF 5-AMINODEHYDROLEVULINIC ACID AND ITS DERIVATIVES

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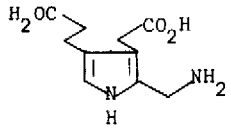
The enzymatic oxidation of porphobilinogen **1** by porphobilinogen oxygenase affords as a main product 3-(β-carboxyethyl)-4-carboxymethyl-5-aminomethyl-5-hydroxy-3-pyrrolin-2-one **2**.



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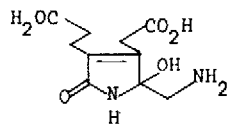
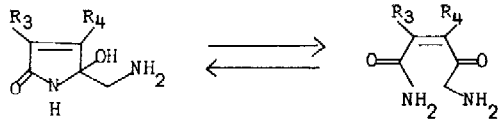


2

Structure **2** was advanced by us on the basis of spectroscopic evidence and of a few selected degradation reactions of **2**[1]. It is a well known fact that free γ-(and δ-) aminoacid esters exist in the cyclic form. Thus, the methyl ester of γ-aminocrotonic acid exist as the Δ^3-pyrrolinone[2], the ethyl esters of N-substituted aminomethylensuccinic acids exist as Δ^4-pyrrolinones[3], and the diethyl esters of meso- and rac-4,5-diaminosuberates cyclize readily to the decahydro-1,5-naphthyridin-2,6-diones[4]. The situation could be different however, in the case of γ-keto-α,β-unsaturated amides, acids, or esters where the tautomeric equilibrium may be displaced toward the open form (Scheme I).



2

Scheme I

Hence, the structure **2** needs a further synthetic confirmation. Moreover, if **2** is the stable form of a γ-keto-α,β-unsaturated amide, then the synthesis of **2** can be planned as a synthesis of the latter compound.

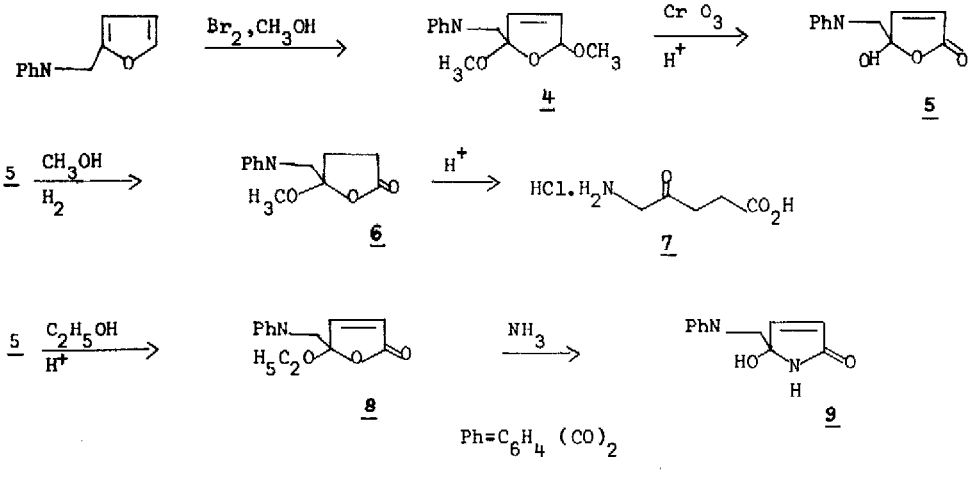
There is a report[5] that describes the preparation of the phthaloyl derivative of 5-

amino-4-keto-2,3-dehydropentanoic acid (dehydroaminolevulinic acid) and of its ethyl ester. Both compounds were described as possesing the open chain structure 3, and not the cyclic pseudo-acid or pseudo-ester structure. This may cast a doubt on the validity of proposing a cyclic structure for the amide derivatives of the γ keto-α,β-unsaturated acids (Scheme I). We repeated the synthesis of 3 and found that the acid as well as the ester exist as the cyclic structures, and that the derived amide is in fact a 5-hydroxy-3-pyrrolin-2-one. N-Phthaloylfurfurylamine was oxidized with bromine in methanol as described[5], and the dimethoxydihydrofuran 4 was obtained as a mixture of isomers (Scheme II). Oxidation of 4 with chromic acid in dilute sulfuric acid afforded 5-phthalimidomethyl-5-hydroxy-2,5-dihydrofuran-2-one 5 in 80% yield: m.p. 74-80° (from water; lit[5] gives m.p. 163° for compound 3, R=H). Structure 5 was secured on the basis of its nuclear magnetic resonance spectrum[6]; nmr ($CDCl_3$), δ 3.37 (b, 1H, OH, disappeared on deuterium exchange with D_2O), 4.15 (d, 2H, CH_2), 6.05 (d, 1H, J=6Hz, =CH-CO), 7.25 (d, 1H, J=6Hz, =CH-C(OH)-CH_2N), 7.78 (m, 4H, C_6H_4); its infrared spectrum, ir (Nujol), 3500 cm^{-1} (OH), 1780 cm^{-1} (lactone CO), 1715 cm^{-1} ($(CO)_2NPh$); and its elemental analysis; Calc. for $C_{13}H_9NO_5$: H, 3.5; C, 60.2. Found: C, 60.3; H, 3.6. The coupling constant of the vinylic protons is compatible only with a cis structure.

Ph.N-CH_2CO.CH=CH-CO_2R

3

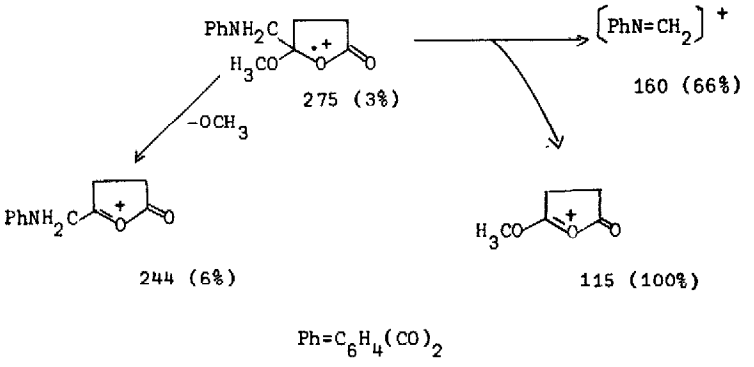
Ph=$C_6H_4(CO)_2$



Scheme II

When 5 dissolved in methanol was reduced with hydrogen over 10% palladium on charcoal at 40 psi the 5-methoxy-tetrahydrofuran 6 was obtained in quantitative yields. It was a mixture

of both possible isomers which were obtained in approximately equal amounts by crystallization from methanol; mp 142° (from methanol), mp 74-76° (from methanol-water). The structure **6** was secured for both isomers by elemental analysis, by their very similar nmr spectra; nmr ($CDCl_3$), δ 2.75 (m, 4H, CH_2CH_2), 3.65 (s, 3H, OCH_3), 4.5 (s, 2H, $\rangle NCH_2$), 7.8 (m, 4H, $C_6H_4(CO)_2$); by their ir spectra (Nujol), 1790 cm^{-1} (lactone CO), 1750 cm^{-1} (Ph $(\underline{CO})_2$); and by their mass spectra (Scheme III).



Scheme III

The existence of two isomers of **6** is by itself an evidence of its cyclic structure. When either isomer was heated under reflux with 6N hydrochloric acid it was transformed into the hydrochloride of 5-aminolevulinic acid **7**.

By treatment of **5** with 5% sulfuric acid in ethanol at 20° during 15 hr the pseudoester **8** was obtained in 60% yield as an inseparable mixture of isomers; mp 140-161° (from ethanol; lit[5] gives mp 97° for structure **3**, R=C_2H_5). The structure of **8** was secured by its nmr spectrum: nmr ($CDCl_3$), δ 1.16 (t, 3H, CH_3), 3.43 (q, 2H, $\underline{CH_2}CH_3$), 4.1 (s, 2H, $\rangle N\text{-}\underline{CH_2}$), 6.05 (d, 1H, J=6Hz, $=\underline{CH}\text{-}CO$), 7.12 (d, 1H, $=\underline{CH}\text{-}C\text{-}OC_2H_5$), 7.72 (d, 4H, C_6H_4); its ir spectrum (Nujol), 1785 cm^{-1}, 1715 cm^{-1}; and its elemental analysis: Calc. for $C_{15}H_{13}NO_5$; C, 62.7; H, 4.5; N, 4.9. Found: C, 62.8; H, 4.7; N, 4.6.

When **8** was treated with ethanol saturated with ammonia and the mixture was kept overnight at room temperature in a closed vessel, ammonolysis took place and the pyrrolinone **9** was obtained in 50% yield; mp 90-92° (from water). Structure **9** was established on the basis of its nmr spectrum (DMSO-d_6), δ 3.45 (b, 1H, OH), 3.85 (s, 2H, CH_2); 5.85 (d, 1H, J=6Hz, =CH-CO), 6.9 (d, 1H, J=6Hz, $=\underline{CH}\text{-}C(OH)\ CH_2$), 7.85 (s, 4H, C_6H_4); 8.2 (s, 1H, NH); its ir spectrum (Nujol) 3550 cm^{-1} (OH), 3450 cm^{-1} (NH), 1785 cm^{-1} (lactone CO), 1715 cm^{-1} (Ph $(CO)_2$); and its mass spectrum: m/e (relative intensity), 258 $[M^+]$ (10%), 240 $[M^+-H_2O$, characteristic fragmentation

of a 5-hydroxy-pyrrolin-2-one[7]] (42%), 161 [Ph $(CO)_2$ $\overset{\cdot+}{N}$-CH_3, formed by H transfer] (100%), 148 [Ph $(CO)_2$ NH_2]$^+$ (80%). The OH and NH peaks in the nmr spectrum disappeared promptly on exchange with D_2O.

These results indicate that the 5-aminodehydrolevulinic acid derivative obtained by the oxidation of the dihydrofuran 4 exist in the pseudoacid form and that its amide is in fact a 5-hydroxy-3-pyrrolin-2-one. Kinetic evidence[8] seemed to lend support to the proposal that the tautomeric equilibrium between the open and cyclic forms of γ-keto-α,β-unsaturated acids is displaced toward the latter forms only when the C=C double bond is substituted with alkyl groups. The data discussed above indicate however, that even cis-acids, esters, and amides, unsubstituted on the double bond, exist entirely in the cyclic hemiacetal structures.

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