The Free Radical Reaction of Thiamine

Previously, the pyrolysis of thiamine disulfide and the reaction of S-anion (II) of thiamine (I) with potassium ferricyanide (III) giving thiochrome have been discussed by A.R. Todd, et al.\(^1\sim3\) They have postulated the reaction mechanism involving a radical process for these reactions. However, no coupling products of the S-radical with the other free radicals have been obtained. Generally, an anion R⁻ reacts with 1-equivalent electron abstracting reagent such as potassium ferricyanide to give a radical R⁻, and then the radical dimerizes.\(^4\) This radical would also be able to couple with some other radicals. For the confirmation of the radical mechanism of this reaction, 4-oxo-2,2,6,6-tetramethylpiperidine-1-oxide (V)\(^6\) or 4-methyl-2,6-di-t-butylnaphthoxy radical\(^7\) was used as stable free radicals to scavenge the S-radical.

In the presence of V, the anion II reacted with III at 5° to give a radical (N), which reacted immediately with V to afford a new derivative of thiamine (VII) accompanied by the disulfide (IX). It is considered that the sulfenamide compound VII would be formed via the coupling intermediate, (VII) or (VII). The reaction mechanism can be illustrated as shown in Chart 1.

VII showed m.p. 179° (from MeOH). Anal. Calcd. for C₃₂H₃₃O₄N₂S: C, 57.91; H, 7.64; N, 16.08; S, 7.36. Found: C, 57.78; H, 7.76; N, 16.29; S, 7.39. UV \(\lambda_{max}\) m.p. (log ε): 235 (4.17); 276 (3.77) (shoulder). IR cm⁻¹ (CHCl₃ solution, 1.0 m/MNaCl, Grating): \(\nu_N\)-H 3620; \(\nu_{\text{as-N-H}}\) 3480; \(\nu_{\text{N-H}}\) 3335; \(\nu_{\text{C=O}}\) 1715. NMR (\(\tau\)) in \(d_4\)-DMSO: 2.08 (singlet); 2.13 (singlet), -N-CHO and -CH= in Pyrimidine. RF value of paper chromatography: 0.70 (n-BuOH, AcOH and H₂O (4:1:5), Toyo-filter paper No. 51). And VII was negative to the thiocchrome test\(^7\) and turned out to be positive after the reduction with cysteine. The hydrolysis of VII with hydrochloric acid at 80° gave 2-methyl-4-amino-5-amino-methylpyrimidine dihydrochloride (X) and 4-oxo-2,2,6,6-tetramethylpiperidine hydrochloride (XI). The reduction of VII with thiophenol in weak acidic aqueous solution at 25°

2) P. Neshit, P. Sykes: Ibid., 1954, 4584.
gave thiamine hydrochloride I and XI quantitatively. Furthermore, high resolution doublefocusing mass spectra were obtained using a JEOL-JMS-OIS mass spectrometer with ionizing voltage of 70 V and 40 V. The mass spectra of VIII contained the expected molecular ion peak at m/e 435.230, and large fragment peak at m/e 122.186=C_{6}H_{5}N_{3}=(Py)^{+};

186.098=C_{6}H_{10}ONS=\left(\begin{array}{c}
\text{CH}_{3} \\
\text{CH}_{3}
\end{array}\right)^{+} \text{and } 249.136=C_{12}H_{17}O_{2}N_{4}=\left(\begin{array}{c}
\text{Py} - N \\
\text{CH}_{3} \\
\text{C} = C \\
\text{R}
\end{array}\right)^{+}. \text{ The}
structure \( \text{III} \) is supported from these facts. A similar experiment has been carried out on a phenoxy radical instead of \( \text{V} \) in order to prove the free radical process more definitely. In this case, the normal coupling product (\( \text{III} \)) was obtained at 0\( ^\circ \) to 5\( ^\circ \) accompanied by the disulfide \( \text{X} \). \( \text{III} \) showed m.p. 197\( ^\circ \) (from MeOH). *Anal. Calcd. for C\(_{27}\)H\(_{32}\)O\(_4\)N\(_2\)S : C, 64.80; H, 8.00; N, 11.20; S, 6.40. Found : C, 64.52; H, 8.04; N, 10.98; S, 6.26. UV \( \lambda_{\max} \) m\(_{\mu}\) (log e) : 234.5 (4.22); 276.5 (4.03).* Further \( \text{XII} \) was negative to the thiocromone test and turned out to be positive after the reduction with cysteine. From these facts, \( \text{XII} \) is confirmed to have normal coupling structure and \( \text{S}-\text{alkyl} \) structure should be excluded for \( \text{XII} \).

Therefore, it has been shown that the reaction of thiamine in thiol form with \( \text{K}_2(\text{Fe(CN)})_6 \) involves a free radical intermediate, since the typical coupling products have been isolated, and that syntheses of new types of thiamine derivatives are accomplished by these methods.

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Components of *Boucerosia aucheriana* Decne

*Boucerosia aucheriana* Decne (Asclepiadaceae) is a plant indigenous to Pakistan and known to have a very bitter taste. A dried collection of whole plants from the vicinity of Peshawar, Pakistan, furnished a mixture of glycosides after usual isolation procedure.\(^1\) The mixture consists of various glycosides and, after mild acid hydrolysis, cymarose, sarmentose, oleandrose and digitoxose were detected as the sugar components.

The aglycone part is also a noncrystalline mixture of diversified esters and resistant to further purification. After alkaline hydrolysis, however, it was partitioned into a crystalline neutral fraction and various acids, i.e. benzoic acid, acetic acid, propionic acid, \( n \)-butyric acid, isovaleric acid and \( n \)-valeric acid.

The neutral fraction holds two closely related components; boucerin, C\(_{27}\)H\(_{32}\)O\(_4\)(\( \text{I} \)), m.p. 239\( ^\circ \) to 241\( ^\circ \), [\( \alpha \)]\(_D\) \( -3.7^\circ \) (c=0.26, MeOH), IR \( \nu_{\max} \) cm\(^{-1}\) : 3356, 1063, 848, NMR \( \tau \) (in pyridine) : 8.93 (singlet, 3H), 8.53 (doublet, 3H, J=6 c.p.s.), 8.33 (singlet, 3H), 4.51 (multiplet, 1H), and dihydroboucerin, C\(_{27}\)H\(_{32}\)O\(_4\)(\( \text{II} \)), m.p. 143\( ^\circ \)/205\( ^\circ \), [\( \alpha \)]\(_D\) \( +3.9^\circ \) (c=0.29, MeOH). IR \( \nu_{\max} \) cm\(^{-1}\) : 3380, 3320, 1043, NMR \( \tau \) (in pyridine) : 8.81 (singlet, 3H), 8.57 (doublet, 3H, J=6 c.p.s.), 8.36 (singlet, 3H). The difference between both compounds lies only in one double bond, thus \( \text{I} \) was transformed to \( \text{II} \) by catalytic hydrogenation. The absence of a carbonyl function is evident from the IR spectra and a normal C\(_1\) steroidal structure with a hydroxyl function at C-20 was anticipated from the NMR data.

Acetylation of \( \text{I} \) and \( \text{II} \) with pyridine-acetic anhydride gave corresponding triacetates: (\( \text{III} \)), C\(_{27}\)H\(_{32}\)O\(_4\), m.p. 147\( ^\circ \) to 149\( ^\circ \), IR \( \nu_{\max} \) cm\(^{-1}\) : 3520, 3430, 1737, 1723, 1260, 1242, NMR \( \tau \) (in CDCl\(_3\)) : 8.98 (6H), 8.81 (doublet, 3H, J=6 c.p.s.), 7.96 (6H), 7.87 (3H), 4.60

\(^{\text{a1}}\) Satisfactory analytical results were obtained for all compounds described in this communication.