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STUDIES ON THE PYRIMIDINE DERIVATIVES. XXXV.

SYNTHESES OF THE BENZO-THIAMINE AND ITS RELATED COMPOUNDS

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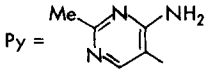
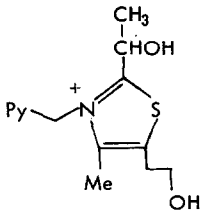
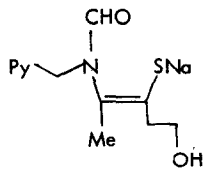
On the mechanism of thiamine action, Breslow (1) proposed that the 2-position of the thiazole ring in thiamine might be the center of thiamine activity. In this connection, Krampitz and his co-workers (2) synthesized I.

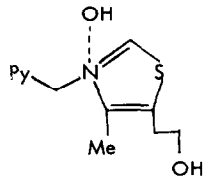




I



II

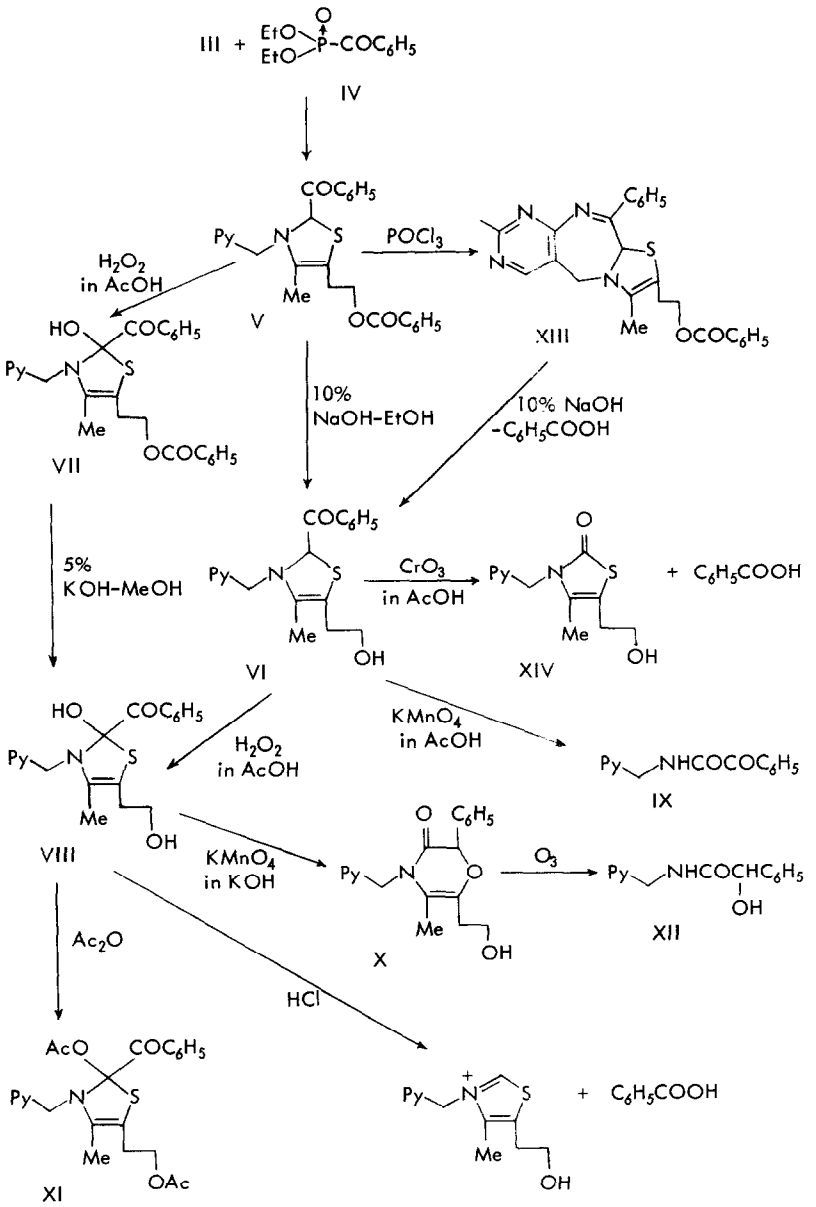


III

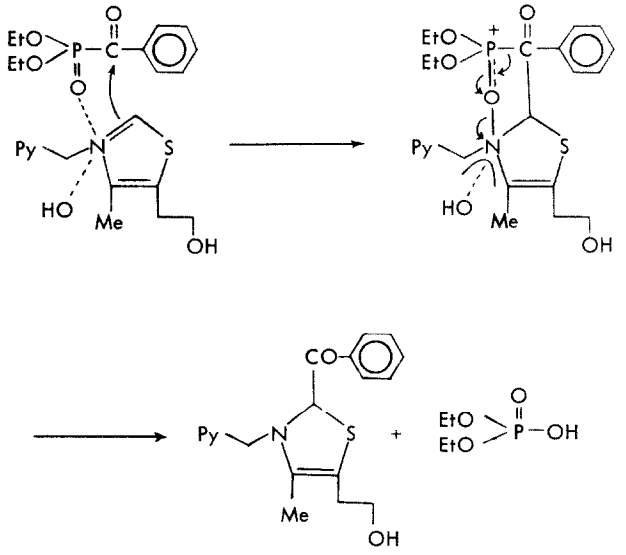
Although it was reported that thiamine hydrochloride reacts with 3 moles of sodium hydroxide to form the sodium salt (II) of a thiol form in which the thiazole ring has been opened (3), we have found that the neutral form of thiamine (III) can be isolated as a crystalline solid under certain condition. When this "neutral form thiamine" was allowed to react with diethyl benzoylphosphonate (IV), 2-benzoyl-

3-(2-methyl-4-amino-5-pyrimidyl)methyl-4-methyl-5-(2-benzoyloxy)ethyl-thiazoline (Benzo-Thiamine) (V) was obtained in 54% yield as a crystalline product, m.p. 163-164° (decomp.). We call this Takamizawa's reaction. On hydrolysis V gave VI. Oxidation of V and VI with hydrogen peroxide in acetic acid let to 2-benzoyl-2-hydroxy-3-(2-methyl-4-amino-5-pyrimidyl)methyl-4-methyl-5-(2-benzoyloxy)ethylthiazoline (VII), m.p. 174-174.5° (decomp.) and 2-benzoyl-2-hydroxy-3-(2-methyl-4-amino-5-pyrimidyl)methyl-4-methyl-5-(2-hydroxy)ethylthiazoline (VIII), m.p. 197-198° (decomp.), respectively. The structures of these new compounds, V, VI, VII, and VIII, were confirmed from the following experiments. VI, on oxidation with chromium trioxide in acetic acid, gave thiamine thiazolone (XIV) and benzoic acid. Treatment of VI with potassium permanganate in acetic acid afforded 2-methyl-4-amino-5-(phenylglyoxaloyl)-aminomethylpyrimidine (IX). Dehydration of V with phosphoryl chloride gave the expected tricyclic compound (XIII), m.p. 196-198° (decomp.). Subsequent ring fission of XIII with sodium hydroxide furnished VI with loss of benzoic acid. VIII, on treatment with acetic anhydride, formed the diacetate (XI), m.p. 160-162° (decomp.). When a solution of VIII in N-hydrochloric acid was allowed to stand at room temperature, thiamine and benzoic acid were obtained in 90% yield. Oxidation of VIII with 4/3 mole of potassium permanganate in N-potassium hydroxide solution gave 2-phenyl-3-oxo-4-(2-methyl-4-amino-5-pyrimidyl)-methyl-5-methyl-6-(2-hydroxy)ethyl-2,3-dihydro-1,4-oxazine (X), m.p. 197-198° (decomp.) in 80% yield. The structure of X follows from that the ozonolysis of X produced 2-methyl-4-amino-5-(mandeloyl)aminomethylpyrimidine (XII).

The authors wish to thank Professor S. Nagakura of Tokyo University for many valuable discussions.


III + (EtO)2P(O)-COC6H5
IV
V
XIII
VII
VI
XIV
VIII
IX
X
XII
XI
H2O2 in AcOH
POCl3
10% NaOH-EtOH
10% NaOH -C6H5COOH
5% KOH-MeOH
CrO3 in AcOH
+ C6H5COOH
KMnO4 in AcOH
KMnO4 in KOH
O3
Ac2O
HCl
+ C6H5COOH

The Mechanism of the Takamizawa's reaction.



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