Tetrahedron Letters No.48, pp. 3599-3604, 1964. Pergamon Press Ltd.
Printed in Great Britain.

STUDIES ON THE PYRIMIDINE DERIVATIVES. XXXV. Supplement ON THE BENZO-THIAMINE

Akira Takamizawa, Yoshiro Sato, Sachiko Tanaka, and Hisako Itoh

Shionogi Research Laboratory, Shionogi & Co., Ltd.,
Fukushima-ku, Osaka, Japan

(Received 7 October 1964)

In a previous communication (1), we reported that neutral thiamine (I), on treatment with diethyl benzoylphosphonate (II), gave a new compound (III) of benzo-thiamine type, which, on oxidation with hydrogen peroxide in acetic acid, led to a pseudo-benzo-thiamine (VII). A series of these related reactions are illustrated in Fig. 1.

At that time, no reasonable explanation was given for the fact that the n.m.r. spectra (60 M c.p.s.) of both III and IV showed a singlet signal pattern about 2.8τ for the benzoyl group, probably introduced into the 2-position of the thiazole ring of thiamine.

Treatment of either III or IV with concentrated hydrochloric acid, gave the same product. This product (XIV), $C_{19}H_{24}N_4O_3S \cdot H_2O$, m.p. 163-164° (decomp.), has an absorption band at 1710 cm^{-1} in the infrared spectrum. Its n.m.r. spectrum exhibited the signals of the NH proton about 2.1τ (broad triplet) and two methylene protons at 5.80τ (d., J=6.2 c.p.s.), indicating the presence of the $-CH_2-NH-$ grouping in XIV. This compound must have been formed by the hydrolytic opening of the ring of III or IV. XIV, on treatment with alcoholic sodium hydroxide or on passing through

Fig. 1

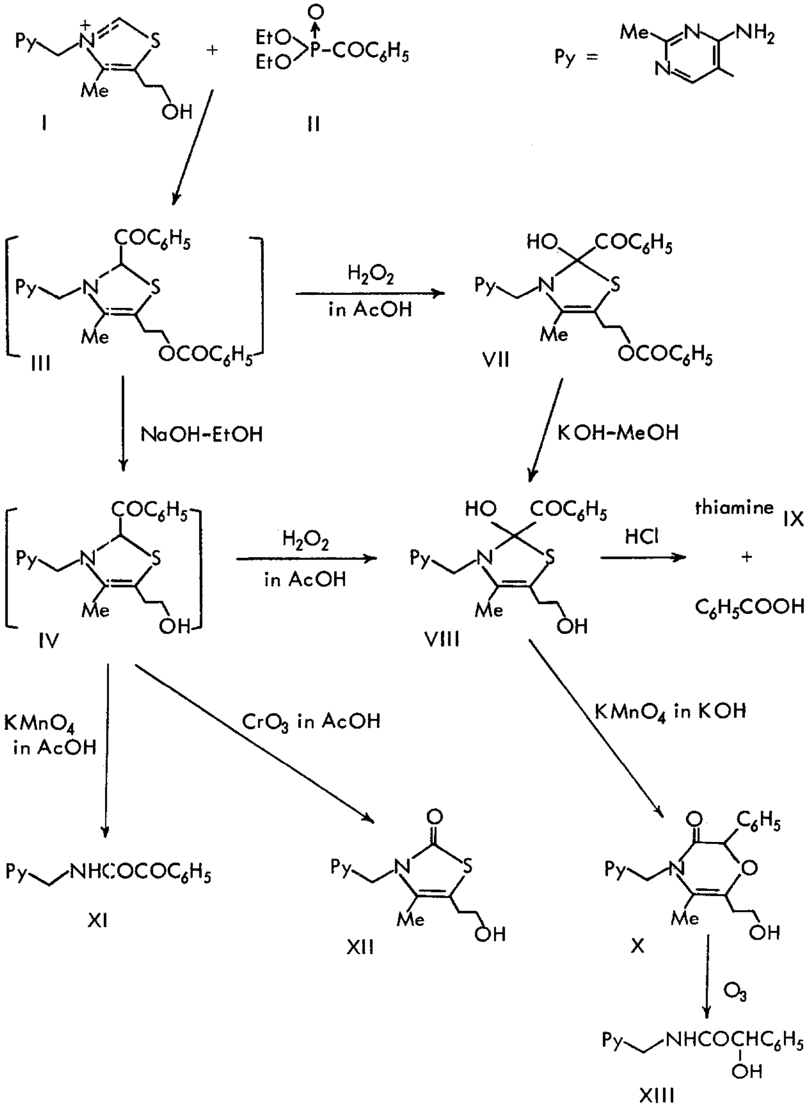
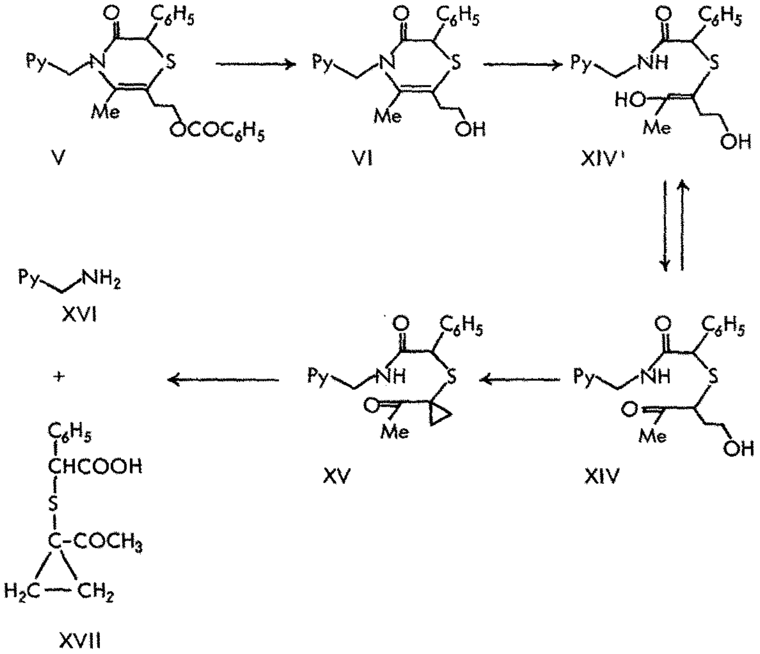

I
II
Py =
III
VII
H2O2 in AcOH
NaOH-EtOH
KOH-MeOH
IV
VIII
H2O2 in AcOH
HCl
thiamine IX
+
C6H5COOH
KMnO4 in AcOH
CrO3 in AcOH
KMnO4 in KOH
XI
XII
X
O3
XIII

Fig. 2

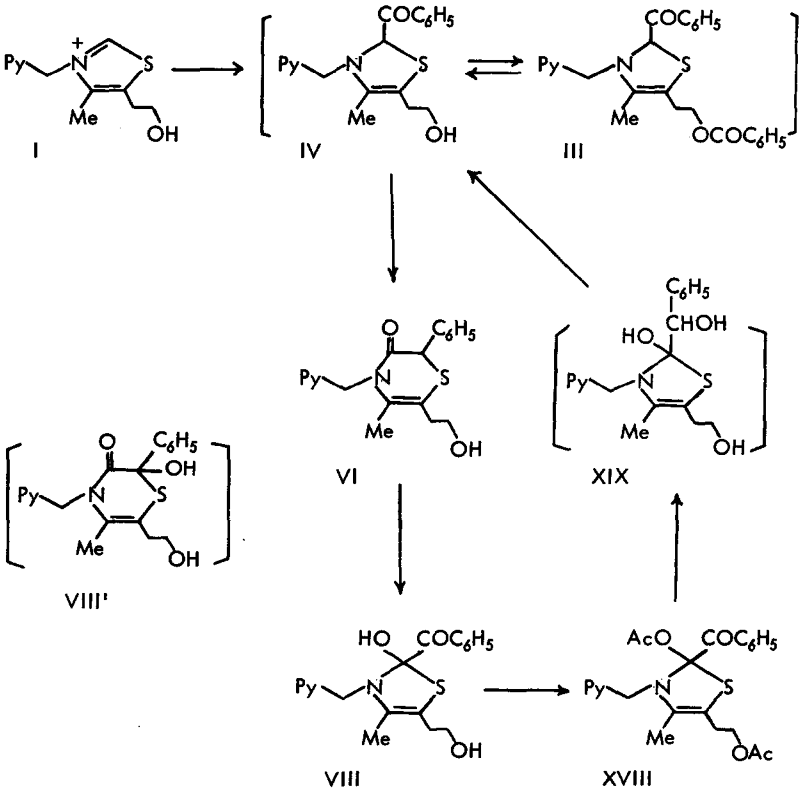


an alumina column, gave XV, $C_{19}H_{22}N_4O_2S$, m.p. 183-184° (decomp.), probably dehydration product of XIV. This compound showed an infrared carbonyl absorption band at 1685 cm^{-1}. In its n.m.r. spectrum, four proton signals of the A_2B_2 type were observed around 8.6τ together with signals for the $-NH-CH_2-$ grouping. These data indicate that XV is S-(1-acetyl)cyclopropylthiomandelyl-(2-methyl-4-amino-5-pyrimidyl)methylamide. On hydrolysis with hydrochloric acid, XV yielded 2-methyl-4-amino-5-aminomethylpyrimidine (XVI) and a carboxylic acid (XVII), $C_{13}H_{14}O_3S$, m.p. 123-124°, of which the infrared spectrum had two strong carbonyl band at 1715 cm^{-1} and 1660 cm^{-1}. The n.m.r. spectrum of XVII showed the signals for phenyl at 2.65 τ(s), $-\overset{|}{\underset{|}{C}}-H$ at 5.38 τ(s), acetyl at 7.85 τ(s) and four protons of the A_2B_2 type around 8.6 τ. This compound must represent an acid fragment of XV and is S-(1-acetyl)cyclopropylthiomandelic acid. XIV is thus S-(1-acetyl-3-hydroxy)propylthiomandelyl-(2-methyl-4-amino-5-pyrimidyl) methylamide.

From these results, it was concluded that the structure proposed previously for III or IV should be corrected as 2-phenyl-3-oxo-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(2-hydroxy or benzoyloxy)ethyl-2,3-dihydro-1,4-thiazine (V or VI). On treatment with either lithium aluminium hydride or sodium borohydride, the diacetate (XVIII) of VIII underwent hydrogenation accompanied by dehydration to yield VI. For the structure of VIII, 2-hydroxy-2-phenyl-3-oxo-4-(2-methyl-4-amino-5-pyrimidyl)methyl-5-methyl-6-(2-hydroxy)ethyl-2,3-dihydro-1,4-thiazine (VIII') may also be conceivable, but this was excluded by the following fact. The n.m.r. spectrum of XVIII showed a signal pattern around 2.3 τ typical of the $-COC_6H_5$ group. In addition, as previously reported, treatment of VIII with hydrochloric acid afforded thiamine and benzoic acid in 90% yield. Reduction of XVIII with sodium borohydride gave VI, as mentioned above. These facts indicate that a thiazoline type of structure (VIII) is a more appropriate one.

In this series of reactions, it is seen that thiazoline derivative (III) which initially formed was easily rearranged to thiazine form (V). V, on treatment with hydrogen peroxide, was again rearranged to thiazoline (VII). The latter, on reduction with either lithium aluminium hydride or sodium borohydride, led to thiazine

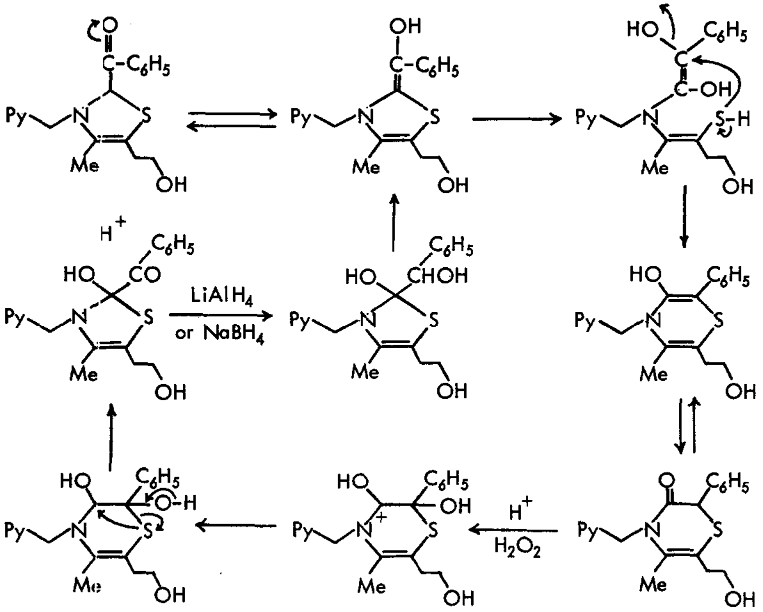
Fig. 3



derivative (VI). The mechanism for these transformations may be considered as outlined in Fig. 4.

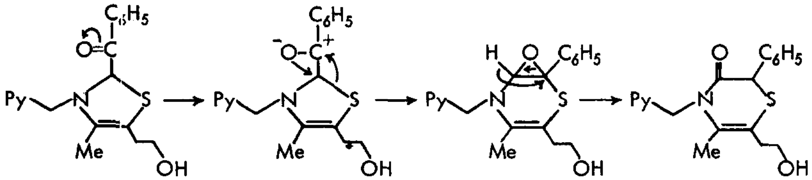
The authors thank Professor S. Nagakura and Professor Emeritus E. Ochiai of Tokyo University for valuable discussions.

Fig. 4*



---

* We have also some interesting for this mechanism.



REFERENCE

1. A. Takamizawa, Y. Sato, and S. Tanaka, Tetrahedron Letters 2803 (1964).