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STUDIES ON PYRIMIDINE DERIVATIVES AND RELATED COMPOUNDS. L.*

REACTION OF THIAMINE WITH ALDEHYDES (I)

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The mechanism, proposed by Breslow (1), for thiamine (B_1) catalysis on the decarboxylation of the adduct of pyruvic acid with B_1 via the zwitter-ion, providing hydroxyethylthiamine (HET) as an intermediate and eliminates an acetaldehyde, has been supported since the success of HET synthesis from B_1 with acetaldehyde by Miller (2) and the isolation of HET or HETDP from a living organism by Carlson (3) or Holzer (4). On the contrary, Wanzlick (5) advocated that the active form of B_1 is the carbene rather the ylid . During the course of the investigation on B_1 chemistry the authors have found interesting information from the reactions of B_1 with aldehydes. Miller et al. obtained HET and its homologues from the reaction of B_1 with aldehydes in the aqueous solution, but the authors obtained colorless crystals (III), m.p. 182-183°, along with benzoin, thiothiamine, bis-2-{4-methyl-5(2-hydroxyethyl)} thiazole, and 2,5-dimethyl-4-aminopyrimidine from the reaction of CO_2 treated B_1-Na with benzaldehyde in toluene or in EtOH. Treatment of III with diluted hydrochloric acid easily decomposed to reproduce B_1 in a quantitative yield. III showed analytical data for $C_{19}H_{22}O_2N_4S$ corresponding to the 1 : 1 adduct of B_1 and benzaldehyde. From the UV spectrum [λ_{max}^{EtOH} mμ 244 (ε 17,800), 275 (ε 8,620)] it was estimated that 2-methyl-4-amino-5-pyrimidinyl group might still remain. IR spectrum showed absorption band at 1687 cm^{-1} (C=O). NMR spectrum (FIG. 1) showed peaks (τ value) at 2.23^s (1H, pyrimidine (pm)-C_6-H), 3.6^b (2H, pm-C_4-NH_2), and at 8.32^s (3H, thiazole (th)-C_4-CH_3) which was a fairly high field as usually found in the th-C_4-CH_3 group indicating the formation of tetrahydrofuran ring accompanied with the characteristic 5H signals between 5.6-8.2 instead of the expected typical triplet-triplet signals due to hydroxyethyl group. From the above-mentioned data, the structure of III was determined to be 2-benzoyl-3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methyl-perhydrofuro[2,3-d] thiazole. This structure was also determined with the authentic sample (6) by their IR comparisons. III was reduced to give IV, m.p. 151-153° in a quantitative yield by treatment with $NaBH_4$ in

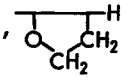
MeOH. The composition of IV corresponded to $C_{19}H_{24}O_2N_4S$ indicating the proceeding of reduction. Moreover, it showed the disappearance of C=O group in its IR spectrum. From the NMR spectral data [τ 2.07^s (1H, pm-C_6-H), 2.71^s (5H, ph), 3.9^b (2H, pm-C_4-NH_2), 5.0^d, 5.45^d (2H, >CH-$\overset{|}{C}$H-O-, J=3.3), 6.0^s (2H, bridge-CH_2-), 7.55^s (3H, pm-C_2-CH_3), 8.60^s (3H, th-C_4-CH_3)], it was clear that the tetrahydrofuran ring remained intact. The methyl signal at 8.60 shifted to a higher field, as much 0.28 p.p.m., than that of III, indicating that the th-C_4-CH_3 group of III was affected by the anisotropic effect of the benzoyl group. Accordingly, it was understandable that the benzoyl group at the C_2 position and the tetrahydrofuran ring might be taking trans configuration from each other. From the similar reaction of B_1-Na with acetaldehyde mentioned above, V was obtained as colorless crystals, m.p. 143-146°, along with the acetoin, and thiothiamine. V was easily decomposed to reproduce B_1 as well as III with diluted hydrochloric acid. The structure of V was confirmed on the basis of the following data: λ_{max}^{EtOH} mμ 236.5 (ε 9.442), 276.5 (ε 4.383); ν_{max}^{Nujol} cm^{-1}: 1720 (C=O), 1028 (C-O-C); τ in $CDCl_3$: 2.15^s (1H, pm-C_6-H), 3.95^b (2H, pm-C_4-NH_2), 6.13 (2H, py-CH_2-), 5.6-6.24^m, 7.45-8.1^m (5H, ), 7.51^s (3H, pm-C_2-CH_3), 7.95^s (3H, CH_3CO-), 8.34^s (3H, th-C_4-CH_3), and at 5.46^s (1H, th-C_2-H). I reacts similarly with isobutyraldehyde, and furfural to give corresponding products (VI, VII), respectively. The same result was obtained from the reaction of B_1-HCl with NEt_3 followed with aldehydes. In all of these cases mentioned above, no HET type products were detected even though reaction mixtures were treated with HCl by the similar method of Miller. On the contrary, from the reaction of B_1-HCl with 2-moles of NaOH followed with benzaldehyde in 50% MeOH in accordance with the method of Miller, colorless crystals (VIII) as HCl-salt (25%), m.p. 204-209° were obtained. VIII was fairly stable to acid and showed analytical data for $C_{19}H_{23}O_2N_4Cl \cdot HCl \cdot \frac{3}{2}H_2O$. UV and NMR spectra are described as follows: λ_{max}^{EtOH} mμ: 239, 270; τ in D_2O: 2.65^m (5H, ph), 3.29^s (1H, pm-C_6-H), 3.52^s (1H, ϕ-$\overset{|}{C}$H-OH), 4.64^s (2H, bridge CH_2-), 6.01^t, 6.77^t (4H, >CH_2-CH_2-O-, J=7.0), 7.52^s, 7.60^s (6H, CH_3X2) intern. ref. D.S.S. From the above-mentioned data, the structure of VIII was determined to be 2-hydroxybenzyl B_1. In this case, the presence of III was not detected entirely during the reaction, indicating III was not the precursor of VIII in this reaction condition at least. It became clear that B_1 has two different ways of the reaction modes with aldehydes. It may be considered from the above facts that the reaction obtaining HET and its homologues proceeds via B_1 ylid and that of the authors obtaining acyl B_1 derivatives rather

Chart 1

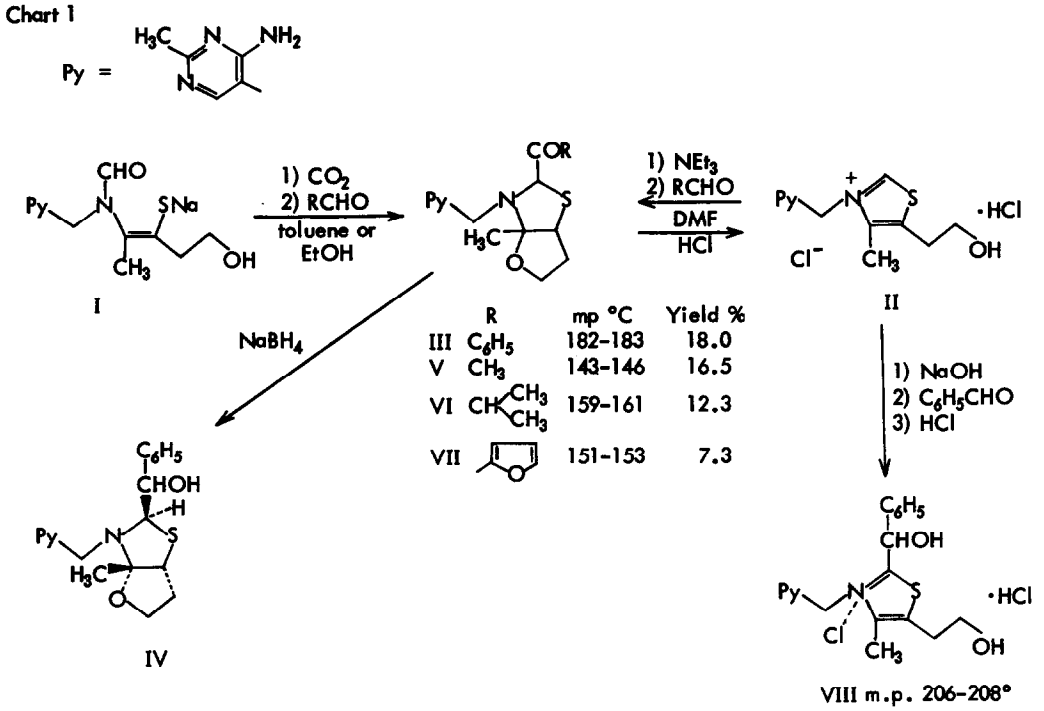
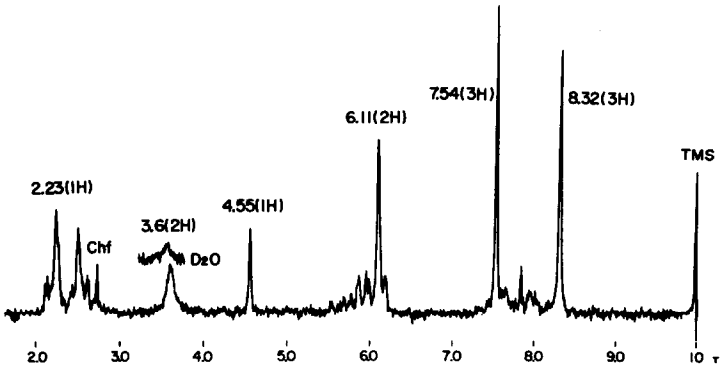


FIG. 1. NMR spectrum of III in $CDCl_3$ (60 Mc).



nucleophilic B_1 carbene. Metzger et al. (7) demonstrated that the reaction of thiazolium ylid or carbene with aldehydes generally proceeded to give acyl type products, however, an evidence was recently revealed that 2-(α-hydroxy)benzyl-3,4-dimethyl-5-(2-hydroxy)ethyl thiazolium iodide was obtained from the reaction of 3,4-dimethyl-5-(2-hydroxy)ethyl thiazolium iodide and benzaldehyde (8). These experiments

Chart 2

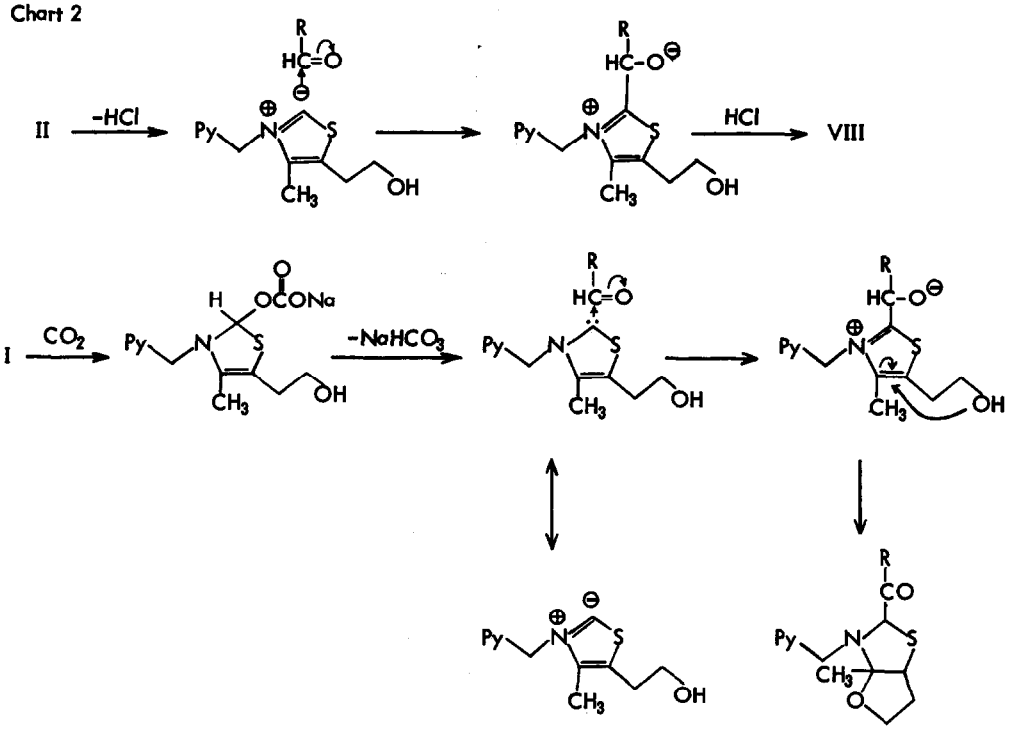
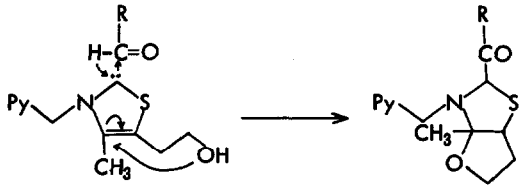


Chart 3



describe that no general correlation between chemical structures and products is established yet in the reaction of azolium compounds with aldehydes. Here, suggested mechanism for the production of acyl B_1 derivatives from I or II by the reaction with aldehydes is offered as shown in Chart 2, nevertheless, it can not be explained fully the evidence obtaining either acyl B_1 or hydroxy alkyl B_1 derivatives quite selectively. So the possibility of the insertion mechanism in this case may be also applicable to some extent (Chart 3). Details for these reactions will be reported and discussed in a full paper. This is the first one stating that both reaction modes proceed quite selectively. It may be considered to be greatly influenced by its complicated chemical structure.

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