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STUDIES ON PYRIMIDINE DERIVATIVES AND RELATED COMPOUNDS. LI.

REACTION OF THIAMINE WITH AMINES (I)

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It has been reported (1) that thiol-thiamine (B_1-Na) (I) reacted with 2-ry amines to give 2-(2-hydroxyethyl)-3,8-dimethyl-4-formyl-4,5-dihydro-1H-pyrimido[4,5-e]-1,4-diazepine (II) by loss of H_2S, and with 1-ry amines to give amine substitution products (III). During the course of the study on the reactivity of B_1-thiazole (B_1-th) C_2-position, the authors (2) found that the reaction of B_1 with aldehydes occurred at the thiazole C_2 position, along with the cyclization of 2-hydroxyethyl group forming a tetrahydrofuran ring, giving the 2-acyl-3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofurothiazoles. Recently, Metzger et al. (3) reported that the benzothiazolium salts reacted with piperidine to give C_2 substitution derivatives by way of ylid or carbene structure of benzothiazolium salts.

Investigation on the reaction of I with various amines has also been undertaken in our laboratory. After passing CO_2 gas into a toluene suspension of I under cooling (pH 8.0-7.5), 2 moles of morpholine were added and the mixture was stirred for 8 hrs. at room temperature. The light brown reaction mixture was concentrated and the residue was extracted with $CHCl_3$. From the extract, VII was obtained as colorless needles, m.p. 143-144° (decomp.) (4) in 78% yield, which showed analytical data for $C_{16}H_{25}N_5O_2S$ corresponding to the 1 : 1 adduct of thiamine and morpholine. From the UV spectrum [λ_{max}^{EtOH}: mμ 237 (ε 8,160), 278.5 (ε 5,580)] it was estimated that the pyrimidine nucleus might be a monocyclic system. IR spectrum showed absorption bands at 3310, 3132 (NH_2), 1672, 1593, 1514 (characteristics), 1112 (morpholine-O-), and 999 (which was anticipated to be due to an another ether bond). NMR (5) spectrum (FIG. 1) showed peaks at 8.42 being attributed to the 3a-methyl of perhydrofuro[2,3-d]thiazole nucleus, 5.6-8.1 (m, 5H) indicating the presence of tetrahydrofuran ring of -CH-CH_2-CH_2-O system, and 4.95 (s, 1H). When an aqueous hydrochloric acid solution of VII was allowed to stand at room temperature, B_1 and morpholine

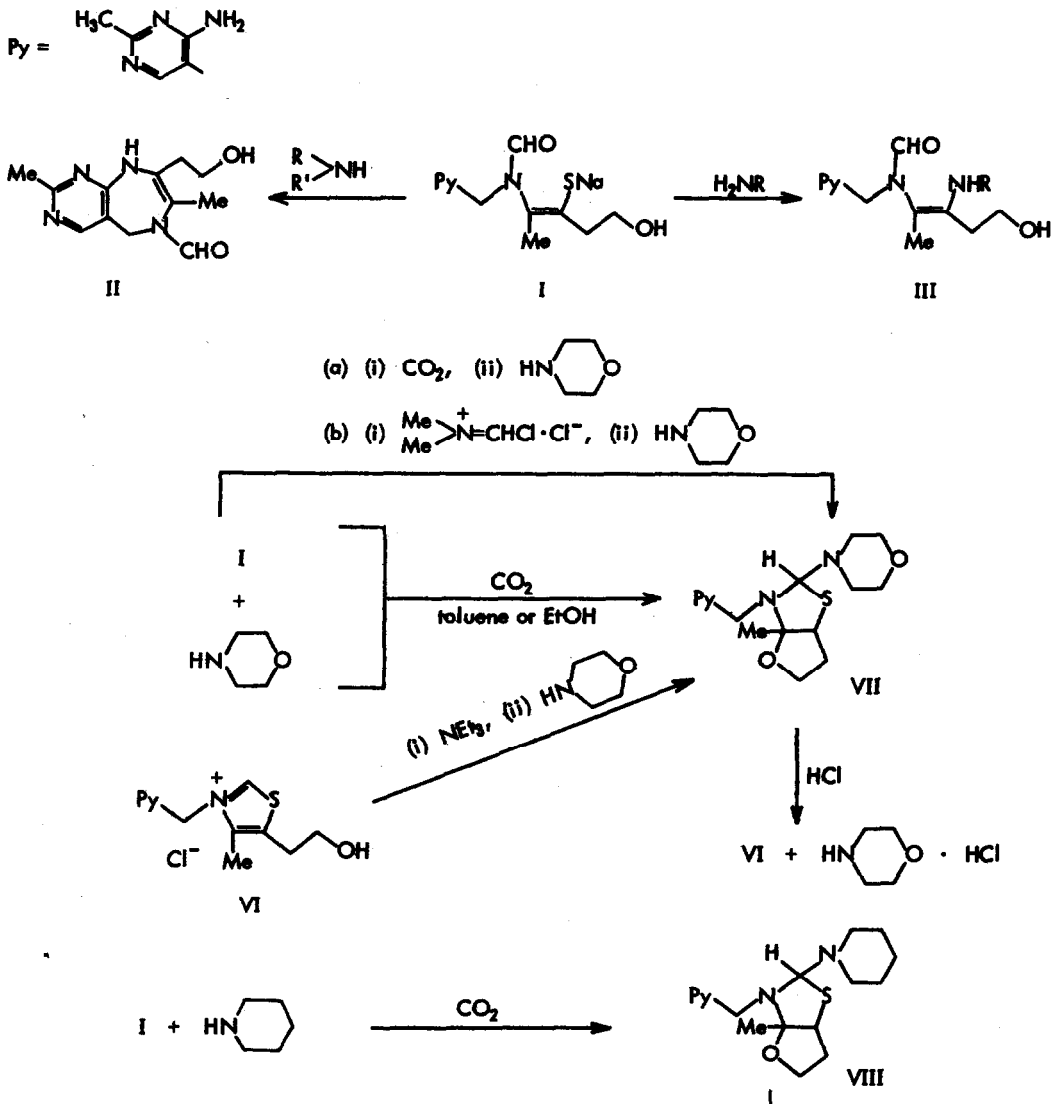
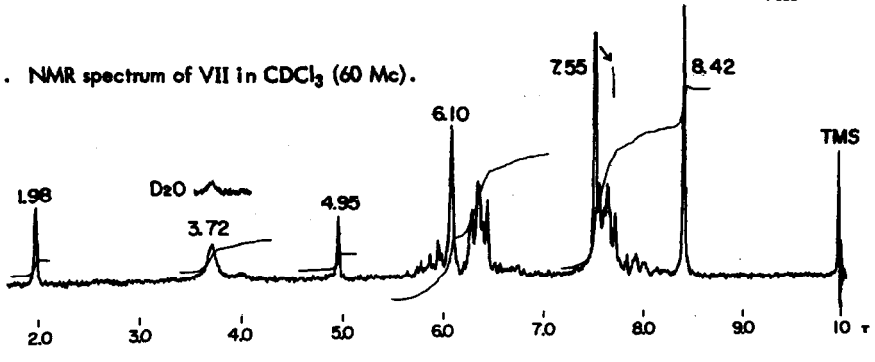
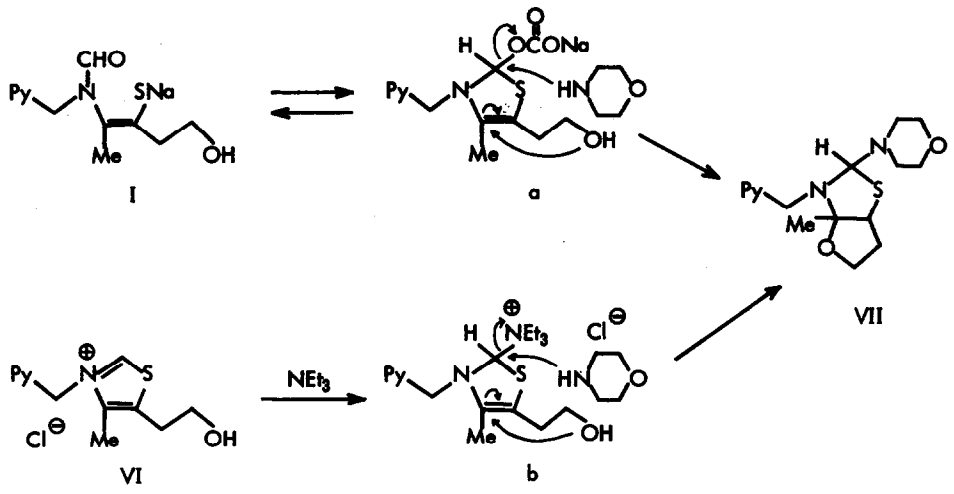


FIG. 1. NMR spectrum of VII in $CDCl_3$ (60 Mc).





were obtained in a quantitative yield. From the data mentioned above, the structure of VII was determined to be 2-morpholino-3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-d]thiazole. VII was also obtained either by the reaction of I with DMF-$COCl_2$ complex (6) followed by treatment with morpholine or the reaction of thiamine-HCl (VI) with NEt_3 followed with morpholine in good yields, respectively. It was found that the reaction of I or VI with piperidine proceeded quite analogously to give 2-piperidino-3-(2-methyl-4-aminopyrimidin-5-yl)methyl-3a-methylperhydrofuro[2,3-d] thiazole (VIII), m.p. 145-147° (decomp.), in 76% yield. The structure of VIII was confirmed on the basis of the following data: λ_{max}^{EtOH} 238.5 (ε 8,400), 280.5 mμ (ε 5,930), ν_{max}^{Nujol}: 3360, 1672, 1604, 1596, 1032 cm^{-1}, NMR signals at 1.96τ (s, 1H, pyrimidine C_6-H), 3.76 (b, 2H, pm-C_4-NH_2), 4.90 (s, 1H, thiazole C_2-), 6.10 (s, 2H, py-CH_2-), 7.55 (s, 3H, pm-C_2-CH_3), 8.46 (s, 3H, th-C_4-CH_3), 5.65-8.1 (m, 5H, cyclic >CH-CH_2-CH_2-O-), 7.63 (m, 4H, piperidine-CH_2-N-CH_2-), 8.52 (m, 6H, pip.-CH_2-CH_2-CH_2-). This reaction hardly proceeds in wet solvents. Moreover, it was nearly clarified that the reaction of aldehydes with B_1 proceeded by way of nucleophilic B_1-carbene. Details of these reactions are now being investigated. Tentative explanation for this reaction mechanism may be described as follows: it seems likely that the treating of CO_2 with I or NEt_3 with VI in anhydrous organic solvent may produce pseudo thiamine type a or b, which further proceed to give VII reacting with amines. This is the first time that amines were introduced at the thiazole C_2 position of B_1. This may be of use in considering the biological behavior of B_1.

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4. All melting points are uncorrected.
5. All NMR spectra were determined on a Varian A-60 in $CDCl_3$ containing tetramethylsilane as an internal reference.
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