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Studies on Pyrimidine Derivatives and Related Compounds. LXXXIII.[1] An Unusual Reaction of Thiamine Ylide with Diaryl Carbodiimide[2]

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Reaction of thiamine with diaryl carbodiimide was found to be quite different from that of the simple thiamine model compound giving unusual (1:2) adduct, S-[1-(2,7-dimethyl-8-aryl-9-arylimino-5,7,8,9-tetrahydroimidazo[1,5-*a*]pyrimido[4,5-*d*]pyrimidin-7-yl)-3-hydroxy-propyl]-N,N'-diaryl isothioureas (IIIa, IIIb). The structure of the (1:2) adduct was elucidated by chemical and spectroscopic evidences, and it was found that the (1:2) adduct (IIIa) underwent a novel acid-catalyzed decomposition reaction to give 7-methyl-2-(N-acetyl-N,N'-di-*p*-tolyl)amidino-1,4-dihydropyrimido[4,5-*d*]pyrimidine(VIIIa). Mechanistic consideration on these reactions was briefly made.

Thiamine ylide is known to be capable of forming various types of adduct with nucleophilic reagents.[4] Heterocumulenes such as isocyanate and isothiocyanate have been reported to react with thiamine and related thiazolium ylides giving (1:2) cycloadduct with a fused spiro cyclic system,[5] and, in the preceding paper, addition reactions of diaryl carbodiimides with thiamine model compounds were also described. In continuation of work related to the studies on nucleophilic reactivity of thiamine ylide, we have investigated the reaction of thiamine ylide with diaryl carbodiimide, and wish to report now that the behavior of thiamine ylide toward diaryl carbodiimide quite differs from that of the previously reported model compounds.[1]

Reaction of thiamine hydrochloride (I) with di-*p*-tolyl carbodiimide (DTCD) (IIa) in the presence of triethylamine (NEt_3) in N,N-dimethylformamide (DMF) afforded an yellow crystalline product (IIIa), mp 181—183° (decomp.), which was analyzed as $C_{42}H_{44}ON_8S \cdot H_2O$ in 35% yield. The molecular formula of IIIa corresponds to an (1:2) adduct of thiamine ylide with DTCD. Reaction of I with diphenyl carbodiimide (DPCD) also gave an (1:2) adduct (IIIb) ($C_{38}H_{36}ON_8S \cdot 2H_2O$, mp 162—164° (decomp.)). The structure of these adducts was elucidated as S-[1-(2,7-dimethyl-8-aryl-9-arylimino-5,7,8,9-tetrahydroimidazo[1,5-*a*]pyrimido[4,5-*d*]pyrimidin-7-yl)-3-hydroxypropyl]-N,N'-diaryl isothioureas (IIIa; Ar=*p*-tolyl, IIIb; Ar=phenyl) by the following chemical and spectroscopic evidences. Acetylation of IIIa by Ac_2O–pyridine yielded an acetate IVa, mp 174—176° (decomp.), which was also obtainable by the reaction of O-acetylthiamine hydrochloride (V) with DTCD under the same condition as employed for the reaction of I with DTCD, indicating that IIIa has a free hydroxyethyl group. Nuclear magnetic resonance (NMR) spectrum of IIIa showed no signal corresponding to pyrimidine-4-NH_2 group, while a methine proton of >CH–CH_2– system and a C–CH_3 group which possibly arised from the thiazolium C_4–CH_3 of thiamine were observed at τ 5.45[t] and τ 8.38[s] respectively. $NaBH_4$ reduction of IIIa afforded a dihydro deriva-

1) Part LXXXII: A. Takamizawa, S. Matsumoto, and S. Sakai, *Chem. Pharm. Bull.* (Tokyo), **22**, 299 (1974).
2) A part of this paper was presented at the 91st Assembly of the Pharmaceutical Society of Japan, Fukuoka, 1971, Abstracts of the papers, p. 657.
3) Location: *Fukushima-ku, Osaka, 553, Japan.*
4) A. Takamizawa, *Vitamins* (Kyoto), **47**, 1 (1973).
5) A. Takamizawa, K. Hirai, S. Matsumoto, and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **16**, 2130 (1968); *idem., ibid.*, **17**, 462 (1969); A. Takamizawa, K. Hirai, S. Matsumoto, S. Sakai, and Y. Nakagawa, *ibid.*, **17**, 910 (1969).

tive VIa ($C_{42}H_{46}ON_8S$, mp 161—164° (decomp.)) which showed a NMR signal at τ 4.90[s] due to a new methine proton. IIIa had an ultraviolet (UV) maximum at 352 mμ (log ε=4.02) due to a conjugated pyrimidine ring, whereas VIa exhibited a maximum at 284 mμ (log ε= 3.98) corresponding to the tetrahydropyrimidopyrimidine chromophore.[6] VIa was found to undergo auto-oxidation to regenerate IIIa in MeOH solution at room temperature, and it is partly decomposed to give a new compound VIIa ($C_{20}H_{22}ON_2S$, mp 121—122°). Infrared (IR) spectrum of VIIa showed a band at 1630 cm^{-1} due to C=N, and its NMR spectrum ex-

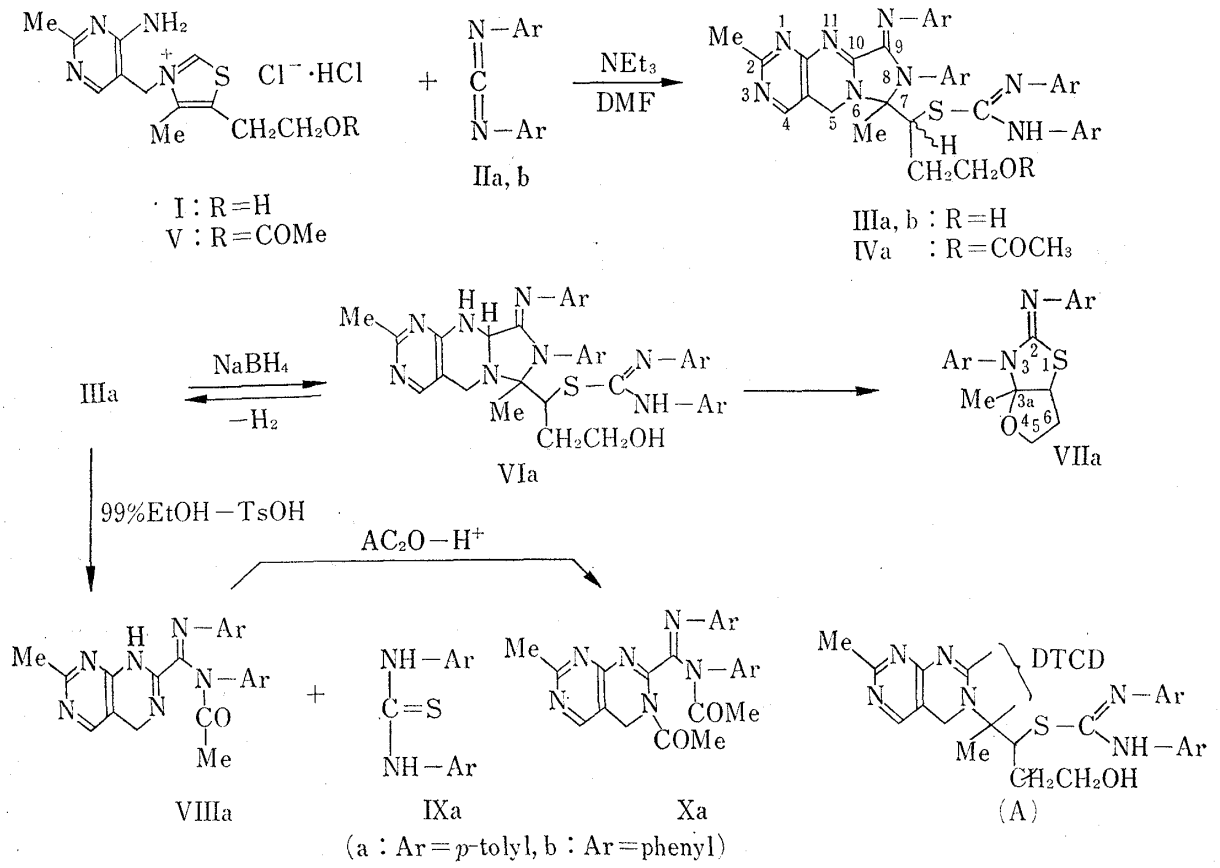


Chart 1

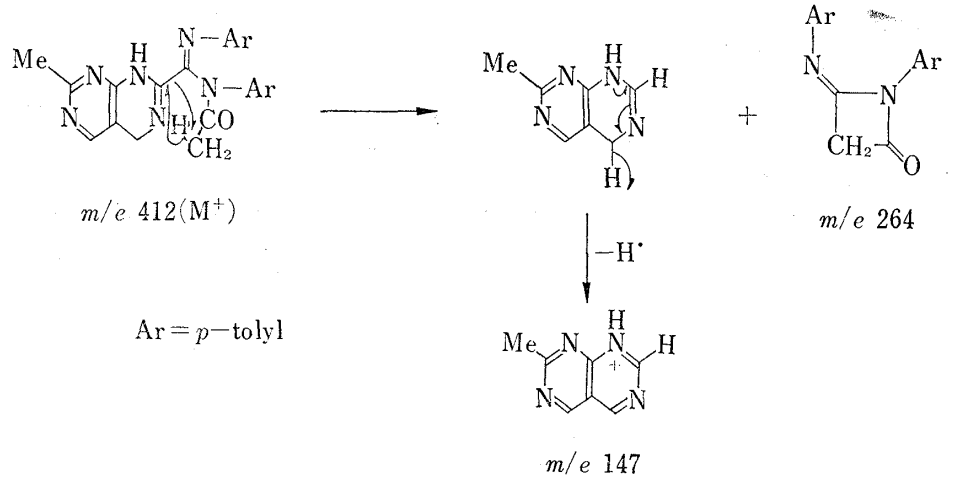


Chart 2

6) A. Takamizawa, K. Hirai, T. Ishiba, and I. Makino, *Chem. Pharm. Bull.* (Tokyo), **19**, 759 (1971).

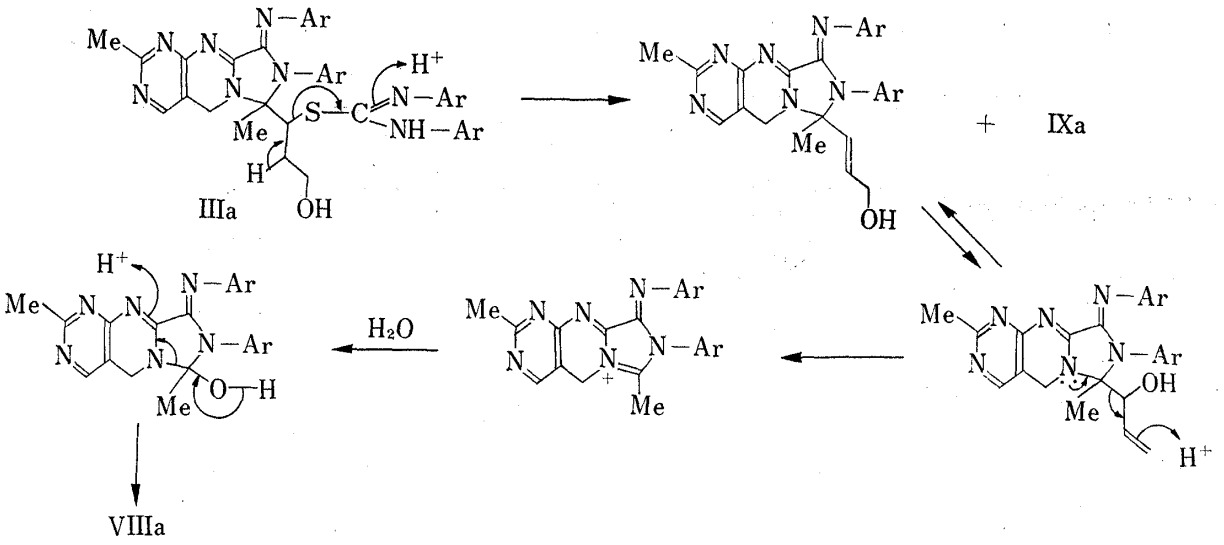


Chart 3

hibited, in addition to the peaks of two tolyl groups (τ 7.60^s, 7.53^s and τ 2.5—3.4^m) signals corresponding to a C–CH_3 (τ 8.48^s) and >$CHCH_2CH_2O$-system (τ 5.7—8.1^m), which are characteristic peaks known for 3a-methylperhydrofuro[2,3-*d*]thiazole ring system.[7] Therefore, the structure of VIIa could be assigned as 2-(*p*-tolyl)imino-3-*p*-tolyl-3a-methylperhydrofuro-[2,3-*d*]thiazole. These evidences cited so far indicate that IIIa should have a partial structure (A), and its full structure (IIIa) could thus be deduced by combining another molecule of DTCD to the partial formula (A). The structure IIIa was further supported by the following evidence. On heating in 99% EtOH in the presence of catalytic amount of *p*-toluenesulfonic acid, IIIa was decomposed to N,N'-di-*p*-tolyl thiourea (IXa) and a sulfur free compound (VIIIa) ($C_{24}H_{24}ON_6$) as an oil. Acetylation of VIIIa afforded a crystalline acetate (Xa), mp 231—232° (decomp.), which showed an UV maximum at 321 mμ (log ε=4.12) due to the conjugated pyrimidine ring. VIIIa had no UV maximum beyond 300 mμ, while it showed an IR band at 1680 cm^{-1} (film) corresponding to an amide carbonyl group. NMR spectrum of VIIIa showed signals due to four methyls (τ 7.45^s, 7.67^s, 7.76^s and 8.10^s), a methylene (τ 5.12^s), eight aryl protons (τ 2.8—3.4^m), pyrimidine-6-H (τ 1.90^s) and a NH proton (τ 1.43^{broad}). Mass spectrum of VIIIa exhibited a molecular ion peak at *m/e* 412 and prominent fragment ions at a) *m/e* 370, b) *m/e* 369, c) *m/e* 264 (base peak) and d) *m/e* 147. The ions a) and b) correspond to M^+–$COCH_2$ and M^+–$COCH_3$ respectively, and the ions c) and d) are considered to be occured by the fragmentations shown in the Chart 2. On the basis of these spectral evidences the structure of VIIIa could be established as 7-methyl-2-(N-acetyl-N,N'-di-*p*-tolyl)amidino-1,4-dihydropyrimido[4,5-*d*]pyrimidine. It is of particularly notable that the acid-catalyzed decomposition of IIIa yielded VIIIa which bears a N-acetyl group. This acetyl group should be originated from the C_7–CH_3 group in IIIa, and a plausible mechanism of the decomposition reaction can be illustrated in the Chart 3. From the mechanistic consideration, the formation of VIIIa from IIIa, therefore, requires IIIa to have an imidazo[1,5-*a*]-pyrimido[4,5-*d*]pyrimidine ring, and the structure of IIIa is thus supported. Theoretically, one diastereoisomer of IIIa can exist, since it has two asymmetric carbons. An epimer, mp 156—157°, could indeed be isolated by fractional crystallization from the mother liquor of IIIa, although only in a small quantity. UV spectrum of the epimer was found to be superimposable to that of IIIa, while its NMR showed the C_7–CH_3 signal at τ 8.31^s which slightly differs from that of IIIa.

7) A. Takamizawa, K. Hirai, Y. Hamashima, S. Matsumoto, and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **16**, 1210 (1968).

The anomality of the reaction of thiamine with diaryl carbodiimide is apparently caused by the intramolecular participation of pyrimidine-4-NH_2 group, which is interesting with regard to the recent theory[8,9] for the mechanism of thiamine catalyzed biochemical reactions where the participation of pyrimidine-4-NH_2 group has been suggested to play an important role. In the case of the reaction of thiamine model compound with diaryl carbodiimide, it has been shown that the bulkiness of the substituent at thiazolium-3 position markedly inhibited the 1,3-dipolar cycloaddition reaction of the (1:1) adduct. In the present reaction, the normal (1: 1) adduct (B) will be initially formed, but the pyrimidinyl methyl moiety in (B) is considered to have a significant steric hindrance for the formation of the normal (1: 2) cycloadduct (C), and the pyrimidine-4-NH_2 group cyclizes to give a tricyclic intermediate (D) as known for the reaction of thiamine derivatives with dialkyl acylphosphonates.[10] The tricyclic intermediate (D) will then undergo ring opening with C–S bond fission to give sulfide anion which adds to the another molecule of DTCD to give (E), and the subsequent cyclization of an arylimino group to the carbon-carbon double bond in (E) will lead to the final product.

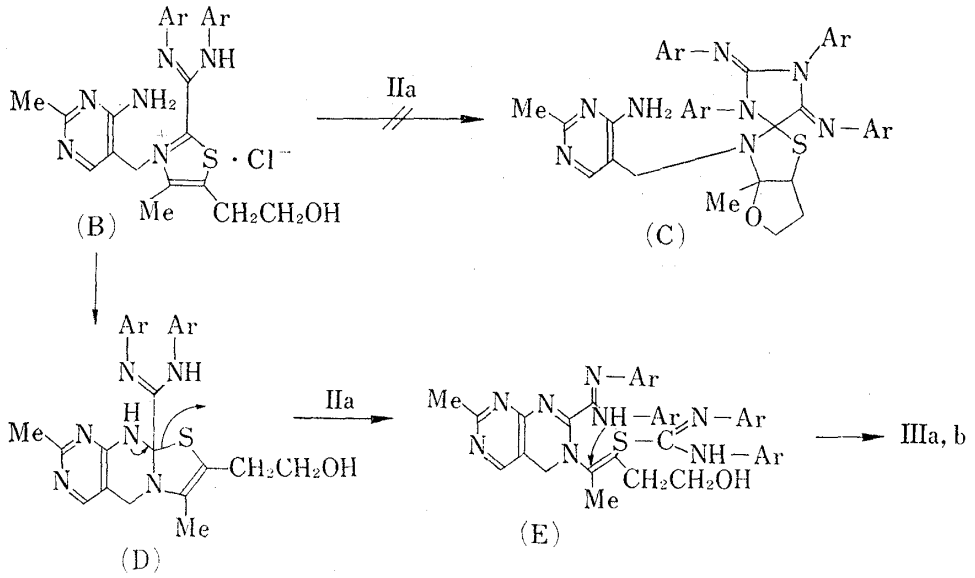


Chart 4

Experimental

All melting points were determined in capillaries and uncorrected. NMR spectra were taken on a Varian Associates A-60 spectrometer in $CDCl_3$ or d_6-DMSO solution with tetramethylsilane (TMS) as an internal standard. UV spectra were taken on a Hitachi EPS-3 spectrophotometer in 99% EtOH. IR spectra were taken in nujol mull on a Japan Spectroscopic Company IR-S spectrophotometer using a NaCl prism unless otherwise indicated. Mass spectrum was taken on a Hitachi RMU-7 mass spectrometer by direct inlet system with ionizing energy 70 eV and ionizing current 80 μA. Column chromatographies were carried out by using SiO_2 (Davision, grade 950).

S-[1-(2,7-Dimethyl-8-*p*-tolyl-9-*p*-tolylimino-5,7,8,9-tetrahydroimidazo[1,5-*a*]pyrimido[4,5-*d*]pyrimidin-7-yl)-3-hydroxypropyl]-N,N′-di-*p*-tolyl Isothiourea (IIIa)——To a suspension of thiamine hydrochloride (I) (3.3 g) in DMF (40 ml) was added NEt_3 (4.0 g), and the mixture was stirred for 30 min at room temperature. Then di-*p*-tolyl carbodiimide (IIa) (4.44 g) was added and the reaction mixture was stirred for 6 hr at 40—45°. After evaporation of DMF *in vacuo*, the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over abs. Na_2SO_4 and evaporated to give an yellow oily residue which crystallized by

8) G.E. Risinger and M.F. Dove, *Chem. Ind.* (London), **1965**, 510.
9) A. Schellenberger, *Angew. Chem.*, **79**, 1050 (1967).
10) A. Takamizawa and H. Satoh, *Chem. Pharm. Bull.* (Tokyo), **18**, 1201 (1970); A. Takamizawa and H. Harada, *ibid.*, **18**, 1402 (1970).

addition of small amount of acetone. The crystals were collected and recrystallized from acetone–MeOH to give IIIa (2.48 g, 35%) as yellow prisms, mp 181—183° (decomp.). *Anal.* Calcd. for $C_{42}H_{44}ON_8S \cdot H_2O$: C, 69.38; H, 6.37; N, 15.42; S, 4.41. Found: C, 69.66; H, 6.48; N, 15.57; S, 4.08. UV λ_{max} mμ (log ε): 352 (4.02). NMR ($CDCl_3$, τ): 8.38^s (3H, C_7–CH_3), 5.45^t (1H, >C<u>H</u>–CH_2–). The mother liquor of IIIa was concentrated *in vacuo* to give a crystalline residue which was dissolved in hot acetone and a small amount of insoluble materials were removed by filtration. The filtrate was then allowed to stand for 3 days at room temperature, and the deposited yellow crystals were collected to give an epimer (52 mg) as yellow prisms, mp 156—157°. *Anal.* Calcd. for $C_{42}H_{44}ON_8S$: C, 71.15; H, 6.26; N, 15.81; S, 4.52. Found: C, 71.01; H, 6.39; N, 15.76; S, 4.61. UV λ_{max} mμ (log ε): 352 (4.02). NMR ($CDCl_3$, τ): 8.31^s (3H, C_7–CH_3).

S-[1-(2,7-Dimethyl-8-phenyl-9-phenylimino-5,7,8,9-tetrahydroimidazo[1,5-*a*]pyrimido[4,5-*d*]pyrimidin-7-yl)-3-hydroxypropyl]-N,N′-diphenyl Isothiourea (IIIb)——Thiamine hydrochloride (I) (3.3 g) and diphenyl carbodiimide (IIb) (3.88 g) were allowed to react according to the procedure employed for the reaction of (I) with IIa. After concentration of the reaction mixture, the resulting residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over abs. Na_2SO_4 and concentrated to give a crystalline residue which was recrystallized from acetone–MeOH to give IIIb (1.23 g, 18%) as yellow prisms, mp 162—164° (decomp.). *Anal.* Calcd. for $C_{38}H_{36}ON_8S \cdot 2H_2O$: C, 66.43; H, 5.58; N, 16.30; S, 4.92. Found: C, 66.90; H, 5.60; N, 16.07; S, 5.00. UV λ_{max} mμ (log ε): 352 (4.01). NMR (d_6-DMSO, τ): 8.28^s (3H, C_7–CH_3).

S-[1-(2,7-Dimethyl-8-*p*-tolyl-9-*p*-tolylimino-5,7,8,9-tetrahydroimidazo[1,5-*a*]pyrimido[4,5-*d*]pyrimidine-7-yl)-3-acetoxypropyl]-N,N′-di-*p*-tolyl Isothiourea (IVa)——a) IIIa (1.5 g) was dissolved in the mixture of Ac_2O (10 ml) and pyridine (40 ml), and the solution was stirred for 6 hr at room temperature. After standing overnight, the reaction mixture was concentrated *in vacuo* to give a crystalline residue which was recrystallized from acetone to give IVa (1.35 g, 85%) as yellow prisms, mp 174—176° (decomp.). *Anal.* Calcd. for $C_{44}H_{46}O_2N_8S$: C, 70.40; H, 6.05; N, 14.94; S, 4.28. Found: C, 70.04; H, 6.08; N, 14.83; S, 4.54. IR ν_{max}^{Nujol} cm^{-1}: 1740 (C=O).

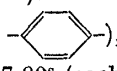
b) O-Acetylthiamine hydrochloride (V) (3.74 g) and di-*p*-tolyl carbodiimide (IIa) (4.44 g) were allowed to react according to the procedure employed for the reaction of I with IIa to give IVa (3.38 g, 45%) which was identified with the compound obtained by the method a) by comparison of their IR spectra.

$NaBH_4$ Reduction of IIIa——To a suspension of IIIa (500 mg) in MeOH (30 ml) was added $NaBH_4$ (40 mg) with vigorous stirring in an ice bath. After stirring for 20 min at 0—5°, the reaction mixture was concentrated *in vacuo* to give a residue which was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over abs. Na_2SO_4 and concentrated *in vacuo* to give a pale yellow residue which was chromatographed with SiO_2–AcOEt system. The first eluate afforded an unidentified oily mixture (120 mg), and the second eluate afforded VIa (230 mg, 45%) as an essentially pure crystalline residue which was washed with ether and dried to give pale yellow crystalline prisms, mp 161—164° (decomp.). *Anal.* Calcd. for $C_{42}H_{46}ON_8S$: C, 70.95; H, 6.53; N, 15.76; S, 4.51. Found: C, 70.77; H, 6.41; N, 15.63; S, 4.72. UV λ_{max} mμ (log ε): 284 (3.98). NMR ($CDCl_3$, τ): 4.90^s (1H, ).

Auto-oxidation and Decomposition of VIa——VIa (120 mg) was dissolved in MeOH (20 ml) by warming at 50—70°, then the solution was stirred for 20 hr at room temperature. After evaporation of MeOH *in vacuo*, acetone was added to the residue and the deposited crystals were collected to give IIIa (14 mg, 12%) which was identified with the authentic sample by IR comparison. The acetone mother liquor was concentrated to give an oily residue consisting of more than two products which was then submitted to a preparative thin layer chromatography by using SiO_2 plate–AcOEt, and a zone of *Rf ca.* 0.55 was cut to give 2-*p*-tolylimino-3-*p*-tolyl-3a-methylperhydrofuro[2,3-*d*]thiazole (VIIa) (22 mg, 39%) as a colorless crystalline solid, mp 121—122°. *Anal.* Calcd. for $C_{20}H_{22}ON_2S$: C, 70.98; H, 6.55; N, 8.28; S, 9.45. Found: C, 70.63; H, 6.66; N, 8.11; S, 9.67. IR ν_{max}^{Nujol} cm^{-1}: 1630 (C=N). NMR ($CDCl_3$, τ): 2.5—3.4^m (8H, 2× ), 5.7—8.1^m (5H, >C<u>H</u>CH_2CH_2O–), 7.53^s, 7.60^s (each 3H, 2×Ar–CH_3), 8.48^s (3H, C_{3a}–CH_3).

7-Methyl-2-(N-acetyl-N,N′-di-*p*-tolyl)amidino-1,4-dihydropyrimido[4,5-*d*]pyrimidine (VIIIa)——To a suspension of IIIa (1 g) in 99% EtOH (50 ml), 5 mg of *p*-toluenesulfonic acid was added, and the mixture was refluxed for 4 hr. After standing overnight at room temperature, the reaction mixture was concentrated to give a residue to which 10% aq. K_2CO_3 solution (20 ml) was added, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over abs. $MgSO_4$ and concentrated to give an oily residue which was chromatographed with SiO_2–AcOEt. The first AcOEt eluate afforded 81 mg (30%) of N,N′-di-*p*-tolyl thiourea (IXa) which was identified with authentic sample by IR comparison. The second eluate afforded VIIIa (85 mg, 14%) as an essentially pure yellow oil. *Anal.* Calcd. for $C_{24}H_{24}ON_6$: C, 69.87; H, 5.87; N, 20.89. Found: C, 69.59; H, 5.72; N, 20.91. IR ν_{max}^{film} cm^{-1}: 1680 (C=O). NMR ($CDCl_3$, τ): 1.43^{broad} (1H, NH), 1.90^s (1H, pyrimidine-6-H), 2.8—3.4^m (8H, 2× ), 5.12^s (2H, pyrimidine-5-CH_2–), 7.45^s, 7.67^s, 7.76^s (each 3H, pyrimidine-2-CH_3 and/or 2×Ar–CH_3), 8.10^s (3H, $COCH_3$). Mass Spectrum *m/e* (percent to base peak): 412 (60), 370 (40), 369 (70), 264 (base peak), 147 (95).

Acetylation of VIIIa——70 mg of VIIIa was dissolved in the mixture of Ac_2O (3 ml) and pyridine (3 ml). To the solution was added 5 mg of *p*-toluenesulfonic acid, and allowed to stand for 18 hr at room temperature.

The reaction mixture was concentrated *in vacuo* to give a crystalline residue which was washed with acetone and recrystallized from acetone to give Xa (54 mg, 70%) as orange prisms, mp 231—232° (decomp.). *Anal.* Calcd. for $C_{26}H_{26}O_2N_6$: C, 68.70; H, 5.76; N, 18.49. Found: C, 68.77; H, 5.68; N, 17.95. IR ν_{max}^{Nujol} cm^{-1}: 1707, 1693 (C=O). UV λ_{max} mμ (log ε): 321 (4.12). NMR ($CDCl_3$, τ): 1.77^s (1H, pyrimidine-6-H), 2.65—3.45^m (8H, 2× ), 5.97 (2H, ABq, J=7.5 Hz, Δ_{AB}=15 Hz, pyrimidine-5-CH_2), 7.30^s (3H, pyrimidine-2-CH_3), 7.61^s, 7.80^s (each 3H, 2×Ar–CH_3), 7.82^s, 8.05^s (each 3H, 2×$COCH_3$).