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# Studies on Pyrimidine Derivatives and Related Compounds. LXXI.[1] Reaction of Thiamine Anhydride with Thiols[2]

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Reactions of thiamine anhydride with various kind of thiophenols were carried out. Disulfide, pyrimido[4,5-*e*][1,4]diazepine, and $SB_1$ type of derivatives were separated. Products distribution was dependent on the $pK_a$ of thiol reacted. The present study reveals new routes to novel thiamine derivatives.

In the preceding report,[1] we described the first example of a reaction of thiamine anhydride (I). This report describes other examples of various types of reaction of I with thiols.

When I was allowed to react with thiophenol in dimethyl formamide (DMF) at room temperature, compound IIb, mp 107—110°, and compound IIIb, mp 148—150°, were obtained in 29 and 34% yield, respectively. Compound IIb has a molecular formula, $C_{24}H_{28}ON_4S_3$, *i.e.*, two moles of thiophenol more than I. Compound IIIb has a molecular formula, $C_{18}H_{20}ON_4S$, equivalent to one mole of thiophenol added to a mole of I from which one mole of $H_2S$ has been lost. The ultraviolet (UV) spectrum of IIb shows shoulders at 237, 257, and 280 mμ, however, IIIb shows absorption maxima at 254 and 305 mμ. The nuclear magnetic resonance (NMR) spectrum[4] of IIb suggests the presence of a $CH_3$-CH< system ($CH_3$-CH<, $\tau$ 8.83, 3H-doublet, $J$=6.5 Hz; $C_2$-methylene, $\tau$ 7.7—8.5, 2H-multiplet, $C_3$-H, $C_4$-H, $C_1$-methylene, $\tau$ 6.2—7.3, 4H-multiplet; pyrimidine $C_2$-$CH_3$, $\tau$ 7.53, 3H-singlet; bridged methylene, $\tau$ 6.15, 5.88, 5.60, 5.33, 2H-AB quartet, $NH_2$, $\tau$ 3.97, deuterium exchangeable 2H-broad singlet). The mass spectrum[5] of IIb shows characteristic ion peaks at *m/e* 122 (base peak, which appears as one of the major peaks in the compounds having (4-amino-2 methyl-5-pyrimidinyl)methyl group[6]), 123 ($CH_2=\overset{+}{S}C_6H_5$), and 375 ($M^+$-$SC_6H_5$) indicating that the phenylthio group attached to the ethyl group. These results suggest the structure N-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-N-[(1-methyl-2-(phenyldithio)-4-(phenylthio)]butyl]formamide for compound IIb. The NMR spectrum of IIIb shows no $NH_2$ signal but a >NH signal appears (2-$CH_3$, $\tau$ 7.45, 3H-singlet; 7-$CH_3$, $\tau$ 7.97, 3H-singlet; 8-$CH_2CH_2$, $\tau$ 7.37, 6.75, 2H-triplets, $J$=7 Hz; 5-methylene, $\tau$ 5.62, 2H-singlet; NH, $\tau$ 3.42 deuterium exchangeable 1H-broad singlet; $C_6H_5$, $\tau$ 2.80, 5H-broad singlet). The mass spectrum of IIIb shows no peak at *m/e* 122 but shows characteristic peaks at *m/e* 340 ($M^+$), 311 ($M^+$-CHO), 231 ($M^+$-$SC_6H_5$), 217 ($M^+$-123), and 123 ($CH_2=\overset{+}{S}$-$C_6H_5$). The UV spectrum of IIIb shows maxima at 254 and 305 mμ (log ε 4.08, 3.97). These results suggest the structure 2,7-dimethyl-6-formyl-8-(2-phenylthioethyl)-5,6-dihydro-9*H*-pyrimido-[4,5-*e*][1,4]diazepine for compound IIIb.

1) Part LXX: A. Takamizawa, K. Hirai, and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **19**, 1022 (1971).
2) A part of this work has appeared in a preliminary form: *Tetrahedron Letters*, **1970**, 437.
3) Location: *Fukushima-ku, Osaka.*
4) NMR spectra were taken with a Varian A-60 spectrometer in $CDCl_3$ containing TMS as an internal reference. Chemical shifts are given as $\tau$ values.
5) Mass spectra were taken with a Hitachi RMU-6E mass spectrometer using a direct inlet system with the ionizing energy at 70 eV and the ionizing current at 80 μA.
6) Y. Oka, S. Kishimoto, and H. Hirano, *Chem. Pharm. Bull.* (Tokyo), **18**, 534 (1970).

The reaction of I with *p*-thiocresol under the same conditions gave the compound IIa, mp 83—83.5°, and the compound IIIa, mp 104—107°, in 35 and 27% yields, respectively. The NMR and mass spectra of IIa gave the similar spectra as those of IIb except for tolyl group instead of phenyl group. Therefore, the compound IIa is the dithio compound. The mass spectrum of IIIa is analogous with that of IIIb and corresponds well to a tolylthioethyl pyrimidodiazepine compound. The NMR spectrum of IIIa also suggests the structure for a tolylthioethyl pyrimidodiazepine compound, however, spectrum taken at room temperature in $d_6$-DMSO shows NH, N-CHO, bridged methylene, and $CH_3$-Ċ=Ċ- signals as two signals, respectively, indicating that this compound is a mixture of isomers in about a 2.5:1 ratio (Fig. 1). This may be ascribed to the presence of isomers due to rotational inhibition around the C-N bond in the N-CHO group.[7] Temperature dependence of the spectrum at 90°, at which temperature the difference in chemical shifts between the two isomers had decreased, and at 120° the two signals collapsed to a singlet (Fig. 1).

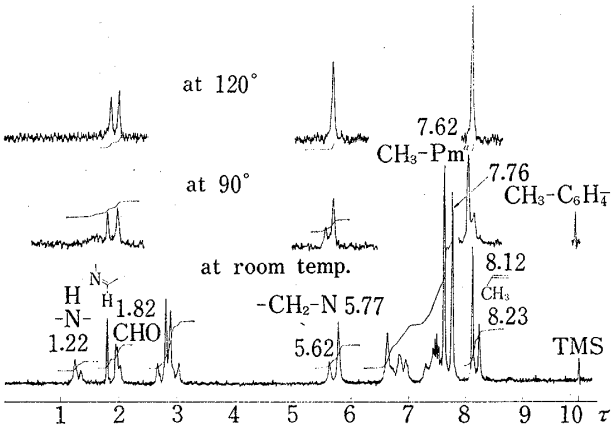


Fig. 1. NMR Spectra of IIIa in $d_6$-DMSO at Different Temperatures

a) Pm=pyrimidine

The reaction of I with *p*-nitrothiophenol in DMF gave the compound IVd, mp 217—220° (decomp.), in 61% yield accompanied by *p*,*p*'-nitrophenyldisulfide and *p*,*p*'-nitrophenylsulfide. The elemental analysis and mass spectrum showed the structural formula $C_{18}H_{19}O_2N_5S_3$. The UV spectrum showed a strong absorption maximum at 329 mμ (log ε 4.40) indicating a pyrimidinylmethylthiazolinethione ($SB_1$) type. Therefore, the structure of IVd was considered to be *p*-nitrophenylthioethyl $SB_1$, and the structure was confirmed by the synthesis from chloroethyl $SB_1$ (VIII) and *p*-nitrothiophenol in DMF.

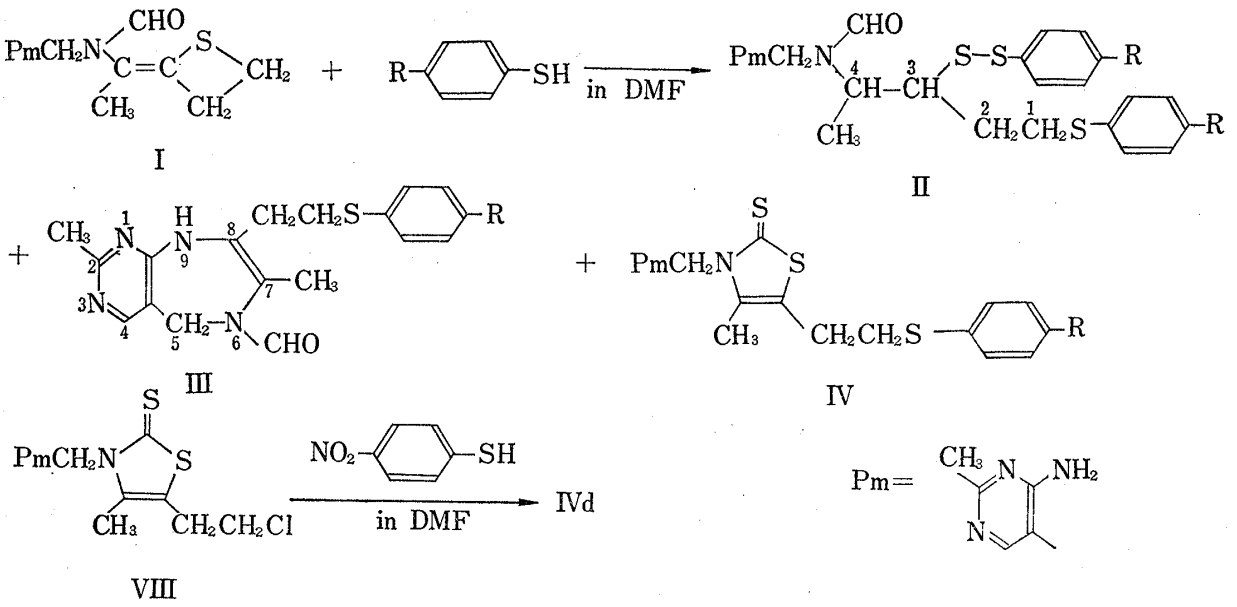


Chart 1

7) L.A. Laplanche and M.T. Rogers, *J. Am. Chem. Soc.*, **86**, 337 (1964); *idem*, *ibid.*, **85**, 3728 (1963).

The reaction of I with *p*-bromothiophenol gave the pyrimidodiazepine compound IIIc and the $SB_1$ type compound IVc in 13 and 12% yield, respectively. In this reaction, addition of piperidine increased the yield of IIIc and decreased that of IVc giving a ratio of 21: 6.4.

Correlation of the p*K*a values of thiols used with product distribution (Table I) revealed that thiols having large p*K*a values give dithio compounds but more acidic thiols afford $SB_1$-type compounds preferentially, and pyrimidodiazepine compounds are yielded by medium p*K*a thiols.

Table I. p$K_a$'s of Thiols and Yields of Products

| R-⟨⟩-SH | | p$K_a$[a] | II (%) | III (%) | IV (%) |
|---|---|---|---|---|---|
| a | R=$CH_3$ | 8.03 | 35 | 27 | — |
| b | R=H | 7.76 | 29 | 34 | — |
| c | R=Br | 6.99 | — | 13 | 12 |
| d | R=$NO_2$ | 5.11 | — | — | 61 |

a) F.G. Bordwell and H.W. Anderson, *J. Am. Chem. Soc.*, **75**, 6019 (1953)

A proposed mechanism involves the addition of thiol to the vinyl group giving VI, while attack of thiol to the tautomeric thioketone VII affords the dithio compound II. Removal of $H_2S$ from VI gives the pyrimidodiazepine compound III[8] and $SB_1$ compound VI is produced *via* the pseudo base IX. These reaction pathways are significantly dependent upon subtle pH differences of the reaction mixtures leading to the formation of three type of products.

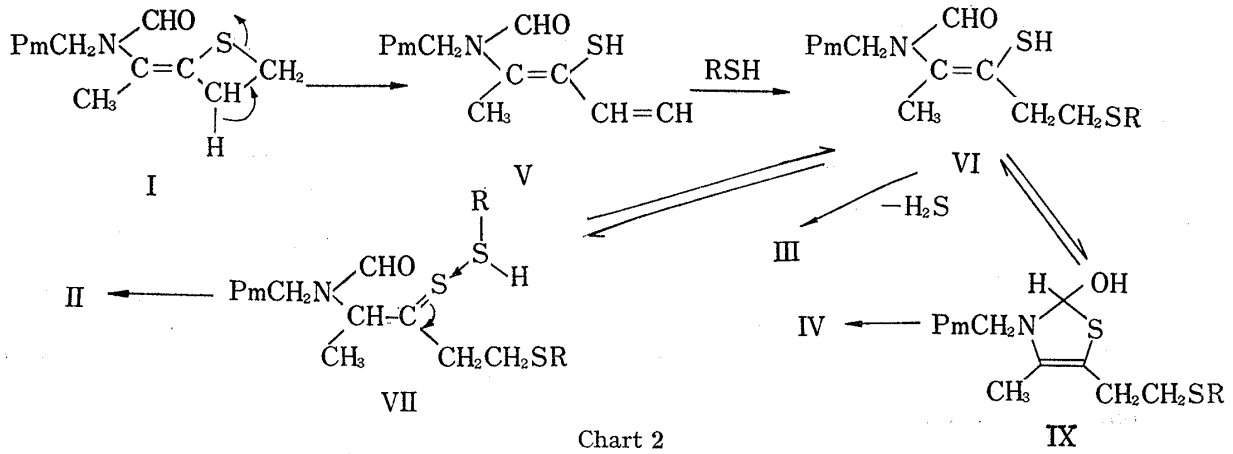


Chart 2

The acidity of thiol used affects the pH of the reaction mixture, a strongly acidic thiol having tendency to incline the equiliblium to a pseudo base IX, thiolation occuring to give $SB_1$ type compound IV. However, when the acidity of the thiol used is not so strong, the inclination toward the pseudo base is inhibited, and conversely, the inclination toward thioketone VII is favored giving the dithio compound II. Pyrimidodiazepine III is formed accompanied by II and IV under conditions where thiol type VI is formed.

## Experimental[9]

**N-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-N-{[1-methyl-2-(phenyldithio)-4-(phenylthio)]butyl}formamide (IIb) and 2,7-Dimethyl-6-formyl-8-(2-phenylthioethyl)-5,6-dihydro-9*H*-pyrimido[4,5-*e*][1,4]diazepine (IIIb)**——To a solution of 0.75 g of thiamine anhydride $2H_2O$ (I) in 10 ml of DMF was added 0.83 g of thiophenol. After stirring for 1 hr at room temp., stirring was continued for 6 hr at 60° and allowed to stand overnight at room temp. The reaction mixture was concentrated *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with $H_2O$, dried over anhyd. $Na_2SO_4$, and evaporated. The residue was chromatographed over silica gel. Elution with acetone gave 0.35 g (29%) of IIb. Recrystal-

8) H. Hirano, *Yakugaku Zasshi*, **77**, 1007 (1957).
9) All melting points were not corrected.

lization from acetone gave colorless prisms of mp 107—110°. *Anal.* Calcd. for $C_{24}H_{28}ON_4S_3$: C, 59.49; H, 5.83; N, 11.56; S, 19.88. Found: C, 59.45; H, 5.78; N, 11.45; S, 19.88. UV $\lambda_{max}^{EtOH}$ m$\mu$ (log $\varepsilon$): 237 (sh), 257 (sh), 280 (sh) (4.26, 4.07, 3.87). Mass Spectrum *m/e*: 484 ($M^+$), 375 ($M^+$-$SC_6H_5$), 123 ($CH_2{=}\overset{+}{S}C_6H_5$), 122 (base peak). NMR $\tau$: 8.83 (3H, d, $J$=6.5 Hz, $C\underline{H}_3$-CH<), 7.53 (3H, s, Pm-2-$CH_3$), 6.15, 5.88, 5.60, 5.33 (2H, AB q, $CH_2$-N), 3.97 (2H, b, $NH_2$), 2.07 (1H, s, CHO), 2.00 (1H, s, Pm-6-H).

Following elution with acetone gave 0.29 g (34%) of IIIb. Recrystallization from AcOEt gave colorless prisms of mp 148—150° (decomp.). *Anal.* Calcd. for $C_{18}H_{20}ON_4S$: C, 63.51; H, 5.92; N, 16.46; S, 9.42. Found: C, 63.40; H, 5.73; N, 16.19; S, 9.47. UV $\lambda_{max}^{EtOH}$ m$\mu$ (log $\varepsilon$): 254, 305 (4.08, 3.97). NMR $\tau$: 7.97 (3H, s, 7-$CH_3$), 7.45 (3H, s, 2-$CH_3$), 7.37 (2H, t, $J$=7 Hz), 6.75 (2H, t, $J$=7 Hz, 8-$CH_2CH_2$), 5.62 (2H, s, 5-$CH_2$), 3.42 (1H, b, NH), 1.83 (1H, s), 1.75 (1H, s, 3-H, CHO). Mass Spectrum *m/e*: 341 ($M^+$+1), 340 ($M^+$) (base peak), 311 ($M^+$-CHO), 231 ($M^+$-$C_6H_5S$), 217 ($M^+$-$CH_2SC_6H_5$), 123 ($M^+$-217).

**N-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-N-[(1-methyl-2-(*p*-tolyldithio)-4-(*p*-tolylthio)]butyl]formamide (IIa) and 2,7-Dimethyl-6-formyl-8-(2-*p*-tolylthioethyl)-5,6-dihydro-9*H*-pyrimido[4,5-*e*][1,4]diazepine (IIIa)**——To a solution of 0.75 g of I in 10 ml of dimethyl formamide (DMF) was added 0.93 g of *p*-thiocresol and worked up as above. Silica gel chromatography with acetone gave 0.45 g (35%) of IIa. Recrystallization from ether gave colorless prisms of mp 83—83.5°. *Anal.* Calcd. for $C_{26}H_{32}ON_4S_3$: C, 60.92; H, 6.29; N, 10.93; S, 18.73. Found: C, 60.84; H, 6.29; N, 10.99; S, 18.76. UV $\lambda_{max}^{EtOH}$ m$\mu$ (log $\varepsilon$): 239 (sh), 255 (sh), 275 (sh) (4.21, 3.98, 3.78). NMR $\tau$: 8.87 (3H, d, $J$=7 Hz, $C\underline{H}_3$-CH<), 7.72 (6H, s, 2X *p*-$C\underline{H}_3$-$C_6H_5$), 7.55 (3H, s, Pm-2-$CH_3$), 6.17, 5.92, 5.62, 5.37 (2H, AB q, N-$CH_2$), 3.97 (2H, b, $NH_2$), 2.08 (1H, s, CHO), 2.03 (1H, s, Pm-6-H). Mass Spectrum *m/e*: 512 ($M^+$), 389 ($M^+$-$SC_6H_4CH_3$), 137 ($CH_2{=}\overset{+}{S}C_6H_4CH_3$), 122 (base peak).

Following eluate with acetone gave 0.24 g (27%) of IIIa. Recrystallization from ether gave colorless prisms of mp 104—107°. *Anal.* Calcd for $C_{19}H_{22}ON_4S$: C, 64.39; H, 6.26; N, 15.81; S, 9.03; O, 4.51. Found: C, 64.39; H, 6.40; N, 15.79; S, 9.20; O, 4.82. UV $\lambda_{max}^{EtOH}$ m$\mu$ (log $\varepsilon$): 258, 305 (4.09, 3.96). NMR $\tau$ ($d_6$-DMSO): 8.23, 8.12 (3H, singlets, 1: 2.5, 7-$CH_3$), 7.76 (3H, s, *p*-$C\underline{H}_3$-$C_6H_4$), 7.62 (3H, s, 2-$CH_3$), 5.77, 5.62 (2H, singlets, 2.5: 1, Pm-$CH_2$-N), 2.95, 2.72 (4H, $A_2B_2$, $J$=8 Hz, S-$C_6\underline{H}_4$-$CH_3$(*p*)), 1.96 (1H, b, CHO), 1.80 (1H, s, 4-H), 1.33, 1.23 (1H, broad singlets, 1: 2.5 NH). Mass Spectrum *m/e*: 355 ($M^+$+1), 354 ($M^+$, base peak), 325 ($M^+$-CHO), 231 ($M^+$-$SC_6H_4CH_3$), 217 ($M^+$-$CH_2$-S-$C_6H_4CH_3$), 137 ($M^+$-217).

**3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-4-methyl-5-(2-*p*-nitrophenylthioethyl)-4-thiazoline-2-thione (IVd)**——a) To a solution of 0.75 g of I and 9 ml of DMF was added 1.15 g of *p*-nitrothiophenol and allowed to stand overnight at room temp. The reaction mixture was concentrated *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with $H_2O$, dried, evaporated. The residue was treated with acetone to separate 0.66 g (61%) of IVd, mp 217—220° (decomp.). *Anal.* Calcd. for $C_{18}H_{19}O_2N_5S_3$: C, 49.88; H, 4.42; O, 7.38; N, 16.16; S, 22.16. Found: C, 49.66; H, 4.51; O, 7.48; N, 15.81; S, 21.63. UV $\lambda_{max}^{EtOH}$ m$\mu$ (log $\varepsilon$): 231, 281 (sh), 329 (4.27, 3.87, 4.40). NMR $\tau$ ($d_6$-DMSO): 7.93 (3H, s, $CH_3$-C=), 7.68 (3H, s, Pm-2-$CH_3$), 4.57 (2H, s, $CH_2$-N), 3.08 (2H, b, $NH_2$). Mass Spectrum *m/e*: 433 ($M^+$).

b) To a solution of 1.57 g of VIII in 20 ml of DMF was added 1.55 g of *p*-nitrothiophenol, stirred for 5 hr at room temp., and allowed to stand overnight at room temp. The reaction mixture was concentrated *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with $H_2O$, dried, and evaporated. The residue was treated with AcOEt to give 1.45 g (54%) of crystals which were identical with IVd obtained above a).

**3-[(4-Amino-2-methyl-5-pyrimidinyl)methyl]-4-methyl-5-(2-*p*-bromophenylthioethyl)-4-thiazoline-2-thione (IVc) and 2,7-Dimethyl-6-formyl-8-(2-*p*-bromophenylthioethyl)-5,6-dihydro-9*H*-pyrimido[4,5-*e*][1,4]diazepine (IIIc)**——a) To a solution of 1.5 g of I and 0.1 g of piperidine in 10 ml of DMF was added 2.84 g of *p*-bromothiophenol under $N_2$ stream. After stirring for 7 hr at 60°, allowed to stand overnight. The reaction mixture was concentrated *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with $H_2O$, dried, evaporated, and the residue was chromatographed on silica gel. The eluate with acetone gave 0.15 g (6.4%) of IVc. Recrystallization from AcOEt gave colorless prisms of mp 165—167°. *Anal.* Calcd. for $C_{18}H_{19}N_4S_3Br$: C, 46.24; H, 4.10; N, 12.01; S, 20.58. Found: C, 46.50; H, 4.25; N, 11.60; S, 20.15. UV $\lambda_{max}^{EtOH}$ m$\mu$ (log $\varepsilon$): 230, 264, 326 (4.27, 4.26, 4.17). NMR $\tau$: 7.95 (3H, s, $CH_3$-C=), 7.57 (3H, s, Pm-2-$CH_3$), 7.15 (2H, t, $J$=5 Hz), 7.07 (2H, t, $J$=5 Hz, $SCH_2CH_2$), 4.65 (2H, s, $CH_2N$), 3.82 (2H, b, $NH_2$), 1.93 (1H, s, Pm-6-H).

Following eluate with acetone gave 0.44 g (21%) of IIIc. Recrystallization from AcOEt gave colorless prisms of mp 146—148°. *Anal.* Calcd. for $C_{18}H_{19}ON_4SBr$: C, 51.55; H, 4.57; N, 13.36; S, 7.64; Br, 19.06. Found: C, 51.78; H, 4.61; N, 13.03; S, 7.37; Br, 19.14. UV $\lambda_{max}^{EtOH}$ m$\mu$ (log $\varepsilon$): 265, 303 (4.25, 4.01). NMR $\tau$: 8.02 (3H, s, $CH_3$-C=), 7.52 (3H, s, Pm-2-$CH_3$), 7.45 (2H, t, $J$=6.5 Hz), 6.85 (2H, t, $J$=6.5 Hz, $SCH_2CH_2$), 5.67 (2H, s, $CH_2N$), 3.53 (1H, b, NH), 1.87 (1H, s, CHO), 1.78 (1H, s, 4-H).

b) Reaction was carried out without piperidine and worked up as above a) to give 0.27 g (13%) of IIIc and 0.28 g (12%) of IVc.

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