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Studies on Xanthine Derivatives. I. Formation of Tricyclic Heterocycles from Hydrolysates of 1-(5-Oxoheptyl)theobromine (Pentoxifylline)

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1-(5-Oxoheptyl)theobromine (I) in alkaline solution was hydrolyzed by heating to give 4-(methylamino)-1-methyl-5-(5-oxoheptyl)aminocarbonylimidazole (II) and *N*-[4-(5-carboxy-1-methylimidazolyl)]-*N*-methyl-*N'*-(5-oxoheptyl)urea (III). When acidified with HCl, II and III were cyclized to 4,4a,5,6,7,8-hexahydro-10-oxo-1,4,4a-trimethyl-1*H*-pyrido[1,2-*a*]-purine (IV) and 4,5,7,8,9,10-hexahydro-5,12-dioxo-1,4,10a-trimethyl-1*H*-pyrido[2',1':2,3]-imidazo[4,5-*f*]oxadiazocine hydrochloride (V), respectively.

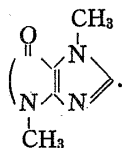
Keywords—pentoxifylline; 1-(5-oxoheptyl)theobromine; alkaline decomposition; acid-catalyzed cyclization; tricyclic heterocycles

We have previously reported¹⁾ the physicochemical properties and stability of pentoxifylline (1-(5-oxoheptyl)theobromine²⁾ (I), which has been developed as a vasodilative drug. The present paper deals with the alkaline hydrolysis of I and acid-catalyzed cyclization of the decomposition products.

It is known that caffeine undergoes alkaline hydrolysis to yield two decomposition products, caffenidine and *N*-[4-(5-carboxy-1-methylimidazolyl)]-*N,N'*-dimethylurea.³⁾ As I has the same 1,3,7-trisubstituted xanthine structure as caffeine, I was expected to undergo alkaline hydrolysis.

Compound I was heated in 1 *N* NaOH for 1 h to give 4-(methylamino)-1-methyl-5-(5-oxoheptyl)aminocarbonylimidazole (II) as a faintly reddish oil and *N*-[4-(5-carboxyl-1-methylimidazolyl)]-*N*-methyl-*N'*-(5-oxoheptyl)urea (III) as colorless needles (mp 128—129°C). The structures of II and III were substantiated by the infrared absorption (IR) and proton nuclear magnetic resonance (¹H-NMR) data (see "Experimental"). The structure of III was confirmed by converting it into the methyl ester (IIIa) and thence into the decarboxylated product (IIIb) (Chart 1).

Compound II was treated with ethanolic hydrogen chloride to precipitate colorless needles (mp 229—231°C). This substance was not the HCl salt of II but was a tricyclic heterocycle (IV·HCl). Neutralization of a solution of IV·HCl with an alkali gave IV as colorless cubes (mp 165—166°C). The IR spectrum of IV showed no absorption bands due to secondary amino and ketone carbonyl groups. The molecular formula of IV was expressed as C₁₂H₁₈N₄O from the results of elemental analyses and mass spectrometry (MS). Furthermore, MS of IV gave peaks at *m/e* 137, 109, 82, 67 and 55 which accorded with a series of fragment peaks of

I.⁴⁾ Accordingly, IV was found to possess the partial structure . In the ¹H-NMR

spectrum of IV, a signal of an acetyl group observed at δ 2.14 in II disappeared and a signal due to a tertiary methyl group was newly observed at δ 1.35. Two signals at δ 2.95 and δ 3.86 assigned to *N*-methyl groups showed almost the same chemical shift values as those of II. In addition, the signals at δ 1.40—2.40 (6H, m), 2.65 (1H, m) and 4.48 (1H, m) were assigned to protons of the piperidine ring. From these data, the structure of IV was identified as 4,4a,5,-

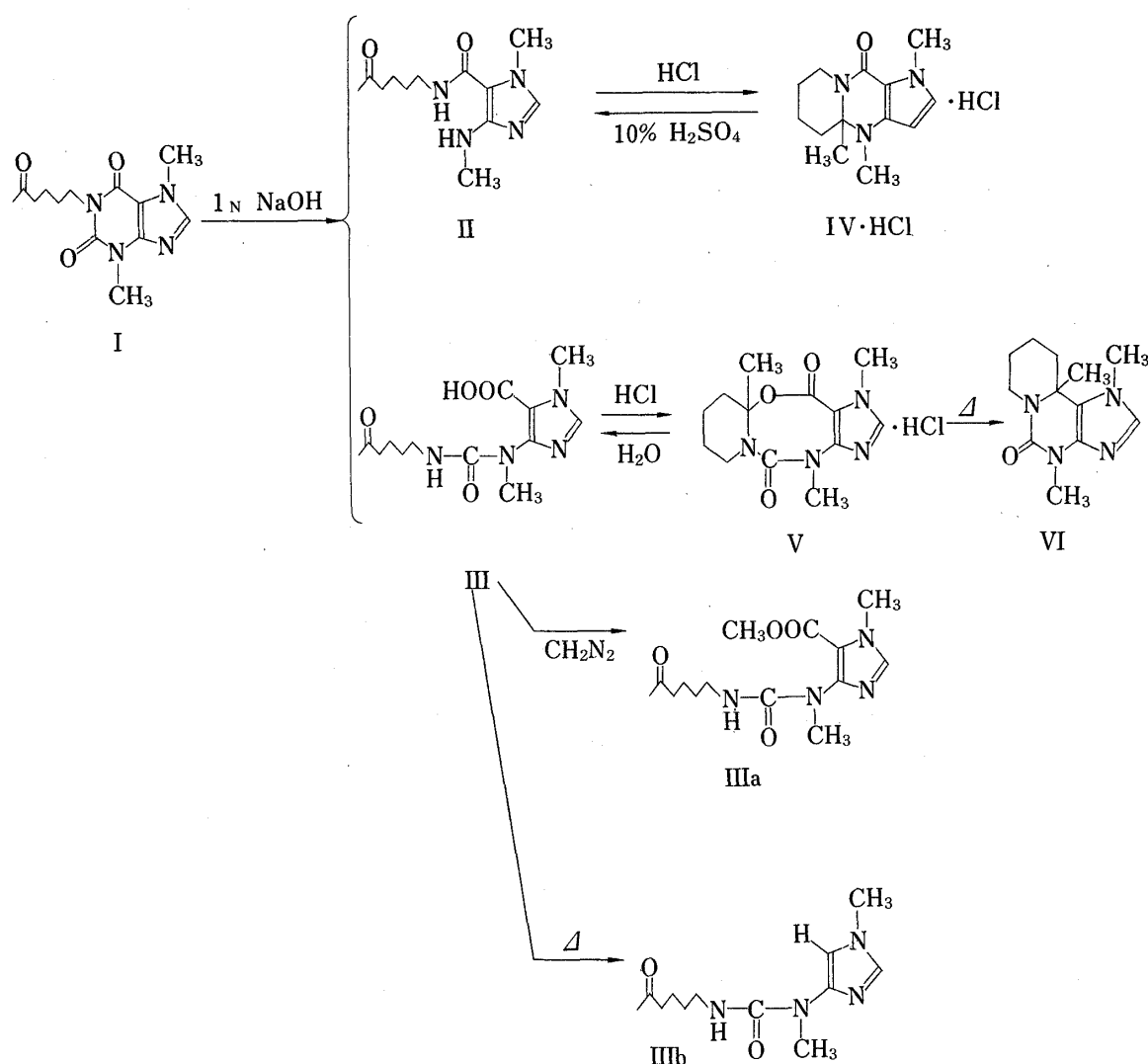


Chart 1

6,7,8-hexahydro-10-oxo-1,4,4a-trimethyl-1*H*-pyrido[1,2-*a*]purine. When it was heated in 10% sulfuric acid, IV was hydrolyzed to II.

Compound IV was supposed to be produced by the initial formation of the 2-hydroxypiperidine ring as a result of acid-catalyzed cyclization of the (5-oxohexyl)amino group followed by nucleophilic attack of the methylamino group.

Having the same (5-oxohexyl)amino group as II, III was expected to produce a cyclic compound on reaction with an acid. Treatment of III with HCl at room temperature afforded, as expected, a tricyclic heterocycle, 4,5,7,8,9,10-hexahydro-5,12-dioxo-1,4,10a-trimethyl-1*H*-pyrido[2',1':2,3]imidazo[4,5-*f*]oxadiazocine hydrochloride (V) as colorless needles (mp 214—216°C). The empirical formula of V was concluded to be C₁₃H₁₉ClN₄O₃ from the results of elemental analyses. The IR spectrum of V did not show absorption bands due to amide and carboxyl groups but displayed lactone absorptions at 1710 and 1200 cm⁻¹. The ¹H-NMR spectrum of V showed a singlet (3H) due to a tertiary methyl group at δ 1.76 and signals due to a piperidine ring at δ 1.40—2.20 (5H, m), 2.60 (1H, m), 3.06 (1H, m) and 4.06 (1H, m). In addition, when fused at 220—230°C, V generated CO₂ gas to produce 4,5,7,8,9,10-hexahydro-5-oxo-1,4,10a-trimethyl-1*H*-pyrido[2,1-*f*]purine (VI). V in aqueous solution underwent hydrolysis to revert to III. These two reactions also substantiated the presence of a lactone group in V.

The molecular formula of VI was established as $C_{12}H_{18}N_4O$, an isomer of IV, from the elemental analyses and MS data. VI was assumed to have a structure in which the three rings are condensed, because the 1H -NMR signal pattern of VI was similar to that of IV. Therefore, the structure of VI could be analyzed by comparison of the 1H -NMR and ultraviolet (UV) spectra of VI with those of IV and known compounds, caffeidine (VII)⁵⁾ and *N*-[4-(1-methylimidazolyl)]-*N,N'*-dimethylurea (VIII).³⁾ The relationships of the chemical shifts of *N*-methyl groups and $\lambda_{\max}$ between IV and VI corresponded well to that between VII and VIII.⁶⁾ As the difference in these spectra between VII and VIII is due to the linkage position of the carbonyl group, the difference between IV and VI might be similar. Accordingly, it is considered that VI as well as VIII has a structure in which a carbonyl group is adjacent to the amino group substituted at the 4 position of the imidazole ring.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Hitachi Model 285 spectrometer, UV spectra on a Hitachi EPS-3T spectrometer, and MS on a JEOL TMS-01SG mass spectrometer. 1H -NMR spectra were measured with a JEOL JNM-MH-100 spectrometer as 10% solution, with tetramethylsilane as an internal standard. The abbreviations used are: s, singlet; d, doublet; t, triplet; m, multiplet; and br s, broad singlet.

Hydrolysis of 1-(5-Oxoheptyl)theobromine (I)—A solution of I (2.0 g) in 1 *N* NaOH (100 ml) was heated under reflux for 1 h and then extracted with CH_2Cl_2 . The CH_2Cl_2 extract was dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to give a brown oil. The oil was purified by silica column chromatography (Wako gel C-200); elution with $CHCl_3$ -MeOH (50:1) afforded 4-(methylamino)-1-methyl-5-(5-oxoheptyl)amino-carbonylimidazole (II) as a faintly reddish oil. Yield: 0.16 g (8.8%). *Anal.* Calcd for $C_{12}H_{20}N_4O_2$: C, 57.12; H, 7.99; N, 22.21. Found: C, 57.01; H, 8.24; N, 22.04. IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 3380 (NH), 3300, 1640 (NHCO), 1720 (CO). 1H -NMR ($CDCl_3$) δ : 1.62 (4H, m, $-CH_2CH_2CH_2CH_2-$), 2.14 (3H, s, CH_3CO-), 2.50 (2H, m, CH_3COCH_2-), 2.90 (3H, s, $-NHCH_3$), 3.38 (2H, m, $-CH_2NHCO-$), 3.84 (3H, s, *N*-1- CH_3 of imidazole ring), 4.14 (1H, br s, $-NHCH_3$, exchangeable with D_2O), 7.10 (1H, br s, $-CH_2NHCO-$, exchangeable with D_2O), 7.20 (1H, s, C-2-H of imidazole ring). UV $\lambda_{\max}^{MeOH}$ nm (log ϵ): 291 (3.93).

After extraction with CH_2Cl_2 , the aqueous layer was neutralized with conc. HCl and concentrated *in vacuo* to give a yellow residue, which was extracted with EtOH. The insoluble material was removed by filtration and the filtrate was concentrated to dryness to afford a pale yellow oil. Treatment of the oil with acetone gave an acetone-insoluble material. The insoluble material was passed through a column of Dowex 50W-8 (H^+ form). The column was eluted with EtOH- H_2O (3:2) and the eluate was evaporated to dryness *in vacuo* to afford a colorless powder, which was crystallized from AcOEt to give *N*-[4-(5-carboxy-1-methylimidazolyl)]-*N*-methyl-*N'*-(5-oxoheptyl)urea (III) as colorless needles. Yield: 0.13 g (6.1%). mp 128–129°C. *Anal.* Calcd for $C_{13}H_{20}N_4O_4$: C, 52.69; H, 6.80; N, 18.91. Found: C, 52.64; H, 6.80; N, 18.82. IR $\nu_{\max}^{KBr}$ cm^{-1} : 3380, 2550–2330 (COOH), 3280, 1640 (CONH), 1710 (COOH, CO). 1H -NMR ($CDCl_3$) δ : 1.54 (4H, m, $-CH_2CH_2CH_2CH_2-$), 2.16 (3H, s, CH_3CO-), 2.48 (2H, m, CH_3COCH_2-), 3.26 (3H, s, $>NCH_3$; 2H, m, $-CH_2NHCO-$), 3.94 (3H, s, *N*-1- CH_3 of imidazole ring), 5.62 (1H, br s, NH, exchangeable with D_2O), 7.54 (1H, s, C-2-H of imidazole ring), 10.50 (1H, br s, COOH, exchangeable with D_2O). UV $\lambda_{\max}^{MeOH}$ nm (log ϵ): 237 (3.87).

***N*-[4-(5-Methoxycarbonyl-1-methylimidazolyl)]-*N*-methyl-*N'*-(5-oxoheptyl)urea (IIIa)**—A solution of diazomethane in Et_2O was added dropwise to a suspension of III (0.5 g) in Et_2O (50 ml), and the mixture was stirred at room temperature for 3 h. The reaction mixture was washed successively with saturated $NaHCO_3$ and H_2O , dried over anhyd. Na_2SO_4 , and concentrated *in vacuo* to give a colorless powder. Recrystallization of this powder from AcOEt gave colorless needles (IIIa). Yield: 0.23 g (44%). mp 108–109°C. *Anal.* Calcd for $C_{14}H_{22}N_4O_4$: C, 54.18; H, 7.14; N, 18.05. Found: C, 54.12; H, 7.02; N, 17.97. IR $\nu_{\max}^{KBr}$ cm^{-1} : 3310, 1635 (CONH), 1720 (CO, $COOCH_3$), 1220, 1110 ($COOCH_3$). 1H -NMR ($CDCl_3$) δ : 1.50 (4H, m, $-CH_2CH_2CH_2CH_2-$), 2.12 (3H, s, CH_3CO-), 2.45 (2H, m, CH_3COCH_2-), 3.19 (3H, s, $>NCH_3$; 2H, m, $-CH_2NHCO-$), 3.86 (3H, s, CH_3OCO-), 3.90 (3H, s, *N*-1- CH_3 of imidazole ring), 5.30 (1H, br s, NH, exchangeable with D_2O), 7.50 (1H, s, C-2-H of imidazole ring). UV $\lambda_{\max}^{MeOH}$ nm (log ϵ): 239 (3.87).

***N*-[4-(1-Methylimidazolyl)]-*N*-methyl-*N'*-(5-oxoheptyl)urea (IIIb)**—When III (0.7 g) was heated at 125–135°C under N_2 gas, it melted, generating CO_2 gas, and changed into a brown oil. This oil was purified by silica column chromatography (Wako gel C-200); elution with $CHCl_3$ -MeOH (50:1) afforded a faintly yellow oil, which was recrystallized from Et_2O to give IIIb as colorless cubes. Yield: 0.20 g (34%). mp 72–74°C. *Anal.* Calcd for $C_{12}H_{20}N_4O_2$: C, 57.12; H, 7.99; N, 22.21. Found: C, 56.92; H, 8.06; N, 22.07. IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 3240, 1645 (CONH), 1705 (CO). 1H -NMR ($CDCl_3$) δ : 1.60 (4H, m, $-CH_2CH_2CH_2CH_2-$), 2.12 (3H, s, CH_3CO-), 2.46 (2H, m, CH_3COCH_2-), 3.19 (3H, s, $>NCH_3$), 3.35 (2H, m, $-CH_2NHCO-$), 3.68 (3H, s,

N-1-CH₃ of imidazole ring), 6.39 (1H, s, C-5-H of imidazole ring), 7.20 (1H, s, C-2-H of imidazole ring), 8.74 (1H, br s, NH, exchangeable with D₂O). UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (log ϵ): 223 (3.96).

4,4a,5,6,7,8-Hexahydro-10-oxo-1,4,4a-trimethyl-1H-pyrido[1,2-a]purine (IV)—Compound II (0.7 g) was dissolved in ethanolic hydrogen chloride and allowed to stand at room temperature overnight. The precipitated crystals were collected by filtration and recrystallized from EtOH to afford colorless needles (IV·HCl), which were dissolved in water and neutralized with 10% NaOH. The precipitated crystals were recrystallized from H₂O to afford colorless cubes (IV). Yield: 0.26 g (40%). mp 165–166°C. *Anal.* Calcd for C₁₂H₁₈N₄O: C, 61.52; H, 7.74; N, 23.91. Found: C, 61.58; H, 7.81; N, 23.85. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1640 (CON). ¹H-NMR (CDCl₃) δ : 1.35 (3H, s, C-4a-CH₃), 1.40–2.40 (6H, m, C-5-H + C-6-H + C-7-H), 2.65 (1H, m, C-8-H), 2.95 (3H, s, N-4-CH₃), 3.86 (3H, s, N-1-CH₃), 4.48 (1H, m, C-8-H), 7.17 (1H, s, C-2-H). MS *m/e*: 234 (M⁺), 219 (M⁺ - CH₃), 137 (137.060; Calcd for C₆H₇N₃O: 137.059), 109 (109.065; Calcd for C₅H₇N₃: 109.064), 82, 67, 55. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (log ϵ): 319 (3.82). $\lambda_{\text{max}}^{0.1N \text{ HCl}}$ nm (log ϵ): 226 (3.91), 312 (3.79). IV·HCl: mp 228–231°C. *Anal.* Calcd for C₁₂H₁₉ClN₄O: C, 53.23; H, 7.07; N, 20.69. Found: C, 53.05; H, 7.07; N, 20.60. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2550 (br), 2320 (br), 1810 (=N⁺H), 1650 (CON). ¹H-NMR (DMSO-*d*₆) δ : 1.36 (3H, s, C-4a-CH₃), 1.40–2.30 (6H, m, C-5-H + C-6-H + C-7-H), 2.64 (1H, m, C-8-H), 2.98 (3H, s, N-4-CH₃), 3.86 (3H, s, N-1-CH₃), 4.22 (1H, m, C-8-H), 8.58 (1H, s, C-2-H). UV $\lambda_{\text{max}}^{0.1N \text{ HCl}}$ nm (log ϵ): 226 (3.91), 312 (3.79).

Hydrolysis of IV—A solution of IV (0.1 g) in 10% H₂SO₄ (10 ml) was refluxed for 3 h. After cooling, it was neutralized with 10% NaOH and then extracted with CH₂Cl₂. The CH₂Cl₂ extract was concentrated *in vacuo* and the residue was subjected to thin layer chromatography (Merck; precoated silica gel plate F₂₅₄, 2 mm thick; solvent, EtOH) to afford unreacted IV and II. These products were identified by IR spectrophotometry.

4,5,7,8,9,10-Hexahydro-5,12-dioxo-1,4,10a-trimethyl-1H-pyrido[2',1':2,3]imidazo[4,5-f]oxadiazocine Hydrochloride (V)—Compound III (0.7 g) was dissolved in ethanolic hydrogen chloride, and Et₂O was added to the solution until it became cloudy. Then, the solution was left overnight. Recrystallization of the precipitated crystals from EtOH–Et₂O afforded colorless needles (V). Yield: 0.21 g (28%). mp 214–216°C. *Anal.* Calcd for C₁₃H₁₉ClN₄O₂: C, 49.61; H, 6.08; N, 17.80; Cl, 11.26. Found: C, 49.52; H, 6.09; N, 17.97; Cl, 11.20. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2500–2300 (=N⁺H), 1710, 1200 (O–CO), 1685 (N–CO–N). ¹H-NMR (CD₃OD) δ : 1.76 (3H, s, C-10a-CH₃), 1.40–2.20 (5H, m, C-8-H + C-9-H + C-10-H), 2.60 (1H, m, C-10-H), 3.00 (1H, m, C-7-H), 3.50 (3H, s, N-4-CH₃), 4.06 (1H, m, C-7-H), 4.12 (3H, s, N-1-CH₃), 9.34 (1H, s, C-2-H). UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (log ϵ): 260 (4.09).

Hydrolysis of V—A solution of V (0.1 g) in H₂O (1 ml) was allowed to stand at room temperature overnight and subjected to thin layer chromatography (Merck; precoated silica gel plate F₂₅₄, 2 mm thick; solvent, EtOH) to give III. III was identified by IR spectrophotometry.

4,5,7,8,9,10-Hexahydro-5-oxo-1,4,10a-trimethyl-1H-pyrido-[2,1-f]purine (VI)—On being heated at 210–230°C for 1 h, V (0.2 g) melted, generating CO₂ gas, and changed into a brown oil. This oil was purified by preparative thin layer chromatography (Merck Kieselgel F₂₅₄) using CHCl₃–MeOH (25: 1) as a developing solvent to give a faintly yellow oil (VI). Yield: 0.06 g (40%). *Anal.* Calcd for C₁₂H₁₈N₄O: C, 61.52; H, 7.74; N, 23.91. Found: C, 61.36; H, 7.89; N, 24.14. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1640 (CON). ¹H-NMR (CDCl₃) δ : 1.58 (3H, s, C-10a-CH₃), 1.30–2.20 (6H, m, C-8-H + C-9-H + C-10-H), 2.98 (1H, m, C-7-H), 3.32 (3H, s, N-4-CH₃), 3.66 (3H, s, N-1-CH₃), 4.56 (1H, m, C-7-H), 7.12 (1H, s, C-2-H). MS *m/e*: 234 (M⁺), 219 (M⁺ - CH₃). UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (log ϵ): 242 (3.75). A solution of HCl in Et₂O was added to VI in EtOH. Recrystallization of the precipitate from EtOH afforded VI·HCl as colorless needles. VI·HCl: mp 169–172°C. *Anal.* Calcd for C₁₂H₁₉ClN₄O: C, 53.23; H, 7.07; N, 20.69. Found: C, 53.20; H, 7.17; N, 20.52.

References and Notes

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- 6) In the NMR and UV spectra of VII, N-1-CH₃ of the imidazole ring was observed at δ 3.9, and methyl protons of the methylamino group substituted at the 4 position of the imidazole ring at δ 2.9, while λ_{max} was at 284 nm (log ϵ : 3.96).⁵⁾ Also, in the NMR and UV spectra of VIII, N-1-CH₃ of the imidazole ring was observed at δ 3.66, and methyl protons of the methylamino group substituted at the 4 position of the imidazole ring at δ 3.15, while λ_{max} was at 221 nm (log ϵ : 3.96).³⁾