Kinetic Measurements——Bovine trypsin was purchased from Worthington Biochemical (lot TRL). The operational molarity of the enzyme preparation was determined by the titration method of Shaw *et al.*[9] The acylation rates of trypsin by *p*-amidinophenyl esters were analyzed using a Union Giken RA/401 stopped-flow spectrophotometer and deacylation rates were determined using a Hitachi UV 200-10 double beam spectrophotometer, following the reported procedure.[3a] The reactions were monitored by measuring the liberation of *p*-amidinophenolate ions at pH 8.0 ($\Delta\varepsilon_{305nm}$: 14000).

Acknowledgement We are grateful to the staff of the Center of Instrumental Analysis of this University for elemental analysis. This work was supported in part by grants from Ministry of Education, Science and Culture, the Yamada Science Foundation, and the Foundation of Research for Medicinal Resources.

9) T. Chase, Jr. and E. Shaw, *Biochem. Biophys. Res. Comm.*, **29**, 508 (1967).

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Synthesis of 9-Substituted 8-Phenyltheophyllines

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Various 9-substituted 8-phenyltheophyllines (III) were prepared in two steps starting from 5,7-dimethyl-2-phenyloxazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-dione (I). Thus, treatment of I with amines afforded 5-(N-substituted benzamidino)-1,3-dimethylbarbituric acids (II). The reaction of II with thionyl chloride or phosphorus oxychloride gave III.

Keywords——5,7-dimethyl-2-phenyloxazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-dione; amines; 5-(N-substituted benzamidino)-1,3-dimethylbarbituric acids; thionyl chloride; phosphorus oxychloride; 9-substituted 8-phenyltheophyllines

We have recently described the synthesis of oxazolo[5,4-*d*]pyrimidines and their conversion into thiazolo[5,4-*d*]pyrimidines.[2] As part of a program directed towards the further exploitation of oxazolo[5,4-*d*]pyrimidines as synthetic intermediates, we now report the conversion of 5,7-dimethyl-2-phenyloxazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-dione (I) into various 9-substituted 8-phenyltheophyllines (III) *via* 5-(N-substituted benzamidino)-1,3-dimethylbarbituric acids (II). Because of the therapeutic importance of theophylline, extensive studies have been carried out on the preparation of its derivatives; however, the synthesis of 9-substituted theophyllines has not been widely investigated.[3]

5-(N-Substituted Benzamidino)-1,3-dimethylbarbituric Acids

Refluxing of I with an excess of the appropriate arylamines in ethanol for 3 hr afforded the corresponding 5-(N-arylbenzamidino)-1,3-dimethylbarbituric acids (IIa—e) in 59—81% yields. Although the structures of IIa—e are isomeric with those of 6-arylamino-5-benzoyl-

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2) K. Senga, J. Sato, and S. Nishigaki, *Heterocycles*, **6**, 689 (1977); K. Senga, J. Sato, K. Shimizu, and S. Nishigaki, *Heterocycles*, **6**, 1919 (1977); K. Senga, J. Sato, and S. Nishigaki, *Chem. Pharm. Bull.*, **26**, 765 (1978).

3) *a*) K. Senga, Y. Kanamori, and S. Nishigaki, *Heterocycles*, **9**, 1437 (1978); *b*) F. Yoneda, M. Higuchi, K. Mori, K. Senga, Y. Kanamori, K. Shimizu, and S. Nishigaki, *Chem. Pharm. Bull.*, **26**, 2905 (1978); *c*) K. Senga, Y. Kanamori, and S. Nishigaki, *Chem. Pharm. Bull.*, **26**, 3240 (1978).

amino-1,3-dimethyluracils, the possibility of formation of the latter compounds was excluded by the fact that refluxing of IIa with 85% hydrazine hydrate in ethanol for 3 hr resulted in hydrolytic fission of the amidino moiety to give the known 5-amino-1,3-dimethylbarbituric acid (V).[4] Moreover, the spectral data for IIa showed marked differences from those of 6-anilino-5-benzoylamino-1,3-dimethyluracil (VIII) (see "Experimental"), which was obtained by the catalytic reduction of 6-anilino-1,3-dimethyl-5-phenylazouracil (VI)[3a] with palladium-carbon to give 5-amino-6-anilino-1,3-dimethyluracil (V) and subsequent treatment with benzoyl chloride (Charts 1 and 2).

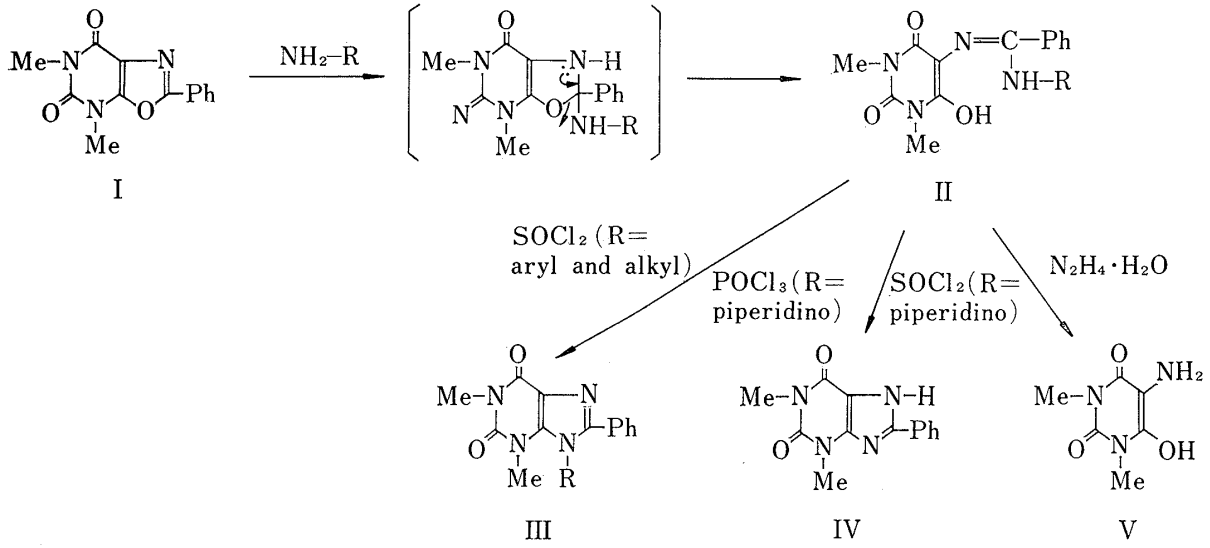


Chart 1

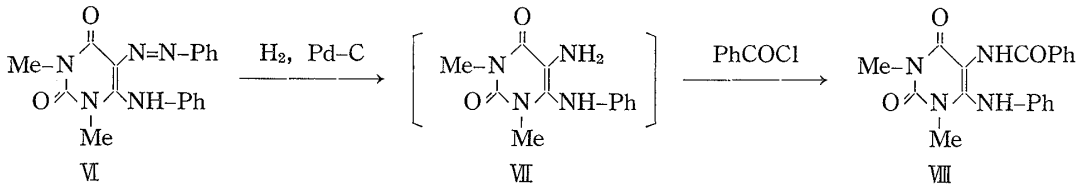


Chart 2

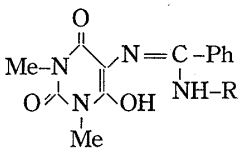
By analogy with the above result, the reaction of I with excess methylamine or benzylamine in ethanol for 2 hr gave the corresponding 5-(N-alkylbenzamidino)-1,3-dimethylbarbituric acid (IIf or g). The yieldes were 78 and 75%, respectively. When compound I was treated with excess N-aminopiperidine in ethanol under the same conditions, 5-(N-piperidinobenzamidino)-1,3-dimethylbarbituric acid (IIh) was obtained in 47% yield. The formation of IIa—h presumably involves the initial nucleophilic attack of amines at position 2 of I and subsequent ring cleavage of the oxazole accompanying the hydrogen transfer. An analogous mechanism has been reported in the reaction of oxazoles with nucleophiles[5] (Table I).

9-Substituted 8-Phenyltheophyllines

Treatment of the appropriate IIa—e with thionyl chloride under reflux for 15 min afforded the desired 9-aryl-8-phenyltheophyllines (IIIa—e)[3b] in 62—87% yields. Similarly, the reaction of IIf or IIg with thionyl chloride provided the corresponding 9-alkyl-8-phenyl-

4) H. Biltz and P. Damm, *Chem. Ber.*, **46**, 3662 (1913).
5) I.J. Turchi and M.J.S. Dewar, *Chem. Rev.*, **75**, 389 (1975) and references cited therein.

TABLE I. 5-(N-Substituted Benzamidino)-1,3-dimethylbarbituric Acids

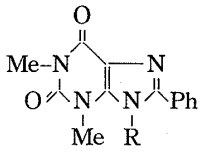


Compd. No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
IIa	C_6H_5	203—205[a]	80	$C_{19}H_{18}N_4O_3$	65.13	5.18	15.99	65.13	5.12	16.25
IIb	4-Br–C_6H_4	229—232[a]	59	$C_{19}H_{17}BrN_4O_3$	53.15	4.00	13.05	53.33	4.06	13.17
IIc	4-Cl–C_6H_4	223—226[a]	61	$C_{19}H_{17}ClN_4O_3 \cdot 1/4H_2O$	58.60	4.54	14.39	58.60	4.45	14.62
IId	4-Me–C_6H_4	220—222[a]	81	$C_{20}H_{20}N_4O_3 \cdot 1/2H_2O$	64.31	5.67	15.01	64.47	5.64	15.06
IIe	4-MeO–C_6H_4	227—229[a]	75	$C_{20}H_{20}N_4O_4$	63.15	5.30	14.73	62.93	5.34	14.69
IIf	Me	272—274[b]	78	$C_{14}H_{16}N_4O_3$	58.32	5.59	19.44	57.95	5.50	19.73
IIg	CH_2–Ph	228—230[b]	75	$C_{20}H_{20}N_4O_3$	65.92	5.53	15.38	65.65	5.54	15.49
IIh		212—213[c]	47	$C_{18}H_{23}N_5O_3$	60.49	6.49	19.60	60.35	6.58	19.36

a) Recrystallized from EtOH.
b) Recrystallized from EtOH-H_2O.
c) Recrystallized from MeOH.

theophyllines (IIIf[3b] and IIIg) in 89 and 28% yields, respectively. In contrast with the above result, refluxing of IIh with thionyl chloride gave 8-phenyltheophylline (IV)[6] instead of the expected 9-piperidino-8-phenyltheophylline (IIIh). The conversion of IIh to IV apparently involves the initial formation of IIIh; however, the mechanism of the subsequent N–N bond cleavage is not yet clear. The cyclization of IIh to IIIh was eventually achieved by refluxing with phosphorus oxychloride for 15 min in 51% yield. A literature survey showed that the compound of type IIIh is the first reported example of a 9-aminotheophylline derivative. It is interesting to note that attempted reduction of IIIh with sodium dithionite in formic acid at 95° for 15 min to give IV resulted in quantitative recovery of the starting material (Table II).

TABLE II. 9-Substituted 9-Phenyltheophyllines



Compd.[a] No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
IIIa	C_6H_5	275—276	81	$C_{19}H_{16}N_4O_2$	68.66	4.85	16.86	68.72	4.90	16.75
IIIb	4-Br–C_6H_4	>300	62	$C_{19}H_{15}BrN_4O_2$	55.47	3.68	13.63	55.52	3.63	13.68
IIIc	4-Cl–C_6H_4	288—291	70	$C_{19}H_{15}ClN_4O_2$	62.19	4.12	15.28	62.43	4.00	15.32
IIId	4-Me–C_6H_4	>300	87	$C_{20}H_{18}N_4O_2$	69.35	5.24	16.18	69.28	5.15	16.08
IIIe	4-MeO–C_6H_4	258—259	87	$C_{20}H_{18}N_4O_3$	66.28	5.01	15.46	66.52	5.01	15.52
IIIf	Me	221—222	89	$C_{14}H_{14}N_4O_2$	62.21	5.22	20.73	62.37	5.42	20.55
IIIg	CH_2–Ph	231—233	28	$C_{20}H_{18}N_4O_2$	69.35	5.24	16.18	69.06	5.19	16.11
IIIh		284—285	51	$C_{18}H_{21}N_5O_2$	63.70	6.24	20.64	63.52	6.09	20.81

a) All compounds were recrystallized from EtOH.

6) K. Senga, K. Shimizu, and S. Nishigaki, *Chem. Pharm. Bull.*, **25**, 495 (1977).

Experimental[7]

5-(N-Substituted Benzamidino)-1,3-dimethylbarbituric Acids (IIa—h) (Table I)——A mixture of 5,7-dimethyl-2-phenyloxazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-dione (I)[3] (0.514 g, 0.002 mol) and an appropriate amine (0.003 mol) in EtOH (15 ml) was refluxed for 3 hr, then the reaction mixture was concentrated *in vacuo* to one-third of the original volume. The precipitates were filtered and recrystallized to give the corresponding IIa—h.

IIa: NMR (DMSO-d_6): δ 3.07 (s, 6H, 2N-Me), 6.67—7.33 (m, 5H, C_6H_5), 7.53 (s, 5H, C_6H_5), 10.63 (br, 1H), 10.87 (br, 1H).

9-Substituted 8-Phenyltheophyllines (IIIa—h) (Table II)——A mixture of the appropriate IIa—h (0.0005 mol) and thionyl chloride (3 ml; for IIIa—g) or phosphorus oxychloride (3 ml; for IIIh) was refluxed for 15 min. The reaction mixture was concentrated *in vacuo* and the residue was triturated with chilled 5% NH_3 (for IIIa—g) or 5% NaOH (for IIIh). The insoluble material was filtered off and recrystallized from EtOH to give the corresponding IIIa—h.

8-Phenyltheophylline (IV)——A mixture of IIh (0.18 g, 0.0005 mol) and thionyl chloride (3 ml) was refluxed for 5 min. The reaction mixture was concentrated *in vacuo* and the residue was triturated with 5% NH_3. The insoluble material was filtered off and recrystallized from DMF to give IV (0.096 g, 75%), which was identical with an authentic sample.[6]

5-Amino-1,3-dimethylbarbituric Acid (V)——A mixture of IIa (0.035 g, 0.001 mol) and 85% hydrazine hydrate (1 ml) in EtOH (10 ml) was refluxed for 3 hr. After cooling, the precipitates were filtered off and recrystallized from EtOH to give V (0.1 g, 60%), which was identical with an authentic sample.[4]

6-Anilino-5-benzoylamino-1,3-dimethyluracil (VIII)——A solution of 6-anilino-1,3-dimethyl-5-phenylazouracil (VI)[3a] (0.36 g, 0.001 mol) in EtOH (200 ml) containing 10% palladium-carbon (0.15 g) was hydrogenated at room temperature and atmospheric pressure. After consumption of hydrogen (22 ml) had stopped, the solution was filtered and concentrated *in vacuo* to dryness. The resulting residue was immediately suspended in pyridine (2.5 ml) containing benzoyl chloride (0.28 g, 0.002 mol) and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated *in vacuo* and the residue was triturated with EtOH. The insoluble material was filtered off and recrystallized from EtOH to give VIII (0.14 g, 40%[8]), mp 168—170°. *Anal.* Calcd for $C_{19}H_{18}N_4O_3 \cdot 1/4H_2O$: C, 64.43; H, 5.27; N, 15.81. Found: C, 64.41; H, 5.42; N, 15.77. IR cm^{-1}: 1695 (CO), 3240 (NH). NMR ($CDCl_3$): δ 3.27 (s, 3H, N–Me), 3.43 (s, 3H, N–Me), 6.67—8.33 (m, 12H, 2NH and $2C_6H_5$). MS *m/e*: 350.

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7) Melting points were taken on a YANACO micro hot-stage melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO IR-E spectrometer from samples mulled in Nujol. NMR spectra were determined at 60 MHz with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL JMS-D 300 spectrometer with a direct inlet system at 70 eV.

8) Calculated on the basis of VI.