

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 ($\Delta\epsilon_{305\text{nm}}$: 14000).

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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

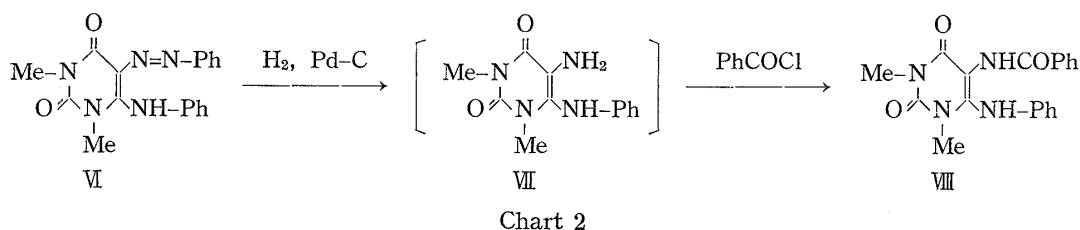
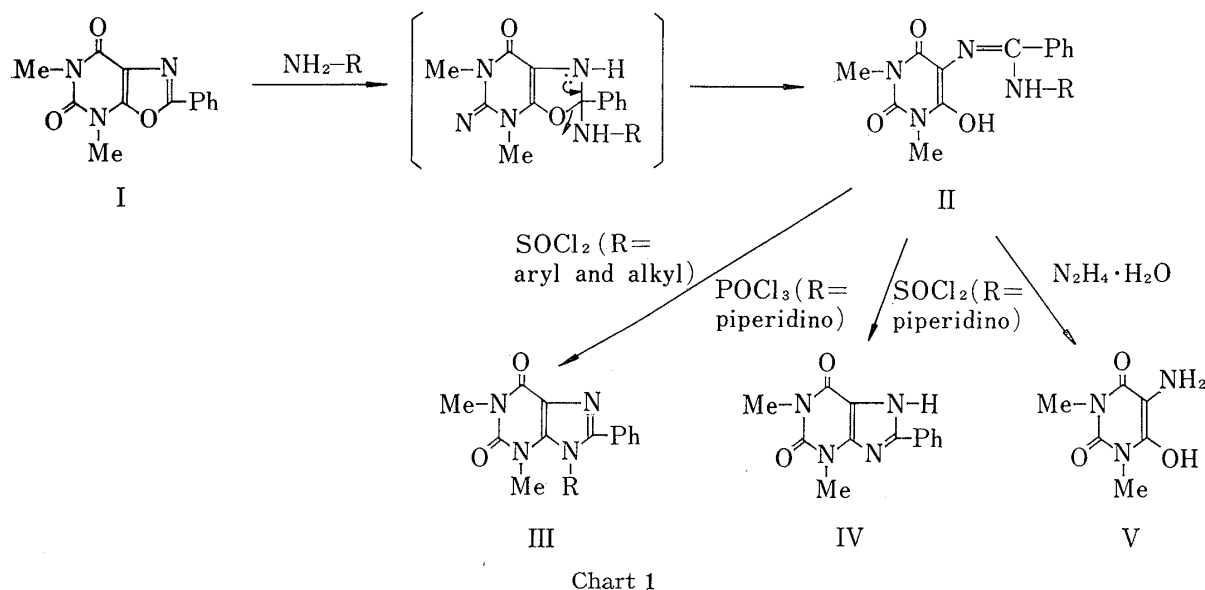
We have recently described the synthesis of oxazolo[5,4-*d*]pyrimidines and their conversion into thiazolo[5,4-*d*]pyrimidines.²⁾ As part of a program directed towards the further exploitation of oxazolo[5,4-*d*]pyrimidines as synthetic intermediates, we now report the conversion of 5,7-dimethyl-2-phenyloxazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-dione (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).



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-alkylbenzamido)-1,3-dimethylbarbituric acid (IIe or g). The yields were 78 and 75%, respectively. When compound I was treated with excess N-aminopiperidine in ethanol under the same conditions, 5-(N-piperidinobenzamido)-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 nucleophiles⁵⁾ (Table I).

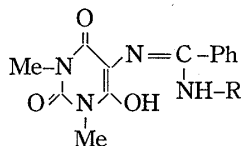
9-Substituted 8-Phenyltheophyllines

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 IIe 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			Found		
					C	H	N	C	H	N
IIa	C ₆ H ₅	203—205 ^{a)}	80	C ₁₉ H ₁₈ N ₄ O ₃	65.13	5.18	15.99	65.13	5.12	16.25
IIb	4-Br-C ₆ H ₄	229—232 ^{a)}	59	C ₁₉ H ₁₇ BrN ₄ O ₃	53.15	4.00	13.05	53.33	4.06	13.17
IIc	4-Cl-C ₆ H ₄	223—226 ^{a)}	61	C ₁₉ H ₁₇ ClN ₄ O ₃ · 1/4H ₂ O	58.60	4.54	14.39	58.60	4.45	14.62
IId	4-Me-C ₆ H ₄	220—222 ^{a)}	81	C ₂₀ H ₂₀ N ₄ O ₃ · 1/2H ₂ O	64.31	5.67	15.01	64.47	5.64	15.06
IIe	4-MeO-C ₆ H ₄	227—229 ^{a)}	75	C ₂₀ H ₂₀ N ₄ O ₄	63.15	5.30	14.73	62.93	5.34	14.69
IIf	Me	272—274 ^{b)}	78	C ₁₄ H ₁₆ N ₄ O 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 ₄ O ₃	65.92	5.53	15.38	65.65	5.54	15.49
IIh		212—213 ^{c)}	47	C ₁₈ H ₂₃ N ₅ O ₃	60.49	6.49	19.60	60.35	6.58	19.36

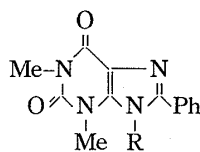
a) Recrystallized from EtOH.

b) Recrystallized from EtOH-H₂O.

c) Recrystallized from MeOH.

theophyllines (III^f^{3b)} and III^g) 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. No. ^{a)}	R	mp (°C)	Yield (%)	Formula	Analysis (%)					
					Calcd			Found		
					C	H	N	C	H	N
IIIa	C ₆ H ₅	275—276	81	C ₁₉ H ₁₆ N ₄ O ₂	68.66	4.85	16.86	68.72	4.90	16.75
IIIb	4-Br-C ₆ H ₄	>300	62	C ₁₉ H ₁₅ BrN ₄ O ₂	55.47	3.68	13.63	55.52	3.63	13.68
IIIc	4-Cl-C ₆ H ₄	288—291	70	C ₁₉ H ₁₅ ClN ₄ O ₂	62.19	4.12	15.28	62.43	4.00	15.32
IIId	4-Me-C ₆ H ₄	>300	87	C ₂₀ H ₁₈ N ₄ O ₂	69.35	5.24	16.18	69.28	5.15	16.08
IIIe	4-MeO-C ₆ H ₄	258—259	87	C ₂₀ H ₁₈ N ₄ O ₃	66.28	5.01	15.46	66.52	5.01	15.52
III ^f	Me	221—222	89	C ₁₄ H ₁₄ N ₄ O ₂	62.21	5.22	20.73	62.37	5.42	20.55
III ^g	CH ₂ -Ph	231—233	28	C ₂₀ H ₁₈ N ₄ O ₂	69.35	5.24	16.18	69.06	5.19	16.11
IIIh		284—285	51	C ₁₈ H ₂₁ N ₅ O 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).

Experimental⁷⁾

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, C₆H₅), 7.53 (s, 5H, C₆H₅), 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% NH₃ (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% NH₃. 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 C₁₉H₁₈N₄O₃·1/4H₂O: 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 (CDCl₃): δ 3.27 (s, 3H, N-Me), 3.43 (s, 3H, N-Me), 6.67—8.33 (m, 12H, 2NH and 2C₆H₅). 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 mullied 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.