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A New, Facile Synthesis of Oxazolo[5,4-*d*]pyrimidines and Their Conversion into Thiazolo[5,4-*d*]pyrimidines[1]

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The condensation of 5-amino-1,3-dimethylbarbituric acid (I) with aromatic aldehydes gave 5-benzylideneamino-1,3-dimethylbarbituric acids (II). Treatment of (II) with thionyl chloride afforded 2-aryl-5,7-dimethyloxazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-diones (IV) in good yields. The reaction of (IV) with phosphorus pentasulfide in pyridine provided 2-aryl-5,7-dimethylthiazolo[5,4-*d*]pyrimidine-4(5H)-one-6(7H)-thiones (VI), which were then converted to 2-aryl-5,7-dimethylthiazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-diones (VII) by the action of 30% hydrogen peroxide in acetic acid or thionyl chloride.

Keywords——5-amino-1,3-dimethylbarbituric acid; aromatic aldehydes; 5-benzylideneamino-1,3-dimethylbarbituric acids; thionyl chloride; 2-aryl-5,7-dimethyloxazolo-[5,4-*d*]pyrimidine-4,6(5H,7H)-diones; phosphorus pentasulfide-pyridine; 2-aryl-5,7-dimethylthiazolo[5,4-*d*]pyrimidine-4(5H)-one-6(7H)-thiones; 30% hydrogen peroxide in acetic acid or thionyl chloride; 2-aryl-5,7-dimethylthiazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-diones

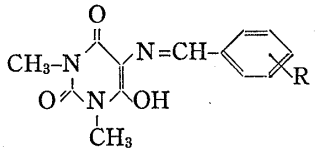
Extensive studies have been carried out during the past few decades on the synthesis of oxazolo[5,4-*d*]pyrimidine derivatives as potential purine antagonists. Oxazolo[5,4-*d*]pyrimidine ring system has generally been prepared by the ring closure of either suitably substituted pyrimidine derivatives or the appropriate oxazole precursors.[3] We now wish to report a new, facile synthetic approach to 2-aryl-5,7-dimethyloxazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-diones (IVa—i) by the reaction of 5-benzylideneamino-1,3-dimethylbarbituric acids (IIa—i) with thionyl chloride. Additionally, we wish to describe the synthesis of 2-aryl-5,7-dimethylthiazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-diones (VIIa—e) *via* 2-aryl-5,7-dimethylthiazolo[5,4-*d*]-pyrimidine-4(5H)-one-6(7H)-thiones (VIa—e) from the appropriate (IV). The compounds, (IVa—i), (VIa—e), and (VIIa—e), are of interest as potential inhibitors of 3′,5′-cyclic AMP phosphodiesterase since these structures are analogous to methylxanthines, especially theophylline.[4]

1) A part of this work has been reported in a preliminary form: K. Senga, J. Sato, and S. Nishigaki, *Heterocycles*, **6**, 689 (1977).
2) Location: *35, Shinanomachi, Shinjuku-ku, Tokyo, 160, Japan.*
3) From pyrimidines: *a*) T.B. Johnson, *Am. Chem. J.*, **34**, 191 (1905); *b*) H. Biltz and K. Strufe, *Ann.*, **404**, 170 (1914); *c*) H. Biltz, K. Strufe, and J. Karte, *Ann.* **404**, 180 (1914); *d*) E.A. Falco, G.B. Elion, E. Burgi, and G.H. Hitchings, *J. Am. Chem. Soc.*, **74**, 4897 (1952); *e*) K. Shirakawa, *Yakugaku Zasshi*, **73**, 643 (1953); *f*) G.D. Hager and C. Kaise, *J. Am. Pharm. Assoc.*, **44**, 193 (1955); *g*) M. Ishidate and H. Yuki, *Chem. Pharm. Bull.* (Tokyo), **8**, 137 (1960); *h*) H. Bredereck, F. Effenberger, and E.H. Schweiger, *Chem. Ber.*, **95**, 956 (1962); *i*) T. Nishiwaki, *Nature*, **211**, 737 (1966); *j*) T. Nishiwaki, *Chem. Pharm. Bull.* (Tokyo), **14**, 1425 (1966); *k*) V.D. Patil and L.B. Townsend, *J. Heterocyclic Chem.*, **8**, 503 (1971). From oxazoles: *l*) A.B.A. Jansen and M. Szelke, *J. Chem. Soc.*, **1961**, 405; *m*) J.P. Ferris and L.E. Orgel, *J. Am. Chem. Soc.*, **88**, 3829 (1966); *n*) Y. Ohtsuka, *Bull. Chem. Soc. Japan*, **43**, 187, 3909 (1970); *o*) M. Sekiya, J. Suzuki, and Y. Kakiya, *Chem. Pharm. Bull.* (Tokyo), **18**, 1233 (1970); *p*) M. Sekiya and J. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **18**, 2242 (1970); *q*) H. Dounchis, *J. Org. Chem.*, **37**, 2583 (1972).
4) The methylxanthines such as caffeine and theophylline have been known to function as inhibitors of 3′,5′-cyclic AMP phosphodiesterase: E.W. Sutherland and T.W. Rall, *J. Biol. Chem.*, **232**, 1077 (1958); R.W. Butcher and E.W. Sutherland, *J. Biol. Chem.*, **277**, 1244 (1962); K.G. Nair, *Biochemistry*, **5**, 150 (1960).

2-Aryl-5,7-dimethyloxazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-diones

The requisite intermediates, (IIa—i), were readily obtained in good yields by refluxing of 5-amino-1,3-dimethylbarbituric acid (I)[5] with the respective aromatic aldehydes in ethanol for 1 hr (Table I).

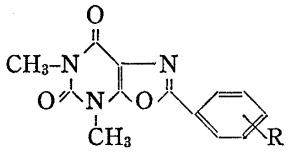
Table I. 5-Benzylideneamino-1,3-dimethylbarbituric Acids



Compd. No.[a]	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIa	H	220	92	$C_{13}H_{13}N_3O_3$	60.22	5.05	16.21	59.99	5.00	15.92
IIb	4-Br	228—229	91	$C_{13}H_{12}BrN_3O_3$	46.17	3.58	12.43	45.99	3.59	12.63
IIc	4-Cl	225—227	91	$C_{13}H_{12}ClN_3O_3$	53.15	4.13	14.31	52.90	4.06	14.60
IId	2,4-Cl_2	209—210	89	$C_{13}H_{11}Cl_2N_3O_3$	47.57	3.39	12.81	47.45	3.64	13.08
IIe	3,4-Cl_2	213—214	85	$C_{13}H_{11}Cl_2N_3O_3$	47.57	3.39	12.81	47.37	3.49	12.54
IIf	4-NO_2	223	87	$C_{13}H_{12}N_4O_5$	51.31	3.98	18.42	51.60	4.05	18.64
IIg	4-Me	217	83	$C_{14}H_{15}N_3O_3$	61.53	5.53	15.38	61.37	5.43	15.16
IIh	4-OMe	231	88	$C_{14}H_{15}N_3O_4$	58.12	5.23	14.53	57.88	5.21	14.51
IIi	3,4-$(OMe)_2$	223—224	90	$C_{15}H_{17}N_3O_5$	56.42	5.37	13.16	56.33	5.31	13.43

a) All compounds were recrystallized from DMF–EtOH.

Table II. 2-Aryl-5,7-dimethyloxazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-diones



Compd. No.[a]	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	IR (Nujol) cm^{-1} (C=O)	
IVa	H	240—242[b]	98	$C_{13}H_{11}N_3O_3$	60.69	4.31	16.34	60.73	4.34	16.54	1715	1670
IVb	4-Br	259	92	$C_{13}H_{10}BrN_3O_3$	46.00	3.00	12.50	46.42	3.01	12.53	1710	1670
IVc	4-Cl	259	90	$C_{13}H_{10}ClN_3O_3$	53.52	3.46	14.54	53.44	3.46	14.49	1710	1675
IVd	2,4-Cl_2	267	92	$C_{13}H_9Cl_2N_3O_3$	47.87	2.78	12.88	47.88	2.80	13.10	1712	1665
IVe	3,4-Cl_2	255—257	89	$C_{13}H_9Cl_2N_3O_3$	47.87	2.78	12.88	27.79	2.78	13.09	1713	1670
IVf	4-NO_2	275	69	$C_{13}H_{10}N_4O_5$	51.66	3.34	18.54	51.56	3.32	18.78	1720	1675
IVg	4-Me	233—235	81	$C_{14}H_{13}N_3O_3$	61.98	4.83	15.49	61.86	4.84	15.52	1715	1675
IVh	4-OMe	267	85	$C_{14}H_{13}N_3O_4$	58.53	4.56	14.63	58.58	4.55	14.87	1705	1660
IVi	3,4-$(OMe)_2$	278—279	95	$C_{15}H_{15}N_3O_5$	56.78	4.77	13.24	56.49	4.72	13.34	1720	1680

a) All compounds were recrystallized from DMF–EtOH.
b) Lit.[3b] mp 237°.

5) H. Biltz and P. Damm, *Chem. Ber.*, **46**, 3662 (1913).

Heating of (IIa) with an excess of thionyl chloride at 55° for 30 min, followed by concentration of the reaction mixture and subsequent addition of 5% aqueous ammonia afforded a high yield of 5,7-dimethyl-2-phenyloxazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-dione (IVa), which was identical with the authentic sample prepared by the reaction of (I) with benzoyl chloride according to the reported procedure.[3b] This reaction was equally applicable to other 5-benzylideneamino-1,3-dimethylbarbituric acids (IIb—i) to give the corresponding oxazolo[5,4-*d*]-pyrimidine derivatives (IVb—i)(Table II).

This new oxazolo[5,4-*d*]pyrimidine synthesis presumably proceeds through the initial formation of the sulfinyl chloride intermediates (IIIa—i) and subsequent elimination of hydrogen chloride and sulfur monoxide (Chart 1). The elimination of hydrogen chloride and sulfur monoxide has been postulated in certain sulfinyl chlorides.[6]

Recently, it was reported that the reaction of 6-amino-5-benzylideneamino-1,3-dimethyluracils with diethyl azodicarboxylate gives the corresponding 8-aryltheophyllines,[7] however, attempted cyclization of (IIa) with this reagent to give (IVa) was found to be unsuccessful, and the starting material was recovered.

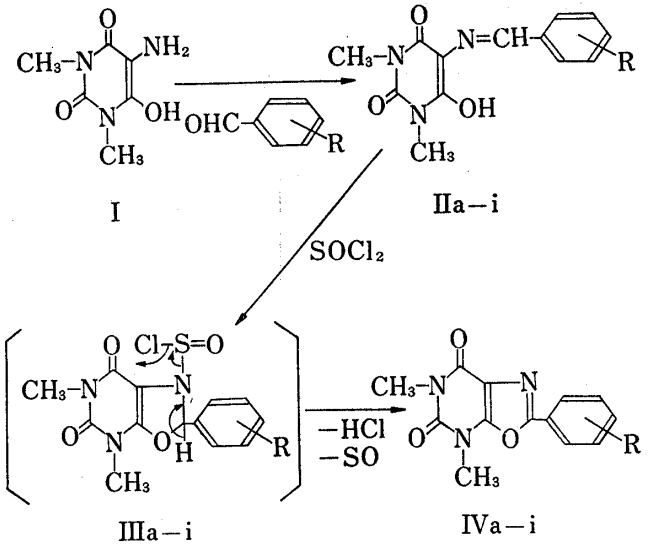
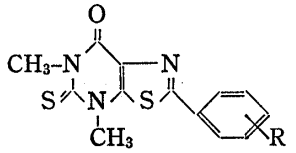


Chart 1

2-Aryl-5,7-dimethylthiazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-diones

Refluxing of (IVa) with an excess of phosphorus pentasulfide in dry pyridine for 8 hr provided an excellent yield of 5,7-dimethyl-2-phenylthiazolo[5,4-*d*]pyrimidine-4(5H)-one-6-

Table III. 2-Aryl-5,7-dimethylthiazolo[5,4-*d*]pyrimidine-4(5H)-one-6(7H)-thiones



Compd. No.[a]	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	IR (Nujol) cm^{-1} (C=O)	(C=S)
VIa	H	264—266	71	$C_{13}H_{11}N_3OS_2$	53.95	3.84	14.52	54.03	3.81	14.74	1686	1270
VIb	4-Br	276—277	95	$C_{13}H_{10}BrN_3OS_2$	42.39	2.74	11.41	42.41	2.72	11.67	1684	1275
VIc	4-Cl	271	90	$C_{13}H_{10}ClN_3OS_2$	48.21	3.12	12.98	48.45	3.17	13.18	1693	1275
VId	4-OMe	274—276	95	$C_{14}H_{13}N_3O_2S_2$	52.64	4.11	13.16	52.38	4.17	13.38	1680	1250
VIe	3,4-$(OMe)_2$	280	98	$C_{15}H_{15}N_3O_3S_2$	51.55	4.34	12.03	51.80	4.38	12.28	1685	1260

a) All compounds were recrystallized from DMF-EtOH.

6) A.J. Krubsack and T. Higa, *Tetrahedron Lett.*, **1968**, 5149; H.M. Relles, *J. Org. Chem.*, 37, 3630 (1972); A.J. Krubsack and T. Higa, *Tetrahedron Lett.*, **1973**, 4515; K. Senga, K. Shimizu, and S. Nishigaki, *Chem. Pharm. Bull.* (Tokyo), **25**, 495 (1977); K. Senga, J. Sato, and S. Nishigaki, *Heterocyles*, **6**, 945 (1977).

7) F. Yoneda, M. Higuchi, K. Senga, K. Shimizu, and S. Nishigaki, *Heterocycles*, **4**, 1759 (1976).

(7H)-thione (VIa) which was isolated after concentration of the reaction mixture and addition of boiling water. This reaction was equally applicable to other oxazolo[5,4-*d*]pyrimidines (IVb, c, h, and i) to give the corresponding thiazolo[5,4-*d*]pyrimidine-4(5H)-one-6(7H)-thiones (VIb—e) (Table III).

The structures of compounds (VIa—e) were assigned by elemental analyses and satisfactory spectral data. In particular, the infrared (IR) spectra of these compounds revealed only one carbonyl absorption band in the region of 1680—1690 cm^{-1}, respectively.

The transformation of (IVa, b, c, h, and i) into (VIa—e) probably involves the initial construction of 2-aryl-5,7-dimethyloxazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-dithiones (Va—e) and subsequent oxazole-thiazole rearrangenemt of (Va—e) (Chart 2). The rearrangement of this type has previously been observed.[3g]

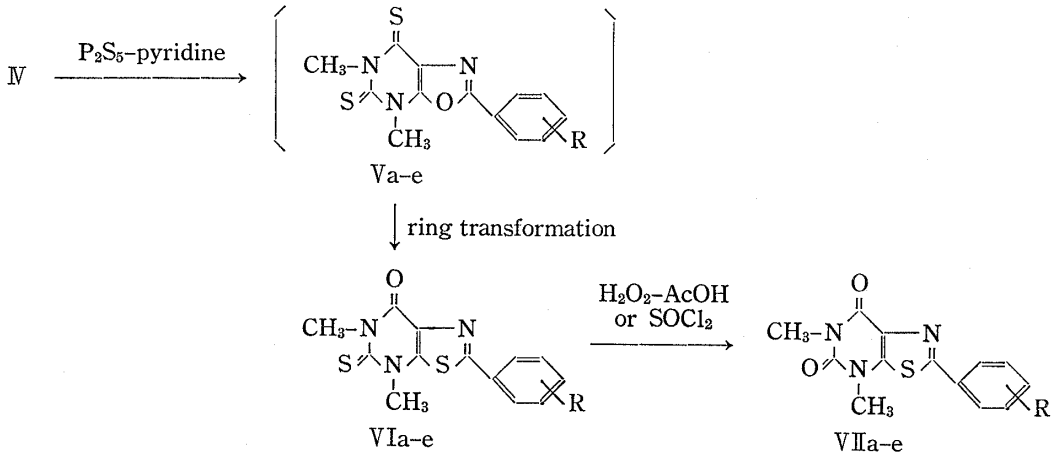
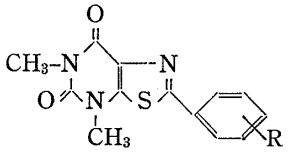


Chart 2

The compounds (VIa—e) thus prepared were treated with 30% hydrogen peroxide in acetic acid at room temperature for 1.5 hr to give the corresponding 2-aryl-5,7-dimethylthiazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-diones (VIIa—e). The conversion of (VIa—e) into(VIIa—e) was also achieved in somewhat better yields by use of thionyl chloride instead of the

Table IV. 2-Aryl-5,7-dimethylthiazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-diones



Compd. No.[a]	R	mp (°C)	Yield (%)[b]	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	IR (Nujol) cm^{-1} (C=O)	
VIIa	H	221—224	88(90)	$C_{13}H_{11}N_3O_2S$	57.12	4.06	15.38	57.37	4.07	15.68	1703	1652
VIIb	4-Br	265—267	77(85)	$C_{13}H_{10}BrN_3O_2S$	44.33	2.87	11.93	44.26	2.85	12.17	1704	1653
VIIc	4-Cl	251	91(95)	$C_{13}H_{10}ClN_3O_2S$	50.73	3.28	13.66	50.62	3.20	13.84	1706	1656
VIId	4-OMe	261	70(91)	$C_{14}H_{13}N_3O_3S$	55.43	4.33	13.85	55.64	4.37	14.10	1695	1650
VIIe	3,4-$(OMe)_2$	280—282	86(91)	$C_{15}H_{15}N_3O_4S$	54.04	4.54	12.61	53.80	4.50	12.33	1690	1650

a) All compounds were recrystallized from EtOH.
b) Yields by Method A. Yields by Method B were indicated in the parentheses.

peroxide (Table IV). Replacement of a sulfur by oxygen with thionyl chloride has recently been reported.[8]

The structures of (VIIa—e) were confirmed by elemental analyses and satisfactory spectral data, especially the presence of two carbonyl absorption bands at 1650—1710 cm^{-1} in their IR spectra.

Experimental[9]

5-Benzylideneamino-1,3-dimethylbarbituric Acids (IIa—i) (Table I)——A mixture of 5-amino-1,3-dimethylbarbituric acid (I)[5] (0.171 g, 0.001 mol) and the respective aromatic aldehydes (0.0013 mol) in EtOH (10 ml) was refluxed for 1 hr. After cooling, the crystals which separated were filtered off and recrystallized to give the corresponding pure product (IIa—i).

2-Aryl-5,7-dimethyloxazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-diones (IVa—i) (Table II)——A mixture of the appropriate (II) (0.001 mol) and $SOCl_2$ (3 ml) was heated at 55° for 30 min with stirring. The reaction mixture was evaporated *in vacuo* and the residue was triturated with chilled 5% aqueous NH_3 (5 ml). The crystals which separated were filtered off, washed well with H_2O, dried, and recrystallized to give the corresponding pure product (IVa—i).

2-Aryl-5,7-dimethylthiazolo[5,4-*d*]pyrimidine-4(5H)-one-6(7H)-thiones (VIa—e) (Table III)——A mixture of the appropriate (IV) (0.001 mol) and P_2S_5 (0.666 g, 0.003 mol) in dry pyridine (10 ml) was refluxed for 8—14 hr. The reaction mixture was evaporated *in vacuo* and the residue was covered with boiling H_2O. The precipitated crystals were filtered off, washed with boiling H_2O, dried, and recrystallized to give the corresponding pure product (VIa—e).

2-Aryl-5,7-dimethylthiazolo[5,4-*d*]pyrimidine-4,6(5H,7H)-diones (VIIa—e) (Table IV)——Method A: To a suspension of the appropriate (VI) (0.00015 mol) in AcOH (1.5 ml), 30% H_2O_2 (0.1 ml) was added dropwise. The mixture was stirred at room temperature for 1.5 hr and the precipitates were filtered off. The crystals were washed well with H_2O, dried, and recrystallized to give the corresponding pure product (VIIa—e).

Method B: A mixture of the appropriate (VI) (0.001 mol) and $SOCl_2$ (1 ml) was refluxed for 10 min. The reaction mixture was evaporated *in vacuo* and the residue was triturated with 5% aqueous NH_3. The crystals which separated were filtered off, washed well with H_2O, and recrystallized to give the corresponding pure product (VIIa—e), which is identical with the sample prepared by Method A.

8) Y. Furukawa, O. Miyashita, and S. Shima, *Chem. Pharm. Bull.* (Tokyo), **24**, 970 (1976); S. Nishigaki, K. Shimizu, and K. Senga, *Chem. Pharm. Bull.* (Tokyo), **25**, 2790 (1977).

9) Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a Japan Spectroscopic Co., Ltd. spectrophotometer, Model IR-E from samples mulled in Nujol.