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Oxidative Cyclization of 6-Amino-5-benzylideneamino-1,3-dimethyluracils with Thionyl Chloride. A Convenient Synthesis of 8-Substituted Theophyllines

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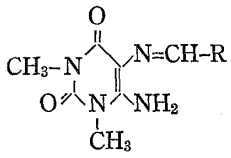
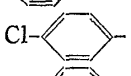
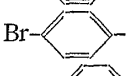
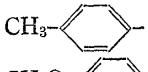
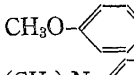
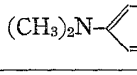
A convenient synthetic method of 8-substituted theophyllines, which consists of the oxidative cyclization of 6-amino-5-benzylideneamino-1,3-dimethyluracils with thionyl chloride, is described.

Keywords——5,6-diamino-1,3-dimethyluracil; aldehydes; 6-amino-5-benzylideneamino-1,3-dimethyluracils; thionyl chloride; oxidative cyclization; 8-substituted theophyllines

Since the successful preparation of uric acid by Traube,[2] 4,5-diaminopyrimidines have been widely employed as the most versatile synthetic intermediates for purine synthesis. Among the several approaches to purines from 4,5-diaminopyrimidines, certain 5-alkylideneamino(and 5-benzylideneamino)-4-aminopyrimidines have been reported to undergo oxidative cyclization to give 8-alkyl(and 8-aryl)purines, and a variety of oxidizing agents have been adopted for this purpose.[3] We now report a convenient synthesis of 8-substituted theophyllines by treatment of 6-amino-5-benzylideneamino-1,3-dimethyluracils with thionyl chloride.

Table I. 6-Amino-5-benzylideneamino-1,3-dimethyluracils[a]

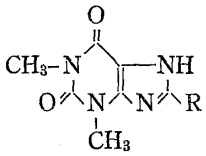


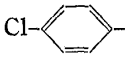
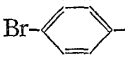
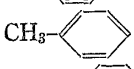
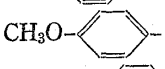
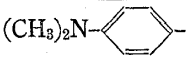
Compd. No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIa		233—235[b]	83	$C_{13}H_{14}O_2N_4$	60.45	5.46	21.70	60.32	5.56	21.83
IIb		221—223	81	$C_{13}H_{13}O_2N_4Cl$	53.33	4.44	19.13	53.26	4.47	19.42
IIc		202	86	$C_{13}H_{13}O_2N_4Br$	46.30	3.89	16.62	46.44	3.94	16.62
IId		230—232	94	$C_{14}H_{16}O_2N_4$	61.75	5.92	20.58	61.57	5.88	20.71
IIe		205—208	92	$C_{14}H_{16}O_3N_4$	58.32	5.59	19.44	58.27	5.57	19.69
IIf		250—253	80	$C_{15}H_{19}O_2N_5$	59.78	6.36	23.24	59.58	6.25	23.26

a) All compounds were recrystallized from EtOH. b) Lit.[6] mp 220°

1) Location: *35, Shinanomachi, Shinjuku-ku, Tokyo, 160, Japan.*
2) W. Traube, *Chem. Ber.*, **33**, 1382 (1900).
3) J.H. Lister, "Fused Pyrimidines, Part II, Purines," ed. by D.J. Brown, Wiley-Interscience, New York, 1971, pp. 69—71, and references cited therein.

Table II. 8-Substituted Theophyllines[a]



Compd. No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IVa		>300[b]	84	$C_{13}H_{12}O_2N_4$	60.93	4.72	21.87	60.78	4.82	22.03
IVb		>300[c]	70	$C_{13}H_{11}O_2N_4Cl$	53.75	3.82	19.29	53.58	3.80	19.31
IVc		>300	68	$C_{13}H_{11}O_2N_4Br$	46.54	3.28	16.71	46.51	3.30	16.74
IVd		>300[c]	70	$C_{14}H_{14}O_2N_4$	62.21	5.22	20.73	62.35	5.01	20.55
IVe		>300[d]	68	$C_{14}H_{14}O_3N_4$	58.73	4.93	19.57	58.46	4.89	19.44
IVf		>300[d]	69	$C_{15}H_{17}O_2N_5$	60.19	5.72	23.40	60.18	5.60	23.67

a) All compounds were recrystallized from DMF.
b) Lit.[6] mp >300°
c) Lit. mp >300° (K. Senga, H. Kanazawa, and S. Nishigaki, *J. Chem. Soc. Chem. Commun.*, **1975**, **155** (1976))
d) Lit. mp >300° (F. Yoneda, S. Matsumoto, and M. Higuchi, *J. Chem. Soc. Chem. Commun.*, **1974**, **551**, (1974))

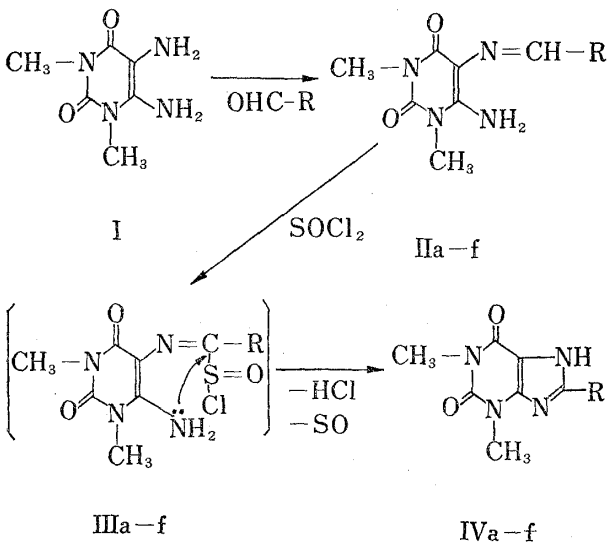


Chart 1

The key intermediates, 6-amino-5-benzylideneamino-1,3-dimethyluracils (IIa—f),[4] were prepared by the condensation of 5,6-diamino-1,3-dimethyluracil (I)[5] with respective aldehydes in according to the reported procedure[6] (Table I). Heating of 6-amino-5-benzylideneamino-1,3-dimethyluracil (IIa)[6] with thionyl chloride at reflux for 5 minutes afforded, after evaporation of the thionyl chloride *in vacuo* and addition of aqueous ammonia, 8-phenyltheophylline (IVa)[6] in a good yield. This reaction was equally applicable to other 6-amino-5-benzylideneamino-1,3-dimethyluracils (IIb—f) to give the corresponding 8-substituted theophyllines (IVb—f) (Table II). The structures of IVa—f were assigned by elemental analyses and the presence of the characteristic secondary amino stretching absorption bands at around 3150 cm^{-1} in their infrared (IR) spectra.[7]

4) The preferential formation of anils (IIa—f) is due to the higher nucleophilic character of the 5-amino group in I: D.J. Brown, "The Pyrimidines," ed. by A. Weissberger, Interscience Publishers, New York, 1962, pp. 324—328.
5) F.F. Blicke and H.C. Godt, *J. Am. Chem. Soc.*, **76**, 2798 (1954).
6) W. Traube and W. Nithack, *Chem. Ber.*, **39**, 227 (1906).
7) The IR spectrum of IVa, IVb, IVd, IVe, and IVf was consistent with that of an authentic sample, respectively (see Table II).

Although the mechanism of this cyclization is not yet clear, the formation of theophyllines presumably involves the oxidative process by the initial formation of the sulfinyl chloride intermediates (IIIa—f) and subsequent cyclization by the loss of hydrogen chloride and sulfur monoxide. The elimination of hydrogen chloride and sulfur monoxide has also been postulated in certain sulfinyl chlorides[8a-c] (Chart 1).

Experimental[9]

6-Amino-5-benzylideneamino-1,3-dimethyluracils (IIa—f) (Table I)——A mixture of 5,6-diamino-1,3-dimethyluracil (I)[5] (0.51 g, 0.003 mole) and an equimolar amount of respective aldehydes in EtOH (20 ml) was refluxed for 1 hr. After cooling, the precipitated solid was filtered and recrystallized from EtOH to give the corresponding pure product (IIa—f).

8-Substituted Theophyllines (IVa—f) (Table II)——A mixture of 6-amino-5-benzylideneamino-1,3-dimethyluracil (0.003 mole) and $SOCl_2$ (5 ml) was refluxed for 5 min. The reaction mixture was evaporated *in vacuo*, and the residue was triturated with aqueous ammonia to give a solid. Recrystallization from dimethylformamide (DMF) gave the corresponding pure product (IVa—f).

8) *a*) A.J. Krubsack and T. Higa, *Tetrahedron Letters*, **1968**, 5149; *b*) H.M. Relles, *J. Org. Chem.*, 23, 3630 (1972); *c*) A.J. Krubsack and T. Higa, *Tetrahedron Letters*, **1973**, 4515.

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

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Effect of Morphine and Its Conjugates on the Isolated Ileal Preparation of Guinea-pig

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The present study was undertaken to reconfirm the previous conclusion that morphine-6-conjugates cause potent analgesia by themselves in mice. For this purpose, inhibitory effect of morphine and its three pairs of 3- and 6-conjugates (glucuronides, ethereal sulfates and phosphates) to nicotine-induced contraction of the isolated guinea-pig ileum was examined. The potency of these conjugates was found to decrease in the following order, morphine-6-sulfate> morphine-6-glucuronide> morphine, morphine-3- and 6-phosphate> morphine-3-glucuronide, morphine-3-sulfate, indicating fairly good accordance with order in their analgesic effects in mice. The present experiment again provided strong suggestion that the above biological effect was attributable to the conjugates themselves.

Keywords——morphine; morphine glucuronides; morphine sulfate esters; morphine phosphate esters; ileum contraction; isolated guinea-pig ileum

Metabolism of morphine has been extensively studied by many workers to elucidate mechanism of the action and development of the tolerance and dependence. Yoshimura, *et al.*[2] showed for the first time that several mammalian species including man excreted morphine-6-

1) Location: *a*) *1-14 Bunkyo-machi, Nagasaki*; *b*),*c*) *3-1-1 Maidashi, Higashi-ku, Fukuoka*; *d*) The author to whom reprint requests should be sent.

2) H. Yoshimura, K. Oguri, and H. Tsukamoto, *Biochem. Pharmacol.*, **18**, 279 (1969); K. Oguri, S. Îda, H. Yoshimura, and H. Tsukamoto, *Chem. Pharm. Bull.* (Tokyo), **18**, 2414 (1970).