[Chem. Pharm. Bull. 21(3) 473—477 (1973)] UDC 547.855'74.04.057

Syntheses and Properties of Some Pyrrolo[2,3-*d*]pyrimidine Derivatives

FUMIO YONEDA, MASATSUGU HIGUCHI,[1a] KEITARO SENGA, MICHIKO KANAHORI and SADAO NISHIGAKI[1b]

Faculty of Pharmaceutical Sciences, Kumamoto University,[1a] and Pharmaceutical Institute, Keio University[1b]

(Received May 19, 1972)

The reaction of 6-amino-1,3-dimethyluracil (I) with phenacyl bromide in DMF gave 1,3-dimethyl-6-phenylpyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione (II) in high yield. The reaction of I and phenacyl bromide in acetic acid afforded the isomeric 1,3-dimethyl-5-phenylpyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione as a byproduct besides II. Nitrosation of II gave 1,3-dimethyl-5-nitroso-6-phenylpyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione (III) along with the corresponding 5-nitro derivative. Ring expansion of III by the Beckmann rearrangement was carried out to give 1,3-dimethyl-5-hydroxy-6-phenylpyrimido[4,5-*d*]-pyrimidine-2,4(1H,3H)-dione. Denitrosation of III by the action of sulfuric acid was observed.

This paper is concerned with preparations of 1,3-dimethylpyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione derivatives and the Beckmann-type ring expansion of 1,3-dimethyl-5-nitrosopyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-diones to 1,3-dimethyl-5-hydroxypyrimido[4,5-*d*]pyrimidine-2,4(1H,3H)-diones.

Refluxing 6-amino-1,3-dimethyluracil (I) with phenacyl bromide in dimethylformamide (DMF) afforded 1,3-dimethyl-6-phenylpyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione (IIa)[2] in high yield. This procedure is an application of the synthetic method of 1,3-dimethylpyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione from I and chloroacetaldehyde.[3] The formation of IIa shows that the reaction of the halogen function of α-halocarbonyl compounds at the 5 position of I is a most probable course of this ring closure reaction. The nuclear magnetic resonance (NMR) spectrum of IIa in DMSO-d_6 showed singlets at 3.25 (N-CH_3) and 3.55 (N-CH_3), a doublet at 6.83 (C_6 H in pyrrole), a multiplet at 7.10—7.90 (C_6H_5), and a broad band at 11.72 ppm (NH in pyrrole). It is interesting to note that the proton at position 5 at 6.83 ppm is split to a doublet (J=2 cps) by the NH proton at position 7. Condensation of I with *p*-chloro- and *p*-bromo-phenacyl bromide likewise gave 6-(*p*-chlorophenyl)-(IIb) and 6-(*p*-bromophenyl)-1,3-dimethylpyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione (IIc), respectively.

When the reaction of I with phenacyl bromide was carried out in acetic acid, the formation of 1,3-dimethyl-5-phenylpyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione (III), the isomer of IIa, was observed besides the main product (IIa). The structure of III was assigned on the basis of the following evidences. Compound (III) shows the presence of a secondary amino stretching absorption band at 3230 cm^{-1}. The NMR spectrum in DMSO-d_6 shows singlets at 3.26 (N-CH_3), 3.37 (N-CH_3), 7.48 (C_6H_5)[4] and 7.68 ppm (C_6 H in pyrrole). No NH absorption typical of the pyrrolo ring was observed. The mass spectrometry reveals a strong parent ion at *m/e* 255. The assigned structure was confirmed with information from its elemental analysis.

1) Location: *a*) *Oe-honmachi, Kumamoto*; *b*) *Shinanomachi, Shinjuku-ku, Tokyo.*
2) Our work on the synthesis of pyrrolo[2,3-*d*]pyrimidines was carried out before a similar report appeared. H. Ogura, M. Sakaguchi, and K. Takeda, *Chem. Pharm. Bull.* (Tokyo), **20**, 404 (1972).
3) C.W. Noell and R.K. Robins, *J. Heterocyclic Chem.*, **1**, 34 (1964).
4) The singlet at 7.48 ppm shows a free rotation of the phenyl group.

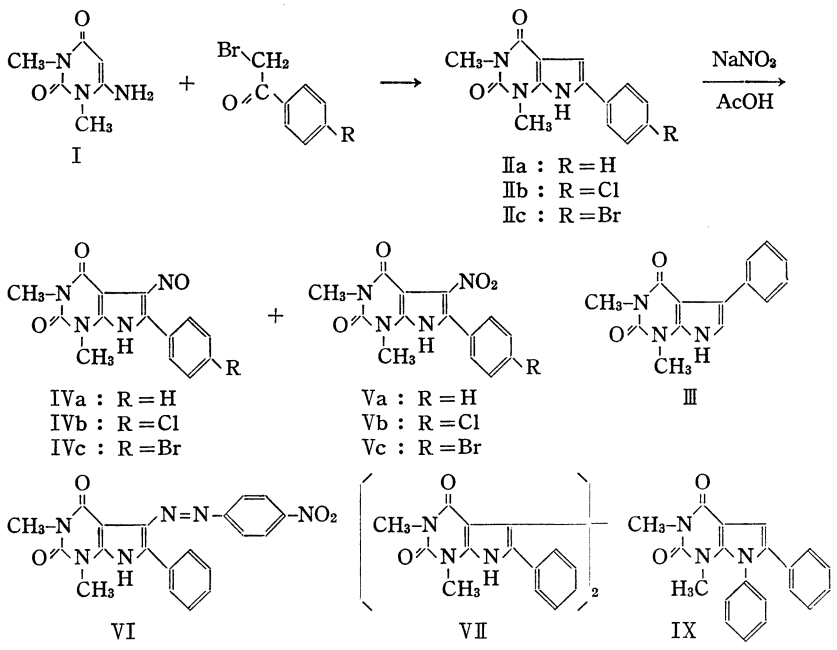


Chart 1

Nitrosation of IIa, IIb and IIc with sodium nitrite in acetic acid gave 6-phenyl -(IVa), 6-(*p*-chlorophenyl)-(IVb) and 6-(*p*-bromophenyl)-1,3-dimethyl-5-nitrosopyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione (IVc) along with the respective 5-nitro derivatives (Va, Vb and Vc). The formation of the nitro derivatives may be caused by oxidation of the corresponding nitroso compounds (IVa, IVb and IVc) by nitrous acid.[5]

1,3-Dimethyl-5-*p*-nitrophenylazo-6-phenylpyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione(VI) was obtained by the conventional coupling reaction of IIa with *p*-nitrobenzenediazonium chloride. The reaction of IIa with diethyl azodicarboxylate underwent dehydrogenative coupling to give 5,5′-bis-(1,3-dimethyl-5-phenylpyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione) (VII), whose structure was ascertained by elemental analysis, molecular weight determination by mass spectrometry and from the similar infrared (IR) spectra with those of IIa.

Next, the reaction of 6-anilino-1,3-dimethyluracil (VIII) and phenacyl bromide in DMF was carried out in order to get 1,3-dimethyl-6,7-diphenylpyrrolo[2,3-*d*]pyrimidine-2,4(1H, 3H)-dione (IX), which has already been synthesized by the condensation of VIII and phenacylpyridinium bromide in low yield.[6] In our case, IX was obtained in 87% yield. All attempts to nitrosate IX were unsuccessful with the starting material being recovered. This would be a behavior ascribed to the decrease of the electron density at position 5 by the introduction of 7-phenyl group.

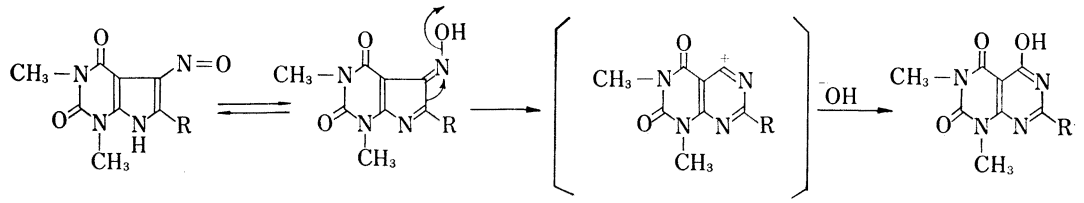
Compounds IVa, IVb and IVc reacted with tosyl chloride in DMF to give the rearranged products, 1,3-dimethyl-5-hydroxy-6-phenylpyrimido[4,5-*d*]pyrimidine-2,4(1H,3H)-diones (Xa, Xb and Xc), which were confirmed in structure by their identical IR spectra to the authentic samples.[7] This is the first example of the conversion of nitrosopyrrole derivative

5) It is known that the oxidation 5-nitrosopyrimidines to 5-nitropyrimidines can be effected with sodium nitrite in sulfuric acid. S. Nishigaki, K. Ogiwara and F. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **19**, 418 (1971).

6) E.C. Taylor and E.E. Garcia, *J. Org. Chem.*, **30**, 655 (1965).

7) *a*) F. Yoneda, and M. Higuchi, *Chem. Commun.*, **1972**, 407; *b*) F. Yoneda and M. Higuchi, *Chem. Pharm. Bull.* (Tokyo), **20**, 2076 (1972).

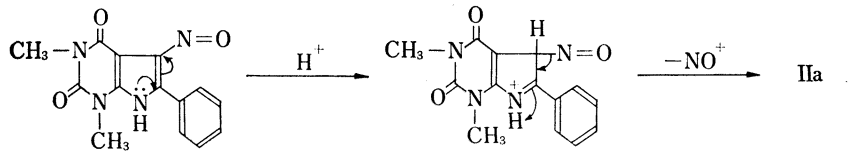
into pyrimidine derivative by the Beckmann rearrangement. Reaction of IVa with phosphorus oxychloride in DMF (Vilsmeier–Haack condition) also gave Xa in good yield. These reactions show that 5-nitrosopyrrolo-pyrimidines apparently react in their imino oxime tautomeric form under these conditions as seen in Chart 2.



IVa, IVb, IVc Xa, Xb, Xc

Chart 2

When IVa was treated with concentrated sulfuric acid in DMF under reflux, the denitrosation took place to give IIa. This type of denitrosation can be rationalized by the following mechanism (Chart 3). The only previously recorded denitrosation is the conversion of 6-amino-5-nitroso-1,3-dimethyluracil to 6-amino-1,3-dimethyl-uracil.[8]



IVa

Chart 3

Experimental[9]

1,3-Dimethyl-6-phenylpyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione (IIa)——A solution of 10 g (0.065 mole) of 6-amino-1,3-dimethyluracil (I) and 13 g (0.065 mole) of phenacyl bromide in 100 ml of DMF was heated under refluxing for 2 hr. After evaporation of the reaction mixture, the residue was treated with H_2O. The precipitated crystals were collected by filtration, washed with H_2O, dried and recrystallized from EtOH of give 12.2 g of colorless needles of IIa.

Under the same conditions, 6-(*p*-chlorophenyl)- (IIb) and 6-(*p*-bromophenyl)-1,3-dimethylpyrrolo[2,3-*d*]-pyrimidine-2,4(1H,3H)-dione (IIc) were obtained by the condensation of I with *p*-chloro- and *p*-bromophenacyl bromide (See Table I).

Reaction of I with Phenacyl Bromide in Acetic Acid——A solution of 1.55 g (0.01 mole) of I and 1.99 g (0.01 mole) of phenacyl bromide in 15 ml of AcOH was heated for 5 hr at 90°. After the reaction mixture was evaporated under reduced pressure, the residue was diluted with 30 ml of H_2O. Separated precipitates were collected by filtration, washed with H_2O and dried to give 0.8 g (31%) of IIa.

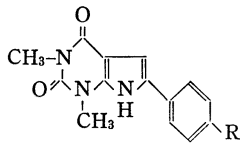
The filtrate was extracted with ether. The extracts were dried (Na_2SO_4) and evaporated. The residue was neutralized with 5% aq. NH_3 to precipitate colorless crystals, which were filtered off and recrystallized from EtOH–H_2O to give 0.4 g (16%) of colorless needles of 1,3-dimethyl-5-phenylpyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione (III), mp 115°. *Anal.* Calcd for $C_{14}H_{13}O_2N_3$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.65; H, 5.10; N, 16.53.

1,3-Dimethyl-5-nitroso-6-phenylpyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione (IVa) and 1,3-Dimethyl-5-nitro-6-phenylpyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione (Va)——To a suspension of 2.55 g (0.01 mole) of

8) E.C. Taylor and E.E. Garcia, *J. Am. Chem. Soc.*, **86**, 4721 (1964).

9) Melting points are uncorrected. Infrared spectra were determined on a Japan Spectroscopic Co., Ltd. spectrophotometer, Model IR-E, from samples mulled in Nujol. NMR spectra were taken at 60 Mc with a Hitachi, Perkin–Elmer Co., Ltd. Model R-20A using tetramethylsilane as the internal reference.

TABLE I. Preparation of 1,3-Dimethyl-6-phenylpyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-diones



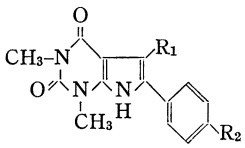
Compound No.	R	mp (°C)	Yield (%)	Appearance (Recryst. solvent)	Formula	Analysis (%) Calcd. C	H	N	Found. C	H	N
IIa	H	298	74	colorless needles (EtOH)	$C_{14}H_{13}O_2N_3$	65.87	5.13	16.46	65.76	5.11	16.31
IIb	Cl	>330	71	colorless needles (EtOH)	$C_{14}H_{12}O_2N_3Cl$	58.03	4.15	14.51	58.32	4.13	14.28
IIc	Br	>330	69	colorless needles (EtOH)	$C_{14}H_{12}O_2N_3Br$	50.31	3.59	12.58	50.10	3.31	12.35

IIa in a mixture of 50 ml of AcOH and 15 ml of H_2O was added little by little a solution of 1 g (0.015 mole) of $NaNO_2$ in 5 ml of H_2O under stirring and cooling at 0°. After stirring for 1 hr at this temperature, the separated crystals were collected by filtration, washed with H_2O and recrystallized from EtOH to give 1.9 g of red needles of IVa, mp 214°.

The mother liquid was allowed to stand at room temperature for 24 hr to precipitate yellow crystals, which were filtered off and recrystallized from EtOH to give 0.75 g of yellow needles of Va, mp 232°.

Similarly, nitrosation of IIb and IIc yielded 6-(*p*-chlorophenyl)- (IVb) and 6-(*p*-bromophenyl-1,3-dimethyl-5-nitrosopyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione (IVc) along with the corresponding 5-nitro derivatives (Vb and Vc) (see Table II).

TABLE II. Preparation of 1,3-Dimethyl-5-nitrosopyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-diones and 1,3-Dimethyl-5-nitropyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-diones



Compound No.	R_1	R_2	mp (°C)	Yield (%)	Appearance (Recryst. solvent)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IVa	NO	H	214	67	red needles (EtOH)	$C_{14}H_{12}O_3N_4$	59.15	4.26	19.71	60.07	4.12	19.50
IVb	NO	Cl	231	76	red needles (EtOH)	$C_{14}H_{11}O_3N_4Cl$	52.75	3.45	17.58	52.96	3.27	17.24
IVc	NO	Br	216	70	red needles (EtOH)	$C_{14}H_{11}O_3N_4Br$	46.29	3.03	15.43	46.49	2.91	15.18
Va	NO_2	H	232	25	yellow needles (EtOH)	$C_{14}H_{12}O_4N_4$	56.00	4.03	18.66	56.12	4.25	18.39
Vb	NO_2	Cl	239	18	yellow needles (EtOH)	$C_{14}H_{11}O_4N_4Cl$	50.24	3.31	16.44	49.99	3.34	16.25
Vc	NO_2	Br	235	20	yellow needles (EtOH)	$C_{14}H_{11}O_4N_4Br$	44.34	2.92	14.78	44.27	3.03	14.56

1,3-Dimethyl-5-*p*-nitrophenylazo-6-phenylpyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione (VI)——To a solution of 2 g (0.008 mole) of IIa in 100 ml of 3N AcOH was added little by little a solution of *p*-nitrophenyldiazonium chloride, which was prepared by treatment of 1.4 g (0.01 mole) of *p*-nitroaniline in 20 ml of 10%

HCl with 0.7 g (0.01 mole) of $NaNO_2$, under stirring and cooling at 0°. The reaction mixture was neutralized to pH 6 with sodium acetate and further stirred for 2 hr. The precipitated red crystals were collected by filtration and recrystallized from DMF to give 2.6 g (81%) of dark red needles, mp>300°. *Anal.* Calcd. for $C_{20}H_{10}O_4N_6$: C, 59.40; H, 3.99; N, 20.78. Found: C, 59.21; H, 4.02; N, 20.65.

5,5′-Bis-(1,3-dimethyl-6-phenylpyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione (VII)——A mixture of 0.5 g (0.002 mole) of IIa, 0.5 g (0.0029 mole) of diethyl azodicarboxylate and 1 ml of sulfolane was heated at 200° for 15 min. After cooling, the reaction mixture was diluted with EtOH to separate crystals. Recrystallization from DMF gave 0.3 g (60%) of colorless prisms of VII, mp>300°. *Anal.* Calcd. for $C_{28}H_{24}O_4N_6$: C, 66.13; H, 4.76; N, 16.53. Found: C, 65.97; H, 4.75; N, 16.24.

1,3-Dimethyl-6,7-diphenylpyrrolo[2,3-*d*]pyrimidine-2,4(1H,3H)-dione (IX)——A mixture of 0.6 g (0.03 mole) of 6-anilino-1,3-dimethyluracil, 0.6 g (0.003 mole) of phenacyl bromide in 10 ml of DMF was heated under refluxing for 10 hr at 190°. After excess of DMF was removed under reduced pressure, the resulting residue was recrystallized from EtOH to give 0.75 g (87.2%) of IX, mp 228—230°, which was in all respects identical with an authentic sample.[6]

1,3-Dimethyl-5-hydroxy-7-phenylpyrimido[4,5-*d*]pyrimidine-2,4(1H,3H)-dione (Xa)——Method A: A mixture of 0.5 g (0.0018 mole) of IVa and 1 g (0.005 mole) of tosyl chloride in 10 ml of DMF was heated under refluxing for 15 min. After cooling, the reaction mixture was diluted with 50 ml of H_2O. The separated precipitates were collected by filtration and recrystallized from DMF to give 0.2 g (40%) of colorless prisms of Xa, mp>320°, which was in all respects identical with an authentic sample.[7]

Method B: To a solution of 0.5 g (0.0018 mole) of IVa in 10 ml of DMF was added 0.8 g (0.005 mole) of $POCl_3$ and heated under refluxing for 1 hr. After evaporation of the reaction mixture, the residue was diluted with H_2O. The precipitated crystals were collected by filtration and recrystallized from DMF to give 0.3 g (60%) of Xa.

Similarly, IVb and IVc were converted into 7-(*p*-chlorophenyl)- (Xb),[7] (mp>330°, 51%) and 7-(*p*-bromophenyl)-1,3-dimethylpyrimido[4,5-*d*]pyrimidine-2,4(1H,3H)-dione (Xc)[7] (mp>330°, 40%).

Reaction of IVa with Sulfuric Acid——To a mixture of 3 ml of concentrated sulfuric acid and 10 ml of DMF was added 0.5 g (0.0018 mole) of IVa and heated for 1 hr at 150°. After cooling, the reaction mixture was diluted with 50 ml of H_2O to precipitate crystals, which were filtered off, washed with H_2O and dried to give 0.1 g (20%) of Xa.

The filtrate was further diluted with 200 ml of H_2O and maintained overnight to precipitate 0.2 g (44%) of IIa.