Pyrrolo[2,3-*d*]pyrimidines. I. 5-Hydroxypyrrolo[2,3-*d*]pyrimidines

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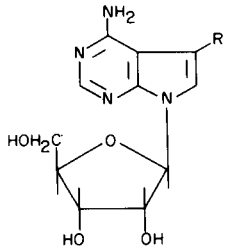
5-Hydroxy-7-alkyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carbonitriles (VIIb-d) and 5-hydroxy-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylic acid, ethyl ester (VIIa) were prepared from 5-carbethoxy-4-chloro-2-phenylpyrimidine (IV) *via* 4-[(cyanomethyl)alkylamino[-2-phenyl-5-pyrimidinecarboxylic acid, ethyl esters (Vb-d) and 4-[(carboxymethyl)amino]-2-phenyl-5-pyrimidinecarboxylic acid, diethyl ester (Va), respectively. The hydroxy group of the pyrrolo-[2,3-*d*]pyrimidines could be methylated, acetylated and tosylated. Hydrolysis of 5-methoxy-7-methyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carbonitrile (IX) afforded the corresponding amide (X).

Although the pyrrolo[2,3-*d*]pyrimidine ring system has been known since 1911 (1), it received little attention until the isolation of antibiotics such as tubercidin (I) (2), toyocamycin (II) (3), and sangivamycin (III) (4), which were all shown to possess the pyrrolo[2,3-*d*]pyrimidine nucleus. Besides their antibiotic properties, these compounds have demonstrated unusual biological properties



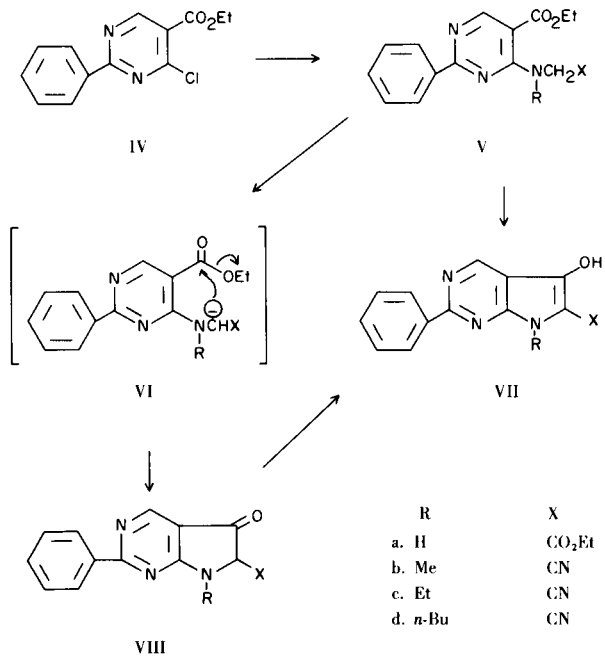
I, R = H, Tubercidin
II, R = CN, Toyocamycin
III, R = $CONH_2$, Sangivamycin

including potent antileukemia activity. It is known, for example, that sangivamycin, which did not show any toxicity in humans at maximally tolerated doses, is presently under clinical trial in the treatment of leukemia (5). The discovery of the remarkable biological activities of these nucleosides has focused considerable attention on pyrrolo-[2,3-*d*]pyrimidines in general as a class of compounds of potential pharmaceutical interest.

A review of the literature has revealed that only a limited number of synthetic routes to the pyrrolo[2,3-*d*]-pyrimidines have been reported. These include: a) cyclization of 4-amino-5-pyrimidineacetic acid esters (1,6,9) or 4-amino-5-pyrimidineacetaldehydes or ketones (7,8); b) the reaction of chloroacetaldehyde with a 4-aminouracil (10,11); c) the reaction of 2-amino-3-cyanopyrroles with methyl orthoformate (12) or formamidine acetate (13); and d) a Fischer indolization-type cyclization of 4-pyrimidyl hydrazones (14).

This paper describes the synthesis of novel 5-hydroxypyrrolo[2,3-*d*]pyrimidines by a process which, to the best of our knowledge, has not been reported previously. 5-Carbethoxy-4-chloro-2-phenylpyrimidine (IV), obtained by treating 5-carbethoxy-4-hydroxy-2-phenylpyrimidine with thionyl chloride, was used as the starting material in this synthesis (Scheme I).

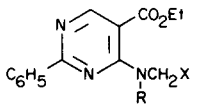
SCHEME I



R	X
a. H	CO_2Et
b. Me	CN
c. Et	CN
d. *n*-Bu	CN

The chloro group of IV was replaced by substituted amines which have incorporated in their structure a methylene

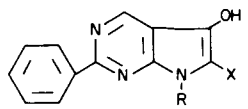
TABLE I



Compound (a)	R	X	M.p., °C	Yield %	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Va	H	CO_2Et	86-88	82	$C_{17}H_{19}N_3O_4$	61.99	5.82	12.76	62.04	5.72	12.94
Vb	Me	CN	86-88	95	$C_{16}H_{16}N_4O_2$	64.85	5.44	18.91	65.08	5.64	18.91
Vc	Et	CN	68-70.5	82	$C_{17}H_{18}N_4O_2$	65.79	5.85	18.05	65.81	6.12	17.85
Vd	*n*-Bu	CN	82-84	81	$C_{19}H_{22}N_4O_2$	67.43	6.55	16.56	67.73	6.43	16.73

(a) The substituted amines required for the preparation of compounds Va-d were commercially available.

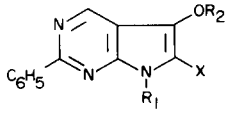
TABLE II



Compound	R	X	M.P., °C	Reaction Period	Yield %	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VIIa	H	CO_2Et	194.5-197	45 min.	86	$C_{15}H_{13}N_3O_3$	63.59	4.63	14.83	63.64	4.48	14.77
VIIb	Me	CN	280-283	15 min.	92	$C_{14}H_{10}N_4O$	67.19	4.03	22.39	67.03	4.06	22.49
VIIc	Et	CN	208 dec	20 min.	44	$C_{15}H_{12}N_4O$	68.17	4.58	21.20	68.00	4.63	21.30
VIId	*n*-Bu	CN	168-172	1 hr.	90	$C_{17}H_{16}N_4O$	69.84	5.52	19.17	69.56	5.46	19.37

TABLE III

Ultraviolet Absorption Date of Pyrrolo[2,3-*d*]pyrimidine Derivatives (a)



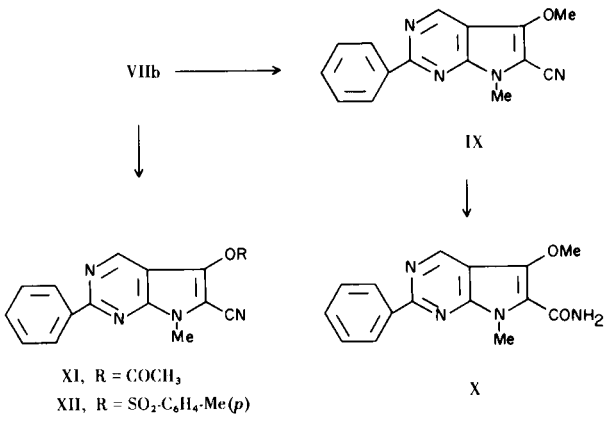
Compound	R_1	R_2	X	λ max mμ	ε max x 10^{-3}
VIIa	H	H	CO_2Et	239	13.4
				270	34.2
VIIb	Me	H	CN	235	13.0
				278	34.2
VIIc	Et	H	CN	236	14.7
				279	35.4
VIId	*n*-Bu	H	CN	233	14.0
				277	34.8
IX	Me	Me	CN	228	15.2
				270	34.2
				308	14.0
X	Me	Me	$CONH_2$	231	14.0
				274	36.8
				309	11.2
XI	Me	$COCH_3$	CN	262	29.4
				315	18.4

(a) Spectra were obtained with a Perkin-Elmer 450 Spectrophotometer in 95% ethanol

group activated by a second functional group, such as a carbethoxy or cyano group. The products thus obtained were intermediates Va-d. Cyclization of Va-d was effected smoothly by treating these compounds with equal molar quantities of sodium ethoxide in ethanol, giving sodium salts of the corresponding 5-hydroxy-2-phenyl-7*H*-pyrrolo-[2,3-*d*]pyrimidines (VIIa-d) in excellent yields. The free pyrrolopyrimidines VIIa-d were obtained by acidification of the sodium salts. This cyclization apparently occurs by an intramolecular Dieckmann-type condensation *via* an intermediate, such as VI, and subsequent tautomerization of VIII to the hydroxypyrrolopyrimidine. Lack of carbonyl absorptions in the infrared spectra of VIIa-d as well as nmr spectral data for these compounds (see experimental), indicates that they exist as 5-hydroxypyrrolo-[2,3-*d*]pyrimidines (VIIa-d)rather than as pyrrolo[2,3-*d*]-pyrimidinones (VIIIa-d). The infrared spectrum of VIIb exhibited an OH absorption band at 3.16 μ and a $-C\equiv N$ stretching band at 4.53 μ.

When the sodium salt of VIIb was allowed to react with methyl iodide in *N*,*N*-dimethylformamide at room temperature, 5-methoxy-7-methyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]-pyrimidine-6-carbonitrile (IX) was formed in quantitative yield (Scheme II). Subsequent treatment of IX with

SCHEME II



30% aqueous sodium hydroxide solution converted the nitrile into the corresponding carboxamide (X). The absence of the $-C\equiv N$ absorption band and the appearance of a 6.06 μ amide carbonyl band in the infrared spectrum of X asserted this transformation. The hydroxy group of VIIb could also be acetylated or tosylated in excellent yield. Thus, refluxing of VIIb in acetic anhydride for 1 hour yielded the acetate XI, and tosylation by a conven-

tional method produced 7-methyl-2-phenyl-5-(*p*-toluenesulfonyloxy)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carbonitrile (XII).

The compounds described in the present report showed mild anti-amoebic and depressant properties when evaluated for pharmacologic activity.

EXPERIMENTAL

The melting points were taken in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. Infrared spectra were obtained in potassium bromide pellets using a Perkin-Elmer 21 spectrophotometer, and nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as the internal reference.

5-Carbethoxy-4-chloro-2-phenylpyrimidine (IV).

A mixture of 5-carbethoxy-4-hydroxy-2-phenylpyrimidine (73 g.) (15) and thionyl chloride (450 ml.) was refluxed for 30 hours. The excess thionyl chloride was removed under reduced pressure. The remaining residue was treated with a large amount of crushed ice and the solid material was collected on a filter giving 75 g. of product, m.p. 128-131°. Recrystallization of the product from petroleum ether raised the m.p. to 130-131°.

Anal. Calcd. for $C_{13}H_{11}ClN_2O_2$: C, 59.44; H, 4.22; N, 10.66; Cl, 13.50. Found: C, 59.22; H, 4.17; N, 10.90; Cl, 13.4.

4-[(Cyanomethyl)methylamino]-2-phenyl-5-pyrimidinecarboxylic Acid Ethyl Ester (Vb) Exemplifies the Preparation of 2-Phenyl-4-substitutedamino-5-pyrimidinecarboxylic Acid, Ethyl Esters (Va-d).

A mixture of methylaminoacetonitrile hydrochloride (10.6 g.) and powdered potassium bicarbonate (10 g.) in 70 ml. of absolute ethanol was heated to reflux for 3/4 hour with mechanical stirring. Compound IV (5.2 g.) was added to the mixture and refluxing was continued for 2 1/2 hours. The mixture was cooled to room temperature, the inorganic salt was removed by filtration, and the filtrate was concentrated under reduced pressure and chilled, causing crystals to separate. The crystals were collected on a filter and washed with water several times. The crude product was recrystallized from absolute ethanol, affording 5.5 g. of product, m.p. 86-88°; ir 3.38 (CH_3), 3.43 (CH_2) and 5.86 μ (C=O); Uv max (95% ethanol) 258 mμ (ϵ, 29,700).

5-Hydroxy-7-alkyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carbonitriles (VIIb-d) and 5-Hydroxy-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylic Acid, Ethyl Ester (VIIa) Were Made as Exemplified by the Preparation of 5-Hydroxy-7-methyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carbonitrile (VIIb).

To a solution containing 0.23 g. of sodium in 45 ml. of absolute ethanol were added 2.9 g. of Vb. The resulting mixture was refluxed for 15 minutes. The reaction mixture was concentrated under reduced pressure and chilled in ice. The resulting precipitate was collected on a filter and dissolved in 70 ml. of hot water. The aqueous solution was acidified with 3 *N* hydrochloric acid to *p*H ~ 2. The solid which separated was collected on a filter, yielding 2.3 g. of product, m.p. 279-281° dec. Recrystallization of the product from absolute ethanol raised the m.p. to 280-283° dec; nmr (DMSO-d_6): δ 3.60 (s, 3H, CH_3N), 7.50 (m, 3H, aromatic), 8.40 (m, 2H, aromatic), 9.10 (s, 1H, pyrimidine), and 11.25 ppm (broad s, 1H, HO–, disappeared on treatment with deuterium oxide.

5-Methoxy-7-methyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carbonitrile (IX).

Compound VIIb was converted into its sodium salt by treatment with an equal molar amount of sodium ethoxide in ethanol, followed by removal of the excess ethanol *in vacuo*. The sodium salt thus obtained (1.7 g.) was dissolved in 20 ml. of DMF to which was added 1.4 g. of methyl iodide. The resulting solution was stirred for 1/2 hour at room temperature, when the dark-orange color disappeared and crystals separated. The mixture was chilled in ice and the precipitate was collected on a filter and washed with water several times. Addition of water to the filtrate caused separation of additional product. The combined product weighed 1.2 g. and melted at 176-179°. Recrystallization from DMF afforded an analytical sample, m.p. 178-180.5°; ir 4.58 (C≡N) and 8.22 μ (C–O–Me); uv max (95% ethanol): 228 (ϵ, 13,900), 270 (ϵ, 34,200, and 308 mμ (ϵ, 13,500); nmr (deuteriochloroform), δ 3.78 (s, 3H, CH_3–N) and 4.22 ppm (s, 3H, CH_3–O).

Anal. Calcd. for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.07; H, 4.66; N, 20.88.

5-Methoxy-7-methyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (X).

Two and one-half grams of IX was added to a mixture of 30% aqueous sodium hydroxide solution (10 ml.) and abolute ethanol (40 ml.). The resulting mixture was refluxed for 2 1/2 hours, then allowed to stand overnight, during which time a precipitate was deposited. The precipitate was collected on a filter and washed with water, giving 2.4 g. of product, m.p. 265-270° dec. Recrystallization from chloroform raised the m.p. to 273-276° dec.; ir 6.06 μ (C=O); nmr (DMSO-d_6), δ 3.25 (s, 2H, H_2N–CO), 4.05 (s, 3H, CH_3–N), and 4.28 ppm (s, 3H, CH_3–O).

Anal. Calcd. for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.79; H, 4.89; N, 19.84.

5-Acetoxy-7-methyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carbontrile (XI).

A mixture of VIIb (1.5 g.) and acetic anhydride (45 ml.) was refluxed for 1 hour, then chilled in ice to allow precipitation of crystals. The crystals were collected on a filter, giving 1.8 g. of product, m.p. 184-188°. Recrystallization of the crude product from acetic anhydride raised the m.p. to 188-190.5°; ir 4.55 (C≡N) and 5.65 μ (C=O); nmr (deuteriochloroform), δ 2.47 (s, 3H, CH_3CO) and 3.94 ppm (s, 3H, CH_3–N).

Anal. Calcd. for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.80; H, 4.01; N, 19.48.

7-Methyl-2-phenyl-5-(*p*-toluenesulfonyloxy)-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carbonitrile (XII).

Two and three-tenths grams of *p*-toluenesulfonyl chloride was dissolved in 15 ml. of ether and added dropwise to an ice-cold pyridine solution containing 2.5 g. of VIIb. The resulting mixture was stirred at room temperature for 2 hours, then poured into ice water, whereupon a precipitate separated. The precipitate was collected on a filter and recrystallized from DMF and water, giving 2.2 g. of product, m.p. 194.5-197.5°; ir 4.56 (C≡N), 7.32, and 8.47 μ (–OSO_2–).

Anal. Calcd. for $C_{21}H_{16}N_4O_3S$: C, 62.36; H, 3.99; N, 13.85; S, 7.93. Found: C, 62.64; H, 4.03; N, 13.84; S, 7.78.

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REFERENCES

(1) T. B. Johnson, *J. Am. Chem. Soc.*, **33**, 758 (1911).

(2) K. Anzai, G. Nakamura and S. Suzuki, *J. Antibiotics* (Tokyo), 10A, 201 (1957).

(3) H. Nishimura, K. Katagiri, K. Sato, M. Mayama, and N. Shimaoka, *ibid.*, 9A, 60 (1956); K. Ohkuma, *ibid.*, 13A, 361 (1960).

(4) K. V. Rao and D. W. Renn, *Antimicrobial Agents and Chemotherapy*, 1963, 77 (1964).

(5) J. A. Cavins, *Proc. Am. Assoc. Cancer Res.*, 7, 12 (1966); C. G. Zubrod, S. Shepartz, J. Leiter, J. M. Endicott, L. M. Carrese, and C. G. Baker, *Cancer Chemotherapy Rept.*, **50**, 496 (1966); J. A. Cavins, T. C. Hall, K. B. Olson, C. L. Khung, J. Horton, J. Colsky, and R. K. Shadduck, *ibid.*, **51**, 197 (1967).

(6) Z. Foeldi, G. V. Fodor, I. Demjen, H. Szekeres, and I. Halmas, *Chem. Ber.*, **75**, 755 (1942); P. Nesbitt and P. Sykes, *J. Chem. Soc.*, 3057 (1954).

(7) J. Davoll, *ibid.*, 131 (1960).

(8) J. A. Montgomery and K. Hewson, *J. Med. Chem.*, **10**, 665 (1967); R. H. Hammer, *J. Pharm. Sci.*, **57**, 1616 (1968).

(9) R. A. Partyka, *U. S. Patent*, 3,311,628 (1967).

(10) C. W. Noell and R. K. Robins, *J. Heterocyclic Chem.*, **1**, 34 (1964).

(11) R. A. West, K. Ledig, and G. H. Hitchings, *British Patent*, 812,366 (1959).

(12) E. C. Taylor and R. W. Hendess, *J. Am. Chem. Soc.*, **86**, 951 (1964); *ibid.*, **87**, 1995 (1965).

(13) R. L. Tolman, R. K. Robins, and L. B. Townsend, *ibid.*, **90**, 524 (1968).

(14) P. A. Crooks and B. Robinson, *Chem. Ind. (London)*, 547 (1967).

(15) P. C. Mitter and J. C. Bardhan, *J. Chem. Soc.*, 2179 (1923).

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