Synthesis of Some 7-Substituted-2,4,8(1*H*,3*H*,7*H*)pyrimido[5,4-*d*]pyrimidinetriones

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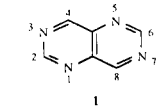
Received February 18, 1986

A synthesis of 2,4,8-pyrimido[5,4-*d*]pyrimidinetriones under mild conditions from ethyl 5-ethoxymethyleneamino-orotate allows the introduction of a variety of substituents regiospecifically into the 7-position. The 7-methyl and 7-benzyl derivatives were methylated with trimethyl phosphate to the 1,3,7-trialkyl derivatives.

J. Heterocyclic Chem., **23**, 1411 (1986).

We are interested in derivatives of the pyrimido[5,4-*d*]-pyrimidine ring system **1** as deaza-analogs of the naturally-occurring antibiotics toxoflavin **2** [1] and fervenulin **3** [2], as "homopurines" [3] related to xanthine and uric acid, and as intermediates in the synthesis of folate analogs. The tetrones **4**, intermediates useful in the synthesis of the coronary vasodilator dipyridamole **5** and derivatives [4], have been prepared previously by fusion of 5-halo- or 5-amino-orotic acids [4-7] with urea or thiourea at temperatures >200°. Similar high-temperature reactions of amino-orotic acid with formamide or formamidine gave the corresponding trione **6** (R = H) [5]; synthesis of a range of 7-substituted derivatives by this route would need symmetrically *N,N'*-disubstituted formamidines which are



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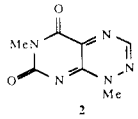

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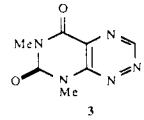

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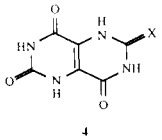

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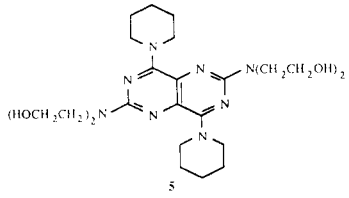

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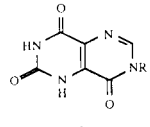

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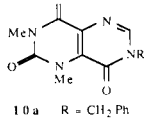

10a R = CH_2Ph
10b R = CH_3

not readily available and which would be unstable under the reaction conditions where more complex or bulkier substituents are required. We here describe a route to 7-substituted pyrimido[5,4-*d*]pyrimidine-2,4,8-triones from ethyl 5-aminoorotate which proceeds under mild conditions, which is tolerant of a wide range of 7-substituents, and which requires only the appropriate primary amine for introduction of the latter.

Ethyl 5-nitroorotate **7** [8] was reduced with aqueous sodium dithionite to the corresponding 5-aminopyrimidine **8**, which on heating with diethoxymethyl acetate was converted into the ethoxymethylene compound **9**. Cyclization to the title compounds **6** was readily effected by heating the latter to reflux with the appropriate primary amine in ethanol (Scheme 1). Structures, reaction conditions and yields are given in Table I. Analytical and nmr

Scheme 1

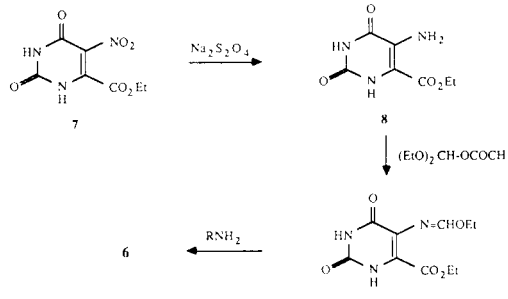

Table I

7-Substituted-pyrimido[5,4-*d*]pyrimidines

Compound # **6**	R	Reaction time (hours)	Yield (%)
a	H	2.5 [a]	72
b	CH_2Ph	2.5	64
c	CH_3	2.5 [a]	59
d	$CH(CH_3)_2$	24	53
e	$(CH_2)_5CH_3$	3	55
f	Morpholinopropyl	3	71
g	Cyclohexylmethyl	1	76
h	$(CH_2)_3Ph$	3	71
i	$C(CH_3)_2CH_2OH$	3	69
j	$(CH_2)_3C(CH_3)_2OH$	3.3	45
k	$(CH(CH_2OH)CH(OH)Ph$	2	73
l	$C(CH_2OH)_3$	3	65
m	3',4'-dimethoxyphenethyl	2.9	73
n	cyclobutyl	3	72
o	cyclopropyl	1.5 [b]	84
p	CH_2CH_2OH	2.75	83
q	$CH_2CH(OH)CH_3$	2.75	75
r	$(CH_2)_3OH$	3.2	79
s	cyclohexyl	0.7	64

[a] Reaction mixture saturated with amine at room temperature, set aside for 3 hours prior to reflux. [b] Reaction mixture stored for 2 hours at room temperature prior to reflux.

Table II

Elemental Analyses

Compound No.	Molecular Formula	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
6a	$C_6H_4N_4O_3$	40.00	2.24	31.11	40.06	2.26	31.05
b	$C_{13}H_{10}N_4O_3$	57.77	3.73	20.73	57.57	3.77	20.66
c	$C_7H_6N_4O_3$	43.30	3.12	28.86	43.30	3.19	28.76
d	$C_9H_{10}N_4O_3$	48.65	4.54	25.20	48.75	4.56	25.10
e	$C_{12}H_{16}N_4O_3$	54.53	6.10	21.20	54.52	6.10	21.20
f	$C_{13}H_{17}N_5O_4$	50.81	5.58	22.79	50.65	5.64	22.72
g	$C_{13}H_{16}N_4O_3$	56.51	5.84	20.28	56.45	5.85	20.23
h	$C_{15}H_{14}N_4O_3$	60.39	4.73	18.78	60.32	4.78	18.72
i	$C_{10}H_{12}N_4O$	47.62	4.80	22.21	47.50	4.86	22.14
j	$C_{13}H_{18}N_4O_4$	53.05	6.16	19.04	53.22	6.19	18.97
k	$C_{15}H_{14}N_4O_5$	54.54	4.27	16.96	54.46	4.32	16.91
l	$C_{10}H_{12}N_4O_6$	42.25	4.26	19.71	42.16	4.33	19.69
m	$C_{16}H_{16}N_4O_5$	55.81	4.69	16.28	55.72	4.74	16.20
n	$C_{10}H_{10}N_4O_3$	51.28	4.30	23.92	51.36	4.39	23.87
o	$C_9H_8N_4O_3$	49.09	3.66	25.25	49.05	3.68	25.41
p	$C_8H_8N_4O_4$	42.86	3.60	25.00	42.93	3.64	24.94
q	$C_9H_{10}N_4O_4$	45.38	4.23	23.53	45.44	4.28	23.49
r	$C_9H_{10}N_4O_4$	45.38	4.23	23.53	45.44	4.28	23.49
s	$C_{12}H_{14}N_4O_3.0.5\ H_2O$	53.13	5.57	20.65	53.27	5.61	20.62

spectroscopic data (Tables II and III) were consistent with the proposed structures.

When the 7-benzyl derivative **6b** was heated under reflux with triethyl phosphate, both nitrogen atoms of the uracil moiety were methylated to yield the 1,3-dimethyl-7-benzyl derivative; the corresponding 1,3,7-trimethyl derivative could be obtained similarly from either the parent molecule **6a** or the 7-methyl derivative **6c**.

EXPERIMENTAL

The ^{1}H-nmr spectra were recorded on Varian FT80A and Perkin-Elmer R24B spectrometers. Chemical shifts (δ) are reported relative to tetramethylsilane (δ 0) as internal standard. Elemental analyses were performed by Atlantic Microlabs Inc., Atlanta, GA.

Ethyl 5-aminoorotate (**8**).

Ethyl 5-Nitroorotate [8] (40 g, 0.175 mole) was added slowly to a stirred solution of sodium bicarbonate (200 g, 2.38 mole) in water (2000 ml). Sodium dithionite (200 g, 0.95 mole) was added portionwise over a half-hour period, and stirring continued for a further one hour at room temperature. The white crystalline amino-derivative (23.7 g, 68%) was filtered off, washed with water and dried for 24 hours at 60°/24 mm Hg. ^{1}H-nmr (d_6-dimethylsulfoxide): δ 1.30 (t, 3H, J = 7.2 Hz), 4.25 (q, 2H, J = 7.2 Hz), 6.00 (s, 2H), 9.6 (s, 1H) [b], 11.4 (s, 1H) [b].

Anal. Calcd. for $C_7H_9N_3O_4$: C, 42.21; H, 4.56; N, 21.10. Found: C, 42.65; H, 4.57; N, 20.69.

Ethyl 5-(Ethoxymethyleneamino)orotate (**9**).

Ethyl 5-aminoorotate (**8**) (54 g, 0.27 mole) was heated under reflux with diethoxymethyl acetate (600 ml) for 1.75 hours. The reaction mixture was allowed to cool to room temperature, and the crystalline ethoxymethylene compound (60.8 g, 93%) filtered off, washed with ethyl acetate, and dried at 60°/24 mm Hg, mp 220°; ^{1}H-nmr (d_6-dimethylsulfoxide): δ 1.26 (t, 6H, J = 7.2 Hz), 4.13 (q, 2H, J = 7.2 Hz), 8.18 (s, 1H), 10.86 (s, 1H) [b], 11.45 (s, 1H) [b].

Anal. Calcd. for $C_{10}H_{13}N_3O_5$: C, 47.06; H, 5.13; N, 16.46. Found: C, 47.01; H, 5.18; N, 16.41.

7-Substituted-2,4,8(1*H*,3*H*,7*H*)pyrimido[5,4-*d*]pyrimidinetriones (**6**).

Ethyl 5-(ethoxymethyleneamino)orotate (**9**), (5.0 g, 0.022 mole) and the relevant amine (0.024 mole) were heated under reflux in ethanol (500 ml) for the time stated in Table I. The reaction mixture was allowed to cool to room temperature, and the crystalline product filtered off and washed with ethanol. The pyrimidopyrimidines **6**, (yields, analytical and spectroscopic data given in Tables I-III), were dried overnight at 50-60° and 25 mm Hg; melting points were all >250°.

7-Benzyl-1,3-dimethyl-2,4,8(1*H*,3*H*7*H*)pyrimido[5,4-*d*]pyrimidinetrione (**10a**).

7-Benzyl- 2,4,8(1*H*,3*H*,7*H*)pyrimido[5,4-*d*]pyrimidinetrione (**6b**) (9.0 g, 0.033 mole) was heated for 4.5 hours under reflux with freshly distilled trimethyl phosphate (90 ml) and anhydrous potassium carbonate (9 g). The reaction mixture was allowed to cool to room temperature, water (100 ml) was added, the precipitated solid removed by filtration and dried at room temperature 25 mm Hg overnight. Column chromatography on silica gel with ethyl acetate as eluent gave the 1,3-dimethyl compound (3.93 g, 40%) as a white crystalline solid, mp 207-208°; ^{1}H-nmr (deuteriochloroform): δ 3.42 (s, 3H), 3.92 (s, 3H), 5.11 (s, 2H), 7.31 (s, 5H), 8.07 (s, 1H).

Anal. Calcd. for $C_{15}H_{14}N_4O_3$: C, 60.39; H, 4.73; N, 18.79. Found: C, 60.28; H, 4.79; N, 18.74.

1,3,7-Trimethyl-2,4,8(1*H*,3*H*,7*H*)pyrimido[5,4-*d*]pyrimidinetrione (**10b**).

Methylation of the parent trioxo-derivative (**6a**) (2.0 g, 0.01 mole) or its 7-methyl derivative with trimethyl phosphate as described above, followed by column chromatography on silica gel with methanol/ethyl acetate (3:7) as eluent, gave the trimethyl compound **10b** [5], (22%), mp >250°; ^{1}H-nmr (deuteriochloroform): δ 3.48 (s, 3H), 3.55 (s, 3H), 3.95 (s, 3H), 8.07 (s, 1H).

Anal. Calcd. for $C_9H_{10}N_4O_3.0.25\ H_2O$: C, 47.68; H, 4.67; N, 24.72. Found: C, 47.71; H, 4.68; N, 24.67.

Table III

^{1}H-NMR Spectra [a]

Compound No.	6-CH (s, 1H)	1,3-NH (2, 2H) [b]	7-Substituent
6a	7.94	[c]	[c]
b	8.32	11.30	5.12 (s, 2H), 7.23 (s, 5H)
c	8.29	10.55	3.50 (s, 3H)
d	8.30	11.20	1.45 (d, 6H, J = 7 Hz), 4.65-5.18 (m, 1H)
e	8.18	11.27	0.59-2.12 (m, 11H), 3.92 (m, 2H)
f	8.25	11.20	1.68-2.08 (m, 2H), 2.13-2.55 (m, 6H), 3.35-3.72 (m, 4H), 3.85-4.18 (m, 2H)
g	8.15	11.00	0.62-2.05 (m, 11H), 3.82 (d, 2H)
h	8.15	11.25	1.70-2.32 (m, 2H), 2.32-2.82 (m, 2H), 3.95 (m, 2H), 7.12 (s, 5H)
i	8.15	11.15	1.58 (s, 6H), 3.82 (s, 2H), 5.05 (s, 1H) [b]
j	8.20	11.25	0.75 (s, 6H), 0.95-1.95 (m, 4H), 2.91-3.20 (m, 2H), 3.90 (m, 2H), 4.28-4.55 (s, 1H) [b]
k	8.32	11.12	3.12-4.20 (m, 3H), 4.65-5.30 (m, 2H), 5.80 (m, 1H), 7.28 (m, 5H)
l	8.07	10.55	4.02 (s, 6H) [b], 5.97 (s, 3H) [b]
m	7.92	11.20	2.91 (m, 2H), 3.67 (s, 6H), 4.17 (m, 4H), 6.75 (m, 3H)
n	8.31	11.12	1.57-2.13 (m, 2H), 2.13-2.81 (m, 4H), 4.92 (m, 1H)
o	8.17	11.45	0.90-1.25 (m, 4H), 3.15-3.57 (m, 1H)
p	8.16	10.05	2.98-4.40 (s, 1H) [b], 3.45-3.82 (m, 2H), 3.88-4.28 (m, 2H)
q	8.15	11.25	1.05 (d, 2H, J = 7 Hz), 3.50-4.20 (m, 2H), 2.90-4.40 (m, 1H) [b], 4.85 (s, 1H) [b]
r	8.20	10.55	1.85 (m, 2H), 3.45 (t, 2H, J = 7 Hz), 4.03 (t, 2H, J = 7 Hz)
s	8.25	11.22	0.92-2.28 (m, 10H), 3.08-3.80 (m, 1H)

[a] Spectra in deuteriodimethylsulfoxide. Chemical shift δ ppm from tetramethylsilane as internal standard. [b] Broad absorption. [c] 1,3,7-NH protons observed as a very broad absorption 10-12.3 ppm.

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