The Synthesis of *lin*-Benzoreumycin, *lin*-Benzo-1-methylxanthine, and *lin*-Benzo-1,9-dimethylxanthine

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Commencing with 7-chloro-3-methylquinazoline-2,4(1*H*,3*H*)-dione (**9a**), a five step synthesis of 7-methylpyrimido[5,4-*g*]-1,2,4-benzotriazine-6,8(7*H*,9*H*)-dione (*lin*-benzoreumycin, **6**) has been accomplished. A synthesis of 1,7-dimethylpyrimido[5,4-*g*]-1,2,4-benzotriazine-6,8(1*H*,7*H*)-dione (*lin*-benzotoxoflavin, **5**) employing an intermediate from the preparation of **6** (*i.e.*, 7-chloro-3-methyl-6-nitroquinazoline-2,4(1*H*,3*H*)-dione, **9b**) was attempted but could not be accomplished beyond the dihydro precursor of **5** (*i.e.*, **12**). Compound **9b** did lead to successful preparations of 7-methylimidazo[4,5-*g*]quinazoline-6,8(5*H*,7*H*)-dione (*lin*-benzo-1-methylxanthine, **7**) and 3,7-dimethylimidazo[4,5-*g*]quinazoline-6,8(5*H*,7*H*)-dione (*lin*-benzo-1,9-dimethylxanthine, **8**) by first reacting **9b** with ammonia (for **7**) or methylamine (for **8**) followed by reductive cyclization in formic acid.

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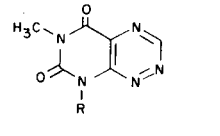
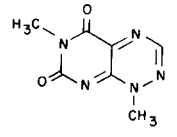
Fervenulin (**1**) [1], toxoflavin (**2**) [2], and reumycin (**3**) [3] are naturally occurring 7-azapteridines [4] that have received varying degrees of attention due to their biological properties [5]. In a continuation of our investigations [6] into pteridines whose heterocyclic rings are separated by well-defined distances [7], the *linear*-benzo-separated [8] analogs of **1**, **2**, and **3** (*i.e.*, **4**, **5**, and **6**, respectively) were sought. The preparation of **4** has been reported elsewhere [6a] whereas the synthesis of 7-methylpyrimido[5,4-*g*]-1,2,4-benzotriazine-6,8(7*H*,9*H*)-dione (*lin*-benzoreumycin, **6**) and a futile effort to prepare 1,7-dimethylpyrimido[5,4-*g*]-1,2,4-benzotriazine-6,8(1*H*,7*H*)-dione (*lin*-benzotoxoflavin, **5**) are presented here. Two methylated *lin*-benzoxanthines (*i.e.*, 7-methylimidazo[4,5-*g*]quinazoline-6,8(5*H*,7*H*)-dione (*lin*-benzo-1-methylxanthine, **7**) [9a] and 3,7-dimethylimidazo[4,5-*g*]quinazoline-6,8(5*H*,7*H*)-dione (*lin*-benzo-1,9-dimethylxanthine, **8**) [9b]) arose from these investigations and their syntheses are also described.



1, R = CH_3
3, R = H



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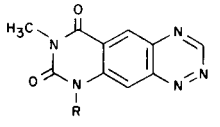
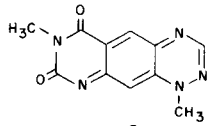


4, R = CH_3
6, R = H



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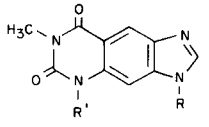
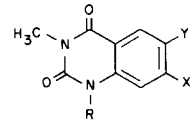


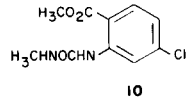
7, R = R' = H
8, R = CH_3, R' = H
14, R = H, R' = CH_3

To achieve the synthesis of **6**, methyl 2-amino-4-chlorobenzoate [6a] was treated with methyl isocyanate in refluxing toluene to give 7-chloro-3-methylquinazoline-2,4-(1*H*,3*H*)-dione (**9a**) without any appearance of the intermediate ureido ester (**10**). Nitration of the dione **9a** with one equivalent of fuming nitric acid in cold, concentrated sulfuric acid yielded **9b**. Reaction of **9b** with hydrazine gave **9c** which, based on a preparation of **4** [6a], was formylated to **9d** for subsequent reductive cyclization to **6**.



9 series, R = H
a, X = Cl, Y = H
b, X = Cl, Y = NO_2
c, X = $NHNH_2$, Y = NO_2
d, X = NHNHCHO, Y = NO_2
e, X = NHN=$CHOC_2H_5$, Y = NO_2
f, X = $N(CH_3)NH_2$, Y = NO_2
g, X = $N(CH_3)NHCHO$, Y = NO_2
h, X = NHNHCHO, Y = NH_2

13 series, R = CH_3
i, X = NHNHCHO, Y = NHCHO
j, X = $NHNH_2$, Y = NHCHO
k, X = NH_2, Y = NO_2
l, X = Y = NH_2
m, X = $NHCH_3$, Y = NO_2
n, X = $NHCH_3$, Y = NH_2
o, X = $N(CH_3)NHCHO$, Y = NH_2
p, X = NH_2, Y = NO_2



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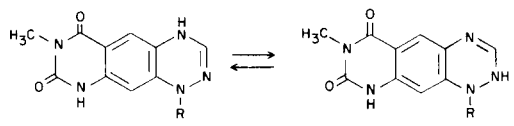
Unfortunately, the insolubility of **9d** in a variety of the customary hydrogenation solvents precluded use of this procedure. As a consequence, **9c** was converted into the more soluble ethoxymethylene derivative **9e** which, following catalytic hydrogenation in ethanol-acetic acid, produced the dihydro tautomers **11a** and **11b**. Subsequent basic hydrogen peroxide oxidation of **11** yielded **6**.

Consideration was next given to attempting a synthesis of **5** *via* oxidation [10] of the dihydro precursor **12**. In this direction, **9b** was treated with methylhydrazine to form **9f**

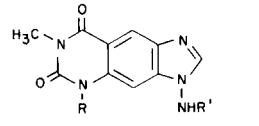


a b

11, R = H
12, R = CH_3

[11]. Formylation of **9f** gave **9g** which, in turn, upon catalytic hydrogenation, was transformed into **12**. Unfortunately, attempted oxidations [10] of **12** consistently resulted in complex mixtures or decomposition [14]. Consequently, the transformation of **12** into **5** was not evaluated further.

The initial plan to **7** and **8** was based on a report [6a] that **13c** gave *lin*-benzotheophylline (**14**) upon catalytic hydrogenation in formic acid. This suggested that **9c** and **9f** would yield *lin*-benzo-1-methylxanthine (**7**) and *lin*-benzo-1,9-methylxanthine (**8**), respectively, when subjected to similar conditions. However, the formylated aminobenzimidazole **15a** was the major product from **9c** with only a trace of **7** detectable by tlc.



15 series R = H 16 series R = CH_3

a, R' = CHO
b, R' = H

Since the formylated derivative of **9c** (*i.e.*, **9d**) also gave **15a** upon hydrogenation in formic acid, the conversion of **9c** into **15a** was viewed [15] as beginning with formylation to **9d** and then proceeding *via* reduction of **9d** to **9h** which underwent formylation to **9i** followed by cyclodehydration to **15a**.

Alternative pathways to **15a** could involve (i) the formation of **11** (from **9h**) and its subsequent ring opening [16] or (ii) the transformylation of **9h** [17] to **9j** followed by cyclodehydration to **15b** and, then, formylation.

Prompted by the failure to obtain **7** from **9c**, a reinvestigation of the catalytic hydrogenation of **13c** in formic acid was conducted and found to, indeed, give **14** (along with **16a** rather than **13d** as originally believed) [6a]. The failure to realize **7** from **9c** was, subsequently, explained as being due to the more rapid reaction of **9c** with formic acid at room temperature relative to **13c**. Thus, it is suggested that **9c** went immediately to **9d** which proceeded further to **15a** as outlined above whereas initial formylation of **13c** to **13d** (and on to **16a** in a manner similar to that described above for the **9d** to **15a** conversion) [18] most likely competed with hydrogenolysis of **13c** to **13k**, the likely [19] precursor to **14** *via* **13***l*.

In contrast to **9c** and **13c**, the presence of the hydrazino methyl substituent on **9f** rendered it incapable of yielding benzimidazoles analogous to **15a** and **16a** upon catalytic hydrogenation in formic acid. Consequently, **9f** gave **8** and **12** (in equal amounts) *via*, possibly, **9m** and **9n** (for **8**) and **9g** and **9o** (for **12**) [21].

To assist in analyzing the hydrogenation reactions of **9c** and **9f**, authentic samples of **7** and **8** were obtained by first reacting **9b** with anhydrous ammonia to give **9p** (for **7**) or methylamine to yield **9m** (for **8**) followed by reductive ring closure in formic acid.

EXPERIMENTAL

General Methods.

All melting points were obtained on a Thomas-Hoover or a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckmann AccuLab 3 spectrophotometer using potassium bromide disks. The pmr spectra were determined in methyl sulfoxide-d_6 at 60 MHz with a Varian EM-360 spectrometer and are reported in parts per million downfield from tetramethylsilane as an internal standard. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Elemental analyses were performed by M-H-W Laboratories, Phoenix Arizona.

For analytical tlc, Eastman precoated silica gel Chromagram sheets with fluorescent indicator (100 μm thick) were used; the spots were detected by irradiation with a Mineralight UVGL-25. The silica gel used for the column chromatographic separation was Baker 60-200 mesh.

7-Chloro-3-methylquinazoline-2,4(1*H*,3*H*)-dione (**9a**).

A mixture of 7.4 g (43 mmoles) of methyl 2-amino-4-chlorobenzoate [6a], 2.24 g (39 mmoles) of methyl isocyanate and 2 ml of triethylamine in 50 ml of dry toluene was heated at 100° for 24 hours. After this period, the mixture was cooled and the resulting precipitate isolated by filtration (4.5 g, 21 mmoles, 50%) and recrystallized from toluene to give **9a** as white crystalline plates; mp 269-271°; pmr: δ 3.2 (s, 3 H, CH_3), 7.05 (d, J = 1 Hz, 1 H, H-8), 7.15 (d of d, J = 5 Hz, J = 1 Hz, 1 H, H-6), 7.85 (d, J = 5 Hz, 1 H, H-5).

Anal. Calcd. for $C_9H_7ClN_2O_2$: C, 51.32; H, 3.34; N, 13.30. Found: C, 51.53; H, 3.60; N, 13.43.

7-Chloro-3-methyl-6-nitroquinazoline-2,4(1*H*,3*H*)-dione (**9b**).

To a mixture of 12.17 g (58 mmoles) of **9a** in 57 ml of concentrated sulfuric acid which was cooled to −10° was added, dropwise, 2.26 ml of fuming nitric acid under mechanical stirring. The addition was done at such a rate as to maintain the reaction temperature at −10°. When all of the solid had dissolved, the mixture was heated on a steam bath for 10 minutes and then poured over ice. The resulting precipitate was isolated by filtration, air dried, and recrystallized from glacial acetic acid to give **9b** (14.58 g, 57 mmoles, 98%) as white crystals, mp 372-374°; pmr: (128°) δ 3.2 (s, 3 H, CH_3), 7.2 (s, 1 H, H-8), 8.35 (s, 1H, H-5), 10.45 (br s, 1 H, NH).

Anal. Calcd. for $C_9H_6ClN_3O_4$: C, 42.49; H, 2.37; N, 16.44. Found: C, 42.05; H, 2.33; N, 16.41.

7-Hydrazino-3-methyl-6-nitroquinazoline-2,4(1*H*,3*H*)-dione (**9c**).

To a magnetically stirred mixture of 10 g (39 mmoles) of **9b** in 300 ml of absolute ethanol at room temperature and under nitrogen was added, dropwise, 33 ml of 95% anhydrous hydrazine. The mixture was then refluxed for 18 hours, cooled and the resulting solid was isolated by filtration (8.8 g, 35 mmoles, 90%) to give **9c** as orange crystals following purification from methyl sulfoxide, mp 279-281°; pmr: δ 3.16 (s, 3 H, CH_3), 4.7 (br s, 2 H, NH_2), 7.05 (s, 1 H, H-8), 8.5 (s, 1 H, H-5), 9.32 (br s, 1 H, NHN), 11.02 (br s, 1 H, NH).

Anal. Calcd. for $C_9H_5N_5O_4$: C, 43.03; H, 3.61; N, 27.88. Found: C, 42.93; H, 3.78; N, 27.64.

7-(2-Formylhydrazino)-3-methyl-6-nitroquinazoline-2,4(1*H*,3*H*)-dione (**9d**).

A mixture of 2 g (7.96 mmoles) of **9c** and 35 ml of 97% formic acid was refluxed for 2 hours with the exclusion of moisture. The excess formic acid was removed *in vacuo* and toluene was added to the residue. The toluene was then removed *in vacuo* to give a residue that was suspended in petroleum ether (60-110°) and then isolated by filtration. Recrystallization of this material from aqueous dimethylformamide gave **9d** (2.1 g, 7.52 mmoles, 94%) as a yellow solid, mp 325-327° dec; ir: 1650 (C=O) cm^{-1}; pmr: δ 3.22 (s, 3 H, CH_3), 6.65 (s, 1 H, H-8), 8.25 (s, 1H, C*H*O), 8.64 (s, 1 H, H-5), 9.66 (br s, 3 H, NH).

Anal. Calcd. for $C_{10}H_9N_5O_5$: C, 43.02; H, 3.25; N, 25.08. Found: C, 42.81; H, 3.50; N, 24.85.

7-[2-(Ethoxymethylene)hydrazino]-3-methyl-6-nitroquinazoline-2,4(1*H*,3*H*)-dione (**9e**).

After refluxing a mixture of 0.65 g (2.59 mmoles) of **9c** in 20 ml of triethyl orthorformate for 2 hours, the precipitated yellow-orange product was isolated by filtration, dried, and recrystallized from dimethylformamide to give **9e** (0.7 g, 2.28 mmoles, 88%) as orange needles; mp 317-318° dec; ir: 1710 (C=O) cm^{-1}; pmr: δ 1.30 (t, J = 8 Hz, 3 H, CH_3), 3.16 (s, 3 H, CH_3), 4.22 (q, J = 8 Hz, 2 H, CH_2), 7.1 (s, 1 H, =CH), 7.22 (s, 1 H, H-8), 8.52 (s, 1 H, H-5), 10.76 (br s, 1 H, NNH), 11.55 (br s, 1 H, NH).

Anal. Calcd. for $C_{12}H_{13}N_5O_5$: C, 46.91; H, 4.26; N, 22.79. Found: C, 46.79; H, 4.47; N, 23.01.

7-Methylpyrimido[5,4-*g*]-1,2,4-benzotriazine-6,8(7*H*,9*H*)-dione (*lin*-Benzoreumycin, **6**).

A mixture of 0.8 g (2.6 mmoles) of **9e**, 25 ml of absolute ethanol and 5 ml of acetic acid, to which a catalytic amount of 10% palladium on charcoal had been added under nitrogen, was treated with 52 psi of hydrogen for 24 hours. The suspension was then filtered to give a solid which was contaminated with catalyst. The solid was freed from the catalyst by dissolving in dimethylformamide, filtering and adding water to the filtrate to reprecipitate the solid. This material (assumed to be **11**) was found to be unstable and was, therefore, dissolved in 25% aqueous sodium hydroxide solution, treated with 30% hydrogen peroxide solution, and neutralized with concentrated hydrochloric acid to give a yellow-orange solid which was isolated by filtration to give **6** (0.16 g, 0.7 mmole, 27%) which recrystallized from methyl sulfoxide as analytically pure orange needles, mp 362-364° dec; ir 1710 (C=O) cm^{-1}; pmr: δ 3.2 (s, 3 H, CH_3), 8.01 (s, 1 H, H-5), 8.6 (s, 1 H, H-10), 10.02 (s, 1 H, H-3), 11.85 (br s, 1 H, NH).

Anal. Calcd. for $C_{10}H_7N_5O_2$: C, 52.41; H, 3.08; N, 30.56. Found: C, 52.23; H, 3.26; N, 30.76.

3-Methyl-7-(1-methylhydrazino)-6-nitroquinazoline-2,4(1*H*,3*H*)-dione (**9f**).

A mixture of 3 g (12 mmoles) of **9b** in 50 ml of absolute ethanol was stirred at room temperature under nitrogen and then 2 g (44 mmoles) of methylhydrazine was added in one portion. This mixture was then refluxed for 2 hours, cooled and the resulting yellow solid isolated by filtration, washed with ethanol and diethyl ether (2.4 g, 9.04 mmoles, 75%) and recrystallized from aqueous methyl sulfoxide to give **9f**, mp 282-283° dec; pmr: δ 3.1 (s, 3 H, CH_3), 3.3 (s, 3 H, CH_3), 4.8 (br s, 2 H, NH_2), 6.5 (s, 1 H, H-8), 7.95 (s, 1 H, H-5), 8.2 (br s, 1 H, NH).

Anal. Calcd. for $C_{10}H_{11}N_5O_4$: C, 45.29; H, 4.18; N, 26.41. Found: C, 45.58; H, 4.35; N, 26.35.

Dihydro-1,7-dimethylpyrimido[5,4-*g*]-1,2,4-benzotriazine-6,8(7*H*,9*H*)-dione (**12**).

A mixture of 1 g (3.8 mmoles) of **9f** in 25 ml of 97% formic acid was refluxed for 2 hours and then the excess formic acid was removed *in vacuo* to give **9g** which was identical to the **9g** whose preparation is given below. Compound **9g** was then redissolved in 25 ml of 97% formic acid and this solution transferred to a hydrogenator bottle. After adding a catalytic amount of 10% palladium on charcoal under nitrogen, the mixture was shaken under 52 psi of hydrogen for 4 hours. The catalyst was removed by filtration and the filtrate was refluxed for 2 hours. After *in vacuo* removal of the excess formic acid, 25 ml of toluene was added to the residue and this new mixture evaporated to dryness *in vacuo* to afford crude **12** (0.85 g, 3.46 mmoles, 91%) which was purified by recrystallization from glacial acetic acid: slow decomposition 270-300°; ir: 1700 (C=O) cm^{-1}; pmr: δ 2.75 (s, 3 H, CH_3), 3.26 (s, 3 H, CH_3), 5.58 (s, 1 H, H-10), 6.32 (s, 1 H, H-5), 6.4 (s, 1 H, H-3), 8.22 (br s, 1 H, NH), 10.8 (br s, 1 H, NH).

Anal. Calcd. for $C_{11}H_{11}N_5O_2$: C, 53.87; H, 4.52; N, 28.56. Found: C, 53.76; H, 4.60; N, 28.49.

7-(2-Formyl-1-methylhydrazino)-3-methyl-6-nitroquinazoline-2,4(1*H*,3*H*)-dione (**9g**).

A mixture of 2 g (7.54 mmoles) of **9f** in 50 ml of 97% formic acid was refluxed for 2 hours. The excess formic acid was removed to near dryness *in vacuo* and 50 ml of toluene added to the residue. The solvents were removed again *in vacuo* and the resulting yellow residue washed with diethyl ether, isolated by filtration, dried and recrystallized as **9g** from methyl sulfoxide (2.14 g, 7.3 mmoles, 97%), mp 289-290°; pmr: δ 3.12 (s, 3 H, CH_3), 3.2 (s, 3 H, CH_3), 6.68 (s, 1 H, H-8), 7.85 (s, 1 H, H-5), 8.01 (s, 1 H, CHO), 10.32 (br s, 1 H, NH), 11.45 (br s, 1 H, NH).

Anal. Calcd. for $C_{11}H_{11}N_5O_5$: C, 45.06; H, 3.78; N, 23.88. Found: C, 44.85; H, 4.04; N, 23.60.

Catalytic Hydrogenation of **9c** in Formic Acid.

A mixture of 0.5 g (2 mmoles) of **9c** in 50 ml of 97% formic acid, to which a catalytic amount of 10% palladium on charcoal was added under nitrogen, was shaken under 52 psi of hydrogen for 12 hours. After removal of the catalyst by filtration, the filtrate was refluxed for 6 hours under nitrogen. The excess formic acid was then evaporated to dryness under reduced pressure and to the residue was added 50 ml of toluene. This resulting mixture was then evaporated *in vacuo* to give 0.53 g of a brown solid which was recrystallized from aqueous dimethylformamide to give **15a** (0.28 g, 1.08 mmoles, 54%) as a light tan solid, mp >325° dec; pmr: δ 3.3 (s, 3 H, CH_3), 7.02 (s, 1 H, H-4), 8.26 (s, 1 H, H-9), 8.45 (s, 1 H, H-2), 8.54 (s, 1 H, C*H*O), 11.42 (br s, 2 H, NH).

Anal. Calcd. for $C_{11}H_9N_5O_3 \cdot \frac{3}{4}H_2O$: C, 48.44; H, 3.88; N, 25.68. Found: C, 48.60; H, 3.99; N, 25.75.

A trace amount of **7** could only be detected by tlc analysis of the crude product using chloroform-methanol (4:1) as the eluting solvent mixture.

Catalytic Hydrogenation of **13c** in Formic Acid.

Using the same procedure as employed for the hydrogenation of **9c** in formic acid, 1 g (3.77 mmoles) of **13c** [6a] gave, after 4 hours of hydrogenation and a 2 hour reflux of the filtrate, 0.9 g of a mixture of two products. These products were isolated by suspending the residue from removal of the formic acid-toluene in ethanol and identified as **14** and **16a** in a 1:2 ratio by pmr and tlc comparisons to authentic **14** [6a] and **16a** (see below).

Catalytic Hydrogenation of **13d** in Formic Acid.

Using a procedure similar to that for the hydrogenation of **9c** in formic acid, 1.8 g (6.14 mmoles) of **13d** [6a] in 100 ml of 97% formic acid was hydrogenated for 4 hours followed by a 2 hour reflux of the filtrate. Following removal of the formic acid-toluene, the residue was suspended in ethanol and filtered to give 1.2 g (4.39 mmoles, 71%) of **16a** as a light tan solid which was purified by recrystallization from aqueous dimethylformamide, mp 281-283° dec; ir: 1650 (C=O) cm^{-1}; pmr: δ 3.3 (s, 3 H, CH_3), 3.43 (s, 3 H, CH_3), 7.21 (s, 1 H, H-4), 8.25 (s, 1 H, H-9), 8.36 (s, 1 H, H-2), 8.48 (s, 1 H, C*H*O), 11.5 (br s, 1 H, NH).

Anal. Calcd. for $C_{12}H_{11}N_5O_3$: C, 52.75; H, 4.06; N, 25.63. Found: C, 52.66; H, 4.08; N, 25.73.

Catalytic Hydrogenation of **9f** in Formic Acid.

Using the same procedure as employed for the hydrogenation of **13c** in formic acid without the need to suspend the residue in ethanol, 1 g (3.77 mmoles) of **9f** gave 0.8 g of a crude mixture of two products in a 1:1 ratio (pmr). Separation of this mixture by silica gel column chromatography (ethyl acetate-methanol, 1:1) yielded **8** with **12** remaining at the origin of the column. This latter component was isolated by dissolution in dimethylformamide and reprecipitating it from the filtrate with water. Both **8** and **12** were found to be identical to those samples prepared by

the other methods described herein.

7-Amino-3-methyl-6-nitroquinazoline-2,4(1*H*,3*H*)-dione (**9p**).

A mixture of 9 g (35 mmoles) of **9b** in 50 ml of ammonia saturated (at room temperature) 1-butanol was heated at 130° for 24 hours in a stainless steel sealed reaction vessel. Following cooling of the reaction vessel, the precipitated solid was isolated by filtration and washed with diethyl ether to give **9p** (6.6 g, 28 mmoles, 80%) as a yellow solid that was recrystallized from aqueous dimethylformamide, mp 358-359°; ir 1700 (C=O) cm^{-1}; pmr: δ 3.19 (s, 3 H, CH_3), 6.52 (s, 1 H, H-8), 7.82 (br s, 2 H, NH_2), 8.54 (s, 1 H, H-5), 11.51 (br s, 1 H, NH).

Anal. Calcd. for $C_9H_8N_4O_4$: C, 45.77; H, 3.41; N, 23.72. Found: C, 45.59; H, 3.49; N, 23.67.

7-Methylimidazo[4,5-*g*]quinazoline-6,8(5*H*,7*H*)-dione (*lin*-Benzo-1-methylxanthine, **7**).

To a suspension of 1 g (4.2 mmoles) of **9p** in 26 ml of 97% formic acid was added 0.2 g of 10% palladium on charcoal under nitrogen. After shaking the resultant mixture under 52 psi of hydrogen for 3 hours, the catalyst was removed by filtration and the filtrate refluxed for 2 hours under nitrogen. The formic acid was removed *in vacuo* and 50 ml of toluene was added to the residue. This mixture was also evaporated to dryness *in vacuo* to give crude **7** that was recrystallized from aqueous dimethylformamide as a light tan powder (0.75 g, 3.3 mmoles, 83%), mp >385° dec; ir 1650 (C=O) cm^{-1}; pmr: δ 3.3 (s, 3 H, CH_3), 7.3 (s, 1 H, H-4), 8.2 (s, 1 H, H-9), 8.4 (s, 1 H, H-2), 11.3 (s, 1 H, NH), 12.6 (br s, 1 H, NH).

Anal. Calcd. for $C_{10}H_8N_4O_2 \cdot \frac{1}{2}H_2O$: C, 53.33; H, 4.02; N, 24.88. Found: C, 53.08; H, 4.00; N, 24.82.

3-Methyl-7-(*N*-methylamino)-6-nitroquinazoline-2,4(1*H*,3*H*)-dione (**9m**).

Using the same procedure as that described for preparing **9p** but replacing the ammonia with methylamine gave **9m** (8.26 g, 33 mmoles, 94%) which was recrystallized from methyl sulfoxide as a yellow solid, mp 318-320° dec; pmr: δ 2.83 (s, 3 H, CH_3), 2.92 (s, 3 H, CH_3), 6.2 (s, 1 H, H-8), 8.0 (br s, 1 H, NH), 8.1 (br s, 1 H, NH), 8.38 (s, 1 H, H-5).

Anal. Calcd. for $C_{10}H_{10}N_4O_4$: C, 48.00; H, 4.03; N, 22.39. Found: C, 47.85; H, 4.12; N, 22.27.

3,7-Dimethylimidazo[4,5-*g*]quinazoline-6,8(5*H*,7*H*)-dione (*lin*-Benzo-1,9-methylxanthine, **8**).

In a manner similar to that used in the synthesis of **7**, a mixture of 6 g (24 mmoles) of **9m** in 70 ml of 97% formic acid yielded **8** (5 g, 22 mmoles, 92%) as white crystals upon recrystallization from methyl sulfoxide, mp >370° dec; pmr: δ 3.25 (s, 3 H, CH_3), 3.75 (s, 3 H, CH_3), 7.08 (s, 1 H, H-4), 8.12 (s, 1 H, H-9), 8.2 (s, 1 H, H-2), 11.35 (br s, 1 H, NH).

Anal. Calcd. for $C_{11}H_{10}N_4O_2$: C, 57.39; H, 4.27; N, 23.72. Found: C, 57.14; H, 4.41; N, 23.47.

REFERENCES AND NOTES

[1a] E. C. Taylor and F. Sowinski, *J. Org. Chem.*, **40**, 2321 (1975); [b] F. Yoneda and T. Nagamatsu, *Bull. Chem. Soc. Japan*, **48**, 2884 (1975).

[2a] F. Yoneda and T. Nagamatsu, *Tetrahedron Letters*, 1577 (1973); [b] F. Yoneda and T. Nagamatsu, *J. Am. Chem. Soc.*, **95**, 5735 (1973); [c] F. Yoneda and T. Nagamatsu, *Chem. Pharm. Bull.*, **23**, 2001 (1975).

[3] S. E. Esipov, M. N. Kolosov and L. A. Saburova, *J. Antibiot.*, **26**, 537 (1973).

[4] D. J. Brown and R. K. Lynn in "Chemistry and Biology of Pteridines", W. Pfleiderer, ed, W. de Gruyter, New York, 1975, pp 575-601.

[5a] For leading references on the biological properties of fervenulin and toxoflavin see the introductory paragraphs of B. K. Billings, J. A. Wagner, P. D. Cook and R. N. Castle, *J. Heterocyclic Chem.*, **12**, 1221 (1975) and H. Yamaguchi, R. Kuwata and F. Yoneda, *ibid.*, **15**, 615 (1978); [b] For the biological properties of reumycin see S. E. Esipov, M. N. Kolosov, L. G. Belyakova, B. P. Baskunov, T. I. Gorokhova, L. A. Saburova, T. G. Terent'eva and S. M. Navashin, German Patent 2,901,537; *Chem. Abstr.*, **93**, 186415n (1980) and S. M. Navashin, L. P. Ivanitskaya, T. G. Terent'eva and L. V. Egorov, *Farmatisya (Moscow)*, **30**, 55 (1981); *Chem. Abstr.*, **95**, 73566k (1981).

[6a] S. W. Schneller and W. J. Christ, *J. Org. Chem.*, **46**, 1699 (1981); [b] S. W. Schneller and W. J. Christ, *J. Heterocyclic Chem.*, **18**, 539 (1981); [c] S. W. Schneller and W. J. Christ, *ibid.*, **18**, 653 (1981).

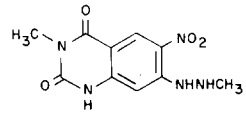
[7] S. W. Schneller and W. J. Christ in "Lectures in Heterocyclic Chemistry", Vol 6, R. N. Castle and T. Kappe, eds, HeteroCorporation, P. O. Box 16000MH, Tampa, FL 33687, USA, 1982, p S-139.

[8] See reference [83] in reference [7] above or note [2] of N. J. Leonard, A. G. Morrice and M. A. Sprecker, *J. Org. Chem.*, **40**, 356 (1975) for an explanation of the use of the *linear* and "benzo" terms as prefixes in defining a particular dimensional analog.

[9a] For representative references on 1-methylxanthine see R. D. Green and L. R. Stanberry, *Biochem. Pharmacol.*, **26**, 37 (1977); J. F. Williams, S. Lowitt, J. B. Polson and A. Szentivanyi, *ibid.*, **27**, 1545 (1978); and, N. C. De, A. Mittelman, S. P. Dutta, C. G. Edmonds, E. E. Jenkins, J. A. McCloskey, C. R. Blakley, M. L. Vestal and G. B. Chheda, *J. Carbohyd. Nucleosides Nucleotides*, **8**, 363 (1981); [b] For representative references on 1,9-dimethylxanthine see W. Pfleiderer and G. Nübel, *Ann. Chem.*, **647**, 155 (1961); D. Lichtenberg, F. Bergmann and Z. Neiman, *J. Chem. Soc. (C)*, 1676 (1971); and, M. A. Croce, G. L. Kramer and D. L. Garbers, *Biochem. Pharmacol.*, **28**, 1227 (1979).

[10] K. T. Finley and L. K. J. Tong in "The Chemistry of the Carbon-Nitrogen Double Bond", S. Patai, ed, Wiley-Interscience, New York, 1970, pp 667-668.

[11] Even though **9f** was the expected product [12] from the reaction of **9b** with methylhydrazine, there was some concern that methylhydrazine could have functioned as a base and removed the N-1 proton of **9b** (which is rendered acidic by the adjacent carbonyl and the *para*-nitro functionalities). Had this occurred, reaction of the resultant $CH_3NH_2NH_2$ [13] with **9b** could have produced **i**, an isomer of **9f**. However, based on the isolation of **8** following the catalytic hydrogenation of **9f** in formic acid described herein, **i** did not form.



[12] R. L. Hinman, *J. Org. Chem.*, **23** 1587 (1958) and T. Denzel and H. Höhn, *J. Heterocyclic Chem.*, **14**, 813 (1977).

[13] F. C. Condon, R. T. Reece, D. G. Shapiro, D. C. Thakkar and T. B. Goldstein, *J. Chem. Soc., Perkin Trans. II*, 1112 (1974).

[14] The major problem in the attempted conversions of **12** into **5** was due to the relative instability of **12** as evidenced by, for example, its total destruction in dilute sodium hydroxide solution.

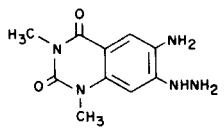
[15] J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **82**, 4592 (1960).

[16] C. Temple, Jr., R. L. McKee and J. A. Montgomery, *J. Org. Chem.*, **28**, 923 (1963).

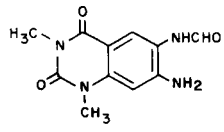
[17a] R. A. Abramovitch and K. Schofield, *J. Chem. Soc.*, 2326 (1955); [b] E. E. Glover, K. T. Rowbottom and D. C. Bishop, *J. Chem. Soc., Perkin Trans. I*, 842 (1973); [c] P. N. Preston in "Benzimidazoles and Congeneric Tricyclic Compounds", Part 1, P. N. Preston, ed, Wiley-Interscience, New York, 1981, p 34.

[18] Evidence that **16a** was formed from **13c** in a sequence of steps similar to that proposed herein for the **9c** → **15a** process was obtained by isolating only **16a** from the catalytic reduction of **13d**.

[19] Initial hydrogenation of **13c** to **ii** followed by hydrogenolysis to **13ℓ** cannot, of course, be ruled out as alternative steps in the mechanism for the conversion of **13c** into **14**. However, if **ii** had formed, the isolation of some *lin*-benzofervenulin (**4**) *via* formylation-ring closure of **ii** should



ii

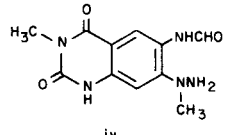


iii

have been observed [6a,20]. Furthermore, hydrogenolysis of **13j** to **iii** as a step in a mechanism to **14**, that would involve a transformylation process, was eliminated from consideration when **14** could not be detected as forming from **13d** under the hydrogenation conditions.

[20] E. C. Taylor, J. W. Barton and W. W. Paudler, *J. Org. Chem.*, **26**, 4961 (1961).

[21] An alternative mechanism involving a transformylation of **9o** to the common intermediate **iv** which could have undergone hydrogenolysis-ring closure to **8** or simple ring closure to **12** was, of course, ruled out since the proposed precursor to **9o** (that is, **9g**) yielded only **12** when subjected to the appropriate conditions as presented herein.



iv