The Synthesis of *proximal*-Benzolumazine, *proximal*-Benzoxanthine, *proximal*-Benzotheophylline and *proximal*-Benzocaffeine (1)

Stewart W. Schneller and William J. Christ*

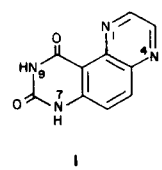
Department of Chemistry, University of South Florida, Tampa, Florida 33620

Received April 20, 1981

The synthesis of pyrazino[2,3-*f*]quinazolin-8,10-(7*H*,9*H*)dione(*proximal*-benzolumazine, **1**), imidazo[4,5-*f*]-quinazolin-7,9-(6*H*,8*H*)-dione (*proximal*-benzoxanthine, **2**), 6,8-dimethylimidazo[4,5-*f*]-quinazolin-7,9-(6*H*,8*H*)-dione (*proximal*-benzotheophylline, **3**), and 1,6,8-trimethylimidazo[4,5-*f*]quinazolin-7,9-(6*H*,8*H*)dione (*proximal*-benzocaffeine, **4**) is reported by commencing with 2-amino-6-chlorobenzamide and proceeding *via* a variety of 5,6-disubstituted-2,4-(1*H*,3*H*)quinazolinediones. Methylation of **3** is shown to yield 3,6,8-trimethylimidazo[4,5-*f*]quinazolin-7,9-(6*H*,8*H*)dione (**15**) and **4** in a ratio of 4:1.

J. Heterocyclic Chem., **18**, 653 (1981).

In spite of the work that has been described on benzo-separated purines (2) and, to a lesser extent, on benzo-separated pteridines (3,4), little information (5-7) has been reported on the *proximal*-benzo series of analogs (8). However, in a continuation of our efforts to satisfy the need for the missing benzo-separated purines and pteridines for biological scrutiny, the synthesis of pyrazino[2,3-*f*]quinazolin-8,10-(7*H*,9*H*)dione (*prox*-benzolumazine, **1**), imidazo[4,5-*f*]quinazolin-7,9-(6*H*,8*H*)-dione (*prox*-benzoxanthine, **2**) (9), 6,8-dimethylimidazo-[4,5-*f*]-quinazolin-7,9-(6*H*,8*H*)dione (*prox*-benzotheophylline, **3**) and 1,6,8-trimethylimidazo[4,5-*f*]quinazolin-7,9-(6*H*,8*H*)-dione (*prox*-benzocaffeine, **4**) has been accomplished.



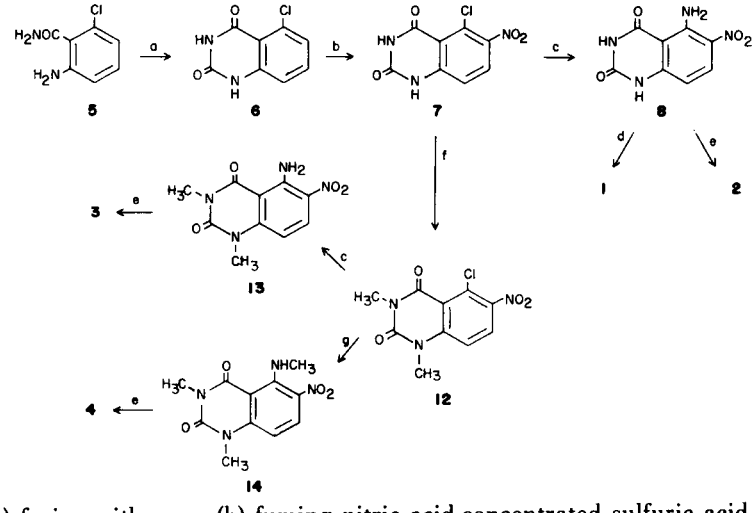
1

2, R=R'=H
3, R=CH_3, R'=H
4, R=R'=CH_3

To achieve these syntheses (see the Scheme) 2-amino-6-chlorobenzamide (**5**) (10) was fused with urea to give 5-chloro-2,4-(1*H*,3*H*)quinazolinedione (**6**) (11a) which, upon carefully controlled stoichiometric nitration, was converted into 5-chloro-6-nitro-2,4-(1*H*,3*H*)quinazoline-

Scheme*

The Synthesis of *prox*-Benzolumazine (**1**), -xanthine (**2**), -thiophylline (**3**) and -caffeine (**4**)



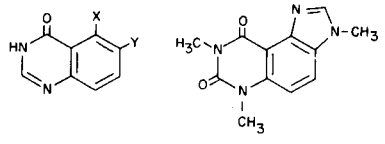
*Reaction conditions: (a) fusion with urea; (b) fuming nitric acid-concentrated sulfuric acid, -10° then warming; (c) 1-butanol saturated with ammonia with heating in a sealed reaction vessel at 140-150° for 24 hours; (d) (i) hydrogenation in 2-methoxyethanol containing a small amount of concentrated hydrochloric acid and 10% palladium-on-charcoal catalyst, (ii) glyoxal at room temperature; (e) hydrogenation in formic acid containing 10% palladium-on-charcoal followed by reflux; (f) dimethyl sulfate-tetraethylammonium hydroxide at 30-35°; (g) the ammonia in reaction condition c was replaced with methylamine.

0022-152X/81/030653-02$02.25

dione (**7**) (11b), a key compound in the preparation of **1-4**. Amination of **7** then produced 5-amino-6-nitro-2,4-(1*H*,3*H*)-quinazolinedione (**8**) (11c). Catalytic hydrogenation of **8** either with subsequent reaction with glyoxal or in the presence of formic acid resulted in **1** (11d) or **2** (11e), respectively.

Compound **2** was previously reported (9), but not fully characterized, as an enzymatic product from the action of xanthine oxidase on *prox*-benzohypoxanthine. However, a more straightforward route to **2**, as shown here, may be necessary (12) to produce a variety of *prox*-nucleosides.

It should also be mentioned that in Leonard's early *proximal* investigations (5) attempts to synthesize the useful intermediate **9** from **10** and ammonia (*i.e.*., a conversion whose 5,6-disubstitution pattern is isomeric with that of the **7** to **8** transformation) led instead to **11** by nitro group displacement. This result was rationalized (5) as being due to a relief in steric strain between the planar C-4 carbonyl and C-5 nitro functionalities of **10** *via* an accommodating tetrahedral intermediate at C-5. The conversion of **7** into **8** supports this conclusion.



9, X = NO_2, Y = NH_2
10, X = NO_2, Y = Cl
11, X = NH_2, Y = Cl

15

For the preparation of **3** and **4**, **7** was methylated with dimethyl sulfate to result in 5-chloro-1,3-dimethyl-6-nitro-2,4-(1*H*,3*H*)quinazolinedione (**12**) (11f). Amination of **12** gave 5-amino-1,3-dimethyl-6-nitro-2,4-(1*H*,3*H*)quinazolinedione (**13**) (11g) while reaction of **12** with methylamine produced 1,3-dimethyl-5-methylamino-6-nitro-2,4-(1*H*,3*H*)-quinazolinedione (**14**) (11h). Catalytic hydrogenation of both **13** and **14** in formic acid formed the desired theophylline (**3**) (11i) and caffeine (**4**) (11j) derivatives, respectively.

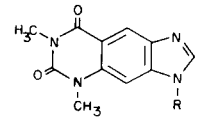
It is interesting to note that methylation of **3** with dimethyl sulfate in 2 *N* sodium hydroxide solution at 40° yielded 3,6,8-trimethylimidazo[4,5-*f*]quinazolin-7,9-(6*H*,8*H*)dione (**15**) (11k) and **4** in a ratio of 4:1. This indicates, not surprisingly, considerable steric crowding around the N-1 center of **3** which severely limits alkylation at that site. Such an isomeric distribution also implies that ribosylation in the *proximal* series should yield a predominance of, or, possibly, exclusively, the necessary *N*-3 nucleosides.

REFERENCES AND NOTES

(1) A preliminary account of this research was presented at the 181st National Meeting of the Americal Chemical Society, Atlanta, GA, March 29-April 3, 1981, ORGN 30.

(2) See references 1 and 2 of R. H. Foster and N. J. Leonard, *J. Org. Chem.*, **44**, 4609 (1979).

(3) S. W. Schneller and W. J. Christ, *ibid.*, **46**, 1699 (1981). It should be noted that the compound numbers for *linear*-benzotheophylline (**i**) and 3,5,7-trimethylimidazo[4,5-*g*]quinazolin-6,8-(5*H*,7*H*)dione (**ii**) were omitted from this paper and should be **11** and **19**, respectively. This error was introduced by the publisher after the galley proofs had been approved and returned.



i, R = H
(should be **11**)
ii, R = CH_3
(should be **19**)

(4) S. W. Schneller and W. J. Christ, *J. Heterocyclic Chem.*, **18**, 539 (1981).

(5) A. G. Morrice, M. A. Sprecker and N. J. Leonard, *J. Org. Chem.*, **40**, 363 (1975).

(6) R. H. Foster and N. J. Leonard, *ibid.*, **45**, 3072 (1980).

(7) E. Cuny, F. W. Lichtenthaler and A. Moser, *Tetrahedron Letters*, **21**, 3029 (1980).

(8) See N. J. Leonard, A. G. Morrice and M. A. Sprecker, *J. Org. Chem.*, **40**, 356 (1975) for an explanation of the use of *proximal* and benzo as prefixes in defining a particular analog.

(9) N. J. Leonard, M. A. Sprecker and A. G. Morrice, *J. Am. Chem. Soc.*, **98**, 3987 (1976).

(10) H. Koopman, *Rec. Trav. Chim.*, **80**, 1075 (1961).

(11) All new compounds gave satisfactory microanalytical data and demonstrated the following properties: (a) **6**, 78%, mp 375° dec; pmr (DMSO-d_6): δ 7.00-7.80 (m, 3 H, aromatic H), 11.2 (br s, 2 H, NH); (b) **7**, 97%, mp dec >340°; pmr (DMSO-d_6): δ 7.25 (d, 1 H, J = 4 Hz, H-8), 8.15 (d, 1 H, J = 4 Hz, H-7), 11.65 (br s, 1 H, NH) 11.75 (br s, 1H, NH); (c) **8**, 84%, mp dec 340°; pmr (DMSO-d_6): δ 6.35 (d, 1 H, J = 5 Hz, H-8), 8.25 (d, 1 H, J = 5 Hz, H-7), 8.60 (br s, 1 H, NH), 9.80 (br s, 1 H, NH), 10.70 (br s, 2 H, NH_2); (d) **1**, 20%, mp dec >350°; pmr (DMSO-d_6 at 118°) δ 7.20 (br s, 2 H, 2 NH), 7.80 (d, 1 H, J = 4 Hz, H-6), 8.30 (d, 1 H, J = 4 Hz, H-5), 8.90 (d, 1 H, J = 1 Hz, H-2 or H-3), 9.00 (d, 1 H, J = 4 Hz, H-2 or H-3); (e) **2**, 22%, mp >370°; pmr (DMSO-d_6): δ 7.20 (d, 1 H, J = 4 Hz, H-5), 7.90 (d, 1 H, J = 4 Hz, H-4), 8.20 (s, 1 H, H-2); (f) **12**; 67%, mp 162-163°; pmr (DMSO-d_6 at 128°): δ 3.20 (s, 3 H, N-1 CH_3), 3.55 (s, 3 H, N-3 CH_3), 7.45 (d, 1 H, J = 5 Hz, H-8), 8.15 (d, 1 H, J = 5 Hz, H-7); (g) **13**; 91%, mp 261-263°; pmr (DMSO-d_6 at 128°): δ 3.20 (s, 3 H, N-1 CH_3), 3.50 (s, 3 H, N-3 CH_3), 5.80-6.90 (br s, 2 H, NH_2), 6.60 (d, 1 H, J = 5 Hz, H-8), 8.15 (d, 1 H, J = 5 Hz, H-7); (h) **14**, 89%, mp 203-205°; pmr (DMSO-d_6 at 108°): δ 2.60 (d, 3 H, J = 3 Hz, $NHCH_3$), 3.15 (s, 3 H, N-1 CH_3), 3.35 (s, 3 H, N-3 CH_3), 6.30 (d, 1 H, J = 5 Hz, H-8), 7.65 (d, 1 H, J = 5 Hz, H-7), 9.50 (br s, 1 H, NH); (i) **3**, 98%, mp >318° dec with sublimation; pmr (DMSO-d_6 at 108°): δ 3.35 (s, 3 H, N-6 CH_3), 3.65 (s, 3 H, N-8 CH_3), 7.20 (d, 1 H, J = 5 Hz, H-5), 8.10 (d, 1 H, J = 5 Hz, H-4), 8.15 (s, 1 H, H-2); (j) **4**, 70%, mp 236-238°; pmr (DMSO-d_6 at 118°): δ 3.35 (s, 3 H, N-6 CH_3), 3.55 (s, 3 H, N-8 CH_3), 4.15 (s, 3 H, N-1 CH_3), 7.30 (d, 1 H, J = 5 Hz, H-5), 8.00 (d, 1 H, J = 5 Hz, H-4), 8.13 (s, 1 H, H-2); (k) **15**, 78%, mp 283-285°; pmr (DMSO-d_6 at 118°): δ 3.20 (s, 3 H, N-6 CH_3), 3.30 (br s, 6 H, N-3 and N-8 CH_3), 7.00 (d, 1 H, J = 5 Hz, H-5), 7.80 (d, 1 H, J = 5 Hz, H-4), 7.85 (s, 1 H, H-2).

(12) G. E. Keyser and N. J. Leonard, *J. Org. Chem.*, **44**, 2989 (1979).