A PRACTICAL APPROACH TO THE SYNTHESIS OF 1,2,3,4,6,7,8,9-OCTAHYDRO-1,3-DIMETHYLPYRIMIDO[2,1-*f*]PURINE-2,4,8-TRIONE

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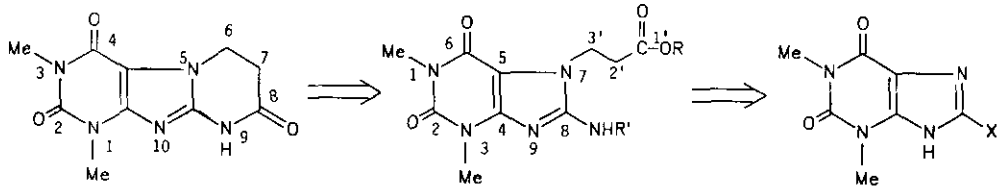
Abstract — A practical synthesis of 1,2,3,4,6,7,8,9-octahydro-1,3-dimethylpyrimido[2,1-*f*]purine-2,4,8-trione, which obviates difficulties encountered in executing the published method, is described.

Our interest in the biological evaluation of 1,2,3,4,6,7,8,9-octahydro-1,3-dimethylpyrimido[2,1-*f*]purine-2,4,8-trione (**1**, NSC-632302) required its preparation in gram quantity. After considerable effort was expended, the preparation described by Pawlowski,[2] at least in our hands, resulted in failure. This result prompted us to devise a simple, workable synthesis of **1** which is reported herein.

The general approach to the synthesis of **1** is shown by the retrosynthetic analysis in Scheme I. The synthesis of target compound (**1**) has been reported by ring closure of either a 3-(8-aminotheophyllin-7-yl)propanoic acid (**2**) or ethyl 3-[8-(benzylamino)theophyllin-7-yl]propanoate (**3**), followed by debenzylation in the latter sequence. Pawlowski reported the N-7 alkylation of 8-bromotheophylline (**4**) using ethyl acrylate in 39% yield and the alkylation of 8-(benzylamino)theophylline (**5**) with ethyl 3-chloropropanoate in 84% yield, respectively. In attempts to duplicate and expand upon these procedures, alkylation of **4** with ethyl

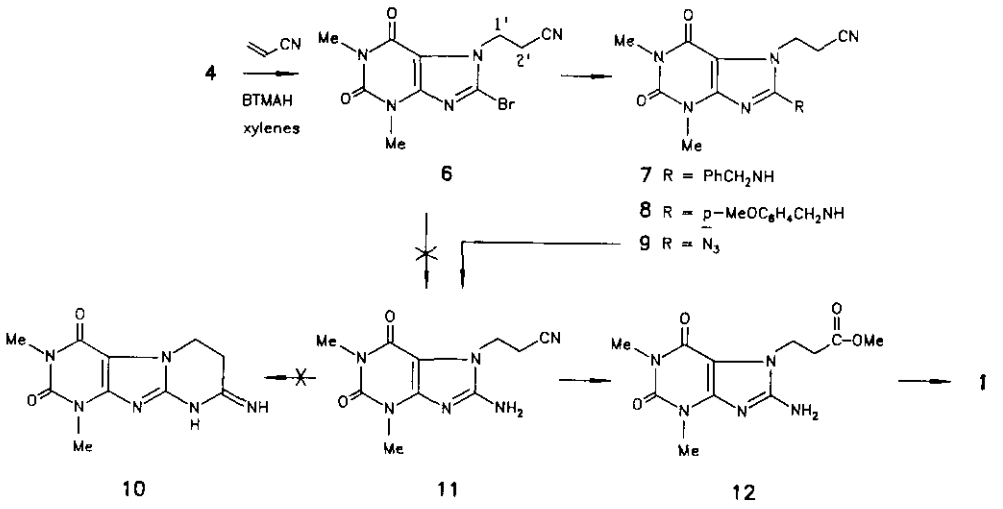


1 | **2** R = R' = H; **3** R = Et, R' = $PhCH_2$ | **4** X = Br; **5** X = $PhCH_2NH$

Scheme I

3-bromopropanoate, 3-chloropropanoic acid, or 3-bromopropiononitrile, under a variety of conditions, gave either very little product or no product at all. Similarly, several attempts to accomplish the alkylation of **4** via conjugate addition of ethyl acrylate[2] were disappointingly unsuccessful. Furthermore, no product was obtained from the 8-benzylamino compound[2] (**5**) when it was heated with ethyl 3-bromopropanoate.

However, when a refluxing solution of **4** and acrylonitrile (Scheme II) in 1,4-dioxane was treated with benzyltrimethylammonium hydroxide (BTMAH) periodically over a period of 10 h, it gave 8-bromo-7-(2-cyanoethyl)theophylline (**6**) in 64% yield. This N-alkylation could be achieved successfully only when BTMAH was added dropwise using a long dropper tube, admitting the reagent directly into the refluxing solution. If during the addition the BTMAH dripped onto the walls of either the condenser or flask and came into direct contact with the vapors, the acrylonitrile polymerized, and no alkylation was observed as determined by tlc and ^{1}H-nmr analysis of the product. A further significant improvement in yield (ca. 95%) was achieved when refluxing xylenes were substituted for 1,4-dioxane as solvent.



Scheme II

The strategy was then altered whereby the 6-bromo group of **6** would be replaced with the amino function, and under the basic conditions of the reaction, the 8-amino group would react with the cyano function to give the amidine (**10**) in a single step. The latter compound should then hydrolyze to give **1**. While ample

precedent exists for this approach,[3] an attempt to displace the 8-bromo group of **6** with ammonia failed, quantitatively giving 8-bromotheophylline (**4**) by a reverse Michael reaction. Thus other methods to introduce the amino group were needed.

The 8-benzylamino derivative (**7**), prepared by treatment of **6** with benzylamine, did not cyclize under the conditions reported by Pawlowski,[2] nor did it cyclize under a variety of other acidic or basic conditions. Removal of the benzyl protecting group to give the free amine to be used in cyclization was unpromising, as only low yields of **11** were obtained. Treatment of **6** with *p*-methoxybenzylamine in 95% ethanol containing triethylamine upon refluxing for 36 h gave **8** in 75% yield. However, the oxidative removal of the *p*-methoxybenzyl group with ammonium cerium(IV) nitrate was also low yielding.

An alternative route, the substitution of azide at position-8 of **6**, was carried out. Reaction of **6** with sodium azide in dimethyl sulfoxide (Me_2SO) at 60°C for 2 h gave the highly crystalline 8-azido-7-(2-cyanoethyl)theophylline (**9**) in 60% yield.[4] Reduction of the azido function was best accomplished (85% yield) using hydrogen and Lindlar's catalyst in 2:3 ethanol—1,4-dioxane.[5] (Other procedures using triphenylphosphine[6] and nickel boride[7] gave **11** in yields of 64% and 30%, respectively.)

Attempts to obtain either the amidine (**10**) or the amide (**1**) directly from **11** were unsuccessful under a variety of conditions. Therefore, **11** was converted to the methyl ester (**12**) by alcoholysis of the cyano group in a solution of methanolic hydrogen chloride at 100 °C for 24 h. Efforts to cyclize **12** using the literature protocol (methanol, conc. sulfuric acid, heat)[2] failed to produce any detectable **1**. However, the cyclization of **12** was found to proceed smoothly in *N*,*N*-dimethylformamide (DMF) and triethylamine to give **1** in 64% yield. The product so obtained had mp >350 °C and was fully characterized by ^1H- and ^{13}C-nmr spectroscopy and by elemental analysis. (See Experimental for details.)

EXPERIMENTAL

Nmr spectra were determined using either a Nicolet NT-200 (200 MHz for ^1H) or a Bruker WM-360 (360 MHz for ^1H or 90 MHz for ^{13}C). Chemical shifts are reported on the δ scale (ppm) downfield from an internal standard of tetramethylsilane. Ir spectra were recorded with either a Perkin—Elmer 710B or 283B spectrophotometer. Thin-layer chromatography was carried out using Silica Gel GF_{254} (E. Merck) aluminum-

backed plates. Column chromatography was performed using Silica Gel 60 (E. Merck) products [70—230 mesh for open columns and 230—400 mesh for medium pressure (flash)]. Evaporation of solvent was generally carried out at ~40 °C under aspirator vacuum. Melting points are uncorrected. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross, GA.

8-Bromo-7-(2-cyanoethyl)theophylline (**6**).

To a suspension of 8-bromotheophylline (**4**, 15 g, 57 mmol) in 350 ml of dry xylenes was added 30 ml (456 mmol) of freshly distilled acrylonitrile, and the mixture was heated under reflux. At this point, 2 ml (4.4 mmol) of 40% benzyltrimethylammonium hydroxide (BTMAH) in MeOH was carefully added directly into the reaction mixture without dripping the reagent on the walls of the reaction flask. (A long dropping tube which extended into the boiling xylene was used.) Additional amounts of acrylonitrile [30 (456 mmol), 20 (304 mmol), and 20 ml (304 mmol)] and BTMAH [2 (4.4 mmol), 2 (4.4 mmol), and 3 ml (6.6 mmol)] were added at 2 h intervals. When the reaction was determined by tlc (5:95,MeOH-$CHCl_3$) to be complete (10 h), the mixture was cooled, and the solvent was evaporated. The residue was diluted with water and extracted with $CHCl_3$. The organic extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated to give the crude product, which was crystallized from $CHCl_3$—MeOH to give 14.2 g (95%) of **6**: mp 192—194 °C; ir (KBr) 2250 cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.00 (t, $J_{1',2'}$ = 6.5 Hz, 2H, H-2'), 3.41 (s, 3H, NMe), 3.56 (s, 2H, NMe), 4.61 (t, $J_{1',2'}$ = 6.5 Hz, 2H, H-1'). Anal. Calcd for $C_{10}H_{10}N_5O_2Br$: C, 38.48; H, 3.23; N, 22.44. Found: C, 38.55; H, 3.28; N, 22.35.

8-Azido-7-(2-cyanoethyl)theophylline (**9**).

To a stirred solution of **6** (6 g, 19.2 mmol) in 100 ml of Me_2SO was added 1.88 g (28.8 mmol) of sodium azide, and the resulting mixture was heated at 60—65 °C for 2 h. The reaction mixture was cooled and diluted with 40 ml of water, and the resulting solid was filtered and dried by suction on a Buchner funnel. The crude product thus obtained was recrystallized from methanol to give 3.23 g (61%) of **9**: mp 310—312 °C; ir (KBr) 2150 cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.00 (t, $J_{1',2'}$ = 6.5 Hz, 2H, H-2'), 3.40 (s, 3H, NMe), 3.57 (s, 3H, NMe), 4.37 (t, $J_{1',2'}$ = 6.5 Hz, 2H, H-1'). Anal. Calcd for $C_{10}H_{10}N_8O_2$: C, 43.80; H, 3.68; N, 40.86. Found: C, 43.84; H, 3.69; N, 40.78.

8-Amino-7-(2-cyanoethyl)theophylline (**11**).

A solution of **9** (2.7 g, 9.78 mmol) in 60 ml of EtOH and 90 ml of 1,4-dioxane containing 1.5 g of Lindlar's

catalyst ($Pd/CaCO_3$ poisoned with lead, Aldrich, cat. no. 20,573-7) was hydrogenated at 50—60 psi and room temperature for 18 h. The mixture was filtered through Celite, and the residue was washed with EtOH. The combined filtrate and washings were concentrated, and the residue was diluted with water and acidified to pH 2 with 10% hydrochloric acid. It was then washed with Et_2O, the aq. layer was adjusted to pH 8 with 10% aq. NaOH, and the solution was thoroughly extracted with dichloromethane. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. The solid thus obtained was recrystallized from 2-methoxyethanol to give 2.06 g (84%) of **11**: mp 260—263 °C; ir (KBr) 3350, 2200 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.95 (t, $J_{1',2'}$ = 6.9 Hz, 2H, H-2'), 3.37 (s, 3H, NMe), 3.49 (s, 3H, NMe), 4.40 (t, $J_{1',2'}$ = 6.9 Hz, 2H, H-1'), 5.90 (br s, 2H, NH_2). Anal. Calcd for $C_{10}H_{12}N_6O_2$: C, 48.38; H, 4.87; N, 33.85. Found: C, 48.44; H, 4.88; N, 33.79.

Methyl 3-(8-aminotheophyllin-7-yl)propanoate (**12**).

A solution of **11** (1.91 g, 7.61 mmol) in 100 ml of dry MeOH satd. with HCl was heated in a sealed tube for 24 h at 100 °C. After cooling the solution to room temperature, the mixture was concentrated, and the residue was adjusted to pH 8 with 1*N* aqueous Na_2CO_3 and thoroughly extracted with $CHCl_3$. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a solid which was recrystallized from 2-methoxyethanol to afford 1.40 g (68.3%) of **12**; mp >320 °C; ir (KBr) 3400, 1730 cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.05 (t, $J_{2',3'}$ = 5.2 Hz, 2H, H-2'), 3.39 (s, 3H, NMe), 3.51 (s, 3H, NMe), 3.72 (s, 3H, OMe), 4.29 (t, $J_{1',2'}$ = 5.2 Hz, 2H, H-3'), 5.37 (br s, 2H, NH_2). Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.96, H, 5.38; N, 24.90. Found: C, 46.70; H, 5.34; N, 24.84.

1,2,3,4,6,7,8,9-Octahydro-1,3-dimethylpyrimido[2,1-f]purine-2,4,8-trione (**1**).

A solution of **12** (0.70 g, 2.49 mmol) in 30 ml of dry *N,N*-dimethylformamide containing 0.9 ml (6.45 mmol) of triethylamine was maintained under a nitrogen atmosphere and heated under reflux for 20 h. The mixture was concentrated, and the residue was thoroughly extracted with $CHCl_3$. The combined extracts were washed with water, brine, dried ($MgSO_4$), and evaporated to give a white solid which was recrystallized from 2-methoxyethanol to yield 0.42 g (64%) of **1**: mp >350 °C (lit.[2] mp >340 °C); ^1H nmr (Me_2SO-d_6): δ 2.84 (t, $J_{6,7}$ = 7.2 Hz, 2H, H-7), 3.21 (s, 3H, NMe), 3.38 (s, 3H, NMe), 4.32 (t, $J_{6,7}$ = 7.2 Hz, 2H, H-6), 8.23 (s, 1H, NH); ^{13}C nmr (Me_2SO-d_6): δ 26.8, 28.9, 29.3, 38.4, 102.3, 146.7, 147.5, 150.7, 153.1, 162.0, 166.7. Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 48.21; H, 4.46; N, 28.04.

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REFERENCES

1. Present address: Department of Chemistry, The University of Tennessee, Knoxville, TN 37996-1600, U.S.A.
2. M. Pawlowski, *Pharmazie*, 1987, **42**, 371.
3. (a) Jahangir, M. A. Brook, D. B. MacLean, and H. L. Holland, *Tetrahedron*, 1987, **43**, 5761; (b) Jahangir, M. A. Brook, D. B. MacLean, and H. L. Holland, *Can. J. Chem.*, 1987, **65**, 2362; (c) D. B. Repke, Jahangir, R. D. Clark, and D. B. MacLean, *J. Chem. Soc., Chem. Commun.*, 1988, 439; (d) D. B. Repke, Jahangir, R. D. Clark, and J. T. Nelson, *Heterocycles*, 1988, **27**, 2289; (e) D. B. Repke, Jahangir, R. D. Clark, J. T. Nelson, and D. B. MacLean, *Tetrahedron*, 1989, **45**, 2541.
4. D. Hesek, M. Tegza, A. Rybar, and F. Považanec, *Synthesis*, 1989, 681.
5. E. J. Corey, K. C. Nicolau, R. D. Balanson, and Y. Machida, *Synthesis*, 1975, 590.
6. N. Knouzi, M. Vaultier, and R. Carrie, *Bull. Soc. Chim. Fr.*, 1985, 815 .
7. J. C. Sarma and R. P. Sharma, *Chem. Ind.*, 1987, 764.

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