Synthesis of Purinobenzodiazepine and Purinobenzotriazocine Derivatives, Two New Heterocyclic Ring Systems

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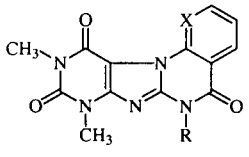
Received July 15, 1998

The preparation of two new heterocyclic ring systems, purinobenzodiazepine and purinobenzotriazocine derivatives by the condensation of 8-aminotheophylline or 8-hydrazinotheophylline with *o*-carboxybenzaldehyde or *o*-carboxyacetophenone is described.

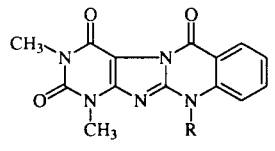
J. Heterocyclic Chem., **36**, 639 (1999).

Presently there is increasing interest in the development of synthetic antitumor drugs belonging to the broad class of DNA-intercalating agents. The majority of these antitumor drugs have common general structures, comprising a tri- or tetracyclic planar chromophore [1-3].

We recently described further examples of this class, such as a number of purinoquinazolines **1a** and **2** [4], purinopyridopyrimidine **1b** [5], purinobenzothiazine **3** and pyridothiazinopurine **4** [6] derivatives, all of which are new heterocyclic ring systems.



1a, X = CH
1b, X = N
R = H, CH_3, $(CH_2)_nNR_2$



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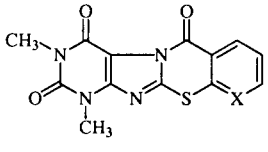
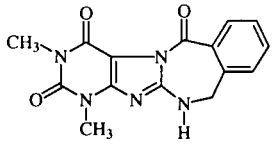


3, X = CH
4, X = N

Some of these new heterocycles, **1a,b,** were recently functionalized with an alkylamino-substituted side chain [5], since this has frequently been associated with improved DNA binding properties. Pursuing our interest in this field, our attention is now focused on the development of new, almost planar heteropolycyclic compounds. In this paper we report the synthesis of novel fused tetracyclic 2,4-benzodiazepinopurine **5** and 2,3,5-benzotriazocinopurine **6** derivatives, which represent new heterocyclic ring systems.



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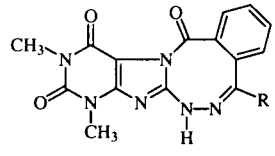


6

The 1,3-dimethyl-11,12-dihydro[2,4]benzodiazepino-[3,2-*f*]purine-2,4,6(1*H*,3*H*)-trione **5** was obtained by condensation of 8-aminotheophylline **7** [7,8] with 2-carboxybenzaldehyde to give the Schiff base **8** in essentially quantitative yield (95%), as summarized in Scheme 1. Reduction of the imine double bond of **8** with sodium borohydride in methanol solution provided the sodium salt of the intermediate derivative **9**, which was obtained by treatment of its ethanolic suspension with hydrochloric acid. Compound **9** was then cyclized to **5** by heating at 300° in a Pyrex tube.

By reaction with dimethyl sulfate in acetonitrile solution, in the presence of potassium carbonate [9], compound **5** afforded **10** in good yield (64%) (Scheme 1).

Analytical, ir, uv, ^1H nmr and mass spectral data of compound **5** were consistent with the proposed structure (Table 1). The assignment of the structure of **5** was supported by considerations emerging from an examination of the uv spectra. In fact, the uv spectra of **5**, which showed an absorption maximum at λ = 205, ε = 36387, appeared closely related to that of purinoquinazoline **1a** [4] (λ_{max} = 222, ε = 29088) and of purinopyridopyrimidine **1b** [5] (λ_{max} = 220, ε = 16267), but different from that of the linear tetracyclic purinoquinazoline **2** [4] (λ_{max} = 245, ε = 21805) (unpublished results). Although the chromophores of compounds **1a-b** and **5** were lightly different, the data supported the structure proposed for **5**. Moreover, cyclization on the N(9) of theophylline is not likely, due to the steric hindrance of the 3-methyl group [10].

The 8-hydrazinotheophylline **11**, which was obtained following a described procedure [11], represented the starting material for the preparation of the title heterocyclic 6,5,8,6 system **6**. In fact **11** and 2-carboxybenzaldheyde were allowed to react in ethylene glycol at reflux for 2 hours, to yield (52%) the desired 1,3-dimethyl-[2,3,5]benzotriazocino[5,4-*f*]purine-2,4,6(1*H*,3*H*)-trione **6**, as shown in Scheme 2.

Scheme 1

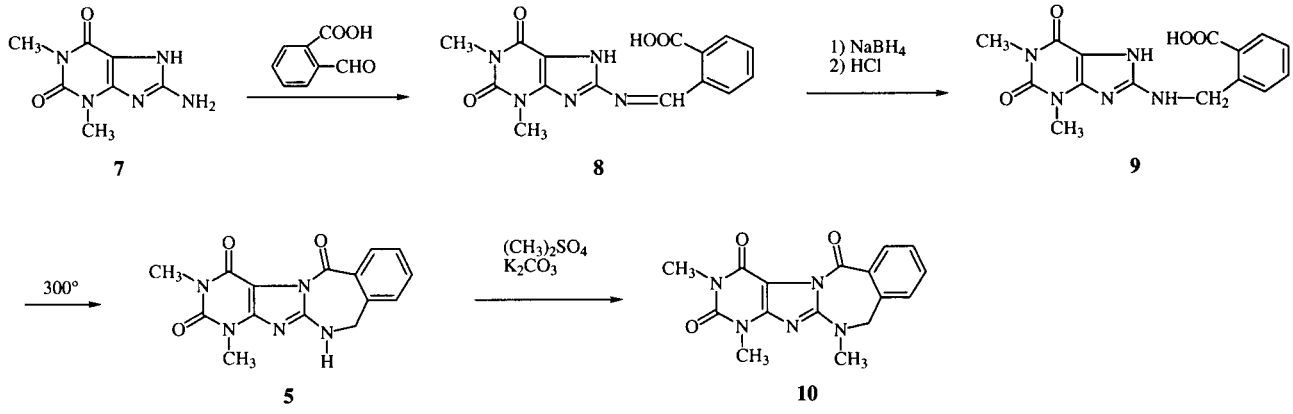
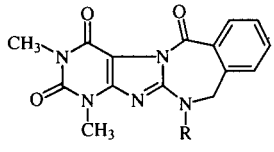


Table 1

Physical and Spectral Data of Compounds **5** and **10**.



No.	R	Yield (%)	Mp (°C) (recrystallization solvent)	^{1}H-NMR (δ ppm) [a]	MS m/z	Molecular Formula	Analysis (%) Calcd./Found		
							C	H	N
5	H	36	>300 (methanol)	3.27 (s, 3H, 3-CH_3), 3.49 (s, 3H, 1-CH_3), 5.11 (d, 2H, 11-CH_2), 7.30-8.20 (m, 4H, Ar-H)	311 (M^+)	$C_{15}H_{13}N_5O_3$	56.57 56.55	3.73 3.80	23.56 23.68
10	CH_3	64	>300 (dimethyl-formamide)	3.27 (s, 3H, 3-CH_3), 3.44 (s, 3H, 1-CH_3), 3.85 (s, 3H, 12-CH_3), 5.08 (s, 2H, 11-CH_2), 7.40-8.30 (m, 4H, Ar-H)	325 (M^+)	$C_{16}H_{15}N_5O_3$	57.88 57.95	4.21 4.19	22.50 22.39

[a] Recorded on a Bruker AC-200.

Scheme 2

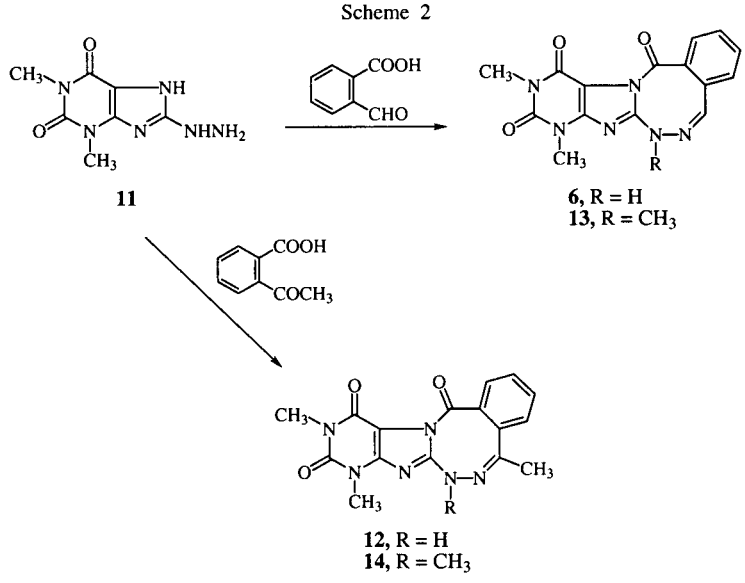
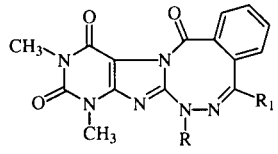


Table II

Physical and Spectral Data of Compounds **6**, **12-14**.



No.	R	R_1	Yield (%)	Mp (°C) (recrystallization solvent)	^{1}H-NMR (δ ppm)	MS m/z	Molecular Formula	Analysis (%) Calcd./Found C	H	N
6	H	H	52	>300 dec (dimethyl-formamide)	3.25 (s, 3H, 1-CH_3), 3.46 (s, 3H, 3-CH_3), 7.52-8.02 (m, 4H, Ar-H), 8.59 (s, 1H, 11-CH), 14.0 (bs, 1H, 13-NH, exch)	324 (M^+)	$C_{15}H_{12}N_6O_3$	55.50 55.35	3.70 3.64	25.90 25.68
12	H	CH_3	40	>300 dec (dimethyl-formamide)	2.62 (s, 3H, 11-CH_3), 3.25 (s, 3H, 1-CH_3), 3.45 (s, 3H, 3-CH_3), 7.71-8.01 (m, 4H, Ar-H), 14.0 (bs, 1H, 13-NH, exch)	338 (M^+)	$C_{16}H_{14}N_6O_3$	56.80 56.74	4.14 4.24	24.85 24.76
13	CH_3	H	65	280 (dimethyl-formamide)	3.27 (s, 3H, 1-CH_3), 3.46 (s, 3H, 3-CH_3), 3.77 (s, 3H, 13-CH_3), 7.94-9.31 (m, 4H, Ar-H), 8.64 (s, 1H, 11-CH)	338 (M^+)	$C_{16}H_{14}N_6O_3$	56.80 56.95	4.14 3.51	24.85 25.07
14	CH_3	CH_3	69	285 (dimethyl-) formamide)	2.60 (s, 3H, 11-CH_3), 3.25 (s, 3H, 1-CH_3), 3.43 (s, 3H, 3-CH_3), 3.75 (s, 3H, 13-CH_3), 7.90-8.31 (m, 4H, Ar-H)	352 (M^+)	$C_{17}H_{16}N_6O_3$	57.95 57.66	4.54 4.42	23.86 23.57

The relatively simple reaction conditions were also used in the reaction between 8-hydrazinotheophylline **11** and 2-carboxyacetophenone, to obtain the methyl derivative **12**; the isomeric methyl derivative **13** and the dimethyl derivative **14** were synthesized by methylation of **6** and **12**, respectively, under the same reaction conditions used to obtain **10** (Scheme 2). The proposed structures of the novel derivative **6** (uv: λ_{max} = 211, ε = 13933), and of the methyl derivatives **12**, **13** and **14** were proved by analytical, ir, ^{1}H nmr and mass spectral data (Table II).

It is our intention to functionalize these new compounds with alkylamino side chains, as previously described [5], with the objective to obtain new compounds to assay for antiproliferative activity.

EXPERIMENTAL

Melting points were determined using a Reichert Köfler hot-stage apparatus and are uncorrected. Infrared spectra were obtained on a PYE/UNICAM Model PU 9561 spectrophotometer as Nujol mulls. Nuclear magnetic resonance spectra were recorded on a Varian CFT-20 spectrometer, unless otherwise reported, in dimethyl sulfoxide solution, using tetramethylsilane as the internal standard. Mass spectra were obtained on a Hewlett-Packard 5988 A spectrometer using a direct injection probe and an electron beam energy of 70 eV. Magnesium sulfate was always used as the drying agent. Evaporations were made *in vacuo* (rotating evaporator). Analytical tlc was carried out on Merck 0.2 mm precoated silica gel aluminium sheets (60 F-254). Elemental analyses were performed by our Analytical Laboratory.

8-[*N*-(2-Carboxyphenyl)methylene]aminotheophylline **8**.

A mixture of 8-aminotheophylline **7** (0.975 g, 5 mmoles) and 2-carboxybenzaldehyde (0.78 g, 5 mmoles) was heated at 120° for 1 hour in absence of a solvent. After cooling, the reaction mixture was treated with ethanol and the solid was collected to give 0.790 g (95% yield) of the pure Schiff base **8**, mp >300°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 3.24 (s, 3H, 1-CH_3), 3.37 (s, 3H, 3-CH_3), 7.16 (s, 1H, N=CH), 7.68-7.89 (m, 4H, Ar-H), 12.10 (br s, 1H, COOH); ms: m/z 327 (M^+), 133 (100).

Anal. Calcd. for $C_{15}H_{13}N_5O_4$: C, 55.05; H, 4.00; N, 21.40. Found: C, 54.99; H, 4.01; N, 21.27.

8-[*N*-(2-Carboxyphenyl)methyl]aminotheophylline **9**.

Sodium borohydride (0.21 g, 5.5 mmoles) was added in small portions to an ice-cooled methanol suspension of **8** (0.45 g, 1.4 mmoles). The reaction mixture was allowed to stir at 0° for 3 hours. The insoluble starting material was filtered and the solution was concentrated to dryness to obtain the sodium salt of **9** (71.9% yield) with methanol-ether as the recrystallization solvent.

A suspension of the above salt in a small amount of ethanol was acidified with concentrated hydrochloric acid and the mixture was allowed to stir at room temperature for 30 minutes. The solid product was collected and purified by recrystallization from dimethylformamide to obtain 0.19 g (41% yield) of **9**, mp 287° dec; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 3.16 (s, 3H, 1-CH_3), 3.35 (s, 3H, 3-CH_3), 4.77 (d, 2H, NH-CH_2), 7.31-7.94 (m, 5H, Ar-H+NH), 11.51 (br s, 1H, COOH); ms: m/z 329 (M^+).

Anal. Calcd. for $C_{15}H_{15}N_5O_4$: C, 54.71; H, 4.56; N, 21.28. Found: C, 54.66; H, 4.55; N, 21.01.

1,3-Dimethyl-11,12-dihydro[2,4]benzodiazepino[3,2-*f*]purine-2,4,6(1*H*,3*H*)-trione **5**.

N-(2-Carboxyphenylmethyl)-8-theophyllinamine **9** (0.30 g, 0.9 mmole) was heated at 300° in a Pyrex tube for 30 minutes. After cooling the crude product was purified by recrystallization to give 0.15 g (36% yield) of pure **5** (Table I).

1,3,12-Trimethyl-11,12-dihydro[2,4]benzodiazepino[3,2-*f*]purine-2,4,6(1*H*,3*H*)-trione **10**.

A solution of dimethyl sulfate (0.38 ml, 4 mmoles) in acetone (2 ml) was added dropwise to an ice-cooled suspension of anhydrous potassium carbonate (0.138 g, 1 mmole) and **5** (0.300 g, 1 mmole) in acetonitrile (5 ml). The reaction mixture was allowed to stir at room temperature for 24 hours. The solid was collected, washed with water and purified by recrystallization (Table I).

1,3-Dimethyl[2,3,5]benzotriazocino[5,4-*f*]purine-2,4,6(1*H*,3*H*)-trione **6** and 1,3,11-Trimethyl[2,3,5]benzotriazocino-[5,4-*f*]purine-2,4,6(1*H*,3*H*)-trione **12**.

General Procedure.

A mixture of 8-hydrazinotheophylline **11** (0.1 g, 0.47 mmole) and the appropriate 2-carboxycarbonyl compound (0.5 mmole) was heated in ethylene glycol at 220° for 2 hours. After cooling the reaction mixture was filtered and the recovered solid product was washed with few portions of ethyl ether to give the pure title derivatives (Table II).

1,3,13-Trimethyl[2,3,5]benzotriazocino[5,4-*f*]purine-2,4,6(1*H*,3*H*)-trione **13** and 1,3,11,13-Tetramethyl[2,3,5]benzo-triazocino[5,4-*f*]purine-2,4,6(1*H*,3*H*)-trione **14**.

General Procedure.

A solution of dimethyl sulfate (0.28 ml, 3 mmoles) in acetone (2 ml) was added dropwise to an ice-cooled suspension of anhydrous potassium carbonate (0.051 g, 0.37 mmole) and **5** or **12** (0.37 mmole) in acetonitrile (5 ml). The reaction mixture was allowed to stir at room temperature for 24 hours. The solid was collected, washed with water and the methyl derivatives **13-14** were purified by recrystallization (Table II).

Acknowledgment.

This work was supported by grants from the Ministry of University and Scientific and Technological Research (MURST) (Research fund 60%).

REFERENCES AND NOTES

[1] B. C. Baguley, *Anti-Cancer Drug Res.*, **6**, 1-35 (1991).

[2] W. A. Denny, *Anti-Cancer Drug Res.*, **4**, 241 (1989).

[3] U. Pindur and G. Fisher, *Curr. Med. Chem.*, **3**, 379 (1996).

[4] A. Da Settimo, G. Primofiore, M. C. Bertacchi, F. Da Settimo and A. M. Marini, *J. Heterocyclic Chem.*, **32**, 941 (1995).

[5] A. Da Settimo, A. M. Marini, G. Primofiore, F. Da Settimo, S. Salerno, G. Viola, L. Dalla Via, and S. Marciani Magno, *Eur. J. Med. Chem.*, **33**, 685 (1998).

[6] A. Da Settimo, A. M. Marini, G. Primofiore, F. Da Settimo and D. Bertini, *J. Heterocyclic Chem.*, **35**, 57 (1998).

[7] B. F. Duesel, H. Berman and R. J. Schachter, *J. Am. Pharm. Assoc.*, **43**, 619 (1954).

[8] J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, **82**, 3773 (1960).

[9] D. Descours and D. Festal, *Synthesis,* 1033 (1983).

[10] D. S. Bariana, *J. Med. Chem.*, **14**, 543 (1971).

[11] H. Priewe and A. Poljak, *Chem. Ber.*, **88**, 1932 (1955).