Benzimidazole Condensed Ring Systems. 7 [1]. An Entry to Substituted 1*H*,6*H*-2,6a,10b-Triazafluoranthene-1,3,6-(2*H*)-triones and Related Systems as Possible Chemotherapeutic Agents

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The syntheses of some derivatives of three new benzimidazole condensed ring systems; namely, 1*H*,6*H*-2,6a,10b-triazafluoranthene-1,3,6(2*H*)-trione (**3**), 1*H*,8*H*,11*H*-12-oxa-2,3a,7b-triazabenz[*e*]acephenanthrylene-1,3,8,11(2*H*)-tetrone (**4**) and 1*H*,4*H*-2,5,6a,10b-tetrazafluoranthene-1,3,4,6(2*H*,5*H*)-tetrone (**10**) are described. Two compounds exhibited *in vitro* antibacterial activity. Four compounds were screened for *in vitro* anti-HIV activity and three compounds were evaluated for antileukemic potency but were inactive.

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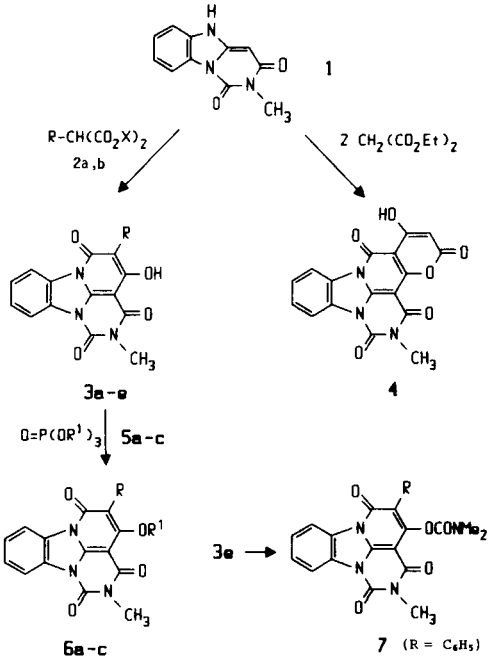
In continuation of our previous work on pyrimido[1,6-*a*]-benzimidazoles [2,3], we became interested in studying the reactivity of 2-methylpyrimido[1,6-*a*]benzimidazole-1,3-(2*H*,5*H*)-diones (**1**) [3] towards some unsubstituted and monosubstituted malonate esters. Our interest in **1** stemmed from the observation that its structure would comprise a 1,3-binucleophilic center. Thus reacting **1**, readily accessible from ethyl 1*H*-benzimidazole-2-acetate and methyl isocyanate [3], with the selected diethyl monosubstituted malonates **2a** at high temperature in the presence of trichlorophenol resulted in excellent yields of the respective 4-hydroxy-2-methyl-5-substituted-1*H*,6*H*-2,6a,-10b-triazafluoranthene-1,3,6(2*H*)-triones **3a-c**. Compound **3b** could also be obtained by fusing **1** with bis-2,4,6-trichlorophenyl ethylmalonate (**2b**). On the other hand, reacting **1** with dimethyl malonate under similar conditions afforded a good yield of 9-hydroxy-2-methyl-1*H*,8*H*,11*H*-12-oxa-2,3a,7b-triazabenz[*e*]acephenanthrylene-1,3,8,11(2*H*)-tetrone (**4**). Alkylation of **3** with trialkyl phosphates **5** yielded the corresponding 4-alkoxy derivative **6**. Carbamoylation of compound **3e** with *N,N*-dimethyl carbamoyl chloride yielded the 4-(*N,N*-dimethylcarbamoyloxy) derivative **7** (Scheme 1).

Scheme 1



2a: X = C_2H_5 **2b**: X = $C_6H_2Cl_3$

3a-e: R-Key see Table 1

6	R	R¹
a	CH_3	CH_3
b	C_4H_9-n	C_4H_9-n
c	$CH_2C_6H_5$	C_2H_5

In the light of these results together with our previous findings of the interaction of ethyl 1*H*-benzimidazole-2-acetate and 1*H*-benzimidazole-2-acetonitrile with ethoxycarbonyl isocyanate (**9**) [2], we were prompted to investigate the behaviour of 2-methyl-1*H*-benzimidazole (**8**) with **9**. Refluxing **8** with two equivalents of **9** in bromobenzene afforded 1*H*,4*H*-2,5,6a,10b-tetrazafluoranthene-1,3,4,6-(2*H*,5*H*)-tetrone (**10**). The latter, on methylation with trimethyl phosphate (**5a**), yielded the 2,5-dimethyl derivative **11**. The result of this condensation, which involved the CH_3, N-1 and N-3 of compound **8**, is different from our previous findings concerning the condensation of **8** and

Scheme 2

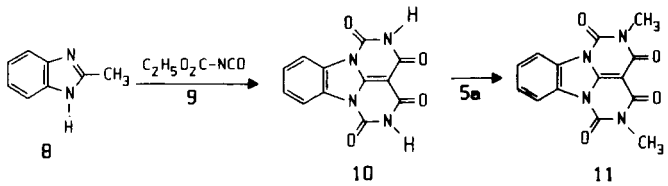


Table 1

4-Hydroxy-2-methyl-5-substituted-1*H*,6*H*-2,6a,10-triazafluoranthene-1,3,6(2*H*)-triones **3a-c**

Compound No.	R	Yield %	Mp (°C)	Recrystallization solvent	Molecular fromula Molecular weight	Analysis, % Calcd./Found C	H	N
3a	CH_3	87	302-305	DMF	$C_{15}H_{11}N_3O_4$ 297.26	60.60 60.42	3.73 3.71	14.14 14.19
3b	C_2H_5	96	272-275	DMF	$C_{16}H_{13}N_3O_4$ 311.29	61.73 61.60	4.21 4.26	13.50 13.51
3c	C_4H_9	87	226-229	DMF	$C_{18}H_{17}N_3O_4$ 339.34	63.70 63.66	5.05 4.95	12.38 12.48
3d	$CH_2C_6H_5$	88	270-273	DMF/H_2O	$C_{21}H_{15}N_3O_4$ 373.35	67.55 67.45	4.05 4.25	11.26 11.17
3e	C_6H_5	89	275-276	DMF/H_2O	$C_{20}H_{13}N_3O_4$ 359.33	66.85 67.01	3.65 3.75	11.70 11.77

^{1}H-nmr (δppm) of **3a**: 2.3 (s, CH_3), 3.7 (s, NCH_3), 7.6-8.0 (m, 2 ArH at C-8 and C-9), 8.3-8.7 (m, 2 ArH at C-7 and C-10). ^{1}H-nmr (δppm) of **3b**: 1.3 (t, J = 7 Hz, CH_3-ethyl), 2.8 (q, CH_2), 3.7 (s, NCH_3), 7.6-8.0 (m, 2ArH at C-8 and C-9), 8.4-8.8 (m, ArH at C-7 and C-10).

Table 2

Growth Inhibition Zones (mm) and MIC (μg/ml) Values

Compound No.	S. aureus ATCC 25921		E. coli NCTC 10418		C. albicans NCTC 2708	
	i. z.	MIC	i. z.	MIC	i. z.	MIC
3a	16	200	16	>250	20	150
3c	15	---	11	---	15	---
4	17	>250	16	>250	18	>250
6a	16	>250	16	>250	20	>250
6b	15	---	14	---	15	---
7	16	>250	18	150	16	>250
10	16	>250	17	>250	16	>250
Reference	20	---	19	---	24	---

i.z. = Inhibition zones.

reactive malonates [4]. In the latter reaction, which have resulted in the substituted 1*H*-imidazo[4,5,1-*ij*]quinolin-4-ones, the condensation involved N-1 and C-7 of the benzimidazole. The structures assigned to the compounds were substantiated by microanalyses, ir and ^{1}H nmr spectral data.

A survey of the available literature indicated that the prepared compounds belong to new ring systems which may be looked upon as hybrid structures of benzimidazole and 5-deazapteridine or pyrimido[4,5-*d*]pyrimidine nuclei. Since many derivatives of these nuclei proved to possess antimicrobial and anticancer activities [5-8], it was considered of interest to screen some of the new compounds for such activities.

Compounds **3a**, **3c**, **4**, **6a**, **6b**, **7** and **10** were screened for the *in vitro* antimicrobial activity against *Staphylococcus aureus, Escherichia coli* and *Candida albicans* by the agar diffusion method [9]. The compounds were dissolved in dimethyl sulfoxide at a concentration of 2 mg/ml and diluted with phosphate buffer (*p*H 8) to 0.2 mg/ml to be used for growth inhibition zone measurements (Table 2). A control for the solvent was included for each organism. Gentamycin (for *S. aureus* and *E. coli*) and Nystatin (for *C. albicans*) were used as reference compounds at a concentration of 0.2 mg/ml. Compounds which showed inhibition zones >15 mm in diameter were evaluated for their minimal inhibitory concentrations (MIC) (Table 2) against the most sensitive organism using the broth dilution method.

Out of the compounds screened, only **3a** showed activity against *S. aureus* (MIC = 200 μg/ml) and against *C. albicans* (MIC = 150 μg/ml) but was inactive against *E. coli* (MIC >250 μg/ml). On the other hand, compound **7** was active against *E. coli* with an MIC value of 150 μg/ml but was inactive against *S. aureus* and *C. albicans* (MIC >250 μg/ml). In addition the tubes which showed no bacterial growth in the MIC measurements of compounds **3a** and **7** were subcultured in broth agar in order to investigate their minimal bactericidal concentrations (MBC). Both compounds showed MBC >250 μg/ml.

Compounds **4**, **6c**, **7** and **10** were evaluated for *in vitro* anti-HIV activity according to the NCI *in vitro* Anti-Aids drug discovery program [10] but were inactive. Moreover, compounds **3b,c,e** were screened against P338 lymphocytic leukemia in mice according to a standard protocol [10], however they were inactive.

EXPERIMENTAL

Melting points were determined in open-glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 421 spectrophotometer using samples in potassium bromide discs. The ^{1}H nmr spectra were recorded in trifluoroacetic acid (unless otherwise specified) using TMS as an internal standard; the instruments used were the Varian EM 360 at 60 MHz and the XL 200 at 200 MHz.

5-Substituted-4-hydroxy-2-methyl-1*H*,6*H*-2,6a,10b-triazafluoranthene-1,3,6(2*H*)-triones **3a-e** (Table 1).

Method A for **3a-e**.

Compound **1** (1.08 g, 5 mmoles) was heated with the appropriate diethyl monosubstituted malonates (5 ml) in the presence of trichlorophenol (0.5 g) at 280° for 20-30 minutes. After cooling and addition of petroleum ether, the product was filtered and dried; ir: 3300 w, 1740-1730 s (CO), 1680-1670 s (CO), 1630-1590 (w-s) cm^{-1}; ^1H nmr data of **3** and **b** are recorded in Table 1.

Method B for **3b**.

Compound **1** (1.08 g, 5 mmoles) was fused with bis-2,4,6-trichlorophenyl ethylmalonate (**2b**) (2.5 g, 5 mmoles) at 240° for 20-30 minutes. After cooling and addition of petroleum ether, the separated solid was filtered and dried, yield 1.25 g (80%). The melting point and spectral data of the compound were identical with those obtained for **3b** prepared by the above method.

9-Hydroxy-2-methyl-1*H*,8*H*,11*H*-12-oxa-2,3a,7b-triazabenz[*e*]-acephenanthrylene-1,3,8,11(2*H*)-tetrone (**4**).

It was prepared by reacting **1** (1.08 g, 5 mmoles) with dimethyl malonate (5 ml) as described for **3** under method A, yield 1.25 g (71%), mp >300°. It was purified by washing with hot dimethylformamide; ir: 3100 w, 1740 s, 1680 s (CO), 1550 s cm^{-1}; ^1H nmr (DMSO-d_6): 200 MHz, δ 3.4 (s, CH_3), 5.6 (s, H at C-10), 7.6-7.9 (m, 2 ArH at C-5 and C-6), 8.3 (d, H at C-7), 8.6 (d, H at C-4).

Anal. Calcd. for $C_{17}H_9N_3O_6$: C, 58.12; H, 2.58; N, 11.96. Found: C, 58.38; H, 2.74; N, 12.20.

2,5-Dimethyl-4-methoxy-1*H*,6*H*-2,6a,10b-triazafluoranthene-1,3,-6(2*H*)-trione (**6a**).

Compound **3a** (1 g) was refluxed with trimethyl phosphate (**5a**) (15 ml) for 30 minutes in presence of potassium carbonate (0.2 g). After cooling and addition of aqueous ethanol the crystalline product was filtered and dried, yield 0.47 g (45%), mp 266-268° (dimethylformamide); ir: 1740 s, 1680 s, 1650 s, (CO), 1610 w, 1560 s cm^{-1}; ^1H nmr: δ 2.3 (s, CH_3 at C-5), 3.7 (s, NCH_3), 4.1 (s, OCH_3), 7.4-7.9 (m, 2 ArH at C-8 and C-9), 8.4 (dd, H at C-7), 8.7 (d, H at C-10).

Anal. Calcd. for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.67; H, 4.34; N, 13.22.

5-Butyl-4-butoxy-2-methyl-1*H*,6*H*-2,6a,10b-triazafluoranthene-1,3,6(2*H*)-trione (**6b**).

This was similarly prepared from **3c** (1 g) and tributyl phosphate **5c** (15 ml), yield 0.82 g (70%), mp 212-214° (dimethylformamide); ^1H nmr (DMSO-d_6): 200 MHz δ 0.9 (t, J = 7 Hz, CH_3-butyl), 1.0 (t, J = 7 Hz, CH_3-butoxy), 1.0-2.0 (m, 8H, 4 CH_2 of butyl and butoxy), 2.9 (t, CH_2-butyl at C-5), 3.3 (s, NCH_3), 4.1 (t, CH_2O-butoxy), 7.5-7.7 (m, 2 ArH at C-8 and C-9), 8.3 (d, H at C-7), 8.6 (d, H at C-10).

Anal. Calcd. for $C_{22}H_{25}N_3O_4$: C, 66.82; H, 6.37; N, 10.63. Found: C, 66.78; H, 6.43; N, 10.68.

5-Benzyl-4-ethoxy-2-methyl-1*H*,6*H*-2,6a,10b-triazafluoranthene-1,3,6(2*H*)-trione (**6c**).

It was likewise prepared from **3d** (1 g) and triethyl phosphate **5b** (15 ml), yield 0.7 g (67%), mp 258-259° (dimethyl formamide); ir: 1730 s, 1680 s, 1650 s (CO), 1610 w, 1550 s cm^{-1}; ^1H nmr: δ 1.15 (t, J = 7 Hz, CH_3-ethyl), 3.7 (s, NCH_3), 4.1 (s, CH_2-benzyl), 4.2 (q, CH_2-ethyl), 7.2 (s, 5 ArH-benzyl), 7.5-7.9 (m, 2 ArH at C-8 and C-9), 8.4 (d, H at C-7), 8.8 (d, H at C-10).

Anal. Calcd. for $C_{23}H_{19}N_3O_4$: C, 68.82; H, 4.77; N, 10.47. Found: C, 68.62; H, 4.92; N, 10.36.

4-(*N,N*-Dimethylcarbamoyloxy)-2-methyl-5-phenyl-1*H*,6*H*-2,6a,-10b-triazafluoranthene-1,3,6(2*H*)-trione (**7**).

To a stirred solution of **3e** (0.9 g, 2.5 mmoles) in dry pyridine (10 ml), *N,N*-dimethylcarbamoyl chloride (0.4 ml, 4 mmoles) was added. The reaction mixture was stirred at room temperature in the presence of 4-(*N,N*-dimethylamino)pyridine (0.1 g) for 5 hours. Water was then added and the separated product was filtered, washed with water and dried, yield 0.6 g (56%), mp >300° (dimethylformamide); ir: 1750 s, 1700 s, 1680 s, 1650 s (CO), 1610 w, 1570 s cm^{-1}; ^1H nmr: δ 2.8 (s, 6 H, $N(CH_3)_2$), 3.7 (s, NCH_3), 7.4 (s, 5 ArH of phenyl at C-5), 7.6-7.9 (m, 2 Ar H at C-8 and C-9), 8.4 (d, H at C-7), 8.7 (d, H at C-10).

Anal. Calcd. for $C_{23}H_{18}N_4O_5$: C, 64.18; H, 4.22; N, 13.02. Found: C, 64.22; H, 4.4; N, 12.94.

1*H*,4*H*-2,5,6a,10b-tetrazafluoranthene-1,3,4,6(2*H*,5*H*)-tetrone (**10**).

2-Methyl-1*H*-benzimidazole (**8**) (1.32 g, 10 mmoles) and ethoxycarbonyl isocyanate (**9**) (2 ml, 20 mmoles) were refluxed in bromobenzene for 2 hours. After cooling the product was filtered washed with benzene and dried, yield 0.81 g (30%), mp >300° (dimethylformamide); ir: 3300-2500 bm, 1730 s, 1660 s (CO), 1610 w, 1520 m cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.5 (m, 2 ArH at C-8 and C-9), 8.1 (m, 2 ArH at C-7 and C-10).

Anal. Calcd. for $C_{12}H_6N_4O_4$: C, 53.34; H, 2.24; N, 20.74. Found: C, 52.80; H, 2.40; N, 20.60.

2,5-Dimethyl-1*H*,4*H*-2,5,6a,10b-tetrazafluoranthene-1,3,4,6(2*H*,-5*H*)-tetrone (**11**).

It was prepared from **10** (0.6 g) and trimethyl phosphate (**5a**) (10 ml) as described for **6a**, yield 0.33 g (50%), mp >300° (dimethylformamide); ir: 2900 w, 1720 s (CO), 1610 m, 1530 s cm^{-1}; ^1H nmr: δ 3.6 (s, 2 CH_3), 7.6 (m, 2 ArH at C-8 and C-9), 8.4 (m, 2 ArH at C-7 and C-10).

Anal. Calcd. for $C_{14}H_{10}N_4O_4$: C, 56.38; H, 3.38; N, 18.78. Found: C, 56.57; H, 3.50; N, 18.68.

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