Benzimidazole Condensed Ring Systems. 4 [1]. New Approaches to the Synthesis of Substituted Pyrimido[1,6-*a*]-benzimidazole-1,3(2*H*,5*H*)-diones

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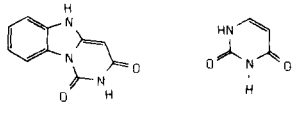
Received October 14, 1988

The synthesis of some substituted 1,3-dioxopyrimido[1,6-*a*]benzimidazole-4-carbonitriles **6a,b** and 4-ethyl carboxylates **6c,d** through condensation of 1*H*-benzimidazole-2-acetonitriles **3a,b** and ethyl 1*H*-benzimidazole-2-acetates **3c,d**, respectively, with ethoxycarbonyl isocyanate **4** are reported. The esters **6c,d** were also obtained by condensing **3c**, or **d** with chlorosulfonyl isocyanate **7**. The alkylation of **5** and **6** with trimethyl or triethyl phosphate **9a**, or **b** to obtain the *N,N*-dialkyl derivatives **10a-e** and **11** are also described. Representative compounds were tested against P-388 lymphocytic leukemia in mice and for herbicidal and plant fungicidal activities but were inactive.

J. Heterocyclic Chem., **26**, 405 (1989).

In connection with our previous work on pyrido[1,2-*a*]-benzimidazoles [2,3] and 2,3-dihydrocyclopenta[4',5':2,3]-pyrido[1,2-*a*]benzimidazoles [1] we became interested in the isosteric pyrimido[1,6-*a*]benzimidazoles. In this respect, our initial effort was directed towards the synthesis of some compounds derived from pyrimido[1,6-*a*]-benzimidazole-1,3-(2*H*,5*H*)dione **1** a molecule comprising a uracil residue **2** within its structure. This fact may add special criterion to the newly designed compounds when screened for biological activities.



1

2

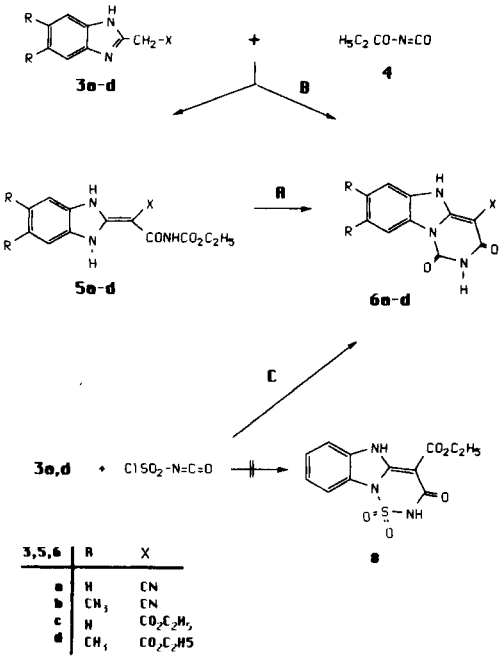
Fig.

The tricyclic system **1** was unknown until 1965, when a short report [4] appeared describing its synthesis by catalytic hydrogenation of 1-(2-nitrophenyl)barbituric acid. The report also described the preparation of 3,4-dihydropyrimido[1,6-*a*]benzimidazol-1(2*H*)-one by cyclizing 2-(2-aminoethyl)benzimidazole with diethyl carbonate. An extension of this work has been reported in 1970 by Nagarajan *et al.* [5] when the amine was condensed with some aldehydes to prepare 1-substituted-1,2,3,4-tetrahydropyrimido[1,6-*a*]benzimidazoles. Later on, Buschauer *et al.* [6] have converted the same amine to 3,4-dihydropyrimido[1,6-*a*]benzimidazol-1(2*H*)-ylidene cyanamide upon condensation with dimethyl *N*-cyanodithioimidocarbonate and to 3,4-dihydropyrimido[1,6-*a*]benzimidazole-1(2*H*)-thione with carbon disulfide. Recently Hammad *et al.* [7] reported the synthesis of 3-trichloromethylpyrimido[1,6-*a*]benzimidazole by condensing 1*H*-benzimidazole-2-acetonitrile with trichloroacetonitrile followed by treatment with ethyl orthoformate.

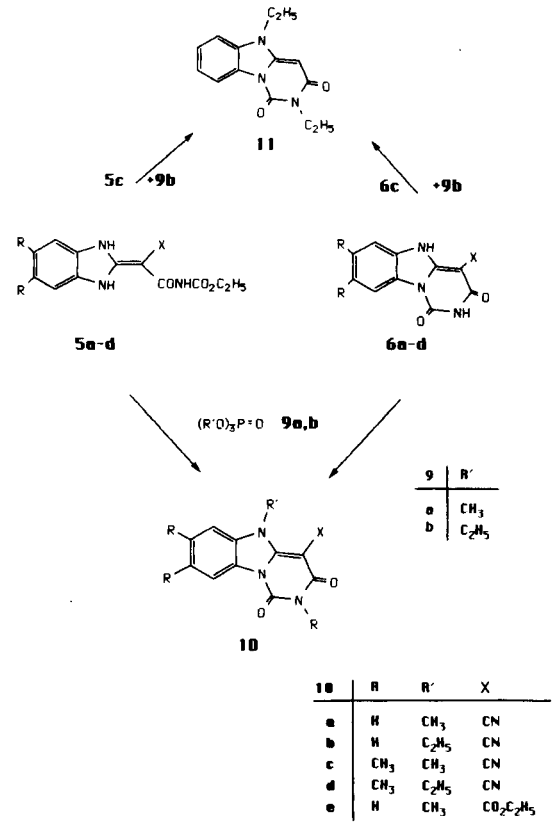
The limited substitution patterns attainable through the aforementioned reactions, motivated the search for an alternative efficient route to the adopted system which would permit the preparation of wider range of substituents for biological screening. In our study, 1*H*-benzimidazole-2-acetonitriles **3a,b** or ethyl 1*H*-benzimidazole-2-acetates **3c,d** were allowed to react with ethoxycarbonyl isocyanate **4** at room temperature to afford the corresponding adducts **5a-d** which were mainly, if not entirely, products of attack on carbon. The assigned structures were substantiated by ^{1}H nmr spectra of all the intermediates which lacked the -CH_2-X protons and the ^{13}C nmr spectrum of compound **5c** which revealed two signals at δ = 156 and 81 ppm attributed to the exocyclic "push-pull" double bond structure.

The intermediates **5a-d** were readily cyclized in boiling bromobenzene to the corresponding 7,8-disubstituted-1,3-dioxo-2*H*,5*H*-pyrimido[1,6-*a*]benzimidazole-4-carbonitriles **6a,b** and 4-ethyl carboxylates **6c,d** in excellent yields (method A, scheme 1). These compounds were also directly obtained, in similar high yields, upon condensing **3a-d** with **4** in boiling bromobenzene (method B). The proposed structures were verified by ir and ^{1}H nmr spectral data. The appearance of strong $C_1=O$ and $C_3=O$ absorptions in the ir spectra confirmed the diacyl imide structure, O=C-N-C=O, within the pyrimido ring. On the other hand, when the proper ethyl 1*H*-benzimidazole-2-acetate **3c,d** was reacted with chlorosulfonyl isocyanate **7** at room temperature, the respective ethyl 1,3-dioxo-2*H*,5*H*-pyrimido[1,6-*a*]benzimidazole-4-carboxylate **6c,d** (method C) was obtained instead of the expected product **8**. The identities of the isolated products were affirmed by elemental analyses, mixed mps, tlc, and spectroscopic

Scheme 1



Scheme 2



determinations. Although this cyclocondensation provides a third new synthetic approach (method C) to the title compounds and considered unique among the known reactions of chlorosulfonyl isocyanate, yet the poor yields of the products would limit its generalization. On the other hand, trials to obtain a product from the interaction of 1*H*-benzimidazole-2-acetonitrile **3a** with **7** were unsuccessful. When the intermediates **5a**, or **b** (X = CN) or their cyclized derivatives **6a**, or **b** were refluxed with excess trimethyl or triethyl phosphate **9a**, or **b** in presence of potassium carbonate the corresponding substituted 2,5-dialkyl-1,3-dioxo-2*H*,5*H*-pyrimido[1,6-*a*]benzimidazoles **10a-d** were obtained in appreciable yields. The reaction of the intermediates involved both cyclization and dialkylation. Analogously, methylation of the intermediate **5c** (X = $COOC_2H_5$) or its cyclized derivative **6c** with trimethyl phosphate **9a** yielded **10e**. Unexpectedly, ethylation of the

Table 1

7,8-Disubstituted 1,3-Dioxo-2*H*,5*H*-pyrimido[1,6-*a*]benzimidazole-4-carbonitriles **6a,b** and 4-Ethyl Carboxylates **6c,d**

Compound No.	R	X	Yield (%)	Mp (°C)	Recrystallization solvent	Molecular formula Molecular weight	Analysis, % Calcd./Found C	H	N
6a	H	CN	96	>300	DMF	$C_{11}H_6N_4O_2$	58.41	2.67	24.77
						226.20	58.15	2.68	24.70
b	CH_3	CN	82	>300	DMF	$C_{13}H_{10}N_4O_2$·	58.71	5.23	21.40
						C_3H_7NO	58.97	5.27	21.46
						327.35			
c	H	$COOC_2H_5$	81	>300	DMF	$C_{13}H_{11}N_3O_4$	57.14	4.06	15.38
						273.25	57.14	3.90	15.50
d	CH_3	$COOC_2H_5$	73	>300	DMF	$C_{15}H_{15}N_3O_4$	59.79	5.02	13.95
						301.30	59.80	5.01	13.93

^{1}H nmr (δ ppm) of **6b**: 2.35 (s, 2 CH_3), 7.4 (s, H at C-6), 8.2 (s, H at C-9).

^{1}H nmr (trifluoroacetic acid (δ ppm) of **6c**: 1.6 (t, J = 7 Hz, CH_3), 4.75 (q, CH_2), 7.7 (s, 3 aromatic H), 8.45 (d, H at C-9).

Table 2

2,5-Dialkyl-7,8-disubstituted-1,3-dioxo-2*H*,5*H*-pyrimido[1,6-*a*]benzimidazole-4-carbonitriles **10a-d**

Compound No.	R'	R	Yield (%)	Mp (°C)	Recrystallization solvent	Molecular formula Molecular weight	Analysis, % Calcd./Found C	H	N
10a	CH_3	H	93	>300	DMF/H_2O	$C_{13}H_{10}N_4O_2$ 254.26	61.41 61.23	3.96 3.86	22.04 21.95
b	C_2H_5	H	76	260-262	DMF	$C_{15}H_{14}N_4O_2$ 282.31	63.82 63.66	4.99 5.05	19.85 19.65
c	CH_3	CH_3	83	>300	DMF	$C_{15}H_{14}N_4O_2$ 282.31	63.82 63.57	4.99 4.90	19.85 19.71
d	C_2H_5	CH_3	74	293-295	DMF/H_2O	$C_{17}H_{18}N_4O_2$ 310.36	65.79 65.70	5.85 5.89	18.05 17.96

Table 3

^{1}H-NMR Data of 2,5-Dialkyl-7,8-disubstituted-1,3-dioxo-2*H*,5*H*-pyrimido[1,6-*a*]benzimidazole-4-carbonitriles **10a-d**

Compound No.	R'	R	^{1}H-NMR (trifluoroacetic acid) (δ ppm)
10a	CH_3	H	3.6 (s, CH_3 at N-5), 4.1 (s, CH_3 at N-2), 7.3-7.8 (m, 3 aromatic H), 8.45 (d, H at C-9)
b	C_2H_5	H	1.4 (t, J = 7 Hz, CH_3-ethyl at N-5), 1.7 (t, J = 7 Hz, CH_3-ethyl at N-2), 4.25 (q, CH_2-ethyl at N-5), 4.6 (q, CH_2-ethyl at N-2), 7.3-7.8 (m, 3 aromatic H), 8.45 (d, H at C-9)
c	CH_3	CH_3	2.45 (s, 2 CH_3 at C-7,8), 3.6 (s, CH_3 at N-5), 4.0 (s, CH_3 at N-2), 7.2 (s, H at C-6), 8.1 (s, H at C-9)
d	C_2H_5	CH_3	1.35 (t, J = 7 Hz, CH_3-ethyl at N-5), 1.6 (t, J = 7 Hz, CH_3-ethyl at N-2), 2.45 (s, 2 CH_3 at C-7,8), 4.2 (q, CH_2-ethyl at N-5), 4.5 (q, CH_2-ethyl at N-2), 7.25 (s, H at C-6), 8.15 (s, H at C-9)

same intermediate **5c** or its tricyclic derivative **6c** with excess triethyl phosphate **9b** using the adopted reaction conditions, resulted in 4-deethoxycarbonylated-2,5-diethylated tricyclic product **11**. These findings were in accordance with those previously observed during the ethylation of ethyl 3-hydroxy-2-phenyl-1-oxo-1*H*,5*H*-pyrimido[1,2-*a*]-benzimidazole-4-carboxylate [3]. The ir spectra revealed the $C_1=O$ and $C_3=O$ absorptions characteristic of the $O=C\text{-}N\text{-}C=O$ structure, and the ^{1}H nmr spectra indicated the proton signals corresponding to N-2 and N-5 dialkyl substituents.

Compounds **6a,c** and **10a-d** were screened against P388 lymphocytic leukemia in mice according to a standard protocol [8] and were inactive. Compounds **6a**, and **10a** were also tested for herbicidal and plant fungicidal activity according to standard protocols but 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 disks. The ^{1}H nmr spectra were recorded on a Varian EM-360 spectrometer using hexadeuteriodimethylsulfoxide as solvent (unless otherwise specified) and tetramethylsilane as the internal standard. The ^{13}C nmr spectrum was recorded on a Varian XL-200 instrument.

2-(1*H*,3*H*-Benzimidazol-2-ylidene)-*N*-ethoxycarbonyl Cyanoacetamide (**5a**).

Ethoxycarbonyl isocyanate **4** [9] (2 ml, 20 mmoles) was added to a stirred solution of **3a** [10] (3.14 g, 20 mmoles) in dry acetone (50 ml). After stirring under dry conditions for 1 hour at room temperature, the resulting white product was filtered, washed with ether and dried, yield 5.1 g (93%), mp >300° (aqueous ethanol); ir: 3500-2700 bm, 2200 s (CN), 1770 s (CO-ester), 1660 m (CO), 1630 s, 1550 w cm^{-1}; ^{1}H nmr: δ 1.3 (t, J = 7 Hz, CH_3), 4.1 (q, J = 7 Hz, CH_2), 7.0-7.6 (m, 4 ArH).

Anal. Calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.41; H, 4.48; N, 20.29.

2-(5,6-Dimethyl-1*H*,3*H*-benzimidazol-2-ylidene)-*N*-ethoxycarbonyl Cyanoacetamide (**5b**).

This was likewise prepared from **4** (2 ml, 20 mmoles) and **3b** [3] (3.7 g, 20 mmoles), yield 5.0 g (84%), mp >300° (ethanol); ir: 3500-2800 bm, 2200 s (CN), 1770 s (CO-ester), 1655 s (CO), 1625 m, 1580 s cm^{-1}; ^{1}H nmr (trifluoroacetic acid): δ 1.5 (t, J = 7 Hz, CH_3-ethyl ester), 2.5 (s, 2 CH_3), 4.5 (q, J = 7 Hz, CH_2-ethyl ester), 7.4 (s, 2 ArH).

Anal. Calcd. for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37; N, 18.66. Found: C, 59.82; H, 5.46; N, 18.26.

Ethyl [(1*H*,3*H*-Benzimidazol-2-ylidene)ethoxycarbonylacetyl]-carbamate (**5c**).

Prepared by reacting **4** (2 ml, 20 mmoles) with **3c** [11] (4.0 g, 20 mmoles) in dry chloroform (75 ml) as described for **5a**. Excess chloroform was then removed under vacuum and the oily residue was mixed with ether and few mls of ethanol. The deposited product was filtered, washed with ether and dried, yield 4.85 g (76%), mp 180-182° (aqueous ethanol); ir: 3500-2800 bm, 1770 s, 1750 s (CO-esters), 1650 s (CO), 1620 s, 1570 s cm^{-1}; ^{1}H nmr: δ 1.25 (t, J = 7 Hz, CH_3 in $=C\text{-}COOC_2H_5$).

$NHCOOC_2H_5$), 4.1 (q, CH_2 in $=C\text{-}COOC_2H_5$), 4.35 (q, CH_2 in $NHCOOC_2H_5$), 7.1-7.9 (m, 4 ArH).

Anal. Calcd. for $C_{15}H_{17}N_3O_5$: C, 56.42; H, 5.37; N, 13.16. Found: C, 56.70; H, 5.30; N, 13.22.

Ethyl [(5,6-Dimethyl-1*H*,3*H*-benzimidazol-2-ylidene)ethoxycarbonylacetyl]carbamate (**5d**).

Prepared from **4** (2 ml, 20 mmoles), and **3d** [3] (4.64 g, 20 mmoles) as described for **5c**, yield 4.5 g (65%), mp 182-185° (aqueous ethanol); ir: 3500-2800 bm, 1755 s (CO-esters), 1650 m (CO), 1620 m, 1570 s cm^{-1}; ^1H nmr: δ 1.25 (t, J = 7 Hz, CH_3 in $=C\text{-}COOC_2H_5$), 1.35 (t, J = 7 Hz, CH_3 in $NHCOOC_2H_5$) 2.25 (s, 2 CH_3), 4.1 (q, CH_2 in $=C\text{-}COOC_2H_5$), 4.35 (q, CH_2 in $NHCOOC_2H_5$), 7.4 (s, 2 ArH).

Anal. Calcd. for $C_{17}H_{21}N_3O_5$: C, 58.78; H, 6.09; N, 12.09. Found: C, 58.90, H, 6.24; N, 12.08.

7,8-Disubstituted 1,3-Dioxo-2*H*,5*H*-pyrimido[1,6-*a*]benzimidazole-4-carbonitriles **6a,b** and 4-Ethyl Carboxylates **6c,d** (Table 1).

Method A for **6a-d**.

The appropriate intermediate **5a-d** (10 mmoles) was refluxed in bromobenzene (50 ml) for 1 hour. After cooling, the product was filtered, washed with benzene, dried and recrystallized; ir of **6a-d**: 3400-2500 bm, 2210 s (CN), 1750 s ($C_1=O$), 1670 s ($C_3=O$), 1640-1520 (s-w) cm^{-1}; ^1H nmr of **6b** and **c** are recorded in Table 1.

Method B for **6a-d**.

The appropriate **3a-d** (10 mmoles) and **4** (1 ml, 10 mmoles) were refluxed in bromobenzene (50 ml) for 2 hours and worked up as described above. The yields of the products were nearly the same as those obtained by method A.

Method C for **6c,d**.

Chlorosulfonyl isocyanate **7** (1 ml, 12 mmoles) was added to a stirred solution of **3c**, or **d** (10 mmoles) in dry chloroform (20 ml) containing drops of triethylamine. After stirring under dry conditions for 10 hours at room temperature, the chloroform was removed under vacuum and the residue was mixed with ethanol. The separated solid was filtered, suspended in water and the medium neutralized with saturated sodium hydrogen carbonate solution. The product was then collected and recrystallized. The yields were 0 .71 g (26%) for **6c** and 0.81 g (27%) for **6d**.

2,5-Dialkyl-7,8-disubstituted-1,3-dioxo-2*H*,5*H*-pyrimido[1,6-*a*]-benzimidazole-4-carbonitriles **10a-d** (Table 2).

Method A.

Compound **6a**, or **b** (10 mmoles) was refluxed with trimethyl or triethyl phosphate **9a**, or **b** (30 ml) for 2 hours in the presence of potassium carbonate (0.5 g). After cooling, water was added and the separated product was filtered, washed with water, dried and recrystallized; ir: 3000-2980 w, 2210 s (CN), 1730 s ($C_1=O$), 1650 s ($C_3=O$), 1620-1585 (w-s) cm^{-1}. The ^1H nmr data are recorded in Table 3.

Method B.

The appropriate **5a**, or **b** (10 mmoles) was reacted with **9a**, or **b** (30 ml) in presence of potassium carbonate (0.5 g) as described under method A. The melting points, yields and spectral data of the compounds were identical with those of the substances prepared by the above method.

Ethyl 2,5-Dimethyl-1,3-dioxo-2*H*,5*H*-pyrimido[1,6-*a*]benzimidazole-4-carboxylate (**10e**).

This was obtained from **6c**, or **5c** (10 mmoles) and trimethyl phosphate **9a** (20 ml) as described for **10** under method A or B, respectively. The yields were 2.41 g (80%) from **6c** and 2.35 g (78%) from **5c**, mp 212-214° (dimethylformamide-water); ir: 3120 w, 2995 w, 1740 s ($C_1=O$), 1690 s (CO-ester), 1650 s ($C_3=O$), 1620 w, 1600 s, 1560 w cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 1.5 (t, J = 7 Hz, CH_3-ethyl), 3.75 (s, CH_3 at N-5), 4.1 (s, CH_3 at N-2), 4.7 (q, J = 7 Hz, CH_2-ethyl), 7.4-7.9 (m, 3 ArH), 8.6 (d, H at C-9).

Anal. Calcd. for $C_{15}H_{15}N_3O_4$: C, 59.79; H, 5.02; N, 13.95. Found: C, 59.56; H, 5.21; N, 13.85.

2,5-Diethylpyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-dione (**11**).

Prepared from **6c**, or **5c** (15 mmoles) and triethyl phosphate **9b** (25 ml) as described for **10** under method A or B, respectively. The yields were 2.2 g (75%) from **6c** and 1.81 g (47%) from **5c**, mp 184-186° (aqueous dimethylformamide); ir: 3100-3000 w, 1710 s ($C_1=O$), 1660 s ($C_3=O$), 1640 w cm^{-1}; ^1H nmr: δ 1.3 (t, J = 7 Hz, CH_3-ethyl at N-5), 1.4 (t, J = 7 Hz, CH_3-ethyl at N-2), 3.9 (q, CH_2-ethyl at N-5), 4.15 (q, CH_2-ethyl at N-2), 5.2 (s, H at C-4), 7.0-7.5 (m, 3 ArH), 8.2 (d, H at C-9).

Anal. Calcd. for $C_{14}H_{15}N_3O$: C, 65.35; H, 5.87; N, 16.33. Found: C, 65.57; H, 5.70; N, 16.30.

Acknowledgements.

The authors are grateful to the Egyptian Ministry of Higher Education and the Austrian Ministry of Science for the financial support of the joint Research Program. They also thank the staff of the Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland, USA, for the anticancer test report.

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