Synthesis of New Benzimidazole Derivatives as Potential Antimicrobial Agents

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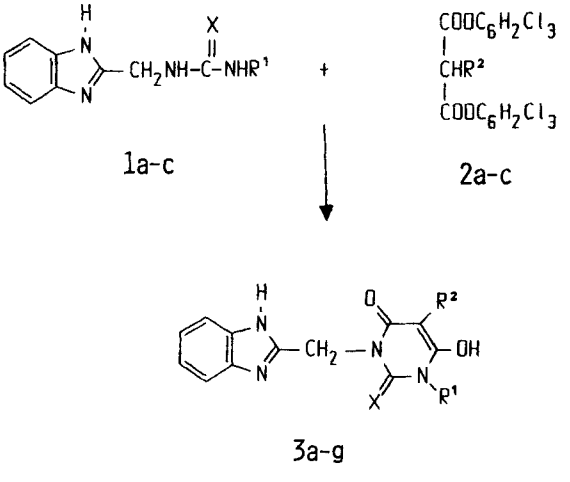
Received April 10, 1990

Barbiturates **3** as possible antimicrobial agents were obtained by reacting the *N,N'*-disubstituted urea **1a** or the thiourea analogues **1b,c** with the magic malonates **2a,b**. On the other hand, reaction of **1a** with ethoxycarbonyl isocyanate (**4**) yielded the substituted *s*-triazine-2,4,6(1*H*,3*H*,5*H*)-trione **5**. The reaction of **4** with 2-aminomethyl-benzimidazole (**6**) gave the allophanate **7** which upon treatment with Na_2CO_3 yielded *N*-(1*H*-benzimidazol-2-yl)urea **8**.

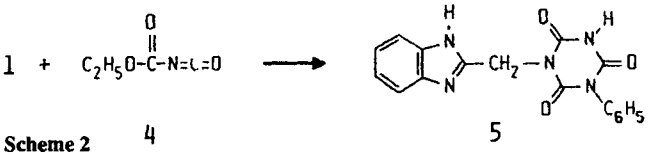
Synthese neuer Benzimidazolderivate als potentiell antimikrobielle Substanzen

Die Barbitursäurederivate **3**, mögliche antimikrobielle Verbindungen, können durch Umsatz der *N,N'*-disubstituierten Harnstoffe **1a** bzw. Thioharnstoffe **1b,c** mit den reaktiven Malonsäureestern **2a,b** synthetisiert werden. Andererseits gibt die Reaktion von **1a** mit Ethoxycarbonylisocyanat (**4**) das *s*-Triazin-2,4,6-(1*H*,3*H*,5*H*)-trion **5**. 2-Aminomethyl-benzimidazol (**6**) liefert mit **4** den Allophansäureester **7**, welcher mit Sodalösung zum Harnstoffderivat **8** verseift wird.

In continuation of our work dealing with the syntheses and antimicrobial properties of several derivatives of pyrido[1,2-*a*]benzimidazole[1-3] and pyrimido[1,6-*a*]benzimidazole[4,5] condensed ring systems, we now report the synthesis and antimicrobial evaluation of some substituted 3-(1*H*-benzimidazol-2-ylmethyl)-6-hydroxypyrimidin-2,4(1*H*,3*H*)-diones (**3a-c**), and 3-(1*H*-benzimidazol-2-ylmethyl)-6-hydroxy-2-thioxopyrimidin-4-(1*H*,3*H*)-ones (**3d-g**) (table 1) and 1-(1*H*-benzimidazol-2-ylmethyl)-3-phenyl-*s*-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (**5**). In such compounds, C-2 of benzimidazole is separated from the selected heterocyclic substituents by one C-atom. The incentive in this direction was based on the previous findings that many benzimidazoles which carry heterocyclic rings at C-2 such as furyl[6], thienyl[7], pyrazinyl[8], quinazolinyl[9], dihydropyrrolyl[9], and thiazolidinyl[10] show antimicrobial and antifungal activities. The observation that an *N,N'*-substituted benzimidazolylurea molecule constitutes a major structural requirement in certain antiviral compounds[11], prompted us to utilize *N*-(1*H*-benzimidazol-2-ylmetyl)-*N'*-phenylurea (**1a**) and its thiourea analogs **1b,c** for the preparation of the final compounds.

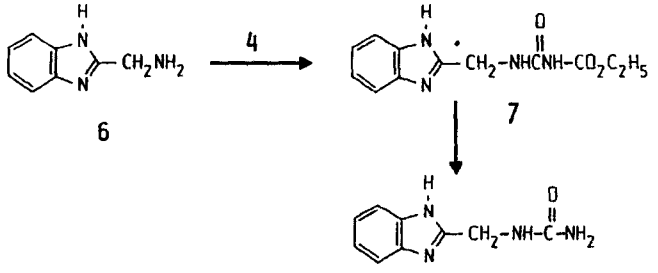


Scheme 1 R^1, R^2 and X-Key see Table 1



Scheme 2 4 5

Compounds **3a-g**, namely, 3-(1*H*-benzimidazol-2-ylmethyl)-6-hydroxypyrimidine-2,4(1*H*,3*H*)-diones (**3a-c**) and their 2-thioxo analogs **3d-g** were prepared in good yields by reacting equimolar quantities of the selected *N,N'*-disubstituted urea **1a**, or thioureas **1b,c** with some bis-2,4,6-trichlorophenyl monosubstituted malonates **2a-c** in refluxing chlorobenzene. Whereas, 1-(1*H*-benzimidazol-2-ylmethyl)-3-phenyl-*s*-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (**5**) was prepared by condensing **1a** with ethoxycarbonyl isocyanate (**4**) in refluxing bromobenzene (scheme 1). The structure of **5** was substantiated by ^{13}C-NMR. Experiments to obtain the 2-thioxo analogues of **5** from **1b** or **c** and **4** at room temp. were abortive. On the other hand, reacting 2-aminomethyl-1*H*-benzimidazole (**6**) with **4** at room temp. yielded *N*-(1*H*-benzimidazol-2-ylmethyl)-*N'*-ethoxycarbonyl urea (**7**) which, unlike **1a-c**, failed to react with **2a** to give a barbituric acid derivative. Refluxing compound **7** with Na_2CO_3-solution resulted in *N*-(1*H*-benzimidazol-2-ylmethyl)urea (**8**) as con-



Scheme 3

  0365-6233/91/0606-0355 $ 3.50 + .25/0

Table 1:

Compound	R^1	R^2	X	Yield %	M.P. °C	Recryst. Solvent	Molecular formula Molecular weight	Analysis, % : Calcd./Found C	H	N	S
3a	C_6H_5	C_2H_5	O	76	255-7	EtOH	$C_{20}H_{18}N_4O_3$ 362.37	66.3 66.6	5.0 5.0	15.5 15.6	
3b	C_6H_5	$CH_2C_6H_5$	O	80	288-91	EtOH	$C_{25}H_{20}N_4O_3$ 424.44	70.7 70.5	4.8 4.8	13.2 13.0	
3c	C_6H_5	C_6H_5	O	58	263-5	DMF/ H_2O	$C_{24}H_{18}N_4O_3.H_2O$ 428.4	67.3 67.5	4.7 4.8	13.1 12.9	
3d	C_4H_9	C_2H_5	S	73	> 300	DMF/ H_2O	$C_{18}H_{22}N_4SO_2$ 358.46	60.3 59.9	6.2 6.0	15.6 15.7	8.9 9.0
3e	$CH_2C_6H_5$	C_2H_5	S	60	278-80	AcOH	$C_{21}H_{20}N_4SO_2$ 392.47	64.3 64.1	5.1 5.1	14.3 14.3	8.2 8.2
3f	C_6H_5	C_2H_5	S	26	> 300	DMF	$C_{20}H_{18}N_4SO_2$ 378.44	63.5 63.8	4.8 4.8	14.8 14.7	8.5 8.9
3g	C_6H_5	$CH_2C_6H_5$	S	23	230-2	AcOH	$C_{25}H_{20}N_4SO_2$ 440.51	68.2 67.9	4.6 4.5	12.7 13.0	

^{1}H-NMR (CF_3COOH) of 3a: δ (ppm) = 1.15 (t, CH_3); 2.35 (q, CH_2-ethyl); 5.75 (s, CH_2); 7.0-7.9 (m, 9 ArH).

firmed by IR, ^{1}H-NMR and microanalytical data. Its mass spectrum was characterized by an $M^{+\cdot}$ of medium intensity. The fragmentation involved a loss of HNCO associated with hydrogen transfer giving 2-aminomethylbenzimidazole at m/z = 147, which constituted the base peak. Further fragmentation of the latter ion, by loss of NH and hydrogen transfer, led to 2-methylbenzimidazole appearing at m/z = 131.

Compounds **3b-g** tested for *in vitro* activity against five *Escherichia coli* strains, five *Klebsiella pneumonia strains*, three *Pseudomonas aeuroginosa* strains, and two *Candida albicans* strains using a disc method[12] but were inactive (MIC > 250 μg/ml).

The authors are grateful to Dr. *Fatma Berto*, Lecturer of Microbiology, Medical Research Institute, University of Alexandria, A.R.E., for performing the antimicrobial screening.

Experimental Part

M.p.'s: Gallenkamp apparatus, uncorrected. - IR-spectra (nujol, unless otherwise specified): Perkin-Elmer 421; wave numbers in cm^{-1}. - ^{1}H-NMR: Varian EM-360, TMS int. stand., δ (ppm): $^{\delta}$TMS = 0 ppm; unless other notation values from CF_3COOH spectra, 60 MHz. - ^{13}C-NMR: Varian XL-200. - M.S: Finnigan 4500. - Elementary analyses: Institut für Organische Chemie, Karl-Franzens-Universität, Graz.

Substituted 3-(1H-benzimidazol-2-ylmethyl)-6-hydroxypyrimidine-2,4 (1H,3H)-diones (**3a-c**) *and3-(1H-benzimidazol-2-ylmethyl)-6-hydroxy-2-thioxopyrimidin-4(1H,3H)-ones* (**3d-g**), *(table 1)*

A solution of the appropriate **1** and **2** (2 mmole of each) in 15 ml of chlorobenzene was refluxed for 1-2h, during which the product partly separated. After cooling, the solid was filtered, washed with benzene, dried and recrystallized. - IR (3a-g): 3200-2600; 1670-1690 (CO); 1600-1500 cm^{-1}.

1-(1H-Benzimidazol-2-ylmethyl)-3-phenyl-s-triazine-2,4,6(1H,3H,5H)-trione (**5**)

To a stirred suspension of 0.93 g (3.5 mmole) of **1a** in 15 ml of bromobenzene, 0.4 ml (4 mmole) ethoxycarbonyl isocyanate (**4**) were added and the mixture was refluxed for 1 h. After cooling the solid was filtered, washed with benzene and crystallized from dimethylformamide; yield 0.7 g (60 %), m.p. >300°C. - IR: 3390 (NH); 3100-2600; 1720; 1660 (CO) cm^{-1}. - ^{13}C-NMR: δ (ppm) = 113 (d, C-5 and C-6 of benzimidazole), 124 (d, C-4 and C-7 of benzimidazole) 127 (d, 2 Ar-C), 131 (d, 2 Ar-C), 133 (d, 2 Ar-C), 147 (s, C-2=O), 147.4 (s, C-6=O), 148 (t, C-2 of benzimidazole), 148.7 (s, C-4=O). - $C_{17}H_{13}N_5O_3$ (335.3) Calc. C 60.9 H 3.9 N 20.9 Found H 4.2 N 20.8.

N-(1H-Benzimidazol-2-ylmethyl)-N'-ethoxycarbonylurea (**7**)

Compound **4** (0.6 ml, 6 mmole) was added to a stirred solution of 2-aminomethylbenzimidazole (**6**) (0.7 g, 5 mmole) in 15 ml of dry chloroform. After stirring under dry conditions for 30 min at room temp., the resulting white product was filtered, washed with ether and crystallized from ethanol; yield 0.8 g (61 %), m.p. 185-7°C. - IR: 3290; 3200; 1730 (CO); 1660 (CO) cm^{-1}. - ^{1}H-NMR: δ (ppm) = 1.35 (t, CH_3, J = 7 Hz), 4.35 (q, CH_2, J = 7 Hz), 5.15 (d, CH_2 at C-2 of benzimidazole, J = 6 Hz), 7.3 [m, 4arom. H). - $C_{12}H_{14}N_4O_3$ (262.3) Calc. C 55.0 H 5.4 N 21.4 Found C 54.7 H 5.1 N 21.6.

N-(1H-Benzimidazol-2-ylmethyl)urea (**8**)

A suspension of 0.26 g (1 mmole) of **6** in 5 ml of sodium carbonate solution (5%) was refluxed for 30 min. The resulting solution was left

overnight to obtain colorless crystals which were filtered and crystallized from water; yield 0.16 g (84%), m.p. 238-41°C. - IR (KBr): 3000 (NH, NH); 1650 (CO); 1610; 1550 cm^{-1}. - ^{1}H-NMR (DMSO-[D_6]): δ (ppm) = 4.39 (d, CH_2, J = 6 Hz), 5.74 (s, NH_2), 6.58 (t, NH of urea J = 6 Hz), 7.15 (m, 4 arom. H), 7.5 (s, NH of imidazole). - MS: m/z (rel. abundance %), 190 (M^+, 45), 147 (100), 131 (25), 119 (70), 91 (25), 44 (25). - $C_9H_{10}N_4O$ (190.2) Calc. C 56.8 H 5.3 N 29.5 Found C 56.6 H 5.3 N 29.7.

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