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Benzimidazole Condensed Ring Systems, III [1]. Synthesis of Some Substituted 2,3-Dihydrocyclopenta-1*H*-[4′,5′: 2,3]pyrido[1,2-a]benzimidazole-11-carbonitriles

El-Sayed A. M. Badawey[1], **Samia M. Rida**[1], **Farid S. G. Soliman**[1], and **Thomas Kappe**[2,*]

[1] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Alexandria, A. R. Egypt
[2] Institute of Organic Chemistry, Karl-Franzens-University Graz, A-8010 Graz, Austria

Summary. The synthesis of compound **3** by condensing 1*H*-benzimidazole-2-acetonitrile (**1**) with ethyl cyclopentanone-2-carboxylate (**2**) in the presence of ammonium acetate is described. Methylation of **3** with trimethyl phosphate yielded the N-methyl derivative **4**. Methods for converting **3** to some of its related derivatives in which the carbonyl function was replaced by Cl, N_3 and amines are also reported.

Keywords. 1*H*-Benzimidazole-2-acetonitrile; Ethyl cyclopentanone-2-carboxylate; Tetracyclic pyrido[1,2-a]benzimidazoles.

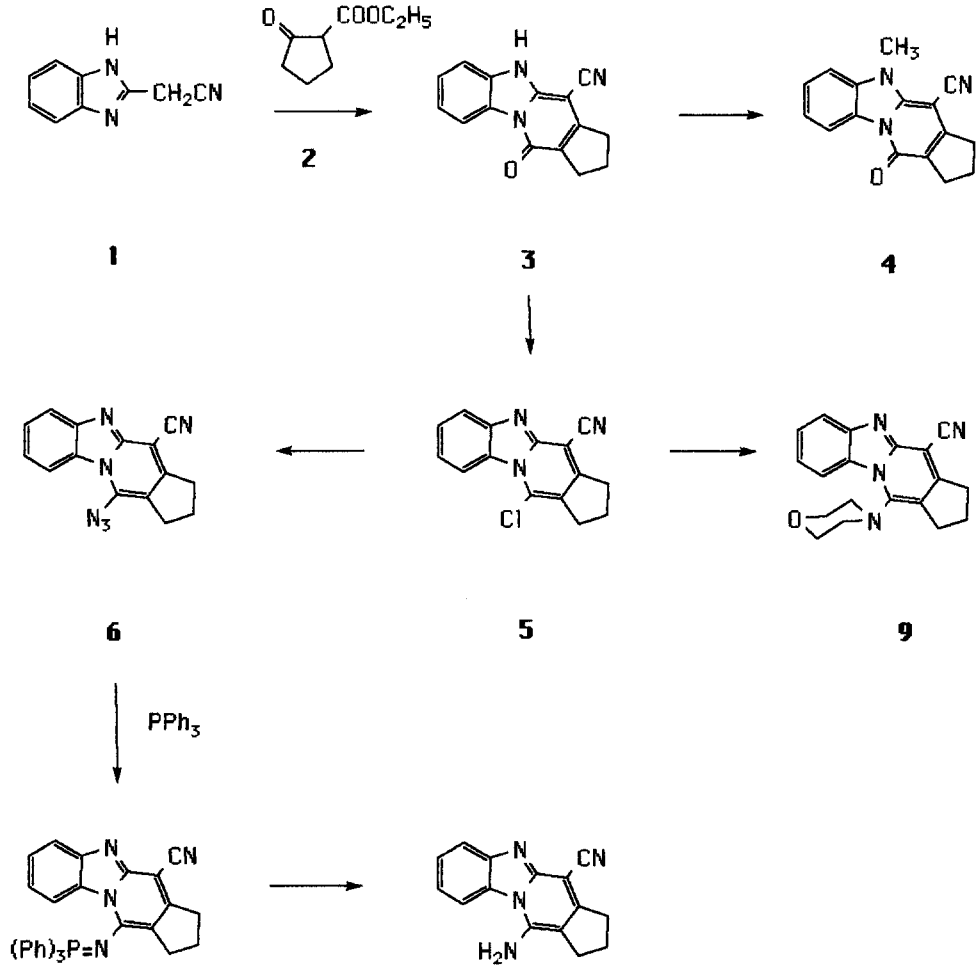
Kondensierte Ringsysteme des Benzimidazols, 3. Mitt. [1].
Synthese von substituierten 2,3-Dihydrocyclopenta[4′,5′: 2,3]pyrido[1,2-a]benzimidazol-11-carbonitrilen

Zusammenfassung. Die Synthese der tetracyclischen Verbindung **3** durch Kondensation von 1*H*-Benzimidazol-2-acetonitril (**1**) mit Cyclopentanon-2-carbonsäureester (**2**) in Gegenwart von Ammonacetat wird beschrieben. Die Methylierung von **3** mit Trimethylphosphat liefert das N-Methylderivat **4**. Die Sauerstoffunktion in **3** kann durch Chlor, Azid und Aminogruppen ersetzt werden.

In the preceeding publication [1] the authors described a facile onestep synthesis of 3-substituted and 2,3-disubstituted-1-oxo-1*H*,5*H*-pyrido[1,2-a]benzimidazole-4-carbonitriles by fusing 1*H*-benzimidazole-2-acetonitrile (**1**) with some β-keto esters in presence of ammonium acetate. We have now extended this cyclocondensation to the synthesis of the titled tetracyclic system as a part of continuing interest in benzimidazole condensed ring systems of potential biological significance [2, 3].

Thus, fusing **1** with ethyl cyclopentanone-2-carboxylate (**2**) in the presence of ammonium acetate afforded 2,3-dihydro-4-oxo-1*H*,4*H*,10*H*-cyclopenta [4′,5′: 2,3]pyrido[1,2-a]benzimidazole-11-carbonitrile (**3**) in high yield. The reaction followed the same pattern as that discussed before [1]. Methylation of **3** with trimethyl phosphate in the presence of potassium carbonate resulted in its 10-methyl derivative **4**. Chlorination of **3** with phosphorus oxychloride yielded 4-

chloro-2,3-dihydro-1*H*-cyclopenta[4′,5′ : 2,3]pyrido[1,2-a]benzimidazole-11-carbonitrile (**5**). Displacement of the 4-chloro atom in the latter with sodium azide gave the 4-azido derivative **6** which was converted to the 4-amino compound **8** through acid hydrolysis of the 4-triphenylphosphoranylideneamino intermediate **7**. Whereas, displacement of this chloro atom with morpholine afforded the 4-morpholino derivative **9** (Scheme 1). The fact that this tetracyclic system comprises a cyclopentane residue within its structure may be of value for the bioactivity, if any, of these compounds.



Scheme 1

Compounds **3**, **5**, and **9** were screened against P-388 lymphocytic leukemia in mice according to a standard protocol [4] and were inactive. Compounds **5** and **6** were screened for *in vitro* activity against three *Staphylococcus aureas* strains (S 14, S 17 and S 18) and two *Escherichia coli* strains (E 21 and E 41) and one *Candida albicans* strain (M 1) using a disc method [5], however, they were inactive.

Experimental

Melting points were determined in open capillary tubes on a Gallenkamp melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 421 spectrometer using samples in potassium bromide disks. The ^{1}H nmr spectra were measured in hexadeuteriodimethylsulfoxide (unless otherwise stated) using *TMS* as an internal standard; the instruments used were the Varian A-60A or the EM 360 at 60 MHz.

2.3-Dihydro-4-oxo-1H,4H,10H-cyclopenta[4',5' : 2,3]pyrido[1,2-a]benzimidazole-11-carbonitrile (**3**)

A mixture of **1** (16 g, 0.1 mol) and **2** (16.3 ml, 0.11 mol) and ammonium acetate (17 g, 0.22 mol) was heated in an oil bath at 140–150° for 30–45 min; during this time ethanol and ammonia were liberated and the reaction mixture gradually solidified. After cooling, the solid was treated with ethanol and the product was filtered and dried, yield 19.7 g (79%), m.p. 300° (dimethylformamide); ir: 3 200–2 600 bm, 2 210 s (CN), 1 660 s (CO), 1 610 w, 1 590 w cm^{-1}. Anal. Calcd. for $C_{15}H_{11}N_3O$: C 72.27, H 4.45, N 16.86. Found: C 72.21, H 4.57, N 16.98.

2,3-Dihydro-10-methyl-4-oxo-1H,4H,10H-cyclopenta[4',5' : 2,3]pyrido[1,2-a]benzimidazole-11-carbonitrile (**4**)

This was prepared by methylating **3** (1.99 g, 8 mmol) with trimethyl phosphate (15 ml) in presence of potassium carbonate (0.2 g) following our previously described procedure [1], yield 2.0 g (95%), m.p. 258–259° (dimethylformamide); ir: 2 205 s (CN), 1 680 s (CO), 1 615 w, 1 600 m cm^{-1}. Anal. Calcd. for $C_{16}H_{13}N_3O$: C 72.99, H 4.98, N 15.96. Found: C 73.03, H 4.76, N 16.15.

4-Chloro-2,3-dihydro-1H-cyclopenta[4',5' : 2,3]pyrido[1,2-a]benzimidazole-11-carbonitrile (**5**)

This was prepared from **3** (9.97 g, 0.04 mol) and phosphorus oxychloride (50 ml) following our previously described method [1], yield 10.4 g (97%), m.p. 250–251° (dimethylformamide); ir: 2 220 s (CN), 1 640 m, 1 605 w, 1 550 m cm^{-1}; ^{1}H nmr (CF_3COOH): δ = 2.5 (m, 2 H at C-2), 3.4 (t, J = 7 Hz, 2 H at C-1), 3.6 (t, J = 7 Hz, 2 H at C-3), 7.9 (S, 3 aromatic H), 8.9 (d, H at C-6). Anal. Calcd. for $C_{15}H_{16}ClN_3$: C 67.29, H 3.76, N 15.70. Found: C 67.52, H 3.94, N 15.50.

4-Azido-2,3-dihydro-1H-cyclopenta[4',5' : 2,3]pyrido[1,2-a]benzimidazole-11-carbonitrile (**6**)

This was prepared by reacting a solution of **5** (1.6 g, 6 mmol) in dimethylformamide (20 ml) with sodium azide (0.46 g, 7 mmol) following our reported conditions [1], yield 1.9 g (98%), m.p. 167°, dec. (dioxane); ir: 2 215 s (CN), 2 150 s (N_3), 1 630 s, 1 600 s, 1 500 s cm^{-1}. Anal. Calcd. for $C_{15}H_{10}N_6$: C 65.68, H 3.68, N 30.64. Found: C 65.82, H 3.89, N 30.42.

2,3-Dihydro-4-(triphenylphosphoranylideneamino)-1H-cyclopenta[4',5' : 2,3]pyrido[1,2-a]benzimidazole-11-carbonitrile (**7**)

This was prepared by reacting a suspension of **6** (1.1 g, 4 mmol) in benzene (10 ml) with a solution of triphenylphosphine (1.31 g, 5 mmol) in benzene (10 ml) following our reported procedure [1], yield 1.77 g (87%), m.p. 300° (dioxane); ir: 2 210 s (CN), 1 630 m, 1 590 s, 1 550 s cm^{-1}. Anal. Calcd. for $C_{33}H_{25}N_4P$: C 77.93, H 4.96, N 11.02. Found: C 77.93, H 5.00, N 10.97.

4-Amino-2,3-dihydro-1H-cyclopenta[4',5' : 2,3]pyrido[1,2-a]benzimidazole-11-carbonitrile (**8**)

Compound **7** (1.53 g, 3 mmol) was hydrolyzed with a mixture of hydrochloric acid (2 *N*) (40 ml) and methanol (40 ml) as previously described [1], yield 0.72 g (97%), m.p. 300° (dimethylformamide); ir:

3 460 s, 3 100–2 500 bm, 2 210 s (CN), 1 660 s, 1 630 s, 1 600 w, 1 570 s cm^{-1}. Anal. Calcd. for $C_{15}H_{12}N_4$: C 72.56, H 4.87, N 22.57. Found: C 72.45, H 4.89, N 22.57.

2,3-Dihydro-4-(1-morpholino)-1H-cyclopenta[4',5':2,3]pyrido[1,2-a]benzimidazole-11-carbonitrile (**9**)

To a stirred suspension of **5** (2.68 g, 10 mmol) in dimethylformamide (25 ml), morpholine (2.6 ml, 30 mmol) was added. Subsequently, the mixture was stirred at 60–80° for 1 hour, during which the required product partly separated out. After cooling and addition of water the product was filtered, yield 2.67 g (84%), m.p. 300° (dimethylformamide – water); ir: 3 000–2 800 w, 2 210 s (CN), 1 640 m, 1 600 m, 1 560 m cm^{-1}; ^{1}H nmr (CF_3COOH): δ = 2.5 (m, 2 H at C-2), 3.3–3.8 (m, 4 H, $H_2C-N-CH_2$ in morpholino + 4 H at C-1 and C-3), 4.4 (m, 4 H, $H_2C-O-CH_2$ in morpholino), 7.9 (s, 3 aromatic H), 8.9 (d, H at C-6). Anal. Calcd. for $C_{19}H_{18}N_4O$: C 71.67, H 5.70, N 17.60. Found: C 71.53, H 5.43, N 17.81.

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References and Notes

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[4] Conducted at the National Cancer Institute, Bethesda, Maryland, USA
[5] Conducted in the Department of Microbiology, Medical Research Institute, University of Alexandria, A.R. Egypt

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