

Base-Catalyzed Cyclization Reactions of 2-[2-(2,4-Dimethyl-3-oxopentyl)]benzimidazoles with Acetic Anhydride and Its Homologs

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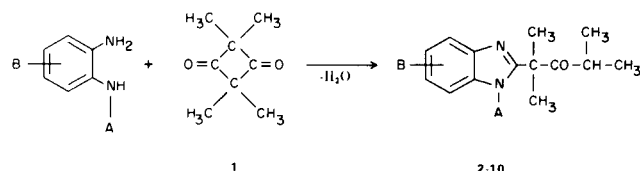
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2-[2-(2,4-Dimethyl-3-oxopentyl)]benzimidazoles (**2-10**) were obtained by allowing *o*-phenylenediamines to react with 2,2,4,4-tetramethyl-1,3-cyclobutanedione (**1**). When refluxed with acetic anhydride (or sterically unhindered homologs) they cyclize in the presence of base to yield the pyrido[1,2-*a*]benzimidazoles (**16-21** and **24, 25**). The 2-[2-(2,4-dimethyl-3-oxopentyl)]imidazolines (**12** and **14**) were obtained by reaction of 1,2-diaminoethane and 1,2-diaminopropane, respectively, with **1**. When allowed to react with acetic anhydride/base, they gave only *N*-acylated products.

2,2,4,4-Tetramethyl-1,3-cyclobutanedione (**1**), the dimer of dimethylketene, reacts in neutral or slightly acidic medium like an aliphatic ketone. Strong, sterically unhindered nucleophiles cleave the cyclobutane ring (1-7).

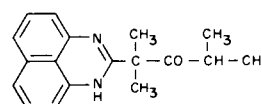
The reaction of **1** with *o*-phenylenediamine was originally carried out by Wedekind and Weisswange in 1906 (8).



In 1969 the structure of the reaction product was established (3).

The formation of the benzimidazoles **2-10** by allowing **1** to react with the corresponding substituted *o*-phenylenediamine using acid catalysis took place in aqueous ethanol at room temperature (8). Best yields could be obtained by using either refluxing toluene or xylene as the solvent in the presence of a catalytic amount of *p*-toluenesulfonic acid. The water formed was removed by azeotropic distillation.

Also, other compounds with two amino groups in positions suitable for cyclization reacted with **1** and yielded heterocycles: 2-[2-(2,4-Dimethyl-3-oxopentyl)]-perimidine (**11**) was obtained by allowing **1** to react with 1,8-diaminonaphthalene.



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The products which were synthesized are shown in Table I.

Our main interest was focused on the assumed "acetyl-derivative", which was obtained by Wedekind and Weisswange (8) by heating **2** with acetic anhydride/sodium acetate after we found out this product was not an acylated **2**. The ir spectrum of this compound showed characteristic absorptions at 3040 ($\text{H}>\text{C}=\text{C}$) and 1700 cm^{-1} ($\text{C}=\text{O}$). The nmr spectrum contained bands of an isopropyl group (1.1 ppm, d, 6 protons; 2.7 ppm, m, 1 proton), and in addition 6 protons at 1.6 ppm (s), 1 proton at 6.1 ppm (s) and 4 aromatic protons at 7.3, 7.7, and 8.3 ppm (m). The mass spectrum showed a parent peak at m/e 254 with 60% relative intensity. The high resolution spectrum indicated the molecular formula $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}$. The main fragmentation resulted by elimination of a methyl radical, followed by loss of carbon monoxide and another methyl radical. Parallel to this fragmentation, the molecule ion lost propylene, an isopropyl radical and carbon monoxide, respectively. Because of these spectroscopic data it was concluded that the reaction of **2** with acetic anhydride/sodium acetate yielded 1,4-dihydro-3-isopropyl-4,4-dimethyl-1-oxopyrido[1,2-*a*]-benzimidazole (**15**).

TABLE I
Reaction of Diamino Compounds with **1**

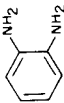
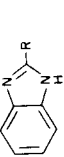
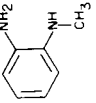
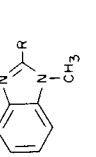
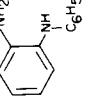
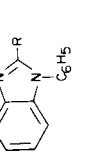
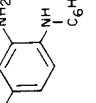
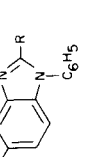
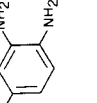
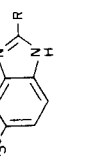
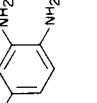
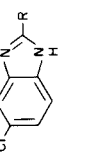
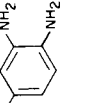
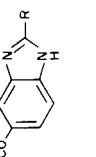
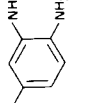
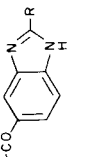
Starting Material	Reaction Product R = -C(CH ₃) ₂ -CO-CH(CH ₃) ₂	Yield %	M.p., °C	Molecular Formula	C	H	N	Cl
					Calculated (Found)			
		95	249-250 (a)	C ₁₄ H ₁₈ N ₂ O				
		93	94-95	C ₁₅ H ₂₀ N ₂ O	73.7 (73.8)	8.3 8.6	11.5 11.6	
		90	96	C ₂₀ H ₂₂ N ₂ O	78.4 (78.6)	7.2 7.1	9.1 9.1	
		79	98-99	C ₂₀ H ₂₂ ClN ₂ O	70.5 (70.5)	6.2 6.3	8.2 8.0	10.4 10.3
		96	146-147	C ₁₅ H ₂₀ N ₂ O	73.7 (73.8)	8.3 8.4	11.5 11.3	
		48	151-153	C ₁₄ H ₁₇ ClN ₂ O	63.5 (63.6)	6.5 6.6	10.6 10.7	13.4 13.7
		82	156	C ₁₅ H ₂₀ N ₂ O ₂	69.2 (69.4)	7.7 7.4	10.8 10.9	
		83	53-56	C ₁₆ H ₂₀ N ₂ O ₃	66.7 (66.4)	7.0 7.3	9.7 9.4	

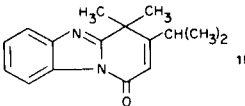
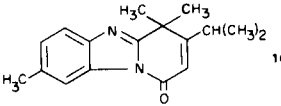
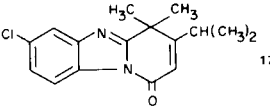
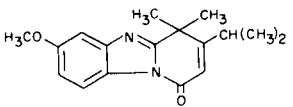
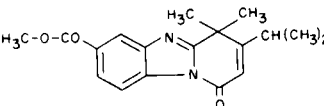
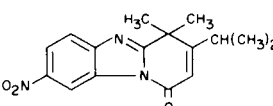
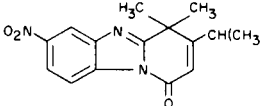
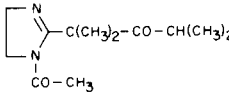
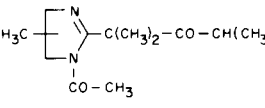
TABLE I (continued)

Starting Material	Reaction Product R = -C(CH ₃) ₂ -CO-CH(CH ₃) ₂	Yield %	M.p., °C	Molecular Formula	C	H	N	Analyses Calculated (Found)
		55	165-168	C ₁₄ H ₁₇ N ₃ O ₃	61.1 (61.1)	6.2 6.1	15.3 15.3)	
		74	170	C ₁₈ H ₂₀ N ₂ O	77.1 (77.4)	7.2 7.2	10.0 9.9)	
		68	78-81 (b) B.p. 160-170° (12 mm.)	C ₁₀ H ₁₈ N ₂ O				
		12	52-55 B.p. 150-160° (0.5 mm.) (c)	C ₁₀ H ₂₀ N ₂ O ₂				
		92	77 B.p. 134-138° (14 mm.)	C ₁₁ H ₂₀ N ₂ O	67.3 (67.5)	10.4 10.4	14.3 14.4)	

(a) M.p. 248-249° (8). (b) M.p. 80-82° (3). (c) B.p. 86-90° (0.15-0.2 mm.) (3).

TABLE II

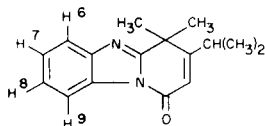
Reaction of the Benzimidazoles **2** and **6-10** and of the
Imidazolines **12** and **13** with Acetic Anhydride-Triethylamine

Starting Material	Reaction Product	Yield %	M.p., °C	Molecular Formula	C	Analyses Calculated (Found)			Cl
						H	N		
2	 15	89	148-150 (a)	C ₁₆ H ₁₈ N ₂ O	75.6 (75.7)	7.1 6.9	11.0 11.0		
6	 16	92	120-124	C ₁₇ H ₂₀ N ₂ O	76.1 (76.2)	7.4 7.6	10.4 10.3		
7	 17	90	163	C ₁₆ H ₁₇ ClN ₂ O	66.6 (66.9)	5.9 6.1	9.7 9.7	12.3 12.7	
8	 18	92	159-161	C ₁₇ H ₂₀ N ₂ O ₂	71.8 (72.0)	7.1 6.9	9.9 9.7		
9	 19	61	163	C ₁₈ H ₂₀ N ₂ O ₃	69.2 (69.4)	6.5 6.3	9.0 9.1		
10	 20A	54	212-214	C ₁₆ H ₁₇ N ₃ O ₃	64.2 (64.4)	5.7 5.7	14.0 14.0		
	 20B	30	144-148	C ₁₆ H ₁₇ N ₃ O ₃	64.2 (64.1)	5.7 5.7	14.0 14.0		
12	 21	87	69-70 B.p. 130-140° (0.5 mm.)	C ₁₂ H ₂₀ N ₂ O ₂	64.3 (64.3)	9.0 8.9	12.5 12.6		
14	 22	88	B.p. 178° (15 mm.)	C ₁₃ H ₂₂ N ₂ O ₂	65.5 (65.2)	9.3 9.6	11.8 11.8		

(a) M.p. 149-151° (8).

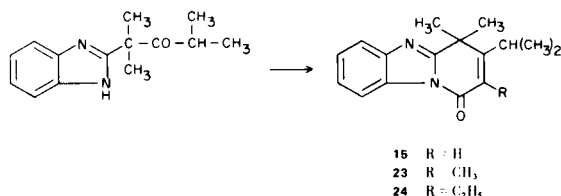
TABLE III

NMR Data of the Aromatic Portions of the 1,4-Dihydro-2-isopropyl-1,1-dimethyl-4-oxopyrido[1,2-*a*]benzimidazoles **15-20**

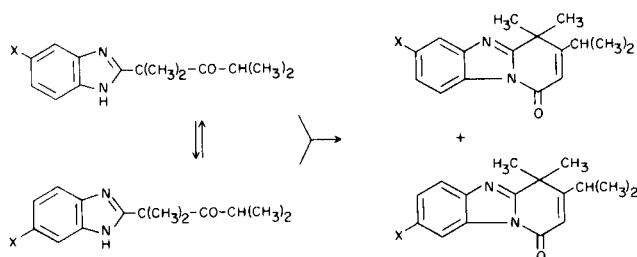


Compound (7- or 8-Substituent)	Chemical shifts of the aromatic protons (a,b,c)			
	H ⁹	H ⁸	H ⁷	H ⁶
15 (H)	8.3 m	7.3 m	7.3 m	7.75 m
16 (8-CH ₃)	8.2 d _m	—	7.2 dd	7.55 d _o
17 (7-Cl)	8.3 d _o	7.35 dd	—	7.8 d _m
18 (7-CH ₃ O)	8.25 d _o	7.0 dd	—	7.3 d _m
19 (7-CH ₃ O-CO)	8.4 d _o	8.15 dd	—	8.55 d _m
20A (8-NO ₂)	9.2 d _m	—	8.3 dd	7.8 d _o
20B (7-NO ₂)	8.55 d _o	8.3 dd	—	8.3 d _m

(a) Measured in deuteriochloroform with TMS as an internal standard. (b) All chemical shifts are expressed in δ -values and are determined by first order analysis. (c) d_o = doublet, *ortho*-coupling with $^3J = 7-10$ Hz; d_m = doublet, *meta*-coupling, $^4J = 1-3$ Hz; dd = doublet of doublets, *ortho*- and *meta*-coupling, m = multiplet.



Because of the tautomeric nature of benzimidazoles (9), the cyclization of the 5(6)-substituted benzimidazoles **6-10** should yield mixtures of 7- and 8-substituted 1,4-dihydro-3-isopropyl-4,4-dimethyl-1-oxopyrido[1,2-*a*]-benzimidazoles.



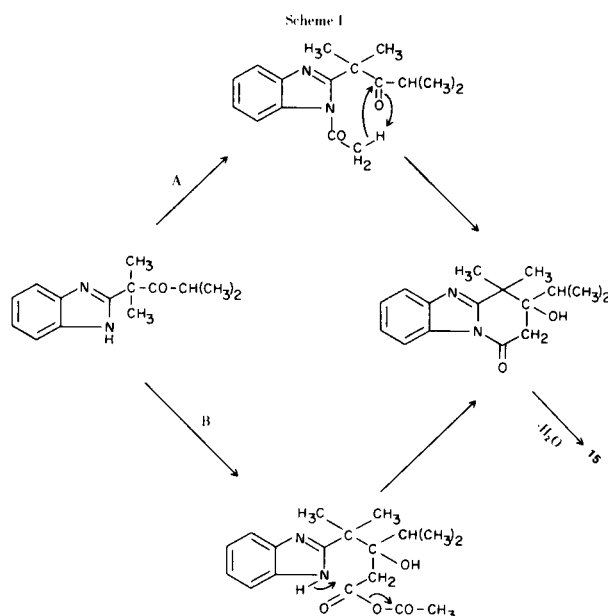
Cyclization of **10** yielded the two isomeric compounds **20A** and **20B**. In all other cases only one isomer has been isolated.

The structures of **16-20** have been determined by nmr-spectroscopy. The nmr spectrum of **2** contained two multiplets at 7.5 (2 protons) and 8.1 ppm (2 protons). Compound **15**, obtained from **2** with acetic anhydride/base showed in its nmr spectrum three multiplets at 8.3 (1 proton), 7.75 (1 proton), and 7.3 ppm (2 protons), respectively. It can be assumed that due to the anisotropic effect of the carbonyl group the signal of the hydrogen in position 9 is shifted to lower field. Making this assumption, the structures of compounds **16-20** can be elucidated by the chemical shifts of their aromatic protons and their coupling patterns (see Table III).

The syntheses of compounds of the type **15** (given in Table II) could be carried out by the method of Wedekind and Weisswange (8). However, a strong organic base (triethylamine) was better than sodium acetate. Also, other anhydrides, those of propionic and *n*-butyric acid, were used successfully. Phenylacetic anhydride did not react, most probably because of steric hindrance.

The imidazoles **12** and **14**, obtained by allowing **1** to react with 1,2-diaminoethane and 1,2-diaminopropane, respectively, did not give cyclized products; only *N*-acylation occurred.

As illustrated by Scheme 1, two reaction mechanisms can be discussed for the cyclization reaction: (1) *N*-acylation, followed by cyclodehydration (route A), and (2) an aldol-like condensation, followed by an *N*-acylating cyclization (route B).



We were unable to determine whether **15** was formed *via* *N*-acylation, followed by cyclodehydration (route A), or *via* an aldol-like intermediate, which could be formed,

if the reaction mechanism was similar to the Perkin condensation (10) (route B). It was not possible to acylate **2** with acetyl chloride or acetic anhydride. This *N*-acetyl intermediate should cyclize with base to yield **15**. The reaction of **15** with isobutyric anhydride did not occur and therefore, an aldol intermediate was not obtained. Furthermore, no reaction took place when the *N*-methylbenzimidazole **3** was allowed to react with acetic anhydride/base. If the reaction mechanism proceeded via route B, an unsaturated acid should have been formed.

EXPERIMENTAL

The melting and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Spectrophotometer, Model 256, the nmr spectra on a Varian Associates Model A 60 Spectrometer. The ir spectra were taken in potassium bromide; the nmr spectra in 10% solutions of deuterated dimethylsulfoxide or in deuteriochloroform with TMS as an internal standard. Mass spectra were taken on a CH5-Apparatus of Varian MAT, Bremen. High resolution measurements were carried out on a MS 9 of AEI Ltd., Manchester. The errors of the obtained values were less than 10 ppm.

Reaction of Diamines with **1**: General Procedure.

1. In Toluene.

Compound **1** (0.15 mole), diamine (0.15 mole), and a trace of *p*-toluenesulfonic acid were refluxed (2-40 hours) in 200 ml. of dry toluene. The water formed was removed by a watertrap. (Aliphatic amines were added dropwise over a period of 2 hours). After filtration and evaporation of the solvent the residue was distilled or recrystallized from ligroin or ligroin-benzene. The yields are given in Table I.

2. In Aqueous Alcohol.

Compound **1** (0.2 mole) and 0.2 mole of *o*-phenylenediamine were dissolved in 125 ml. of warm ethanol. Water (125 ml.) and 5 ml. of concentrated hydrochloric acid were added and the reaction mixture was stirred overnight. After filtration and washing with ethanol-water (1:1), the crystals obtained were recrystallized from methanol. The yield was 61% of **2**, m.p. 248-250°.

When 0.3 mole of *o*-phenylenediamine and 0.2 mole of **1** were used the yield of **2** was 84%.

Reaction of **2**, **6-10**, **12** and **14** with Acetic Anhydride-Triethylamine. General Procedure.

The imidazole (0.1 mole), 20 g. of triethylamine (0.2 mole), and 120 ml. of acetic anhydride were refluxed overnight. After evaporation of the solvent the residue was treated with water. If crystals were obtained they could be recrystallized from

ligroin or ligroin-benzene. If an oil separated it was extracted with ether, the ether solution was dried (sodium sulfate) and distilled.

When **10** was allowed to react with acetic anhydride-triethylamine, a second reaction product (**20B**) was isolated from the mother liquor. This compound was an isomer of **20A**. For the structures of these compounds see Table II and Table III.

The reactions of **2** with anhydrides of propionic and *n*-butyric acid were carried out according to the general procedure already given.

1,4-Dihydro-3-isopropyl-2,4,4-trimethyl-1-oxopyrido[1,2-*a*]benzimidazole (**23**).

Yield, 76%, m.p. 94°; ir (potassium bromide): 1695 cm⁻¹ (CO); nmr (deuteriochloroform): δ 8.4, 7.75 and 7.35 (m, 4, aromatic H), 2.95 (m, 1, CH, J = 7 Hz), 2.22 (s, 3, CH₃), 1.7 (s, 6, CH₃), 1.35 (d, 6, CH₃, J = 7 Hz).

Anal. Calcd. for C₁₇H₂₀N₂O (268.4): C, 76.1; H, 7.5; N, 10.4. Found: C, 75.9; H, 7.4; N, 10.4.

1,4-Dihydro-2-ethyl-3-isopropyl-4,4-dimethyl-1-oxopyrido[1,2-*a*]benzimidazole (**24**).

Yield, 73%, m.p. 134°; ir (potassium bromide): 1700 cm⁻¹ (CO); nmr (deuteriochloroform): δ 8.4, 7.55 and 7.38 (m, 4, aromatic H), 2.75 (m, 1, CH, J = 7 Hz), 2.75 (qu, 2, CH₂, J = 7 Hz), 1.7 (s, 6, CH₃), 1.35 (d, 6, CH₃, J = 7 Hz), 1.22 (t, 3, CH₃, J = 7 Hz).

Anal. Calcd. for C₁₈H₂₂N₂O (282.4): C, 76.6; H, 7.9; N, 9.9. Found: C, 76.5; H, 7.9; N, 10.0.

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