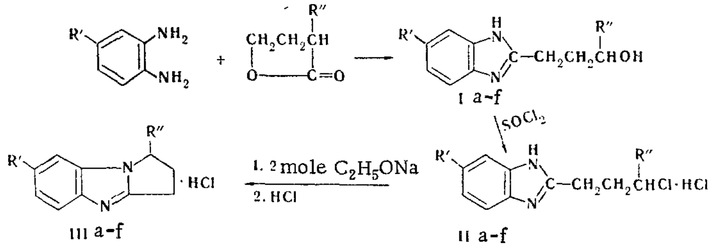
SYNTHESIS OF 1- AND 7-SUBSTITUTED 2,3-DIHYDRO-1H-PYRROLO[1,2-*a*]BENZIMIDAZOLES

Kh. A. Suerbaev and Ch. Sh. Kadyrov

UDC 547.785.5'743.1 : 543.422.25

Cyclization of 5-substituted 2-(γ-chloroalkyl)benzimidazoles in the presence of sodium ethoxide gave some benzene- and pyrroldine-ring-substituted 2,3-dihydro-1H-pyrrolo[1,2-*a*]-benzimidazoles.

2,3-Dihydro-1H-pyrrolo[1,2-*a*]benzimidazole derivatives that contain structural elements that are similar to the natural alkaloid desoxypeganine [1] are of interest as potential physiologically active substances. In order to make pharmacological tests we synthesized a number of benzene- and pyrrolidine-ring-substituted 2,3-dihydro-1H-pyrrolo[1,2-*a*]benzimidazole derivatives via the following scheme:



a R'=H, R''=H; b R'=Cl, R''=H; c R'=H, R''=CH_3; d R'=Cl, R''=CH_3; e R'=H, R''= =C_7H_{15}; f R'=Cl; R''=C_7H_{15}

The starting 2-(γ-hydroxyalkyl)benzimidazoles (I) were obtained from the appropriate o-phenylenediamines and γ-lactones by refluxing equimolecular amounts of them [2] or by condensation under the conditions in [3] (Table 1).

On reaction with excess thionyl chloride, 2-(γ-hydroxyalkyl)benzimidazoles are converted to 2-(γ-chloroalkyl)benzimidazole hydrochlorides (II) (Table 2). The action of 2 moles of sodium ethoxide on the latter gave the corresponding 2,3-dihydro-1H-pyrrollo[1,2-*a*]benzimidazole derivatives (III), which were isolated as the hydrochlorides (Table 3). When we used the method in [3] to synthesize 1-substituted 2,3-dihydro-1H-pyrrolo[1,2-*a*]benzimidazole derivatives we were able to obtain only the 1-methyl derivative (IIIc) but in lower yield (15%).

The structures of the compounds obtained were confirmed by means of the mass and PMR spectra.

EXPERIMENTAL

The PMR spectra were recorded with a C-60-HL spectrometer with an operating frequency of 60 MHz and tetramethylsilane as the standard. The mass spectrum was recorded with an MKh-1303 mass spectrometer.

2-(γ-Hydroxyalkyl)benzimidazoles (I). A) A mixture of equimolecular amounts of o-phenylenediamine and the appropriate γ-butyrolactone was heated in a flask equipped with a Dean–Stark trap. The mixture was heated to the boiling point in the course of 30 min and maintained at this temperature until water

---

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1137-1139, August, 1974. Original article submitted June 25, 1973.

TABLE 1. Compounds I

Compound	mp, °C	Empirical formula	N, %		Hydrochloride mp, °C	Yield, %
			found	calc.		
Ia	163,5—164[a]	$C_{10}H_{12}N_2O$	—	—	157,5—158,5	80
Ib	167—170[b]	$C_{10}H_{11}ClN_2O$	—	—	188—189	60
Ic	122—123[c]	$C_{11}H_{14}N_2O$	—	—	161,5—163	55
Id	138—139	$C_{11}H_{13}ClN_2O$	12,5	12,5	176—178	30
Ie	117—118[d]	$C_{17}H_{26}N_2O$	—	—	98—100	31
If	115—116	$C_{17}H_{25}ClN_2O$	9,0	9,1	171,5—174	28

---

[a] According to [4], mp 161-163°. [b] According to [3], mp 160-164°. [c] According to [2], mp 115-116°. [d] According to [2], mp 111-112°.

TABLE 2. 2-(γ-Chloroalkyl)benzimidazole Hydrochlorides (II)

Compound	mp, °C	Empirical formula	N, %		Yield, %
			found	calc.	
IIa	194—196	$C_{10}H_{11}ClN_2 \cdot HCl$	12,3	12,1	75
IIb	212—213	$C_{10}H_{10}Cl_2N_2 \cdot HCl$	10,9	10,5	80
IIc	217—218	$C_{11}H_{13}ClN_2 \cdot HCl$	11,5	11,4	82
IId	232—233	$C_{11}H_{12}Cl_2N_2 \cdot HCl$	10,2	10,0	74
IIe	170—172	$C_{17}H_{25}ClN_2 \cdot HCl$	9,0	8,5	67
IIf	200—201	$C_{17}H_{24}Cl_2N_2 \cdot HCl$	7,9	7,7	74

TABLE 3. 2,3-Dihydro-1H-pyrrolo[1,2-a]benzimidazole Hydrochlorides (III)

Compound	mp, °C	Empirical formula	N, %		M[a]	Yield, %
			found	calc.		
IIIa	235—237[b]	$C_{10}H_{10}N_2 \cdot HCl$	—	—	—	70
IIIb	236—237	$C_{10}H_9ClN_2 \cdot HCl$	12,5	12,2	192	72
IIIc	188—189[c]	$C_{11}H_{12}N_2 \cdot HCl$	13,7	13,4	172	85
IIId	236—238	$C_{11}H_{11}ClN_2 \cdot HCl$	11,6	11,5	206	40
IIIe	93—95	$C_{17}H_{24}N_2 \cdot HCl$	9,7	9,6	256	38
IIIf	176—178	$C_{17}H_{23}ClN_2 \cdot HCl$	8,9	8,6	290	40

---

[a] By mass spectrometry. [b] The base had mp 115.5-116.5° [3]. [c] The base had mp 68.5-70°.

separation ceased (2-3 h). It was then allowed to stand overnight. The crystallizing mixture was then treated with ether, and the product was purified by recrystallization (from methanol–water or dioxane–heptane).

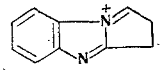
B) A mixture of 0.1 mole of 4-chloro-1,2-phenylenediamine and 0.1 mole of the appropriate γ-butyrolactone in 100 ml of 4 N HCl was refluxed for 5 h under nitrogen, after which it was decolorized three to four times with activated charcoal. Neutralization of the filtrate with ammonium hydroxide gave an oil, which crystallized on standing. The product was purified by recrystallization (from methanol–water or dioxane–petroleum ether).

2-(γ-Chloroalkyl)benzimidazole Hydrochlorides (II). The starting material (II) was refluxed for 30 min with a sevenfold excess of $SOCl_2$, after which the excess $SOCl_2$ was removed by distillation, and the solid residue was treated with ether. The product was purified by reprecipitation from alcohol solution by the addition of ether.

2,3-Dihydro-1H-pyrrolo[1,2-*a*]benzimidazole Hydrochlorides (III). A) Compound IIIa. A solution of 1.46 g (6.3 mmole) of IIa in 15 ml of ethanol was added with stirring in the course of 20 min to 12.6 mmole of sodium ethoxide in 15 ml of ethanol, after which the mixture was refluxed for 2 h. It was then cooled, and the precipitated NaCl (0.715 g) was separated. The filtrate was evaporated to dryness, and the solid residue was recrystallized from ethyl acetate to give 0.7 g (70%) of 2,3-dihydro-1H-pyrrolo[1,2-*a*]benzimidazole with mp 115.5-116.5°. Treatment of the latter with gaseous hydrogen chloride in alcohol gave hydrochloride IIIa as hygroscopic white crystals with mp 235-237° (alcohol–ether).

PMR spectrum (in pyridine) of the free base (δ, ppm): two triplets at 3.6 (J =6.7 Hz) (1-CH$_2$) and 2.75 (J =6.7 Hz) (3-CH$_2$), a two-proton multiplet at 2.25 (2-CH$_2$), and multiplets at 7.0-7.7 (aryl protons).

B) 2,3-Dihydro-1-heptyl-1H-pyrrolo[1,2-*a*]benzimidazole Hydrochloride (IIIe). A solution of 1.93 g (5.86 mmole) of IIe in 15 ml of ethanol was added with stirring in the course of 20 min to 11.7 mmole of sodium ethoxide in 15 ml of ethanol, after which the mixture was stirred for 2 h. The precipitated NaCl was separated, and the filtrate was evaporated to dryness. The oily residue was dissolved in 20 ml of hexane, and the solution was separated from the small amount of NaCl by filtration. The filtrate was again vacuum evaporated, the residue was dissolved in 10 ml of ethanol, and dry HCl was passed through it until it was saturated. The solvent was removed, and the soil residue was purified by reprecipitation from benzene solution by the addition of ether to give 0.65 g (38%) of hydrochloride IIIe with mp 93-95°.

The mass spectrum contains a molecular peak at 256 and M-15, M-29, M-43, M-71, and M-85 peaks corresponding to fragmentation of the hydrocarbon side chain. The most intense peak with m/e 157 corresponds to the  fragment.

LITERATURE CITED

1. Kh. N. Khashimov, M. V. Telezhenetskaya, and S. Yu. Yunusov, Khim. Prirod. Soedin., 5, 456 (1969).
2. A. A. Shazhenov, Ch. Sh. Kadyrov, and P. Kurbanov, Khim. Geterotsikl. Soedin., 641 (1972).
3. A. R. Freedman, D. S. Payne, and A. R. Day, J. Heterocycl. Chem., 3, 257 (1966).
4. W. Reppe et al., Ann, 596, 176, 209 (1955).