RESEARCHES ON IMIDAZOLES

XXXIII. Pyrrolo[1,2-a]Benzimidazoles*

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 3, No. 3, pp. 536–540, 1967

UDC 547.785.5 + 547.759

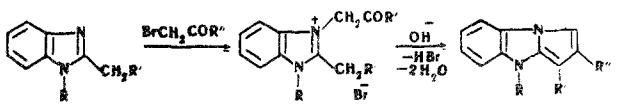
Reaction of 1,2-dialkylbenzimidazoles with α-halogenoketones followed by cyclization of the 1,2-dialkyl-3-β-ketoalkyl(aralkyl)-benzimidazolinium halides in aqueous solution, in the presence of bases, leads to the synthesis of a number of derivatives of a new aromatic tricyclic system, 4H-pyrrolo[1,2-a]benzimidazole.

The literature describes the preparation of 2,3-dihydropyrrolo[1,2-a]-benzimidazole [1–6], and its 1-oxo derivative [7]. The corresponding aromatic system, pyrrolo[1,2-a]benzimidazole, is not known.

In continuation of previous research [8], it was of interest to synthesize derivatives of pyrrolo[1,2-a]-benzimidazole. The starting materials used were the following known compounds: 1,2-dimethylbenzimidazole (XXVI) [9–12], 1-ethyl-2-methylbenzimidazole (XXVII) [11, 14–16], and 1-methyl-2-benzylbenzimidazole (XXVIII) [12], prepared by alkylating the accessible compounds 2-methylbenzimidazole [17] and 2-benzylbenzimidazole with certain alkylating agents (esters of benzenesulfonic acid or alkyl halides).

Heating XXVI–XXVIII with α-halogenoketones in acetone gives good yields of the hitherto undescribed 1,2-dialkyl-3-[β-ketoalkyl(aralkyl)]-benzimidazolinium halides (I–XI, Table 1). Treatment of halides V and VI with picric acid, or treatment of salt I (in the cold) with an equivalent quantity of sodium hydroxide, followed by addition of picric acid, gives the picrates of 1,2-dialkyl-3-[β-ketoalkyl(aralkyl)]benzimidazolinium picrates (XII–XIV). So far it has not been possible to isolate the free benzimidazolinium quaternary bases, or the corresponding enolbetaines, as the compounds investigated were water-soluble.

When the quaternary salts (I–XI) are refluxed with aqueous sodium bicarbonate, as recently described [18], they are cyclized to derivatives of 4H-pyrrolo[1,2-a]benzimidazole (XV–XXV, Table 2). Some of these compounds (XV, XXII) are obtained by reacting the quaternary salts (I, VIII) with sodium hydroxide solution in the cold



Unlike derivatives of pyrrol[1,2-a]imidazole [8], compounds XV–XXV are obtained in high yield, and are more stable, probably as a result of the benzene ring being fused to the imidazole one.

*For Part XXXII see [8].

EXPERIMENTAL

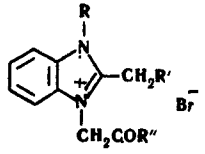
1,2-Dimethylbenzimidazole (XXVI). a) 10 g (0.0712 mole) 2-Methylbenzimidazole [16] was added to a solution of 4.4 g (0.0786 mole) KOH in 135 ml MeOH, the mixture heated to effect solution, cooled, and 11.5 g (0.0794 mole) MeI added dropwise. The whole was refluxed for 8 hr, cooled, the solvent distilled off, and the residue extracted with ether. The ether extract was washed with water, dried over Na_2SO_4, the solvent distilled off, and the residue recrystallized from 200 ml water. Yield 2.2 g (20%) XXVI, mp 109°–112° C (112° [9]). Picrate mp 234°–236° C (237° C [11]).

b) 19 g (0.11 mole) 2-Methylbenzenesulfonate was added in portions, with stirring, to 13.2 g (0.1 mole) 2-methylbenzimidazole at 200°–210° C. The temperature was then raised to 240°–245° C, and held there for 45 min, heating being by means of an oil-bath. The products were then cooled to 70° C, 100 ml water added, the mixture cooled to 15°–16° C, and neutralized with 40% NaOH, the pH being brought to pH 9. The solution was then extracted with $CHCl_3$ (700 ml), the extract washed with water, and dried over Na_2SO_4. The solvent was distilled off, and the residue recrystallized from 250 ml water. Yield 4.6 g (31.5%), mp 106°–112° C (± 2°–3°).

1-Ethyl-2-methylbenzimidazole (XXVII). a) 40 g (0.3 mole) 2-Methylbenzimidazole was added to a solution of 25.4 g (0.45 mole) KOH in 350 ml EtOH, after which 87.3 g (0.6 mole) EtI was added. The mixture was refluxed for 8 hr. cooled, the precipitate of KI filtered off, the filtrate evaporated under vacuum, and acetone added to the residue. The precipitate of 1-ethyl-2-methylbenzimidazole ethiodide (XXIX) was filtered off, colorless crystals, mp 197°–198° C (ex dry EtOH), readily soluble in water and EtOH, insoluble in ether, acetone, and benzene. Found: I 39.77; N 9.21%. Calculated for $C_{12}H_{17}IN_2$: I 40.13; N 8.86%. After removing XXIX, the acetone solution was evaporated under vacuum, the residue dissolved in $CHCl_3$, the solution washed with water, dried over Na_2SO_4, the solvent distilled off, and the residue vacuum-distilled, to give 31 g (64%) XXVII, bp 124°–125° C (1 mm), which crystallized on cooling. Colorless crystals, mp 51°–52.5° C (ex petrol ether). Found: C 74.74; H 7.32; N 17.55%. Calculated for $C_{10}H_{12}N_2$: C 74.94; H 7.54; N 17.48%. Picrate mp 237°–239° C. According to the literature [11] the compound is a liquid bp 110°–112° C (0.3–0.4 mm),

Table 1

1,2-Dialkyl-3-β-ketoalkyl(aralkyl)benzimidazolinium Halides*



Compound	R	R¹	R²	Mp, °C (decomp)	Formula	Found, %				Calculated, %				Yield, %
						C	H	Br	N	C	H	Br	N	
I	CH_3	H	C_6H_5	242—244	$C_{17}H_{17}BrN_2O$	58.75	5.10	22.88	7.92	59.14	4.96	23.14	8.11	87.6
II	CH_3	H	p-BrC_6H_4	268—269	$C_{17}H_{16}Br_2N_2O$			37.68				37.45		77
III	CH_3	H	m-$O_2NC_6H_4$	244—246	$C_{17}H_{16}BrN_3O_3$	51.95	4.35	20.19	10.28	52.32	4.13	20.47	10.76	97
IV	CH_3	H	p-$O_2NC_6H_4$	251—253	$C_{17}H_{16}BrN_3O_3$	52.23	4.20	20.09	10.96	52.32	4.13	20.47	10.76	88.9
V**	C_2H_5	H	CH_3	255—256	$C_{13}H_{17}ClN_2O$***	61.35	6.62	(Cl) 14.05	11.26	61.77	6.78	(Cl) 14.02	11.08	69.6
VI	C_2H_5	H	C_6H_5	234—236	$C_{18}H_{19}BrN_2O$	60.31	5.26	22.26	7.93	60.17	5.33	22.24	7.79	89.8
VII	C_2H_5	H	p-BrC_6H_4	237—238	$C_{18}H_{18}Br_2N_2O$	49.33	4.07	18.60	6.32	49.34	4.14	18.23	6.39	93
								ionic				ionic		
								35.91				36.46		
								total				total		
VIII	C_2H_5	H	p-$O_2NC_6H_4$	250—251	$C_{18}H_{18}BrN_3O_3$	53.53	4.56	19.49	10.01	53.47	4.48	19.76	10.39	100
IX	CH_3	C_6H_5	C_6H_5	199—200	$C_{23}H_{21}BrN_2O$	65.40	5.20	18.63	6.41	65.56	5.02	18.96	6.64	79.6
X	CH_3	C_6H_5	p-BrC_6H_4	203—204	$C_{23}H_{20}Br_2N_2O \cdot H_2O$	53.10	3.90	30.84	5.22	53.30	4.26	30.84	5.40	69.6
XI	CH_3	C_6H_5	p-$O_2NC_6H_4$	181—183	$C_{23}H_{20}BrN_3O_3 \cdot H_2O$	57.23	4.70	16.18	8.25	57.03	4.58	16.49	8.67	86.3

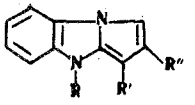
*For analysis the compounds were purified by recrystallization: I, III, IV, VI, VIII ex dry EtOH; II ex MeOH; V was precipitated from dry EtOH with acetone; IX–XI were precipitated from dry EtOH with ether.

**V was the corresponding chloride.

***IR spectra, cm^{-1}: V, ν_{CO} 1737; VII ν_{CO} 1708. The spectra were measured with a UR-10 instrument, using vaseline mulls.

Table 2

Pyrrolo[1, 2-a]benzimidazoles*



Compound	R	R¹	R²	Mp, °C (decomp)	Formula	Found, %			Calculated, %			Yield, %
						C	H	N	C	H	N	
XV	CH_3	H	C_6H_5	109—111	$C_{17}H_{14}N_2$	83.14	5.78	11.45	82.89	5.73	11.37	94.7
XVa	CH_3	H	C_6H_5	202	$C_{17}H_{14}N_2 \cdot C_6H_3N_3O_7$	57.72	3.67		58.10	3.60		
XVI	CH_3	H	p-BrC_6H_4	155—156	$C_{17}H_{13}BrN_2$	62.71	4.00	8.52	62.78	4.03	8.61	85.9
XVIa	CH_3	H	p-BrC_6H_4	200—201	$C_{17}H_{13}BrN_2 \cdot C_6H_3N_3O_7$			12.23			12.61	
XVII	CH_3	H	m-$O_2NC_6H_4$	170,5—171,5	$C_{17}H_{13}N_3O_2$	69.82	4.61	14.33	70.09	4.49	14.42	92.2
XVIII	CH_3	H	p-$O_2NC_6H_4$	180—182	$C_{17}H_{13}N_3O_2$	70.13	4.48	14.11	70.09	4.49	14.42	89.9
XIXa	C_2H_5	H	CH_3	177—178	$C_{13}H_{14}N_2 \cdot C_6H_3N_3O_7$	53.45	3.90	16.63	53.39	4.01	16.38	
XX	C_2H_5	H	C_6H_5	119—120	$C_{18}H_{16}N_2$	82.72	6.28	10.61	83.04	6.19	10.76	96.7
XXa	C_2H_5	H	C_6H_5	192—194	$C_{18}H_{16}N_2 \cdot C_6H_3N_3O_7$	58.49	3.97	14.03	58.89	3.91	14.31	
XXI	C_2H_5	H	p-BrC_6H_4	123—124	$C_{18}H_{15}BrN_2$**	63.85	4.37	7.99	63.72	4.46	8.26	95
XXIa	C_2H_5	H	p-BrC_6H_4	205—207	$C_{18}H_{15}BrN_2 \cdot C_6H_3N_3O_7$	50.41	3.15		50.70	3.19		
XXII	C_2H_5	H	p-$O_2NC_6H_4$	118—121	$C_{18}H_{15}N_3O_2$	70.47	4.72	13.77	70.81	4.95	13.76	80.9
XXIIa	C_2H_5	H	p-$O_2NC_6H_4$	185—186	$C_{18}H_{15}N_3O_2 \cdot C_6H_3N_3O_7$			15.98			15.72	
XXIII	CH_3	C_6H_5	C_6H_5	157—159	$C_{23}H_{18}N_2$	85.70	5.80	8.49	85.68	5.63	8.69	96
XXIV	CH_3	C_6H_5	p-BrC_6H_4	156—158	$C_{23}H_{17}BrN_2$***	68.76	4.52	6.78	68.83	4.27	6.98	99
XXV	CH_3	C_6H_5	p-$O_2NC_6H_4$	184—185	$C_{23}H_{17}N_3O_2$	75.60	4.79	11.08	75.19	4.66	11.44	92

*For analysis the compounds were purified by recrystallization: **XV**, **XVI**, **XIXa**, **XX** ex EtOH; **XVa**, **XXIIa** ex Me_2CO; **XVIa**, **XIXa**, **XXIa** ex glacial AcOH; **XVII**, **XXIII** ex dimethylformamide; **XVIII**, **XXIV**, **XXV**: ex EtOH-dimethylformamide (4:1); **XIXa** ex water; **XXII** by precipitation with petrol ether from acetone.

**Found: Br 23.32%. Calculated: Br 23.56%.

***Found: Br 20.01%. Calculated for: 19.91%.

picrate mp 236°–237° C; according to [15, 16], undoubtedly erroneous, it has mp 178°–180° C.

b) Prepared by alkylating 2-methylbenzimidazole with ethylbenzenesulfonate, as described for XXVI (b). Yield 50%, bp 135°–137° C (3 mm), mp 47°–52° C (± 2°–3°).

1-Methyl-2-benzylbenzimidazole (XXVII). Prepared by alkylating 2-benzylbenzimidazole with methyl benzenesulfonate, as described for XXVI (b). Yield 61.5%, bp 208°–210° C (3 mm), mp 69°–71° C (ex petrol ether) (77°–78° C [12]). Found: C 81.37; H 6.36; N 12.54%. Calculated for $C_{15}H_{14}N_2$: C 81.04; H 6.35; N 12.60%.

1, 2-Dialkyl(aralkyl)benzimidazolinium halides (I–XI, Table 1). A solution of 0.01 mole 1, 2-dialkylbenzimidazole and 0.01 mole α-halogenoketone in 30–50 ml acetone was refluxed for 3–5 hr (1 hr for nitrophenacylbromides). The precipitate was filtered off, and washed with acetone. Colorless or dull white (in the case of nitro compounds) crystals, slightly soluble in cold water, readily soluble in EtOH, insoluble in ether, acetone, and benzene. Some salts were hygroscopic.

1, 2-Dialkyl-3-[β-ketoalkyl(aralkyl)]benzimidazolinium picrates (XII–XIV). a) 0.0011 mole NaOH (as a 36% aqueous solution) was added to a solution of 0.001 mole benzimidazolinium halide I in 30 ml water, excess alkali was neutralized with AcOH, bringing the solution to pH 5, an aqueous solution of picric acid was added, and the precipitate filtered off. The product was 1, 2-dimethyl-3-phenacylbenzimidazolinium picrate (XII), yellow crystals mp 167°–168° C (ex water). Mixed mp with the picrate of XVa 130°–150° C. Found: C 56.16; H 4.26; N 14.17%. Calculated for $C_{23}H_{19}N_5O_8$: C 55.98; H 3.88; N 14.19%. IR spectrum: 1700 cm^{-1} (ν_{CO}).

b) An aqueous solution of picric acid was added to a solution of 0.001 mole benzimidazolinium halide V or VI in water (30–50 ml), the precipitate filtered off, and recrystallized from water. 1-Ethyl-2-methyl-3-acetonylbenzimidazolinium picrate (XIII) yellow crystals mp 157°–159° C. Mixed mp with picrate XIXa 147°–150° C. Found: C 51.61; H 4.58; N 15.94%. Calculated for $C_{19}H_{19}N_5O_8$: C 51.23; H 4.30; N 15.72%. IR spectrum: 1747 cm^{-1} (ν_{CO}). 1-Ethyl-2-methyl-3-phenacylbenzimidazolinium picrate (XIV) yellow crystals, mp 158°–160° C, mixed mp with picrate XXa 148°–156° C. Found: C 56.78; H 4.14; N 13.84%. Calculated for $C_{24}H_{21}N_5O_8$: C 56.80; H 4.17; N 13.80%. IR spectrum: 1698 cm^{-1} (ν_{CO}).

Pyrrolo[1, 2-a]benzoimidazoles (XV–XXV, Table 2). a) 0.0105 mole $NaHCO_3$ was added to a hot solution of 0.01 mole 1, 2-dialkyl-3-[β-ketoalkyl(aralkyl)]benzimidazolinium halide in water (50–500 ml), and the whole refluxed for 2–8 hr. The reaction gave rise to a precipitate, which, after cooling, was filtered off, and washed with water. Colorless (XV), dull white (XVI, XX, XXI, XXIII, XXIV), or red (XVII, XVIII, XXII, XXV) crystals, soluble in most organic solvents, insoluble in water.

b) 5–10 ml 36% Aqueous NaOH was added, in the cold, to a solution of 0.001 mole benzimidazolinium halide in 30–50 ml water. A precipitate quickly formed, and was filtered off, and washed with water. Compounds XV and XXII were obtained in good yield by this method.

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2 August 1965

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