

STUDIES IN THE IMIDAZOLE SERIES

XL. Synthesis of New Di-, Tri-, and Tetrasubstituted Derivatives of Pyrrolo[1,2-*a*]Benzimidazole*

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 5, pp. 865-868, 1969

UDC 547.785.5'741.07

A study was made of the action of primary and secondary α -halogen ketones on 1,2-di- and 1,2,5,6-tetrasubstituted derivatives of benzimidazole. The peculiarities of the structure of the residues of the ketone in position 3 of the quaternary salts of benzimidazole affected the process of their intramolecular cyclization under the action of sodium bicarbonate. A number of new di-, tri-, and tetrasubstituted derivatives of pyrrolo[1,2-*a*]benzimidazole were obtained.

In continuing studies [1, 2] with the object of obtaining new di-, tri-, and tetra-substituted derivatives of pyrrolo[1,2-*a*]benzimidazole for biological tests, it was of interest to investigate in more detail the quaternization by primary and secondary α -halogen ketones of 1,2-di and 1,2,5,6-tetrasubstituted derivatives of benzimidazole, and also to elucidate the effect of the peculiarities of the structure of the ketone residue in position 3 of the quaternary salts of benzimidazole on the process of closure of the pyrrole ring.

It was found that during the interaction of 1,2-di- and 1,2,5,6-tetrasubstituted derivatives of benzimidazole (XXXVII-XL, XLII) both with primary and secondary α -bromo ketones of the aliphatic, aliphatic-aromatic and heterocyclic series in acetone, the corresponding quaternary salts of benzimidazole (I-XIX, Table 1) are formed. In certain cases with secondary bromo ketones there is a decrease in the yields of the salts up to 28-36% (VI, X, and XV) which is apparently on account of the lower stability of these halogen ketones or spatial difficulties. The reaction does not proceed so readily with the α -chloro ketones, and prolonged boiling is required (up to 20 hrs in comparison with 1-3 hrs in the case of bromo ketones) to produce a yield of approximately 50% (V).

The structure of the ketone residue in position 3 of the benzimidazole salts has a much greater effect on the process of their intramolecular condensation in an aqueous solution of NaHCO_3 and on the physicochemical properties of the pyrrolobenzimidazoles obtained. Thus halogenides of 3-phenacylbenzimidazole (IV-VI, XI-XIII, XVI, XVIII, and XIX), irrespective of the nature of the substitutes in the *n*-position of the benzene nucleus of the ketone, readily undergo cyclization with the formation of the corresponding 2-arylsubstituted pyrrolobenzimidazoles (XXII-XXIV, XXVIII-XXX, XXXIII, XXXV, and XXXVI, Table 2).

Bromides of benzimidazole (I, II, VII-IX, XIV, and XVII, Table 1), containing residues of aliphatic and heterocyclic ketones in position 3 are also converted

into alkylpyrrolobenzimidazoles with satisfactory yields. These substances, as distinct from the arylpyrrolobenzimidazoles, have low melting points or are liquid compounds unstable in air. For the analysis they were characterized in the form of hydrochlorides or picrates (XX, XXI, XXV-XXVII, XXXI, XXXII, and XXXIV, Table 2).

On heating the bromides of 3-(α -phenylacetyl)benzimidazole (III, VII, and X, Table 1) in an aqueous solution of NaHCO_3 , the reaction proceeds in a different manner. In the case of compound VIII pyrrolobenzimidazole (XXVI) was obtained with a satisfactory yield. Compounds III and X undergo cleavage with the formation of the corresponding 1,2-diakylbenzimidazoles (XXXVII and XL), as has been observed for certain halogenides of 3- β -ketoalkyl(aralkyl)imidazole [3, 4]. One should note that electron donor substitutes (CH_3 group) in the benzene ring of 1,2-disubstituted derivatives of benzimidazole have no effect either on their reaction of quaternization, or on the process of cyclization of benzimidazole salts.

After the experimental part of our article had been completed, a letter to the editor by F. S. Babichev and A. F. Babicheva [5] appeared in which it was reported that these authors, independently of our studies [1, 2], synthesized certain derivatives of pyrrolo[1,2-*a*]benzimidazole by an analogous method.

EXPERIMENTAL

1,2-Dimethyl-, 1-Ethyl-2-Methyl- and 1-Methyl-2-Benzylbenzimidazoles (XXXVII-XXXIX) were prepared previously [2].

1-Methyl-2-ethylbenzimidazole (XL) was obtained by methylation of 2-ethylbenzimidazole [6] by two methods. With methyl iodide (as described for the synthesis of 1-methylbenzimidazole [7]) and with the methyl ester of benzosulfo acid (as described for the synthesis of 1,2-dimethylbenzimidazole [2]). The yields were 66% and 37% respectively. Bp 148-150° C. Picrate, mp 245-246° C. According to data in the literature [8], the mp is 54.5-55.5° C. The picrate has an mp of 235-236° C.

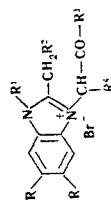
2,5,6-Trimethylbenzimidazole (XLI) was obtained by boiling 4,5-diamino-*o*-xylof with acetic acid, as described for 2-methylbenzimidazole [6]. Yield, 97%, mp. 235-237° C (from dimethylformamide). According to data in the literature [9], the mp is 233-234° C, and according to other data [10], the mp is 229-231° C.

1,2,5,6-Tetramethylbenzimidazole (XLII) was obtained by methylation of compound XLI with methyl iodide in an analogous manner to compound XL. Yield 86%, mp 165-167° C. According to data in the literature [9], the mp is 164° C.

Halogenides of 1,2-dialkyl-3- β -ketoalkyl(aralkyl)benzimidazole (I-XIX, Table 1) were prepared by the interaction between compounds XXXVII-XL, XLII and α -halogenketones according to a previously described method [2].

*For part XXXIX, see [11].

Table 1



Compound	R	R ¹	R ²	R ³	R ⁴	Mp, °C (decomp.) ^a	Empirical formula	Found, %				Calculated, %				Yield, %
								C	H	Br	N	C	H	Br	N	
I	H	CH ₃	H	CH ₃	CH ₃	255—257	C ₁₈ H ₁₇ BrN ₂ O	52.40	5.74	27.10	9.33	52.53	5.76	26.88	9.42	79
II ^b	H	CH ₃	H	CH ₃	C ₆ H ₅	236—238	C ₁₈ H ₁₇ BrN ₂ O	55.16	6.72	24.28	8.40	55.39	6.51	24.57	8.61	68
III	H	CH ₃	H	CH ₃	C ₆ H ₅	217—218	C ₁₈ H ₁₇ BrN ₂ O	59.68	5.59	22.30	7.81	60.17	5.33	22.24	7.80	69
IV	H	CH ₃	H	<i>p</i> -CH ₃ -C ₆ H ₄	H	235—237	C ₁₈ H ₁₇ BrN ₂ O	59.77	5.32	22.04	7.69	60.17	5.33	22.24	7.79	89
V ^c	H	CH ₃	H	<i>p</i> -CH ₃ O-C ₆ H ₄	H	211—213	C ₁₈ H ₁₇ BrN ₂ O	61.74	6.14	10.30	7.82	61.99	6.07	10.14	8.03	49
VI	H	CH ₃	H	<i>p</i> -C ₆ H ₅ -C ₆ H ₄	CH ₃	243—244	C ₁₈ H ₁₇ BrN ₂ O	65.97	5.41	18.12	6.25	66.21	5.32	18.35	6.43	36
VII ^b	H	C ₂ H ₅	H	CH ₃	CH ₃	261—262	C ₁₈ H ₁₇ BrN ₂ O	53.90	5.96	26.04	8.86	54.03	6.15	25.67	9.01	79
VIII	H	C ₂ H ₅	H	CH ₃	C ₆ H ₅	216—217	C ₁₈ H ₁₇ BrN ₂ O	61.41	5.77	21.76	7.48	61.13	5.67	21.41	7.50	62
IX	H	C ₂ H ₅	H	CH ₃	C ₆ H ₅	223—224	C ₁₈ H ₁₇ BrN ₂ O	52.21	4.67	22.01	7.35	52.60	4.69	21.89	7.67	92
X	H	C ₂ H ₅	H	CH ₃	C ₆ H ₅	241—242	C ₁₈ H ₁₇ BrN ₂ O	60.71	5.66	21.58	7.71	61.13	5.67	21.41	7.50	28
XI	H	CH ₃	CH ₃	CH ₃	H	226—228	C ₁₈ H ₁₇ BrN ₂ O	60.02	5.26	22.51	7.56	60.17	5.33	22.24	7.79	80
XII	H	CH ₃	CH ₃	<i>p</i> -BrC ₆ H ₄	H	233—234	C ₁₈ H ₁₇ BrN ₂ O	49.15	4.37	36.16	—	49.34	4.14	36.48	—	77
XIII	H	CH ₃	CH ₃	<i>p</i> -O ₂ NC ₆ H ₄	H	244—246	C ₁₈ H ₁₇ BrN ₂ O	53.61	4.61	19.85	10.45	53.47	4.48	19.76	10.39	84
XIV	H	CH ₃	CH ₃	CH ₃	H	213—215	C ₁₈ H ₁₇ BrN ₂ O	60.14	5.01	—	8.13	60.17	5.33	—	7.79	83
XV	H	CH ₃	C ₆ H ₅	CH ₃	CH ₃	217—219	C ₁₈ H ₁₇ BrN ₂ O	61.26	5.90	21.52	7.13	61.13	5.67	21.40	7.50	30
XVI	H	CH ₃	C ₆ H ₅	<i>m</i> -O ₂ NC ₆ H ₄	H	213—215	C ₁₈ H ₁₇ BrN ₂ O	59.29	4.26	17.41	9.09	59.24	4.30	17.13	9.01	78
XVII	CH ₃	CH ₃	H	CH ₃	H	264—266	C ₁₈ H ₁₇ BrN ₂ O	53.68	6.41	25.85	9.23	54.02	6.15	25.67	9.00	95
XVIII	CH ₃	CH ₃	H	C ₆ H ₅	H	232—234	C ₁₈ H ₁₇ BrN ₂ O	60.76	5.61	21.64	7.67	61.13	5.67	21.40	7.50	88
XIX	CH ₃	CH ₃	H	<i>n</i> -BrC ₆ H ₄	H	254—255	C ₁₈ H ₁₇ BrN ₂ O	50.37	4.43	35.56	6.09	50.44	4.45	35.34	6.19	86

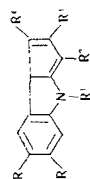
^a For analysis the compounds were purified by crystallization from anhydrous ethanol (I, II, IV, V, VII, IX—XV, and XVII—XIX), ethanol (VI), and by precipitation with ether from anhydrous ethanol (III, VIII, and XVI).

^b The values of ν_{CO} in cm^{-1} in the IR spectra (recorded in vaseline oil in the UR-10 apparatus) are: 1723 (II), 1735 (VII).

^c Compound V represent the corresponding chloride.

^d C₄H₃S=thienyl-2. Found %: S 8.44. Calculated, %: S 8.78.

Table 2



Com- pound	R	R ¹	R ²	R ³	R ⁴	Mp, °C (decomp) ^a	Empirical formula	Found, %			Calculated, %			Yield, %
								C	H	N	C	H	N	
XX	H	CH ₃	H	CH ₃	CH ₃	114—116 ^c	C ₁₈ H ₁₆ N ₂ · HCl · 2H ₂ O	57.80	6.69	10.21	57.66	7.07	10.34	74
XXI	H	CH ₃	H	CH ₃	C ₆ H ₇	136—138	C ₁₈ H ₁₆ N ₂ · C ₆ H ₅ N ₃ O ₇	55.44	4.74	15.53	55.38	4.65	15.38	70
XXII ^b	H	CH ₃	H	<i>p</i> -CH ₃ C ₆ H ₄	H	131—132	C ₁₈ H ₁₆ N ₂	83.23	6.25	10.86	83.04	6.19	10.76	67
XXIII	H	CH ₃	H	<i>p</i> -CH ₃ OC ₆ H ₄	H	141—142	C ₁₈ H ₁₆ N ₂ O	78.56	5.65	10.16	78.23	5.84	10.14	84
XXIV ^b	H	CH ₃	H	<i>p</i> -C ₆ H ₅ C ₆ H ₄	CH ₃	191—192	C ₂₂ H ₂₀ N ₂	85.40	5.92	8.19	85.68	5.99	8.33	91
XXV	H	C ₆ H ₅	H	CH ₃	CH ₃	138—140	C ₁₇ H ₁₆ N ₂ · C ₆ H ₅ N ₃ O ₇	54.33	4.17	15.75	54.42	4.34	15.87	78
XXVI	H	C ₆ H ₅	H	CH ₃	C ₆ H ₅	139—140	C ₁₇ H ₁₆ N ₂ · C ₆ H ₅ N ₃ O ₇	59.30	4.16	13.78	59.65	4.20	13.91	82
XXVII ^b	H	C ₆ H ₅	H	C ₆ H ₅ S ^d	H	178—179	C ₁₈ H ₁₆ N ₂ · C ₆ H ₅ N ₃ O ₇	53.06	3.41	14.09	53.33	3.46	14.13	79
XXVIII ^b	H	CH ₃	CH ₃	C ₆ H ₅	H	136—137 ^e	C ₁₈ H ₁₆ N ₂	83.12	6.32	10.48	83.04	6.19	10.76	97
XXIX	H	CH ₃	CH ₃	<i>p</i> -BrC ₆ H ₄	H	162—163	C ₁₈ H ₁₆ N ₂ · C ₆ H ₅ N ₃ O ₇	63.79	4.46	8.13	63.72	4.45	8.26	91
XXX	H	CH ₃	CH ₃	<i>p</i> -O ₂ NC ₆ H ₄	H	143—144	C ₁₈ H ₁₆ N ₂ O ₂	71.20	5.00	—	70.80	4.95	—	83
XXXI	H	CH ₃	CH ₃	CH ₃	CH ₃	152—153	C ₁₈ H ₁₆ N ₂ · C ₆ H ₅ N ₃ O ₇	59.24	4.01	14.43	58.89	3.91	14.31	86
XXXII ^b	H	CH ₃	C ₆ H ₅	CH ₃	CH ₃	172—173	C ₁₈ H ₁₆ N ₂ · C ₆ H ₅ N ₃ O ₇	59.48	4.38	14.28	59.64	4.20	13.91	87
XXXIII ^b	H	CH ₃	C ₆ H ₅	<i>m</i> -O ₂ NC ₆ H ₄	H	170—172	C ₂₂ H ₁₇ N ₃ O ₂	74.75	4.96	11.17	75.19	4.66	11.44	97
XXXIV	CH ₃	CH ₃	H	CH ₃	CH ₃	207—208	C ₁₈ H ₁₆ N ₂ · C ₆ H ₅ N ₃ O ₇	54.24	4.18	15.93	54.42	4.34	15.86	90
XXXV	CH ₃	CH ₃	H	C ₆ H ₅	H	149—150	C ₁₈ H ₁₆ N ₂	83.43	6.79	10.35	83.17	6.61	10.21	98
XXXVI	CH ₃	CH ₃	H	<i>p</i> -BrC ₆ H ₄	H	203—204	C ₁₈ H ₁₇ BrN ₂ · g	64.78	4.89	7.88	64.59	4.85	7.93	82

^aFor analysis the compounds were purified by crystallization from: acetone (XXI); ethanol (XXII, XXIII, and XXXI); dimethylformamide (XXIV, XXVIII-XXX, XXXIII, XXXV, and XXXVI); water (XXV, XXVII); a 1 : 1 mixture of acetone and water (XXVI, and XXXII); a 4:1 mixture of dimethylformamide and water (XXXIV); and by precipitation with ether from anhydrous ethanol (XX). ^bUV spectra (recorded in alcoholic solutions in the EPS-3 apparatus). Compounds, λ_{max}, nm (log ε): XXII, 330 (3.80), 283 (4.20); XXIV, 369 (4.60), 256 (4.22); XXXIII, 268 (4.35). ^cFound, %: C 13.34. Calculated, %: C 13.09. ^dPicrate with a mp of 151–153° C (from water, decomp.). ^eFound, %: N 16.30. Calculated, %: N 16.39. According to data in the literature [5] of the base of XX, 96° C., mp C₁₈H₁₆N₂ · C₆H₅thienyl-2. ^fThe compound is chromatographically pure. Picrate, mp 155–156° C (from water, decomp.). ^gFound, %: C 58.70; H 4.02; N 14.11, mp Calculated for C₁₈H₁₆N₂ · C₆H₅N₃O₇, %: C 58.89; H 3.91; N 14.31. According to data in the literature [5], mp of the base of XXVIII is 167° C. ^hFound, %: Br 23.56. ⁱFound, %: Br 22.74. Calculated, %: Br 22.62.

Pyrrolo[1,2-*b*]benzimidazoles (XX-XXXVI, Table 2) were obtained by boiling compounds I, II, IV-IX, and XI-XIX in an aqueous solution of NaHCO₃ by previously described methods [1,2]. The bases of compounds XX, XXI, XXV-XXVII, XXXI, XXXII and XXXIV were extracted with ether. Because of their instability they were characterized as hydrochlorides or picrates. On heating compounds III and X under the same conditions, extraction of the reaction solutions with ether and addition of picric acid, picrates of 1,2-dialkylbenzimidazoles XXXVII (mp 235-237° C) and XL (mp. 245-246° C) were isolated with yields of 35% and 77% respectively.

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21 June 1967

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