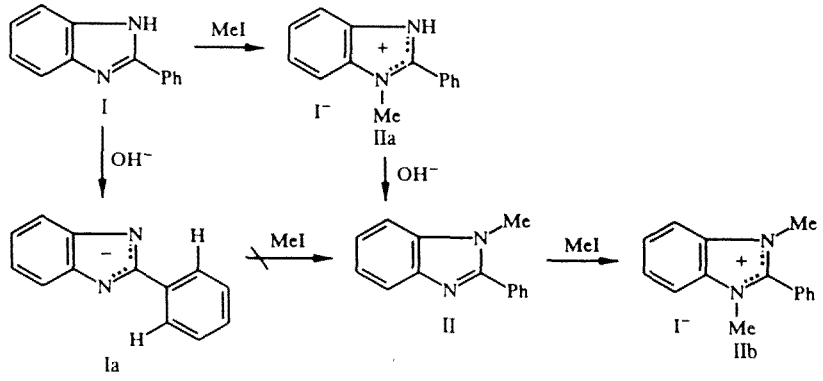
Chemistry of Heterocyclic Compounds, Vol. 32, No. 6, 1996

INVESTIGATIONS OF UNSATURATED AZOLES. 13.* SYNTHESIS AND SOME REACTIONS OF 1-ALKYLBENZIMIDAZOLES

I. I. Popov

Methods of direct alkylation of benzimidazoles by haloalkanes in homogeneous medium and under phase transfer catalysis conditions together with cyanoethylation by acrylonitrile are reported. The dealkylation of quaternary benzimidazole salts was also studied.

Until recently, methylation of the silver salt of 2-phenylbenzimidazole (I) was used in the synthesis of 1-methyl-2-phenylbenzimidazole (II) since I does not react with methyl iodide in alcoholic KOH solution [2, 3]. The inertness of I is evidently caused by steric factors. This proposal is supported by dipole moment and Kerr effect data, according to which the dihedral angles between the benzimidazole and phenyl rings in I and II are 48° and 65° respectively [4]. In this connection, it is logical to assume that deprotonation of I in alcoholic KOH solution causes elimination of the interaction between the protons of the phenyl and N–H groups, a significant decrease in the dihedral angle, and a flattening of the molecule. As a consequence, this increases the shielding of the mesomeric N-anion Ia by the neighboring protons of the phenyl ring and blocks attack of the anion by haloalkane. On this basis, alkylation of I in neutral medium as the free base seemed promising. In fact, II was obtained in 72% yield by refluxing a solution of I with methyl iodide in alcohol for 2 h and subsequent treatment of the product with base.



Alkylation of benzimidazoles by haloalkanes with a large excess of powdered KOH and acetone at 20°C gave 1-alkylbenzimidazoles in high yield [5]. Addition of powdered NaCl to the KOH-acetone mixture gives an improvement in the alkylation process by avoiding conglomeration of base and precipitation on the walls of the reactor, thus keeping to a minimum the consumption of base and solvent [6]. Variation of the conditions of the model reaction of alkylation of 2-methylbenzi-

*For communication 12 see [1].

Rostov State University, Rostov-on-Don 344090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 781-792, June, 1996. Original article submitted February 21, 1996.

 0009-3122/96/3206-0672$15.00

TABLE 1. Conditions for Alkylation of 2-Methylbenzimidazole by Methyl Iodide

Experimental No.	Base, g		NaCl, g	Base/NaCl ratio (by weight)	Yield of IVa	
					g	%
1	KOH	1,34	—	1 : 0	1,8	61,6
2	KOH	1,34	1,34	1 : 1	2,0	68,5
3	KOH	1,34	2,0	1 : 1,5	2,2	75,7
4	KOH	1,34	2,7	1 : 2	2,9	99,3
5	NaOH	0,8	—	1 : 0	2,6	89,0
6	NaOH	0,8	0,8	1 : 1	2,8	95,0

TABLE 2. Relation of the Duration of Cyanoethylation of 2-R-Benzimidazoles III on pK_a Values and 2-R Substituents

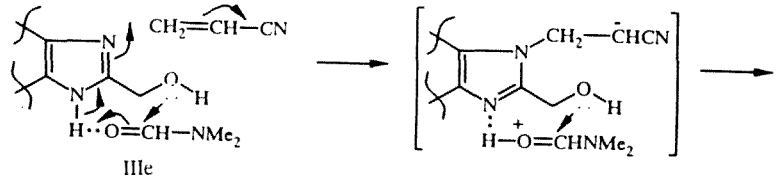
Starting material	IIIa	IIIb	IIIc	IIId	IIIe	IIIf
R	CH_3	C_2H_5	C_3H_7	C_4H_9	CH_2OH	$CH(OH)CH_3$
pK_a	6,19	6,20	6,20	6,23	6,28	6,25
Time, h	16	19	23	30	5	6
Cyanoethylation product	Va	Vb	Vc	Vd	Ve	Vf

midazole (IIIa) by methyl iodide under phase transfer catalytic conditions showed the optimal ratio of sodium chloride and base to be 2:1 for KOH and 1:1 for NaOH based on the yield of 1,2-dimethylbenzimidazole (IVa) (Table 1).

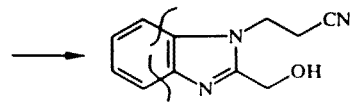
According to TLC data (chloroform/alumina) the benzimidazole alkylation products usually contain residues of the starting material and traces of quaternary 1,3-dialkylbenzimidazolium salts under these conditions. Chromatographically pure 1-alkylbenzimidazoles are separated from the benzimidazole alkylation reaction mixture in a two phase system which is formed by mixing a saturated solution of sodium hydroxide (30-50%) with aqueous polar aprotic solvents (acetone, DMSO or their mixture) [6]. In these conditions the benzimidazoles are solvated and dissolve in a small volume of solvent. Employment of quaternary benzylammonium salts as catalysts proves useful, especially for the alkylation of benzimidazoles by aminochloroalkanes and other low-reactivity alkylating reagents. Thus benzimidazole is alkylated by β-diethylaminoethyl chloride in 92% yield in a two-phase water–acetone system in the presence of triethylbenzylammonium chloride (TEBAC) [6]. Compound II was synthesized in 84% yield under similar conditions. Evidently, under phase transfer catalysis, compound I reacts with methyl iodide at the interface as the free base to form salt IIa which is rapidly neutralized by base. With an excess of methyl iodide under these conditions there is an almost quantitative yield of the difficultly soluble 1,3-dimethyl-2-phenylbenzimidazolium iodide IIb which can also be prepared by quaternization of II using methyl iodide in refluxing alcoholic solution. We were unable to convert quaternary salt IIb to base II by refluxing it in sodium bicarbonate solution.

The reported method for cyanoethylation of benzimidazole with acrylonitrile by heating in dioxane or aqueous dioxane [7, 8] seemed unsuitable for 2-alkylbenzimidazoles IIIa-f. Synthesis of 1-cyanoethylbenzimidazoles Va-f was achieved by heating IIIa-f with acrylonitrile in DMF solution. The rate of the reaction is mainly determined by steric factors and the nature of the benzimidazole ring substituent. The basicity does not appear to have a large importance, as shown by the closeness of the basicity constants [9] for IIIa-f (pK_a in water) and the time taken to complete the cyanoethylation (Table 2).

The marked ease of cyanoethylation of the 2-hydroxyalkylbenzimidazoles IIIe, f compared with the 2-alkylbenzimidazoles IIIa-d as shown by their reaction rates is evidently due to a specific solvation of the NH and OH protons in IIIe, f by DMF which allows not only stabilization of the intermediate addition product transition state but also transfer of the NH group proton to the α-C atom of the cyanoethyl group.



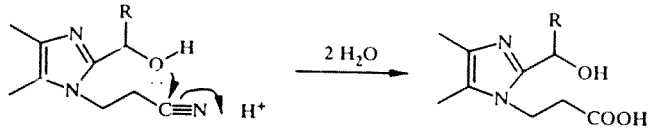
IIIe



Ve

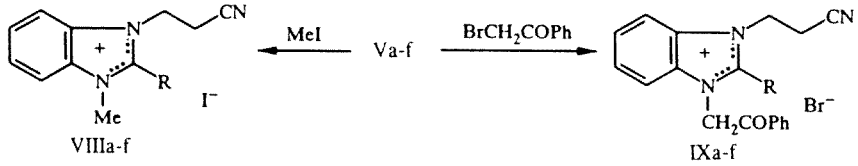
The IR spectrum of Ve clearly shows an absorption band for the nitrile group at 2265 cm^{-1} and the PMR spectrum shows two triplet signals at 4.5 and 2.8 ppm for the cyanoethyl group.

Hydrolysis of Va-d and Ve, f by sulfuric acid at 20°C gives unexpected results. In the first case the amides VIa-d are formed and in the second the carboxylic acids VIIe, f. A more thorough hydrolysis of nitriles Ve, f is evidently promoted by an anchimeric effect of the hydroxyl group. This is a rare example of a neighboring group effect through a seven-membered ring cyclic transition state (see [10]).



Ve, f VIIe, f

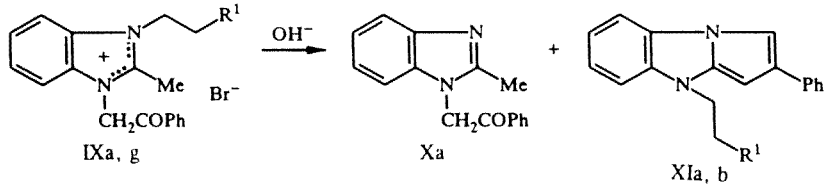
Compounds Va-f are readily quaternized by methyl iodide or phenacyl bromide when refluxed in alcohol or acetone. When iodomethylate VIIIa is heated with aqueous base solution, fission of the cyanoethyl group occurs to give 1,2-dimethylbenzimidazole (IVa).



VIIIa-f IXa-f

VIII, IX a R = Me, b R = Et, c R = C_3H_7, d R = Bu, e R = CH_2OH, f R = CH(OH)Me

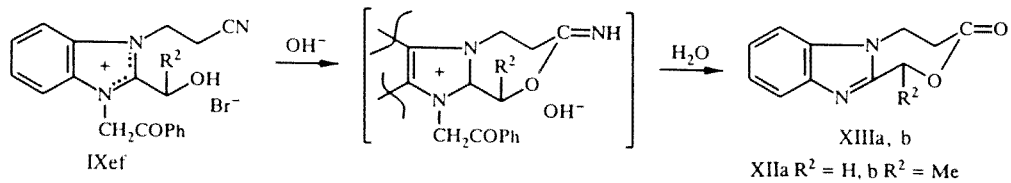
The action of a solution of alkali, ammonia, or simply heating in water causes fission of the cyanoethyl group of IXa to give 1-phenacyl-2-methylbenzimidazole (Xa). Heating salt IXa with aqueous sodium carbonate in the presence of sodium bisulfite gives Xa with a small amount of 2-phenyl-9-β-cyanoethylpyrrolo[1,2-a]benzimidazole (XIa). Salt IXg (obtained by refluxing amide VIa with phenacyl bromide in alcohol-acetone solution) and 5% sodium hydroxide solution gives Xa together with acid XIb.



IXa, g Xa XIa, b

IX, XI a R^1 = CN; IX g R^1 = $CONH_2$; XI b R^1 = COOH

Dealkylation of the phenacyl salts IXe, f by heating in an aqueous solution of sodium bicarbonate and bisulfate occurs in another direction. In this case, the presence of the neighboring hydroxyl group leads to an intramolecular cyclization involving the cyanoethyl group. Hydrolytic cleavage of the phenacyl group and ammonia then gives esters XIIa, b.



IXe,f XIIIa, b

XIIa R^2 = H, b R^2 = Me

TABLE 3. Parameters for the Compounds Synthesized

Compound	R	Empirical formula	mp, °C	Yield, %
1	2	3	4	5
Va	CH_3	$C_{11}H_{11}N_3$	88; 89...90 [7]	85
Vb	C_2H_5	$C_{12}H_{13}N_3$	79	86
Vc	n-C_3H_7	$C_{13}H_{15}N_3$	72...73	82
Vd	n-C_4H_9	$C_{14}H_{17}N_3$	60	70
Ve	CH_2OH	$C_{11}H_{11}N_3O$	158...159	91
Vf	$CH(OH)CH_3$	$C_{12}H_{13}N_3O$	122	87
VIa	CH_3	$C_{11}H_{13}N_3O$	194; 196 [16]	98
VIb	C_2H_5	$C_{12}H_{15}N_3O$	153...154	97
VIc	n-C_3H_7	$C_{13}H_{17}N_3O$	197; 198...200 [16]	99
VId	n-C_4H_9	$C_{14}H_{19}N_3O$	178	96
VIIe	CH_2OH	$C_{11}H_{12}N_2O_3$	210 †	92
VIIf	$CH(OH)CH_3$	$C_{12}H_{14}N_2O_3$	184 †	94
VIIIa	CH_3	$C_{12}H_{14}IN_3$	158...159	72
VIIIb	C_2H_5	$C_{13}H_{16}IN_3$	233	68
VIIIc	n-C_3H_7	$C_{14}H_{18}IN_3$	148	66
VIIId	n-C_4H_9	$C_{15}H_{20}IN_3$	192	70
VIIIe	CH_2OH	$C_{12}H_{14}IN_3O$	189...190	74
VIIIf	$CH(OH)CH_3$	$C_{13}H_{16}IN_3O$	154	75
VIIIg	$CH_2CH{-}CH_2$	$C_{14}H_{16}BrN_3O$	187	82
VIIIh	$CH_2C{\equiv}CH$	$C_{14}H_{14}BrN_3O$	186...188	79
IXa	CH_3	$C_{19}H_{18}BrN_3O$	202	93
IXb	C_2H_5	$C_{20}H_{20}BrN_3O$	158	94
IXc	n-C_3H_7	$C_{21}H_{22}BrN_3O$	209	95
IXd	n-C_4H_9	$C_{22}H_{24}BrN_3O$	172...173	94
IXe	CH_2OH	$C_{19}H_{18}BrN_3O_2$	205	82
IXf	$CH(OH)CH_3$	$C_{20}H_{20}BrN_3O_2$	182...183	81
IXg	$CONH_2$	$C_{19}H_{20}BrN_3O_2$	256	80
Xa	CH_3	$C_{16}H_{14}N_2O$	161	78
XIa	CN	$C_{19}H_{15}N_3$	166	5
XIb	COOH	$C_{19}H_{16}N_2O_2$	74	15
XIIa	H	$C_{11}H_{10}N_2O_2$	82	54
XIIb	CH_3	$C_{12}H_{12}N_2O_2$	95	56
XIIIa	$CH_2CH{-}CH_2$	$C_{11}H_{12}N_2O$	96	49
XIIIb	$CH_2C{\equiv}CH$	$C_{11}H_{10}N_2O$	120	38
XIIIc	$CH_2CBr{-}CH_2$	$C_{11}H_{11}BrN_2O$	57	51
XIVa	$CH_2CH{-}CH_2$	$C_{14}H_{16}N_2O \cdot C_6H_3N_3O_7$	117	19
XIVb	$CH_2C{\equiv}CH$	$C_{14}H_{12}N_2O \cdot C_6H_3N_3O_7$	193	5
XIVc	$CH_2CBr{-}CH_2$	$C_{14}H_{14}Br_2N_2O \cdot C_6H_3N_3O_7$	220	18
XVa	C_2H_5	$C_{11}H_{14}N_2O$	162...163	68
XVb	$CH_2CH{-}CH_2$	$C_{12}H_{14}N_2O$	97,5	54
XVc	$CH_2CBr{-}CH_2$	$C_{12}H_{13}BrN_2O \cdot C_6H_3N_3O_7$	154	56

TABLE 3. (Continued)

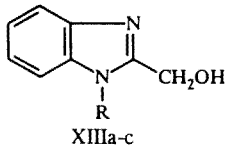
1	2	3	4	5
XVd	$CH_2CH_2N(C_2H_5)_2$	$C_{15}H_{23}N_3O \cdot C_6H_3N_3O_7$	120	79
XVe	$CH_2C_6H_5$	$C_{16}H_{16}N_2O$	130	75
XVI		$C_{11}H_{10}N_2O$	96...98	40
XXa	$CH_2CH{=}CH_2$	$C_{14}H_{16}N_2O_3 \cdot H_2O$	127	23
XXb‡	$CH_2C{\equiv}CH$	$C_{14}H_{14}N_2O_3 \cdot H_2O$	163	43
XXc‡	CH_3	$C_{12}H_{14}N_2O_3 \cdot H_2O$	193...195	61
XXIIa	$CH_2CH{=}CH_2$	$C_{11}H_{11}ClN_2$	68	41
XXIIb	$CH_2C{\equiv}CH$	$C_{11}H_9ClN_2$	90	54
XXIIc	$CH_2CBr{=}CH_2$	$C_{11}H_{10}ClBrN_2$	158	30
XXIId	CH_2CH_2CN	$C_{11}H_{10}ClN_3$	112	59
XXIIIa	$CH_2CH{=}CH_2$	$C_{22}H_{20}N_4 \cdot C_6H_3N_3O_7$	209	49
XXIIIb	$CH_2C{\equiv}CH$	$C_{22}H_{16}N_4 \cdot C_6H_3N_3O_7$	273	16
XXIIIc	$CH_2CBr{=}CH_2$	$C_{22}H_{18}Br_2N_4 \cdot C_6H_3N_3O_7$	239...240	27

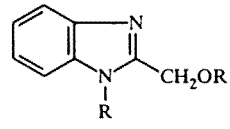
*Compound V crystallizes from toluene, XXII from toluene with hexane, VI and VII from DMF, XIa and XXc from aqueous DMF, XIII from water, XIV, XV, XVI from aqueous alcohol, VIII, IX, XI, XII, XXIII from alcohol.

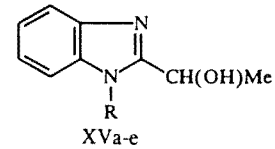
†With decomposition.

‡Tarring on recrystallization.

As a rule, alkylation of 2-hydroxyalkylbenzimidazoles in basic medium gives N- and O-dialkyl side products together with their quaternization products. In addition, the methyl derivatives IVe, f are obtained in good yield by alkylation of carbinols IIIe, g using dimethyl sulfate with cooling in ice and a minimal excess of base. Compounds XVa-e were synthesized successfully under similar conditions.


XIIIa-c

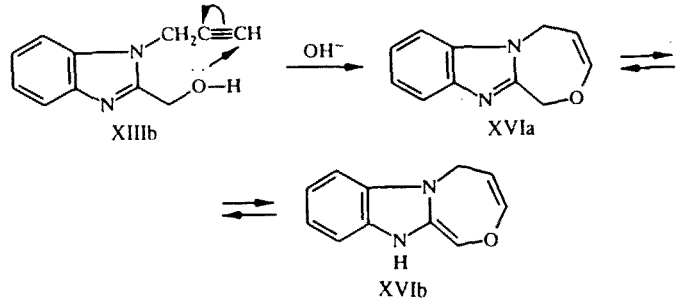

XIVa-c


XVa-e

XIII, XIV a R = $CH_2CH{=}CH_2$, b R = $CH_2C{\equiv}CH$, c R = $CH_2CBr{=}CH_2$;
XV a R = Et, b R = $CH_2CH{=}CH_2$, c R = $CH_2CBr{=}CH_2$, d R = $CH_2CH_2NEt_2$, e R = CH_2Ph

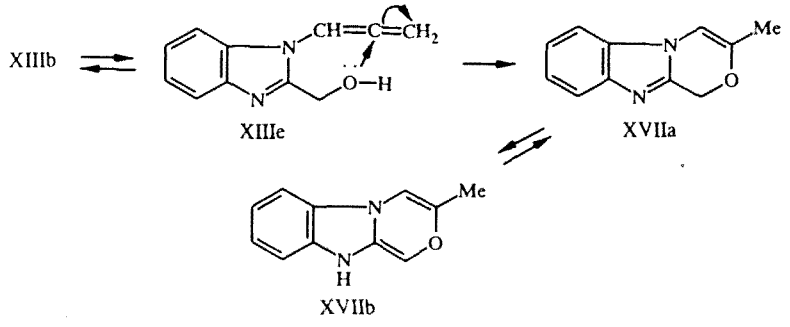
Compound IVe was obtained in high yield under phase transfer catalytic conditions by treating carbinol IIIe with methyl iodide. With allyl bromide and 2,3-dibromopropene, significant amounts of ethers XIVa-c are obtained under similar conditions. Lowering the yields of the latter is achieved by carrying out the alkylation with a molar concentration ratio of IIIe:NaOH:alkenebromide of 1:2:1.5 at a temperature below 5°C. Variation of the aprotic solvent (acetone, THF, DMSO, or dioxane) does not have a significant effect on this reaction. Alkylation of carbinol IIIe by 1,2,3-tribromopropane under phase transfer catalysis (NaOH, acetone, 20°C) gives XIIIc and XIVc via a parallel occurring dehydrobromination process. Furthermore, the PMR spectrum of the reaction products shows signals for XIIIb at 1.75 ppm (1H, s, $\equiv$CH), its isomer XIIId (R is $C{\equiv}C{-}CH_3$) at 1.95 ppm (3H, s, CH_3), and signals for the protons of Favorskii reaction products of XIIIb with acetone at the acetylene group at 1.1 (6H, s, CH_3), $\equiv C{-}C(CH_3)_2OH$, and 2.4 ppm (3H, t, $\equiv C{-}C(CH_3){=}CH_2$). A similar reaction of the propargyl group is observed in the reaction of the same benzimidazole with propargyl bromide in these conditions. The PMR spectrum of the reaction products shows signals for allene protons at 5.4 (1H, t, $-CH{=}C{=}$) and 4.6 (2H, d, $={=}CH_2$), the isomeric methylacetylene group at 1.9 ppm (3H, s, $\equiv C{-}CH_3$) and fragments $\equiv C{-}C(CH_3)_2OH$ at 1.1 (3H, s) and $\equiv C{-}C(CH_3){=}CH_2$ at 2.4 ppm (3H, t). Treatment of carbinol IIIe with propargyl bromide in acetone in the presence of powdered NaOH gives not only XIIIb and XIVb but also the products of a side reaction of the propargyl group with acetone. A smoother reaction of carbinol IIIe with propargyl bromide occurs when exchanging acetone for DMSO. The yield is increased to 38%. However, as a result of an intramolecular addition of the hydroxyl group to the propargyl function, the cyclic

ether XVI is formed, which is encouraged by increase in temperature and concentration of base in the final stage of the reaction.



XIIIb XVIa XVIb

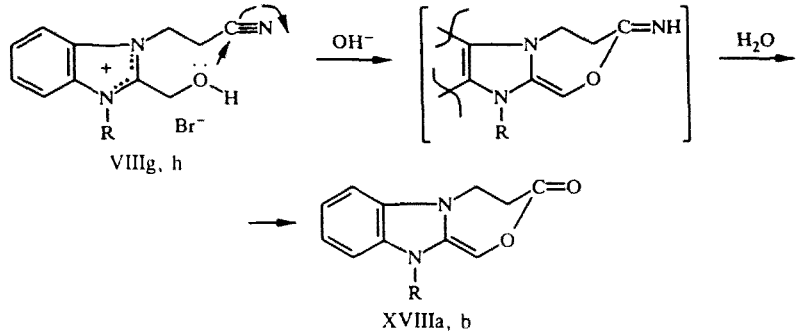
Bearing in mind the ease of isomerization of a propargyl group to allyl, occurring in benzimidazoles [11, 12], a reaction of carbinol XIIIb to allene XIIIe with subsequent intramolecular cyclization to tautomer XVII was expected.



XIIIb XIIIe XVIIa XVIIb

However, the PMR spectrum of the product showed the absence of methyl proton signals, i.e., evidently here the rate of intramolecular cyclization of carbinol XIIIb to XVI significantly exceeds the rate of an acetylene-allene rearrangement.

Refluxing iodomethylate VIIIe with aqueous sodium bicarbonate solution occurred with fission of the cyanoethyl group to give carbinol IVe in 62% yield. It seemed that carbinols XIIIa, b could be prepared similarly. The quaternary salts VIIIg, h were made by refluxing salt Ve with allyl or propargyl bromides. However, refluxing salt VIIIg with sodium bicarbonate gave the carbinol XIIIa in only 5% yield. In this case a concurrent fission of the allyl group occurs to give the starting carbinol. By contrast, dealkylation of VIIIh in the same conditions gave XIIIb in good (56%) yield. This dealkylation reaction is accompanied by an intramolecular cyclization involving the cyanoethyl group to give low yields (5-10%) of the oily compounds XVIIIa, b (R_f 0.8 on aluminium oxide in chloroform).

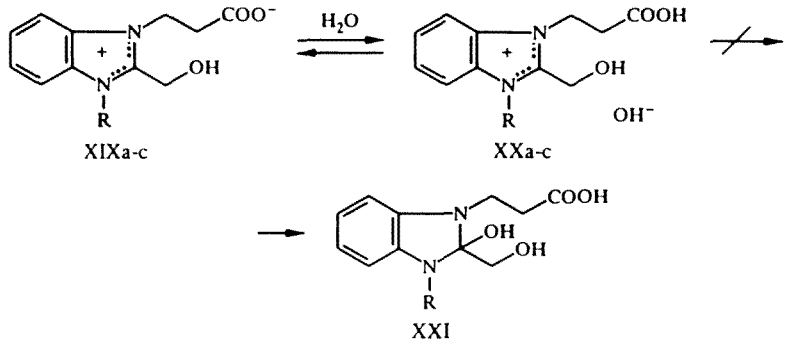


VIIIg, h XVIIIa, b

VIIIg, XVIIIa R = $CH_2CH{=}CH_2$; VIIIh, XVIIIb, R = $CH_2C{\equiv}CH$

The IR spectra of XVIIIa, b show a strong absorption at 1730 cm^{-1} (C=O) typical of cyclic esters and the spectrum of XVIIIb an additional band at 2230 cm^{-1} (≡CH). The intramolecular cyclization mechanism for VIIIg, h is apparently similar to that for formation of ester XIIa.

When VIIIg, h and VIIIa are treated with sulfuric acid at 20°C the nitrile group is converted to carboxyl as in the acid hydrolysis of carbinols Ve, f. It might have been expected that the products would be isolated as the betaines XIX when the reaction mixture was neutralized.

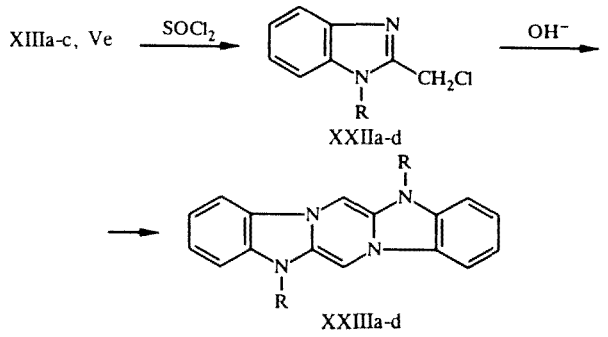


XIXa-c XXa-c XXI

XXa R = $CH_2CH=CH_2$, b R = $CH_2C{\equiv}CH$, c R = Me

However, the presence of an unionized carboxyl group in the IR spectra (strong band at 1730 cm^{-1}) infers the structure of the hydrated betaine hydroxides XXa-c. The possible formation of the pseudobase XXI is improbable. It is difficult to visualize attack of the imidazolium ring by the hydroxyl anion with the presence of the carboxyl group in the molecule. Compounds XXa, b are separated from the reaction mixture as hygroscopic oily products solidifying to the crystallohydrate when dried initially in air and then over P_2O_5. Compounds XXa, b could not be purified by crystallization since they tarred upon heating with solvent. Upon prolonged standing over P_2O_5, XXa, b partially undergo reaction to the cyclic esters XVIIIa, b. Attempts to realize this reaction by fusing XXa, b with P_2O_5 or refluxing with thionyl chloride in dioxane were unsuccessful due to tarring of the reaction mixture.

Refluxing carbinols XIIIa-c or Ve with thionyl chloride in dioxane gives the 2-chloromethylbenzimidazole XXIIa-d in high yields. Treatment of XXIIa-c with 50% NaOH in the presence of acetone for 5 h at 25°C gives only traces of the cyclic compounds XXIIIa-c; exchange of acetone for DMSO allows completion of the cyclization within one hour (see [13]).



XXIIa-d XXIIIa-d

XXII, XXIII a R = $CH_2CH=CH_2$, b R = $CH_2C{\equiv}CH$, c R = $CH_2CBr=CH_2$;
XXIId R = CH_2CH_2CN; XXIIIdR = H

Reaction of XXIId with base under these conditions causes fission of cyanoethyl group. In the IR spectrum of the product, the nitrile (C ≡ N) band at 2265 cm^{-1} is absent and in the PMR spectrum the signals for the cyanoethylene methylene protons. These data confirm the structure as XXIIId, which had been obtained earlier by treating 2-chloromethylbenzimidazole with bases [13, 14].

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument and PMR spectra on a Tesla BS-487 instrument (80 MHz) in CCl_4 solvent with HMDS internal standard. Chromatography was carried out on Brockmann activity grade III Al_2O_3 in ether. Physicochemical parameters for the compounds prepared are given in Table 3.

Elemental analytical data for C, H, and N have been presented to the editor and agree with calculated values.

1,2-Dimethylbenzimidazole (IVa). A. Methyl iodide (1.25 ml, 0.02 mole) was added with vigorous stirring at 20°C to a mixture of 2-methylbenzimidazole (IIIa, 2.64 g, 0.02 mole), TEBAC (50 mg), alkali (0.02 mole) triturated with NaCl,

and acetone (2.6 ml). The reaction mixture was stirred for 0.5 h, diluted with water in the ratio 1:2, and the precipitate filtered off. The amount of added sodium chloride and yield of IVa are given in Table 1.

B. To a solution of sodium hydroxide (50 g, 1.25 mole) in water (50 ml) there were added compound IIIa (132 g, 1 mole), acetone (130 ml), and methyl iodide (68.5 ml, 1.1 mole) with cooling in iced water and intensive stirring during 2 h. The product was then stirred for 2 h at 20°C, poured into cold water, neutralized with 10% HCl, and the precipitate filtered. After drying, the weight was 130 g. Following removal of the mother liquor an additional 9 g of IVa was obtained. The overall yield was 139 g (95%) with mp 110-111°C (lit. data: mp 112°C [3]).

1-Methyl-2-phenylbenzimidazole (II). A. A solution of 2-phenylbenzimidazole (I, 19.4 g, 0.1 mole) in alcohol (200 ml) was refluxed with methyl iodide (10.7 ml, 0.17 mole) for 2 h using a reflux condenser, cooled, KOH (7 g) added, and heated until complete solution of the base. The precipitated potassium iodide was filtered, the alcohol distilled off, and the residue extracted with benzene. The solvent was removed and II was distilled *in vacuo* to give 15 g (72%) with mp 97-98°C (from benzene-petroleum ether, 1:5). Lit, mp 98°C [3].

B. Compound II was synthesized in 84% yield under phase transfer catalytic conditions as described for IVa (method B).

1,3-Dimethyl-2-phenylbenzimidazolium Iodide (IIb). Compound I (1.94 g, 0.01 mole), acetone (10 ml), and methyl iodide (2 ml, 0.03 mole) were added to a solution of sodium hydroxide (3 g) in water (3 ml). The product was initially crimson-violet but became colorless upon further mixing. The precipitated iodide IIb (2.7 g, 80%) with mp 290°C (from water) was filtered off.

1-β-Cyanoethylbenzimidazoles (Va-f). A solution of the benzimidazole IIIa-f (0.1 mole) in DMF (10 ml) was refluxed for 5-30 h with acrylonitrile (8 ml, 0.12 mole) in the presence of triethylbenzylammonium hydroxide. The end of the reaction was determined by TLC on Al_2O_3 in $CHCl_3$. Compounds Ve, f precipitated when the reaction mixture was cooled and were filtered off. For separation of Va-d the reaction mixture was diluted with water and the oily product extracted with a mixture of ether-chloroform (2:1). The solvent was removed and the residue dried over P_2O_5. The shiny, snow white crystals (from toluene) were readily soluble in alcohol. IR spectrum: 2265 cm^{-1} (C≡N). PMR spectrum for Ve (CF_3COOH, δ, ppm): 7.3 (4H, m, arom.), 4.55 (2H, t, NCH_2), 2.8 (2H, t, CH_2CN), 5.1 (2H, s, CH_2O). 2-Phenyl- and 2-benzylbenzimidazoles IIIg, h (R = C_6H_5 and R = $CH_2C_6H_5$) did not react with acrylonitrile under similar conditions.

Hydrolysis of Va-f. Concentrated sulfuric acid (5 ml) was added to Va-f (0.01 mole) and the product left for one day at 20°C and diluted with water (10 ml). The precipitated acids VIIe,f were filtered off and washed with alcohol or acetone. For separation of amides VIa-d the reaction mixture after dilution with water was basified with 20% NaOH to pH 8 with cooling. The precipitate was filtered and washed with alcohol and acetone. IR spectrum of VIa-d, 1680 cm^{-1}; VIe, f, 1700 cm^{-1} (C=O bands). Hydrolysis of VIIIa and VIIIg,h was carried out similarly to Va-f in concentrated sulfuric acid. The reaction product was diluted with water (1:1), concentrated ammonia added to pH 5-6, and the precipitated XXa-c filtered and dried over P_2O_5. IR spectrum: 1730 cm^{-1}.

1-(β-Cyanoethyl)-3-methylbenzimidazolium Iodides (VIIIa-f). A solution of Va-f (5 mmole) in ethanol (5 ml) was refluxed for 3 h with methyl iodide (0.5 ml, 1.1 g, 7.5 mmole). After cooling, the precipitated VIIIa-f was filtered and washed with several drops of alcohol to give snow white needles (from alcohol) which were readily soluble in water.

1(β-Cyanoethyl)-3-phenacylbenzimidazolium Bromides (IXa-f). Phenacyl bromide (2 g, 0.01 mole) was added to a warm solution of Va-f (0.01 mole) and the product was refluxed for 15 min on a water bath and left overnight. The precipitated bromides IXa-f were filtered, washed with acetone, and crystallized from alcohol. The snow white crystals dissolved readily in water. IR spectrum: 2260 cm^{-1} (C≡N), 1700 cm^{-1} (C=O). To prepare IXg, a solution of amide VIa (2.2 g, 0.01 mole) in alcohol (6 ml) and acetone (3 ml) was refluxed with phenacyl bromide (2 g, 0.01 mole) for 6 h. The salt formed was precipitated from the cooled solution using diethyl ether.

Reaction of IXa, g and IXe, f with Bases. A. Sodium bicarbonate (0.84 g, 0.01 mole) and triethylbenzylammonium hydroxide (50 mg) were added to a solution of bromide IXa (3.84 g, 0.01 mole) in water (40 ml) and held on a steam bath for 12 h. The yellow-green precipitate formed on cooling was filtered, washed with water, and dried. Chromatography on alumina in benzene and collection of the first fraction gave XIa (0.14 g). IR spectrum: 2265 cm^{-1} (C≡N). The second fraction gave 1-phenacyl-2-methylbenzimidazole (Xa, 1.95 g, 78%). IR spectrum: 1700 cm^{-1} (C=O).

B. Salt IXg (3.6 g, 0.01 mole) was heated with NaOH solution (5%, 1 ml) on a steam bath. After cooling, the mixture of Xa and XIb was filtered, dried, and chromatographed on alumina in chloroform, separating Xa in the first fraction and acid XIb in the second. IR spectrum for XIb: 1690 (C=O), 3400 cm^{-1} (OH).

C. A solution of salt IXe, f (0.01 mole), sodium carbonate (1.1 g, 0.01 mole), and sodium sulfite (1.3 g, 0.01 mole) in water (40 ml) was heated on a steam bath for 7 h. After cooling, the yellowish precipitate was filtered off to give XIIa, b. IR spectrum: 1715 cm^{-1} (C=O).

1-Methyl-2-α-hydroxyalkylbenzimidazoles (IVe, f). A. Methyl iodide (13.5 ml, 0.22 mole) was added dropwise with vigorous stirring to a solution of carbinol IIIe (29.6 g, 0.2 mole) in acetone (30 ml) and 40% NaOH (22 ml). The product was stirred for 1 h and the precipitated IVe filtered. Yield 28 g (86%), mp 121°C (lit. mp 125-130°C [5]). Carbinol IVf was obtained similarly in 90.6% yield.

B. Carbinol IIIf (16.2 g, 0.1 mole) and ethanol (15 ml) were added to a solution of 80% KOH (7 g, 0.1 mole) in water (20 ml). Dimethyl sulfate (14.2 ml, 0.15 mole) was added with stirring and cooling in ice over 5 h, the reaction mixture was stirred at 20°C for 1.5 h, and the precipitated sodium sulfate filtered off. After distillation of alcohol, the oily residue started to crystallize when it was filtered and washed with ether to give IVf (13.2 g, 75%).

C. A solution of iodomethylate VIIIa (3.4 g, 0.01 mole), sodium bicarbonate (1.7 g, 0.02 mole), and sodium sulfite (0.6 g, 5 mmole) in water (10 ml) was heated on a water bath for 5 h, diluted with water (10 ml), and the IVe precipitate filtered off (1 g, 62%).

1-Alkyl-2-α-hydroxyethylbenzimidazoles (XVa-e). Ethyl bromide (1.2 ml, 15 mmole) was added dropwise over 0.5 h with stirring to a solution of carbinol IIIf (1.62 g, 0.01 mole) and KOH (0.7 g, 0.01 mole) in alcohol (3 ml) and water (1 ml). The product was left overnight or stirred for 6 h, and the precipitated potassium bromide filtered off, and washed with alcohol. After distillation of the alcohol, water (5 ml) was added to the residue and the precipitate was filtered and washed with ether. Compounds XVb-e were obtained similarly to XVa.

Reaction of IIIe with 2,3-Dibromopropane, Allyl-, and Propargyl Bromide. A. The alkenyl (alkynyl) halide (15 mmole) was added with vigorous stirring and cooling in ice to a mixture of powdered NaOH (3 g), TEBAC (0.6 g), carbinol IIIe (1.48 g, 0.01 mole), and acetone (3 ml). The product was stirred for 2 h at 20°C, diluted with water, extracted with ether, and chromatographed collecting ethers XIVa-c in the first fraction and carbinols XIIIa-c in the second. PMR spectra of XIVa-c as follows: XIVa, 7.5-7.1 (4H, m, arom.), 5.6 (2H, m, CH=), 5.1 (2H, d, $=CH_2$, J = 12 Hz), 5.0 (2H, d, OCH_2, J = 12 Hz), 4.6 (2H, d, $=CH_2$, J = 6 Hz), 4.5 (2H, s, CH_2O), 3.8 (2H, d, NCH_2, J = 6 Hz); XIVb, 7.6-7.1 (4H, m, arom.), 5.1 (2H, s, $OCH_2C\equiv$), 4.7 (2H, s, CH_2O), 4.1 (2H, s, NCH_2), 1.7 (2H, s, $\equiv CH$); XIVc, 7.6-7.1 (4H, m, arom.), 5.4 (2H, s, OCH_2), 5.1 (2H, s, $=CH_2$), 5.0 (2H, s, $=CH_2$), 4.7 (2H, s, CH_2O), 4.0 (2H, s, NCH_2).

B. Propargyl bromide (1.4 ml, 1.8 g, 15 mmole) was added dropwise at 5°C with stirring to a mixture of powdered NaOH (3 g) in DMSO (5 ml), carbinol IIIe (1.48 g, 0.01 mole), and TEBAC (0.6 g). The product was stirred for 3 h at 20-25°C, NaOH (3 g) added, and the product heated at 70°C for 2 h, diluted with water (10 ml), and extracted with ether. Chromatography gave 1,5-dihydro-2,6-oxazepino[3,4-a]benzimidazole (XVI) in the first fraction of eluent and XIIIb in the second. R_f values for XIIIb and XVI were 0.2 and 0.9 in chloroform and 0.1 and 0.6 in toluene. IR spectrum: 1080 (COC), 1620, 1670 cm^{-1} (C=C, C=N). PMR spectrum (CF_3COOH): 7.4 (5H, m, arom., 3-H), 6.7 (1H, m, 4-H), 5.5 (2H, m, NCH_2), 5.0 ppm (2H, s, CH_2O).

1-R-2-Chloromethylbenzimidazoles (XXIIa-d). Thionyl chloride (1 ml, 1.8 g, 15 mmole) was added portionwise with stirring to a suspension of carbinol XIIIa-c or Ve (0.01 mole) in anhydrous dioxane (4 ml). The product was heated at 60°C for 2 h, cooled, neutralized with ammonia, extracted with ether-chloroform (3:1), and chromatographed. PMR spectrum: 5.1 ppm (2H, s, CH_2Cl).

The pyrazino[1,2-a: 4,5-a']bisbenzimidazoles XXIIIa-c were obtained by [13], chromatographed, and the oily products converted to the picrates.

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