INVESTIGATION OF BENZIMIDAZOLE DERIVATIVES

XXIX.* SYNTHESIS OF BIS(1-BENZIMIDAZOLYL)ALKANES AND THEIR BEHAVIOR TOWARD SOME NUCLEOPHILIC AGENTS

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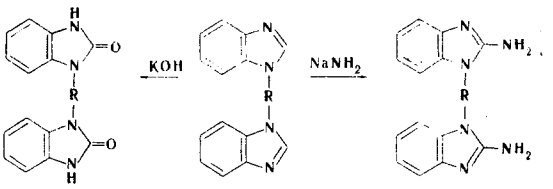
A number of bis(1-benzimidazolyl)alkanes (I) were synthesized, and their behavior toward sodium amide and potassium hydroxide was studied. While compounds with n=3-5 (Ic–Ie) are aminated by $NaNH_2$ and hydroxylated by KOH to give diamines (II) and bisbenzimidazolones (III), Ia,b with n=1, 2 decomposed under the influence of these reagents. Considerations regarding the possible reasons for this phenomenon are stated.

It has been shown that bis(1-benzimidazolyl)methane (Ia) [2] and 1,2-bis(benzimidazolyl)ethane (Ib) [3] do not undergo amination by sodium amide. The reasons for this could not be ascertained, although it was assumed to be due to the steric hindrance to reactions at the 2 position that is created by the closely located benzimidazole rings. The successful amination of 1-tert-butylbenzimidazole [4] – a compound with a bulky substituent in the 1 position – demonstrated that steric effects cannot bear the responsibility for the inert behavior of Ia and Ib with respect to sodium amide. In this connection, it seemed of interest to synthesize bis(1-benzimidazolyl)alkanes with far-removed benzimidazolyl substituents and to test their behavior toward sodium amide and potassium hydroxide (the latter reagent reminds one of sodium amide with respect to its effective mechanism) [5]. We obtained I (Table 1) in good yields by the action of the appropriate dihalo derivatives on benzimidazole in alcoholic alkali (Ia-f) or in neutral media (Ig).

It was found that of all of the I compounds, only bis(1-benzimidazolyl)propane (Ic), bis(1-benzimidazolyl)butane (Id), and bis(1-benzimidazolyl)pentane (Ie) are aminated by sodium amide and hydroxylated by alkali to give diamines (II) or bisbenzimidazolones (III, Table 1). Moreover, the amination proceeds at higher temperatures (130-160°C) than in the case of simple 1-alkylbenzimidazoles (110-115°), and the reaction product is obtained in low yield and is difficult to purify.



IIIc-e I a-g IIc-e

a R=CH_2 b R=$(CH_2)_2$ c R=$(CH_2)_3$ d R=$(CH_2)_4$ e R=$(CH_2)_5$

f R=CH_2–C$_6$H$_4$–CH_2; g R=CH_2OCH_2

Compounds Ia,b,f,g do not react with sodium amide in xylene solution, while a reaction accompanied by the evolution of gases (CO_2, NH_3, H_2, and hydrocarbons) is observed in dimethylaniline. Only in the amination of If were we able to isolate 25% of the starting compound and 13% of the benzimidazole. Compounds Ia, b,

*See [1] for communication XXVIII.

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TABLE 1. Characteristics of I-III

Compound	mp, °C (crystallization solvent)	Empirical formula	Found, %			Calc., %			Yield, %
			C	H	N	C	H	N	
Ic	137—138 (xylene)	$C_{17}H_{16}N_4 \cdot 1/2H_2O$	72,0	6,1	19,9	71,6	6,0	19,6	59
Id	171—172 (aqueous alcohol)	$C_{18}H_{18}N_4$	74,7	6,7	19,4	74,5	6,3	19,3	83
Ie	58—70 (water)	$C_{19}H_{20}N_4 \cdot 2H_2O$	66,7	7,2	16,3	67,0	7,1	16,5	39
If	209—210 (aqueous alcohol)	$C_{22}H_{18}N_4$	78,2	5,5	16,3	78,1	5,4	16,6	100
Ig	186—186,5 (benzene)	$C_{16}H_{14}N_4O \cdot 1/2H_2O$	68,9	5,0	20,3	68,8	5,4	20,1	37
IIc	231—232 (water)	$C_{17}H_{18}N_6$	66,7	6,1	26,6	66,6	5,9	27,4	16
IId	286—288* (aqueous alcohol)	$C_{18}H_{20}N_6 \cdot 1/2H_2O$	65,7	6,8	25,5	65,6	6,4	25,5	28
IIe	225—226* (aqueous alcohol)	$C_{19}H_{22}N_6 \cdot 1/2H_2O$	66,5	7,0	24,9	66,4	6,8	24,5	30
IIIc	246—247 (acetic acid)	$C_{17}H_{16}N_4O_2$	66,6	5,4	18,6	66,2	5,2	18,2	50
IIId	331—332* (acetic acid)	$C_{18}H_{18}N_4O_2$	66,7	5,8	17,1	67,1	5,6	17,4	80,7
IIIe	218—219* (acetic acid)	$C_{19}H_{20}N_4O_2$	67,7	6,2	16,5	67,8	6,0	16,7	90,6

* These compounds melt with decomposition.

TABLE 2. Ionization Constants and Behavior toward Sodium Amide and Anhydrous Alkali of Some Bisbenzimidazolylalkanes

Compound	$pK_a^{25°}$ (water : alcohol 1 : 1)	Behavior toward sodium amide	Behavior toward anhydrous alkali
Ia	4.22	Not aminated	Decomposed to a benzimidazole
Ib	4.56	Destructively decompsed	Decomposed to a benzimidazole
Ic	5.02	Aminated	Hydroxylated
Id	5.13	Aminated	Hydroxylated
Ie	5.17	Aminated	Hydroxylated
If	4.80	Decomposed to a benzimidazole	Decomposed to a benzimidazole
Ig	4.38	Not aminated	Decomposed to a benzimidazole

f,g are apparently decomposed under severe conditions under the influence of $NaNH_2$. More precisely, in addition to forming benzimidazole, the starting compounds are destroyed under the influence of potassium hydroxide. Moreover, in all cases we isolated a benzimidazole (in 42-88% yield). The splitting out of the N-substituent (isopropyl, methoxymethyl) on fusion of N-substituted benzimidazoles with potassium hydroxide has also been previously observed [4, 5].

The difference in the behavior of Ic,d,e and Ia,b,f,g is apparently explained in part by the reduced basicity of the latter (Table 2). It has been previously shown that the basicity is the most important factor that influences the Chichibabin reaction (because of the necessity of the prior coordination of the pyridine N atom with the Na^+ ions in sodium amide), and a decrease in the basicity of benzimidazole derivatives to pK_a 4.2-4.5 can completely prevent their amination. The decrease in basicity in Ia,b,f,g is due to the mutual electron-acceptor effect of the two closely located benzimidazole groupings (Ia,b) or even of the oxygen (Ig) and p-phenylene (If) bridges. On the other hand, the benzimidazole groupings in Ic,d,e have practically no effect on one another, and the pK_a values of Ic,d,e and the readily aminated 1-alkylbenzimidazoles are practically identical. In addition, the certain difficulty in the amination and hydroxylation of Ic,d,e and the decomposition of molecules of other bis(1-benzimidazolyl)alkanes by the action of $NaNH_2$ may be partially due to the instability of the alkylene chain with respect to the action of caustic reagents such as sodium amide and KOH.

Finally, a last factor, which, in our opinion, should not be disregarded, is the presence in I of two identical N atoms of the pyridine type, which compete with one another for coordination with sodium amide. The equivalence of these N atoms may make sorption of a molecule of the heterocyclic derivative on the surface of the $NaNH_2$ too brief and ineffective for the occurrence of the Chichibabin reaction.

The interaction of all of these factors apparently also determines the different behavior of I toward sodium amide and alkali.

EXPERIMENTAL

1,3-Bis(1-benzimidazolyl)propane (Ic). A 45-g (0.38 mole) sample of benzimidazole and 30 g (0.19 mole) of 1-chloro-3-bromopropane were added successively to a solution of 25 g (0.45 mole) of 85% KOH in 400 ml of alcohol. The mixture was refluxed for 4 h, after which 24.4 g of a mixture of KCl and KBr was removed

by filtration, and the alcohol was removed from the filtrate by distillation. The semicrystalline residue was dissolved in 300 ml of chloroform, and the solution was washed with 10% NaOH solution and dried with Na_2SO_4. The chloroform was removed, and the residue was triturated with ether. The precipitated Ic was removed by filtration and dried to give 30.5 g of colorless needles with mp 137-138°. 1,4-Bis(1-benzimidazolyl)butane (Id) was similarly obtained.

1,5-Bis(1-benzimidazolyl)pentane (Ie). This compound was obtained similarly but with several differences in the isolation procedure. Removal of the chloroform left a brown oil, which was dissolved in 5% HCl. The solution was made alkaline with 10% NaOH solution to give a yellowish precipitate in 70% yield. The product was recrystallized from water to give colorless needles of the dihydrate of Ie with mp 58-70°. The dihydrate lost water on drying over P_2O_5 to give a sticky caramel-like mass that could be drawn into long threads. The yield was 39%. This mass crystallized again on storage in a desiccator to give a crystal hydrate containing one molecule of water and two molecules of base. Compound Ie was quite soluble in chloroform, alcohol, and ethyl acetate, only slightly soluble in benzene, and insoluble in ether and petroleum ether.

ω,ω'-Bis(1-benzimidazolyl)-p-xylene (If). A 28.32-g (0.24 mole) sample of benzimidazole and a solution of 21 g (0.12 mole) of p-xylylene dichloride in 200 ml of alcohol were added to a solution of 15.84 g (0.28 mole) of 85% KOH in 200 ml of alcohol, and the mixture was refluxed for 4 h. It was then cooled, and water was added until precipitation was complete. The yield of colorless needles with mp 209-210° was quantitative. PMR spectrum, δ, ppm ($CDCl_3$, 10% by volume): 5.10 (singlet, four CH_2 protons), 6.92 (singlet, four protons of the phenylene bridge), 7.05 (center of a multiplet, eight protons of the benzene rings), 7.70 (singlet, two protons of the imidazole rings).

1,2-Bis(1-benzimidazolyl)dimethyl Ether (Ig). A 1.75-ml (0.01 mole) sample of bischloromethyl ether was added with stirring to a cooled (to 0°) suspension of 4.72 g (0.04 mole) of benzimidazole in 100 ml of absolute xylene, and the mixture was refluxed for 2 h. The resulting oil was separated and treated with water, and the crystals of Ig that formed were removed by filtration and dried to give 2 g of colorless fibrous crystals.

1,3-Bis(2-amino-1-benzimidazolyl)propane (IIc). A mixture of 5.52 g (0.02 mole) of Ic and 3.9 g (0.1 mole) of sodium amide was heated in 60 ml of absolute dimethylaniline for 1.5 h at 135-155°. The evolved hydrogen (320 ml) was collected. The mixture was then cooled and diluted with 10 ml of water. The sticky precipitate was removed by filtration and dissolved in water. The solution was extracted with chloroform, and the chloroform was evaporated to give 1 g of pale-rose crystals. IR spectrum (mineral oil), cm^{-1}: ν_{as} 3435, ν_s 3335, δ 1650 (NH_2). The chloroform-insoluble residue yielded a high-melting side product with mp > 360° (from dimethylformamide). The structure of this side product could not be ascertained, but it did not contain an amino group.

1,4-Bis(2-amino-1-benzimidazolyl)butane (IIb). This compound was obtained as pale-rose crystals via the method used to prepare IId. IR spectrum (mineral oil), cm^{-1}: ν_{as} 3425, ν_s 3310, δ 1660 (NH_2).

1,5-Bis(2-amino-1-benzimidazolyl)pentane (IIe). This compound was obtained as pale-rose crystals by the action of $NaNH_2$ on Ie, as in the preparation of IIa. IR spectrum ($CHCl_3$), cm^{-1}: ν_{as} 3492, ν_s 3409, δ 1636 (NH_2).

Attempted Amination of Bis(1-benzimidazolyl)methane (Ia), 1,2-Bis(1-benzimidazolyl)ethane (Ib), ω,ω'-Bis(1-benzimidazolyl)-p-xylene (If), and 1,2-Bis(1-benzimidazolyl)dimethyl Ether (Ig.) The amination of 0.01 mole of the above-indicated substances with 0.05 mole of sodium amide in absolute xylene at 139° for 2 h was unsuccessful. The starting materials were recovered in 50-90% yields and were identified by chromatography and from the IR spectra of mixtures. Destructive decomposition of substances Ia,b,f,g (recorded by the evolution of CO_2, NH_3, H_2, and gases that decolorize bromine water) occurred in absolute dimethylaniline at 130-150°. In the amination of If, we were able to isolate 25% of the starting compound and 13% benzimidazole. The amination of bis(1-benzimidazolyl)methane yielded a high-melting product [mp > 360° (from DMF)] that was only slightly soluble in the usual organic solvents. The structure of this product could not be ascertained, but it did not contain an amino group.

1,3-Bis(benzimidazol-2-on-1-yl)propane (IIIc). A 2.76-g (0.01 mole) sample of Ic was fused with 5.6 g (0.1 mole) of anhydrous powdered KOH at 240-260° in a Kjeldahl flask. Hydrogen evolution (340 ml) ceased after 40 min. The cooled gray-green melt was treated with 5% HCl until it gave an acid reaction to Congo Red. The precipitate was removed by filtration, washed with water, and dried to give 1.15 g of pale-rose crystals. IR spectrum (mineral oil): ν_{CO} 1710 cm^{-1}.

1,4-Bis(benzimidazol-2-on-1-yl)butane (IIId). This compound was obtained as rose crystals by the method used to prepare IIIc. IR spectrum (mineral oil), cm^{-1}: 1724 (shoulder) and 1695 (C=O).

1,5-Bis(benzimidazol-2-on-1-yl)pentane (IIIe). This compound was obtained as pale-rose crystals by the method used to prepare IIIc. IR spectrum ($CHCl_3$), cm^{-1}: 3478 (N–H), 1710 (C=O).

Attempted Hydroxylation of Ia,b,g. Fusion of 0.01 mole of the above-indicated substances with 0.1 mole of anhydrous powdered KOH at 200-250° gave benzimidazole in 42-88% yield. The hydroxylation product was identified by chromatography and mixed-melting-point determination.

Ionization Constants. These were determined at 25 ± 1° by potentiometric titration of 0.001 M solutions of the bases in 50% (by weight) aqueous alcohol with 0.01 N HCl with an LPU-01 potentiometer and were calculated by the usual method.

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