DIRECT HYDROXYLATION OF IMIDAZOLES NEW METHOD FOR THE SYNTHESIS OF 2-IMIDAZOLONES, ARYLIMIDAZOLONES, AND PERIMIDONES*

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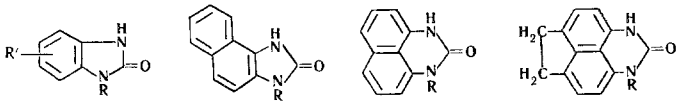
It is shown that the N-substituted derivatives of 4,5-diphenylimidazole, benzimidazole, naphth-[1,2]imidazole, perimidine, and aceperimidine are hydroxylated by alkali metal hydroxides to give the corresponding 2-imidazolones and perimidones in high yields.

Chichibabin's studies [1, 2] on the hydroxylation of nitrogen heterocycles to their 2-hydroxy derivatives have received less development than sodium amide amination. Up to now, several pyridines [1,3-5], quinolines [1,2], benzoquinolines [2], isoquinoline [2], and phenanthridine [6] have been successfully used in this reaction. We have found that hydroxylation by means of fused anhydrous alkali is to a great degree characteristic for N-substituted benzimidazoles, naphth[1,2]imidazoles, 1,8-naphthimidazoles (perimidines), and aceperimidines. The corresponding N-substituted benzimidazolones (I), naphth[1,2]imidazolones (II), perimidones (III), and aceperimidones (IV) are obtained in high yields (Table 1).

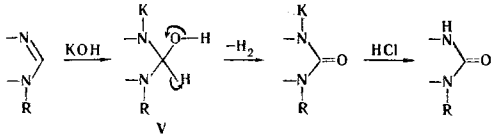


I II III IV

Uncondensed imidazoles (for example, 1-methyl-4,5-diphenylimidazole) are also hydroxylated at the 2 position but with considerably greater difficulty. This is the first case of the direct hydroxylation of five-membered nitrogen heterocycles.

This method should be considered to be the most simple and effective route for the synthesis of N-monosubstituted 2-imidazolones, which, until now, were less accessible than imidazolones without substituents or with two identical substituents on the nitrogen atoms [7,8]. This is explained by the fact that only N-disubstituted imidazolones are formed on attempts to obtain I-IV by the direct alkylation or aralkylation of imidazolones, regardless of the ratio of the reagents [9].

The hydroxylation of imidazoles apparently proceeds in accordance with the scheme



V

*The material in this paper regarding the synthesis of perimidones and aceperimidones should be considered as communication V of our series entitled "Heterocyclic Analogs of Pleiadiene." See [16] for communication IV.

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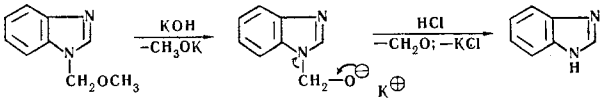
TABLE 1. N-Monosubstituted 2-Imidazolones and Perimidones

2-Imidazolone	Hydroxylation conditions		Mp °C	Crystallization solvent	$\nu_{C=O}$, cm^{-1}	Empirical formula	Found, %		Calculated, %		Yield, %
	temp., °C	reaction time, min					C	H	C	H	
1-Methyl-4,5-diphenylimidazolone	370—400	180	292†	Ethanol	1688	$C_{16}H_{14}N_2O$	76,52	5,40	76,77	5,63	30
1-Methylbenzimidazolone	230—250	20	192‡	Ethanol	1712	$C_8H_8N_2O$	—	—	—	—	90
1-Methyl-5-methoxybenzimidazolone	230—250	20	290—291	Ethanol	1693	$C_9H_{10}N_2O_2$	60,37	5,41	60,66	5,65	85
1-Benzylbenzimidazolone	230—250	20	201—202**	Butanol	1695	$C_{14}H_{12}N_2O$	—	—	—	—	90
1-Benzyl-5,6-dimethylbenzimidazolone	250—270	20	239—240	Ethanol	1695	$C_{16}H_{16}N_2O$	75,99	6,30	76,16	6,40	85
1-Phenylbenzimidazolone	290—320	120	203—204	Ethanol	1710	$C_{13}H_{10}N_2O$	—	—	—	—	20
1-(p-Methoxyphenyl)benzimidazolone	230—250	30	320	Ethanol	1690	$C_{14}H_{12}N_2O_2$	69,94	4,68	69,98	5,03	70
3-Methylnaphth[1,2]imidazolone	250—280	30	293—294	Ethanol	1695	$C_{12}H_{10}N_2O$	72,69	5,23	72,71	5,08	90
1-Methylperimidone*	160—170	5	229—230	Acetic acid	1724	$C_{12}H_{10}N_2O$	—	—	—	—	90
1-Ethylperimidone	160—170	10	224—225	Acetic acid	1690	$C_{13}H_{12}N_2O$	73,37	5,55	73,56	5,70	87
1-Methoxymethylperimidone	200—230	30	305	Aqueous ethanol	1725	$C_{13}H_{12}N_2O_2$	68,60	5,95	68,40	5,74	82
1-Methylaceperimidone	170—180	10	269—270	Acetic acid	1689	$C_{14}H_{12}N_2O$	75,07	5,12	74,98	5,39	81

*This compound was described by us in [16].
†mp 289-290° [17].
‡mp 190-192° [9].
**mp 197-200° [18].

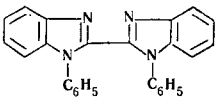
Any derivatives of imidazole systems which contain substituents that are inert with respect to alkali (alkyl, aralkyl, aryl, alkoxy, etc.) on the nitrogen atom or in the aromatic rings enter into the reaction. The hydroxylation process is readily observed from hydrogen evolution, which usually lasts for 10 to 30 min (sometimes longer). In contrast to imidazole derivatives, the hydroxylation of six-membered nitrogen heterocycles generally requires heating for many hours [1-5]. The temperature at which hydrogen is evolved is in qualitatively good agreement with the magnitude of the positive charge on the μ-carbon atom of the imidazole ring. Perimidines, for which the positive charge, as calculated by the Hückel MO method [10], is a maximum at the 2 position, are therefore hydroxlyated particularly readily, while uncondensed imidazoles are hydroxylated with difficulty. To the best of our knowledge, the hydroxylation of 1-methyl-4,5-diphenylimidazole is the only example of nucleophilic substitution of a hydrogen atom in the 2 position of uncondensed imidazoles.

Another factor which affects the hydroxylation (as in amination [11]) is the basicity of the compound, which ensures the necessary coordination of the metal atom with the nitrogen atom. Only this can explain the great difficulty (reaction time and temperature) involved in the hydroxylation of 1-phenylbenzimidazole (pK_a 4.32 [11]) and 1-methoxymethylperimidine (pK_a 4.96 [12]) as compared with their N-alkyl analogs (pK_a 5.5-5.9 [11, 12]). The action of alkali on the still less basic 1-methoxymethylbenzimidazole (pK_a 4.17) results in cleavage of a methoxymethyl group (compare this with the action of sodium amide on this compound [13]), as a result of which benzimidazole is formed and formaldehyde is evolved:



The dependence of the hydroxylation on the basicity indicates the importance of the first step in the reaction, viz., addition of the elements of KOH to the C=N bond of the imidazole ring with the formation of an adduct of the V type. On the other hand, the step involving aromatization of the adduct apparently has no effect on the course of the reaction. Thus perimidines are hydroxylated particularly readily (the combination of an extremely high basicity [12] with a high positive charge on the C_2 atom [10]), despite the difficulty involved in the aromatization of their 2,3-dihydro derivatives [15].

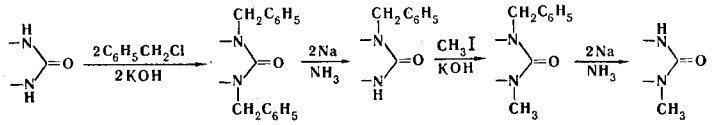
The hydroxylation of 1-phenylbenzimidazole, as in the amination of this compound [14], proceeds very peculiarly, and the yield of the 2-hydroxy derivative is low. The major process is apparently opening of the imidazole ring, which is accompanied by profound resinification. A side product (15%) was isolated from the reaction mixture, which, on the basis of the extremely simple IR spectrum (absence of absorption above 3100 cm^{-1} and minimum absorption from 1520 to 1700 cm^{-1}, which attests to the high degree of symmetry), the molecular weight, and elementary analysis, we assigned the 1-phenyl-2-(1'-phenyl-2'-benzimidazolyl)-benzimidazole structure (VI).



VI

Although the formation of this sort of product is an extremely characteristic side process for the Chichibabin reaction, it has not previously been noted during hydroxylation.

In view of the fact that the N-monosubstituted perimidones were previously unknown, we accomplished an alternative synthesis of 1-methylperimidone to prove the structures of the products of hydroxylation of perimidones via the following scheme (1-methylbenzimidazolone was similarly obtained):



The IR spectra* of crystalline samples of the perimidones and 1-methylaceperimidone obtained contain a strong absorption band at 1690-1730 cm^{-1} which is characteristic for the valence vibrations of the C=O group (see Table 1). Thus III and IV, like 2-imidazolones [7], exist primarily in the oxo form in the crystalline state.

*The IR spectra in mineral oil were obtained with a UR-20 spectrometer.

The success obtained in experiments on the hydroxylation of nitrogen-containing heterocycles compelled us to undertake the direct alkoxylation of N-substituted imidazoles with sodium alkoxides. However, only decomposition of sodium methoxide was observed during the reaction of dry sodium methoxide at 200-300° with 1-ethylbenzimidazole and 1-methylperimidine, and the starting compounds were recovered unchanged from the reaction mixtures.

EXPERIMENTAL

General Hydroxylation Method. The appropriate imidazole (0.01 mole) was melted in a Kjeldahl flask with 0.05 mole of anhydrous powdered potassium hydroxide (or sodium hydroxide) at a temperature which ensured uniform hydrogen evolution. When hydrogen evolution ceased, the mixture was cooled and treated with 5% hydrochloric acid unitl it gave an acid reaction to Congo red. The precipitate was filtered, washed with water, and recrystallized (in the case of N-alkyl and N-benzyl derivatives of benzimidazole and naphthimidazole, the crude products were already sufficiently pure for synthetic purposes).

Hydroxylation of 1-Phenylbenzimidazole. A mixture of 1 g (0.005 mole) of 1-phenylbenzimidazole and 1.4 g (0.025 mole) of anhydrous powdered KOH was heated at 270-320° for 1.5-2 h until hydrogen evolution ceased. The liquid mass solidified at the end of the heating period. The melt was treated with water after cooling. The resulting solution was filtered, and 0.21 g (20%) of 1-phenyl-2-benzimidazolone with mp 203-204° (in agreement with the melting point reported in [14]) was isolated from the filtrate with hydrochloric acid.

The alkali-insoluble residue was treated with chloroform, and the chloroform solution was passed through a column filled with aluminum oxide. The first fraction yielded 0.15 g (15%) of VI in the form of light-yellow needles with mp 189° (from alcohol). Found %: C 80.62; H 4.63; mol. wt. (Rast method) 345. $C_{26}H_{18}N_4$. Calc. %: C 80.78; H 4.70; mol. wt. 386.5.

Hydroxylation of 1-Methoxymethylbenzimidazole. 1-Methoxymethylbenzimidazole [1.6 g (0.01 mole)] was fused with 2.8 g (0.05 mole) of anhydrous powdered KOH at 270-300°. The reaction mixture was held at this temperature until the evolution of gaseous products had ceased. The mixture was cooled, and the melt was treated with 5% HCl until it gave an acid reaction to Congo red. The mixture was filtered, and the filtrate was treated with ammonia to give 0.9 g (80%) of benzimidazole with mp 174° (from water). The structure of the product was proved by elementary analysis, the identity of the IR spectral characteristics with those of an authentic sample, and a mixed-melting-point determination.

Alternative Synthesis of 1-Methylperimidone

A) 1,3-Dibenzylperimidone. A mixture of 1.8 g (0.01 mole) of perimidone, 7.5 g (0.06 mole) of benzyl chloride, and 4.2 g (0.06 mole) of KOH in 50 ml of alcohol was refluxed under nitrogen for 3 h. The mixture was filtered, and the solvent was removed from the filtrate by distillation. The residue was treated with ether and filtered to give 2.9 g (80%) of colorless crystals with mp 190-191° (from alcohol). Found %: C 82.26; H 5.79; N 7.97. $C_{25}H_{20}N_2O$. Calc. %: C 82.39; H 5.53; N 7.68.

B) 1-Benzylperimidone. Sodium metal [0.23 g (0.01 g-atom)] was added in lumps to a suspension of 1.8 g (0.005 mole) of 1,3-dibenzylperimidone in 50 ml of liquid ammonia. The reaction mixture was stirred for 1 h at −70 to −80°, and the ammonia was evaporated in a stream of nitrogen or ammonia. After the ammonia had evaporated, 30 ml of water was added, and the grey precipitate, which is a mixture of the starting compound, perimidone, and 1-benzylperimidone, was filtered. The precipitate was treated with chloroform and passed through a column filled with aluminum oxide to give 0.9 g (65%) of 1-benzylperimidone in the form of colorless plates with mp 270-271° (from alcohol). Found %: C 78.56; H 5.02; N 10.36. $C_{18}H_{14}N_2O$. Calc. %: C 78.82; H 5.14; N 10.21.

C) 1-Methyl-3-benzylperimidone. Potassium hydroxide [0.75 g (0.01 mole)] was added to a solution of 1.3 g (0.005 mole) of 1-benzylperimidone in 30 ml of alcohol, and 0.6 ml (0.01 mole) of methyl iodide was added. The mixture was refluxed for 3 h, cooled, the potassium iodide was filtered, and the solvent was removed from the filtrate by distillation. The residue was treated with water and filtered to give 1.1 g (80%) of colorless crystals with mp 185-186° (from alcohol). Found %: C 78.97; H 5.14; N 9.62. $C_{19}H_{14}N_2O$. Calc. %: C 79.14; H 5.9; N 9.71.

D) 1-Methylperimidone. This was obtained in the same way as 1-benzylperimidone from 1.4 g (0.005 mole) of 1-methyl-3-benzylperimidone and 0.23 g (0.01 g-atom) of sodium in 50 ml of liquid ammonia. A

total of 0.7 g (80%) of crude product was isolated, which, after recrystallization from acetic acid, was obtained as colorless prisms with mp 229-230°. This product did not depress the melting point of the hydroxylation product.

We also obtained 1-methylbenzimidazolone via a similar scheme. Of all of the intermediates, only 1-methyl-3-benzylbenzimidazolone with mp 89-90° (from aqueous alcohol) has not yet been reported. Found %: C 75.39; H 5.67. $C_{15}H_{14}N_2O$. Calc. %: C 75.60; H 5.92.

Attempted Ethoxylation of 1-Ethylbenzimidazole and 1-Methylperimidine. A mixture of 4.6 g (0.03 mole) of 1-ethylbenzimidazole and sodium ethoxide [obtained from 3 g (0.11 g-atom) of sodium via the method described in [19] was heated at 200-300° until the evolution of gaseous products (ethylene and hydrogen as a result of decomposition of sodium ethoxide) ceased. The mixture was cooled, and treated with water; chloroform extraction yielded 3.7 g (81%) of unchanged starting compound. No traces whatsoever of 2-ethoxy derivative were detected in the chloroform solution or in the aqueous solution.

1-Methylperimidone (7%) was isolated along with the starting compound (80%) by the action of sodium ethoxide on 1-methylperimidine under nitrogen (200-300°, 1 h). The formation of 1-methylperimidone is probably a result of hydroxylation of 1-methylperimidine by sodium hydroxide, which could form in small amounts by thermal decomposition of sodium ethoxide or as a result of partial hydrolysis during all of the operations for the preparation of sodium ethoxide.

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