NITRATION OF 5(6)-HYDROXYBENZIMIDAZOLE AND ITS DERIVATIVES

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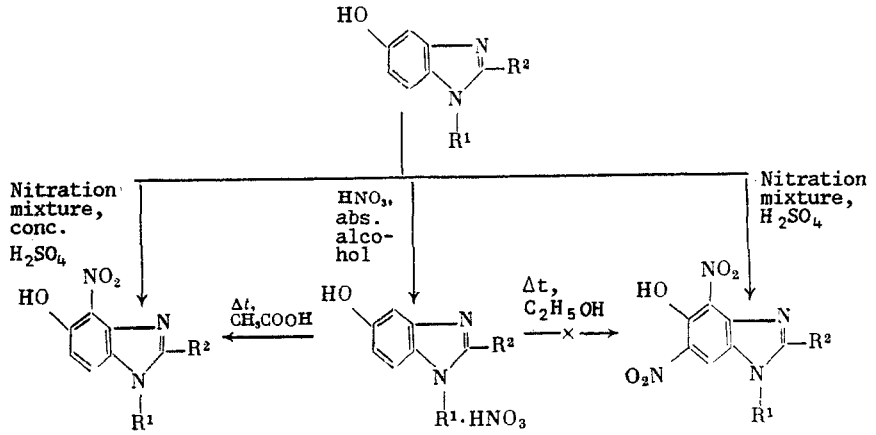
Nitration of 5(6)-hydroxybenzimidazole and its derivatives takes place with the formation of mono- and dinitro-derivatives; in the latter case, the primary substitution is, as a rule, in position 4.

In a continuation of our study of the reactivity of 5(6)-hydroxybenzimidazole (I) and its derivatives towards electrophilic substituents [1, 2] we turned to one of the most studied substitution reactions in aromatic systems — nitration — the orientation of which is determined by the peculiarities of the electronic structure of the benzimidazole ring.

Nitration of benzimidazole derivatives [3], benzimidazolone, and 1,3-dimethylbenzimidazolone [4] takes place quite readily with the successive formation of 5-nitro- and 5,6-dinitro-derivatives, thereby confirming the high reactivity of the 5- and 6-positions calculated by allowing for electronic effects within the framework of the LCAO–MO perturbation theory [5]. In the case where electron-donor substituents are present at position 5, an uncoordinated orientation effect is observed: whereas these substituents activate position 4 to a great extent, the imino group of the heterocycle directs a substituent to position 6. By virtue of the factors mentioned, the substituting group can enter into both reactive positions 4 and 6, and the primary orientation of the substituent is determined by the magnitude and nature of the electron-donor effect of the substituent at position 5. Thus, it has been shown that nitration of 5-chloro-, 5-methyl, and 5-ethoxybenzimidazole is accompanied by the formation of 4,6-dinitro derivatives, the first nitro group entering into position 6 [6]. On the other hand, as we have established [2], halogenation of 2-methyl(I) (II) and 1-ethyl-2-methyl(I) (III) generally involves the 4 position first and only then position 6, i.e., the hydroxy group proves to exert a stronger effect than the imino group of the imidazole ring. Bearing in mind the results which provide evidence that the nitration of (I) and its derivatives might proceed ambiguously, we used in this study different reactants and reaction conditions with allowance for the fact that diluted HNO_3 can facilitate oxidation while the use of nitrating mixture entails the possibility of sulfonation of (I)-(III).

In the first place, we examined the possibility of using a nitration mixture in conc. H_2SO_4. Although this is traditionally used for the nitration of aromatic compounds, in the present case it carried the risk of a secondary sulfonation reaction. However, by carrying out the reaction with cooling it was possible not only to prevent undesirable side reactions but also to make use of a property of H_2SO_4 — the suppression of oxidative secondary reactions [7]



$R^1 = R^2 = H$; $R^1 = H$ and $R^2 = CH_3$; $R^1 = C_2H_5$ and $R^2 = CH_3$

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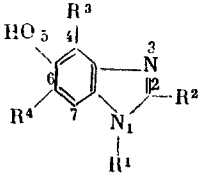
TABLE 1. Products of Nitration of Derivatives of 5(6)-Hydroxybenzimidazole



R^1	R^2	R^3	R^4	Method	Yield, %	Mp, °C	Found / Calculated, % C	Found / Calculated, % H	Empirical formula	Solvent	δ, ppm: 2—CH_3	δ, ppm: 1—CH_2—CH_3	δ, ppm: H^6	δ, ppm: H^7	δ, ppm: H^2	$J_{H^6H^7}$, Hz
H	H	NO_2	H	a b	92,3 94,6	222–224(decomp.) hydrochloride 236–238(decomp.)[9]	47,32 46,93	3,13 2,82	$C_7H_5N_3O_3$	D_2O	–	–	7,84 d (1H)	8,31 d (1H)	8,82 s (1H)	9,2
H	H	NO_2	NO_2	–	89,3	>285 (decomp.)	37,35 37,52	2,17 1,79	$C_7H_4N_4O_5$	$(CD_3)_2SO$	–	–	–	8,90 s (1H)	9,02 s (1H)	–
H	Me	NO_2	H	a b	40,7 41,5	254–256(decomp.) hydrochloride >230 (decomp.)	49,42 49,76	3,82 3,63	$C_8H_7N_3O_3$	D_2O	2,85 s(3H)	–	7,22 d (1H)	7,89 d (1H)	–	9,0
H	Me	NO_2	NO_2	–	67,3	>300 (decomp.)	39,59 40,35	2,76 2,52	$C_8H_6N_4O_5$	CF_3COOH	2,75 s(3H)	–	–	8,50 s (1H)	–	–
Et	Me	NO_2	H	a b	63,3 78,8	183–185 hydrochloride >200 (decomp.)	54,55 54,32	4,83 4,98	$C_{10}H_{11}N_3O_3$	D_2O	2,79 s(3H)	1,47 t (3H) 4,29 q (2H)	6,79 d (1H)	7,33 d (1H)	–	9,0
Et	Me	NO_2	NO_2	–	80,1	254–256	44,87 45,13	3,82 3,76	$C_{10}H_{10}N_4O_5$	$(CD_3)_2SO$	2,68 s(3H)	1,30 t (3H) 4,30 q (2H)	–	8,50 s (1H)	–	–

Thus, both mono- and dinitro derivatives of (I)-(III) are obtained in quite high yield, with the observation that the hydrochlorides form only mononitro derivatives of (I)-(III). No trinitro derivatives were obtained.

The action of an excess of nitric acid on (I)-(III) in absolute alcohol yielded addition products, the so-called nitrates of the starting materials, which on heating in CH_3COOH were converted into the ring-substituted mononitro derivatives of (I)-(III). It was noted here that this method of preparing 4-nitro derivatives from the corresponding nitrates made it possible to obtain the mononitro derivative exclusively, and only in the case of (III) were traces of disubstituted product observed, in addition to the 4-nitro-(III); this provides some confirmation of an increase in the reactivity of positions 4 and 6 on N-alkylation of the benzimidazole ring. The dinitro derivative could be removed by conversion of the mixed product into the hydrochlorides and recrystallization of the mononitro derivative of (III) from absolute alcohol. In addition, it was noted that prolonged boiling of the nitrates of (I)-(III) in alcohol did not lead to ring-substitution although this proceeded readily in acetic acid.

It was also established that nitration of (I)-(III) by potassium nitrate in sulfuric acid did not lead to the selective formation of 4-mono- or 4-6-dinitro derivatives but only to their mixture with the starting material.

From the overall results obtained for the nitration of 5(6)-hydroxybenzimidazole and its derivatives one can conclude that the two positions ortho to the hydroxy group (4 and 6) are nonequivalent and substituents are preferentially directed to position 4. In contrast to 5-alkyl, 5-halo, and 5-alkoxy derivatives of benzimidazole, introduction of a hydroxy group into position 5 leads to a change in the orientation of the substitution, and the substituting group (nitro, halo, etc.) is preferentially directed to position 4 (and not 6 [6]), which corresponds to the peculiarities of the electronic structure of benzimidazole which determine its asymmetry and the increase in double bond character between the carbon atoms in positions 4-5 and 6-7. The preferred orientation of substituents into position 4 in 3-hydroxyquinoline is explained by similar reasoning [8].

Thus, the structure of the heterocycle stipulates its chemical behavior in aromatic substitution reactions. The structure of the compounds prepared was confirmed by their NMR spectra: in the monosubstituted derivatives of (I)-(III) signals of the H^4 proton were absent, and signals from H^6 and H^7 were doublets with spin–spin coupling constants $J_{6,7}$ = 9.0-9.2 Hz. Introduction of a second substituent into the benzene ring led to the disappearance of the H^6 signal and the H^7 signal became a singlet. The signals of the OH- and NH-protons were not recorded (see Table 1).

EXPERIMENTAL

NMR spectra were obtained on a Varian T-60 in D_2O, $(CD_3)_2SO$, or CF_3COOH with t-BuOH as internal standard. Chemical shifts were recalculated from TMS (δ 1.27 ppm).

Monotitration of (I)-(III). a) In 10 ml conc. H_2SO_4 was dissolved, with stirring, 0.005 mole (I) or its derivative, and a nitrating mixture made from 0.36 ml (0.0055 mole) 68% HNO_3 and 0.4 ml conc. H_2SO_4 was cautiously added dropwise. After stirring for 0.5-1.5 h the 4-nitro derivative of (I)-(III) was isolated by pouring the ice-water or by neutralizing with aqueous ammonia and the product recrystallized from aqueous alcohol.

b) In 30 ml abs. alcohol was dissolved, with stirring, 0.005 mole (I) or its derivative, and 0.66 ml (0.01 mole) 68% HNO_3 added dropwise and the mixture stirred for a further 10-30 min. The precipitated nitrate of (I)-(III) was separated, washed with acetone and dried in air. A solution of the precipitate in a minimum amount of AcOH was stirred 10-30 min at 70-75°C. The precipitate of the nitro derivative of (I)-(III) which was deposited on cooling was separated, dried in air, and recrystallized from aqueous alcohol.

The hydrochlorides of the 4-nitro derivatives of (I)-(III) were prepared by treating the base with an alcoholic solution of HCl and subsequent recrystallization from abs. alcohol.

Dinitration of (I)-(III). In 10 ml conc. H_2SO_4 was dissolved, with stirring, 0.005 mole (I) or its derivative, and a nitrating mixture made from 0.99 ml (0.015 mole) 68% HNO_3 and 1.5 ml conc. H_2SO_4 cautiously added dropwise. At the end of the stirring period (1.0-3.0 h) the 4,6-dinitro derivative of (I)-(III) was isolated by pouring into ice-water or by neutralizing with aqueous ammonia followed by recrystallization from aqueous alcohol.

The method for the preparation of the starting materials is given in [10]. Physicochemical properties of the products are given in Table 1.

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