RESEARCH IN THE IMIDAZOLE SERIES

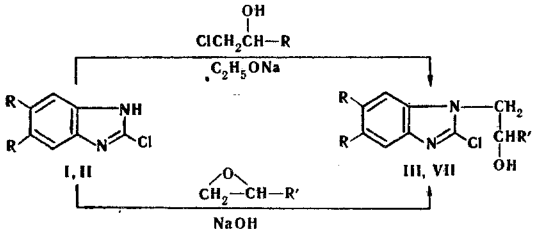
LXXX.* REACTION OF 2-CHLOROBENZIMIDAZOLES WITH OLEFIN OXIDES AND β-HALO ALCOHOLS

V. S. Ponomar', P. M. Kochergin,
O. S. Anisimova, Yu. N. Sheinker,
B. A. Priimenko, and M. V. Povstyanoi

UDC 547.785.5:543.51

It was established on the basis of an investigation of the mass spectra that in the reaction of 2-chlorobenzimidazoles with unsymmetrical olefin oxides and secondary β-halo alcohols, of the two possible isomers only 1-[β-alkyl(aryl)-β-hydroxyethyl] derivatives of benzimidazole are formed.

In a continuation of our research on the synthesis of 2,3-dihydro derivatives of imidazo[1,2-*a*]benzimidazole [2] and thiazolo [3,2-*a*]benzimidazole [3], which seem of interest for biological testing, we made a detailed study of the reaction of 2-chlorobenzimidazole (I) and its 5,6-dimethyl derivative (II) with olefin oxides and β-halo alcohols. In both cases the reactions proceed readily in the cold or on heating in lower alcohols in the presence of an equimolar amount of sodium alkoxide (when β-halo alcohols are used) or a catalytic amount of alkali (when olefin oxides are used) to give III-VII (Table 1). Depending on the site of cleavage of the epoxide ring, the reaction of benzimidazole derivatives I and II with unsymmetrical olefin oxides may give two isomers – α-alkyl(aryl)- (structure A) and β-alkyl(aryl)-substituted (structure B) 1-β hydroxyethyl-2-chlorobenzimidazoles. In all cases we isolated only one isomer, for which we proposed structure B on the basis of research by Krasuskii [4] and an analysis of the mass spectra of III and IV and their deutero analogs. The intense molecular ion peaks in the spectra of both compounds – 210/212 (III) and 272/274 (IV) – correspond to the proposed structures A and B. The most favorable process for the fragmentation of the molecular ions for these structures should be cleavage of the $C=C$ bond in the α position relative to the OH group. Fragmentation of this sort will give stable fragments a and a' (structure A) and b and b' (structure B).

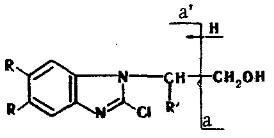


$R=H, CH_3$; $R'=CH_3, C_6H_5, C_6H_4NO_2\text{-}p$

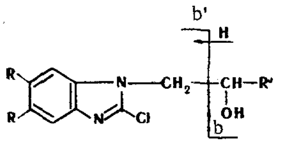
---

*See [1] for communication LXXIX.

Zaporozhe Medical Institute. S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1284-1286, September, 1975. Original article submitted December 17, 1976.

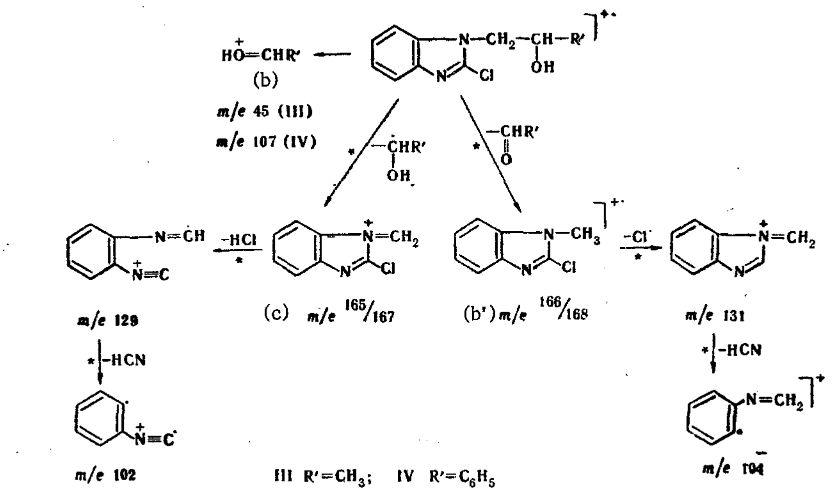


A



B

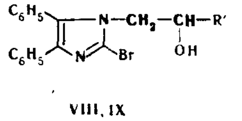
The spectra of III and IV contain intense peaks with m/e 166/168, 165/167, 45 (III), and 107 (IV), the formation of which may be explained only proceeding from the existence of the substance in the 1-[β-alkyl(aryl)-β-hydroxyethyl]-2-chlorobenzimidazole form.



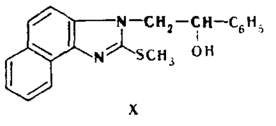
III R'=CH₃; IV R'=C₆H₅

The correctness of the proposed scheme is confirmed by data on the fragmentation of deutero-substituted III and IV. As one should have expected, an increase of one unit in the mass numbers of ions b and b' is observed in the spectra of III-D and IV-D, inasmuch as the compositions of these fragments include the hydrogen atom of the hydroxyl group. The mass number of ion c obtained during elimination of $\dot{C}H(OH)R'$ from the molecular ion remains unchanged. At the same time, the $\overset{+}{C}H_2OH$ and $[M-CH_2O]^{+\cdot}$ fragments expected in the case of fragmentation of molecular ion A are not observed in the spectrum.

According to the mass spectral data, unsymmetrical olefin oxides react similarly with 4,5-diphenylimidazole and naphthimidazole derivatives (VIII-X), the synthesis of which was described in [5, 6].



VIII, IX



X

VIII R'=CH₃; IX R'=C₆H₅

TABLE 1. 1-β-Hydroxyalkyl(aralkyl)-2-chlorobenzimidazoles (III-VII)

Compound	R	R'	mp, °C	Empirical formula	Found, %				Calc., %				ν_{OH}, cm⁻¹	Yield, %
					C	H	Cl	N	C	H	Cl	N		
III	H	CH_3	127—129	$C_{10}H_{11}ClN_2O$	56,7	5,0	16,8	13,3	57,0	5,3	16,8	13,3	3250	44
IV	H	C_6H_5	147—149	$C_{15}H_{18}ClN_2O$	66,4	4,7	13,1	10,5	66,1	4,8	13,0	10,3	3160	62—73
V	H	$C_6H_4NO_2$-*p*	187—189	$C_{15}H_{12}ClN_3O_3$	56,7	3,8	10,9	13,2	56,7	3,8	11,2	13,2	3160	68—69
VI	CH_3	CH_3	149—151	$C_{12}H_{15}ClN_2O$	60,1	6,3	15,0	11,7	60,4	6,3	14,9	11,7	3300	58
VII	CH_3	$C_6H_4NO_2$-*p*	198—200	$C_{17}H_{16}ClN_3O_3$	58,9	4,6	10,1	12,2	59,0	4,7	10,3	12,2	3250	92—93

The presence of peaks of $[M-HCOR']^{+\cdot}$ fragments and the absence of $[M-CH_2O]^{+\cdot}$ and $[M-\dot{C}H_2OH]^{+\cdot}$ ions are characteristic for the spectra of these compounds, and this indicates the existence of VIII-X also exclusively in the B form.

Thus the reaction of unsymmetrical olefin oxides with all of the investigated imidazole derivatives proceeds only via a pathway giving β-alkyl(aryl)-β-hydroxyethyl derivatives.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The mass spectra were recorded with an MKh-1303 spectrometer at an ionizing-electron energy of 50 eV. The compounds were chromatographed on standard Silufol UV-254 plates in chloroform–methanol (95 : 5). The spots were developed in UV light or with iodine vapors in a moist chamber.

1-β-Hydroxyalkyl(aralkyl)-2-chlorobenzimidazoles (III-VII, Table 1). A) A 0.02-0.03-g sample of NaOH and 0.06 mole of propylene oxide, 0.02 mole of styrene oxide, or 0.015 mole of p-nitrostyrene oxide were added to a solution of 0.015 mole of 2-chlorobenzimidazole I [7] or II [8] in 25-35 ml of ethanol, after which the mixture was refluxed for 4-5 h, cooled, and diluted with water. The resulting precipitate was removed by filtration and washed with water.

B) A 0.05-mole sample of I or II and 0.075 mole of styrene chlorohydrin or 0.05 mole of p-nitrostyrene chlorohydrin were added successively to a solution of 0.05 mole of sodium ethoxide in 75-100 ml of absolute ethanol, after which the mixture was refluxed for 4-6 h (until it was neutral or weakly acidic). It was then cooled and diluted with water, and the resulting precipitate was removed by filtration and washed with water. No melting-point depressions were observed for mixtures of alcohols IV, V, and VII with the corresponding samples obtained by method A. The individuality of the compounds was established by chromatography (R_f values): III 0.33, IV 0.48, and V 0.38. Compounds III-VII were colorless or pale-yellow (V, VII) crystalline substances of basic character and were purified for analysis by crystallization from aqueous acetone (III, IV, and VI) and methanol (V, VII). Absorption bands of an OH group at 3160-3310 cm^{-1} were observed in the IR spectra of III-VI.

LITERATURE CITED

1. M. I. Yurchenko, P. M. Kochergin, and A. N. Krasovskii, Khim. Geterotsikl. Soedin., 693 (1974).
2. P. M. Kochergin, M. V. Povstyanoi, B. A. Priimenko, and V. S. Ponomar', Khim. Geterotsikl. Soedin., 129 (1970).
3. P. M. Kochergin, A. N. Krasovskii, and A. B. Roman, USSR Author's Certificate No. 355174; Byul. Izobr., No. 31 (1972).
4. K. A. Krasuskii, Zh. Russk. Fiz.-Khim. Obshchestva, 39, 460, 1469 (1907).
5. B. A. Priimenko and P. M. Kochergin, Khim. Geterotsikl. Soedin., 1248 (1971).
6. M. V. Povstyanoi and P. M. Kochergin, Khim. Geterotsikl. Soedin., 816 (1972).
7. D. Harrison, J. T. Ralph, and A. C. Smith, J. Chem. Soc., 2930 (1963).
8. N. P. Bednyagina, G. N. Tyurenkova, and I. V. Panov, Zh. Obshch. Khim., 34, 1575 (1964).