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# INVESTIGATIONS OF UNSATURATED AZOLES. 14*. REACTION OF BENZIMIDAZOLE AND ITS DERIVATIVES WITH p-NITROSTYRENE OXIDE. QUATERNARY AMMONIUM BASES

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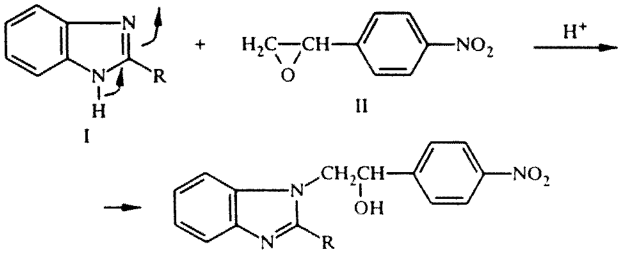
*The reactions of benzimidazole and its 2- and 1-alkyl, 2-mercapto, and 2-amino derivatives with p-nitrostyrene oxide have been studied.*

Styrene oxide reacts with benzimidazole at 110-120°C in DMF in the presence of strong bases to form 1-(2-hydroxyethyl-2-phenyl)benzimidazole, which is a starting material for the synthesis of 1-styrylbenzimidazole [2, 3]. The reaction of benzimidazole with p-nitrostyrene oxide has not been studied.

We have shown that benzimidazole (Ia) and the 2-hydroxy-alkylbenzimidazoles (Id, e) react with p-nitrostyrene oxide (II) when refluxed in alcohol with a catalytic amount of acid to form the carbinols IIIa, d, e in good yield. By contrast, the 2-alkylbenzimidazoles Ib, c do not react with oxirane II under these conditions. Carbinols IIIb, c could be prepared in moderate yield only upon prolonged refluxing of Ib, c with II in DMF solution.



III

I, III a R = H; b R = Me; c R = Et, d R = CH$_2$OH; e R = CH(OH)Me

The basicity constants of Ib, c and Id, e differ little (p$K_a$ in water 6.2, 6.2, 6.28, and 6.25 respectively [4]). Hence the ease of hydroxyalkylation of Id, e by oxirane II is evidently due to the influence of the hydroxyalkyl group via the seven-membered transition state A during the nucleophilic attack of the heterocyclic tertiary nitrogen atom on the oxirane ring (see [1].)

Conversion of IIIa-e to the p-nitrostyrylbenzimidazoles via dehydration using KOH was unsuccessful (as in the case of [3]) due to tarring of the reaction mixture.

Benzimidazole (Va) and its monoalkylated derivatives Vb-d do not react when fused with oxirane II in neutral medium and they undergo tarring when heated with mineral acid or strong base catalyst in the reaction mixture. Treatment of the benzimidazole-2-thiones VIa-d with oxirane II leads to desulfuration and gives the benzimidazol-2-ones Va-d through a process similar to that when thiourea is treated with ethylene oxide [5]. This reaction is an interesting route from the available benzimidazole-2-thiones [6] to the corresponding benzimidazol-2-ones.

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*For communication 13, see [1].

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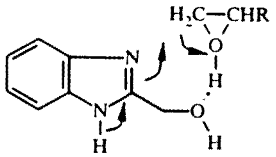
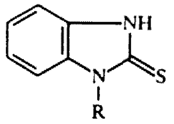
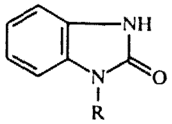


A

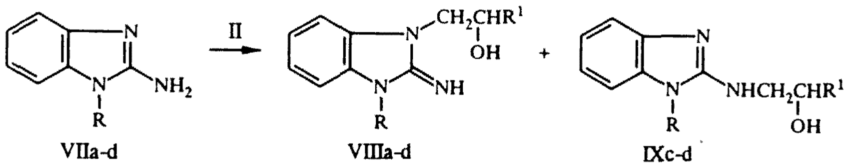


VIa-d

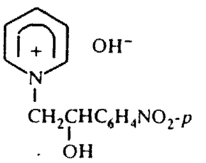


Va-d

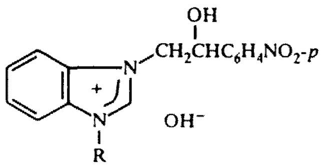
A similar reaction of 2-aminobenzimidazole VIIa with p-nitrostyrene oxide in the presence of methyl chloroformate [7] gives a high yield of 1,3-dihydroxyalkyl-2-iminobenzimidazoline VIIIa; with oxirane II, 1-methyl-2-aminobenzimidazole (VIIb) gives the imino derivative VIIIb. Moreover, treatment of amines VIIc, d with II gives the 2-iminobenzimidazolines VIIIc, d together with the 1-alkyl-2-hydroxyalkylamino derivatives IXc, d through reaction at the amino group (see [7]).



The known reaction of pyridine with ethylene oxide and HI gives $\beta$-hydroxyethylpyridinium iodide [8]. We have found that pyridine reacts with oxirane II with brief heating in alcohol plus a catalytic amount of pyridine hydrochloride to give the carbinol hydroxide X (after treatment of the reaction mixture with water and ammonium hydroxide). Analogously to the pyridine, the 1-alkylbenzimidazoles XIa-f react with II to form XIIa-f in moderate yield.



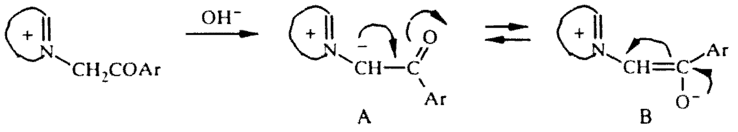
X



XIIa-f

Under these reaction conditions, it might have been expected that XIIa-f would further react to give a 2-hydroxybenzimidazolium pseudo base or o-phenylenediamines resulting from imidazole ring opening. However, the PMR spectrum of XIIa shows a signal at 10 ppm, typical of the 2-H proton in 1,3-dialkylbenzimidazolium cations, and the IR spectrum the absence of an amide C═O group absorption, thus excluding alternative structures.

In examples of 1-alkyl-3-phenacylbenzimidazolium bromides containing a nitro group, the transition from a phenacyl salt to compounds with an ylid (A) or ylene (enolbetaine) (B) structure [9] has been demonstrated previously.



Such a change from phenacyl bromide to anhydro base is usually accompanied by a yellow coloration, typical of the ylid.

However, treatment with potassium carbonate solution of the phenacyl bromides XIII (prepared by quaternization of the 1-alkylbenzimidazoles XIa-j with phenacyl or p-bromophenacyl bromides) gives pale colored crystals. The compounds do not contain ionic halogen and show parameters which differ from the starting materials (see Table 1). The position of the carbonyl group absorption at 1710 $cm^{-1}$ in the IR spectra does not change when going from the phenacyl salt XIII to compound XIV, hence confirming the structure of the phenacyl cations in the compounds described.

TABLE 1. Parameters for Compounds Synthesized

| Compound | R | R$^1$ | mp, °C* | Found, % |  |  |  | Empirical formula | Calculated, % |  |  |  | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  | C | H | Br | N |  | C | H | Br | N |  |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| IIIa | H |  | 196...199 | 63,6 | 4,5 |  | 14,6 | $C_{15}H_{13}N_3O_3$ | 63,6 | 4,6 |  | 14,8 | 67 |
| IIIb | $CH_3$ |  | 220...221 | 64,2 | 5,4 |  | 14,1 | $C_{16}H_{15}N_3O_3$ | 64,6 | 5,1 |  | 14,2 | 17 |
| IIIc | $C_2H_5$ |  | 192...193 | 65,3 | 5,2 |  | 13,1 | $C_{17}H_{17}N_3O_3$ | 65,7 | 5,5 |  | 13,5 | 12 |
| IIId | $CH_2OH$ |  | 182...183 | 60,9 | 4,9 |  | 13,8 | $C_{16}H_{15}N_3O_4$ | 61,3 | 4,8 |  | 13,4 | 42 |
| IIIe | $CH(OH)CH_3$ |  | 209 | 62,8 | 5,2 |  | 13,1 | $C_{17}H_{17}N_3O_4$ | 62,4 | 5,8 |  | 12,8 | 49 |
| VIIIa | $CH_2CH(OH)C_6H_4NO_2$ | $C_6H_4NO_2$-*p* | 221 | 59,2 | 4,2 |  | 15,5 | $C_{23}H_{21}N_5O_6$ | 59,6 | 4,6 |  | 15,1 | 63 |
| VIIIb | $CH_3$ | $C_6H_4NO_2$-*p* | 193...194 | 61,2 | 5,0 |  | 17,6 | $C_{16}H_{16}N_4O_3$ | 61,5 | 5,2 |  | 17,9 | 63 |
| VIIIc | $C_2H_5$ | $C_6H_4NO_2$-*p* | 177...178 | 62,3 | 5,4 |  | 17,5 | $C_{17}H_{18}N_4O_3$ | 62,6 | 5,5 |  | 17,2 | 65 |
| VIIId | $CH_2C_6H_5$ | $C_6H_4NO_2$-*p* | 169 | 67,7 | 5,0 |  | 14,8 | $C_{22}H_{20}N_4O_3$ | 68,0 | 5,2 |  | 14,4 | 23 |
| IXc | $C_2H_5$ | $C_6H_4NO_2$-*p* | 250 | 62,2 | 5,3 |  | 17,6 | $C_{17}H_{18}N_4O_3$ | 62,6 | 5,5 |  | 17,2 | 23 |
| IXd, | $CH_2C_6H_5$ | $C_6H_4NO_2$-*p* | 250 | 67,6 | 5,1 |  | 14,6 | $C_{22}H_{20}N_4O_3$ | 69,0 | 5,2 |  | 14,4 | 67 |
| X, |  |  | 250 | 60,0 | 5,0 |  | 10,6 | $C_{13}H_{12}N_2O_4$ | 59,8 | 13,1 |  | 10,7 | 86 |
| XIIa | $CH_3$ |  | 183 | 61,0 | 5,6 |  | 13,5 | $C_{16}H_{17}N_3O_4$ | 60,9 | 5,4 |  | 13,3 | 14 |
| XIIb | $C_2H_5$ |  | 215 | 62,0 | 5,8 |  | 13,0 | $C_{17}H_{19}N_3O_4$ | 62,0 | 5,8 |  | 12,7 | 22 |
| XIIc | $CH_2C_6H_5$ |  | 239 | 67,8 | 5,6 |  | 10,5 | $C_{22}H_{21}N_3O_4$ | 67,5 | 5,4 |  | 10,7 | 27 |
| XIId | $CH_2CH{=}CH_2$ |  | 139 | 63,5 | 5,3 |  | 12,5 | $C_{18}H_{19}N_3O_4$ | 63,3 | 5,6 |  | 12,3 | 22 |
| XIIe | $CH_2OH$ |  | 272 | 64,0 | 5,4 |  | 14,2 | $C_{16}H_{17}N_3O_5$ | 64,3 | 5,7 |  |  | 16 |
| XIIf | $CH_2CH_2N(C_2H_5)_2$ |  | 275 | 63,0 | 7,2 |  | 14,3 | $C_{21}H_{28}N_4O_4$ | 63,1 | 7,0 |  | 14,0 | 26 |

TABLE 1. (Continued)

| Compound | R | R$^1$ | mp, °C* | Found, % |  |  |  | Empirical formula | Calculated, % |  |  |  | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  | C | H | Br | N |  | C | H | Br | N |  |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| XIIIa | $C_2H_5$ | H | 112...113 | 59,3 | 4,8 | 23,5 | 8,4 | $C_{17}H_{17}BrN_2O$ | 59,1 | 4,9 | 23,1 | 8,1 | 83 |
| XIIIb | $C_2H_5$ | Br | 198 | 48,4 | 3,5 | 37,8 | 6,9 | $C_{17}H_{16}Br_2N_2O$ | 48,1 | 3,8 | 37,7 | 6,6 | 97 |
| XIIIc | $CH_2OH$ | H | 183 | 55,1 | 4,4 | 23,3 | 8,3 | $C_{16}H_{15}BrN_2O_2$ | 55,3 | 4,3 | 23,1 | 8,1 | 68 |
| XIIId | $CH_2OH$ | Br | 239 | 45,3 | 3,2 | 37,8 | 6,9 | $C_{16}H_{14}Br_2N_2O_2$ | 45,1 | 3,3 | 37,6 | 6,6 | 51 |
| XIIIe | $CH_2COC_6H_5$ | H | 178 | 63,6 | 4,4 | 17,8 | 6,3 | $C_{23}H_{19}BrN_2O_2$ | 63,4 | 4,4 | 18,4 | 6,4 | 59 |
| XIIIf | $CH_2C_6H_5$ | Br | 125...126 | 54,0 | 3,6 | 33,1 | 5,6 | $C_{22}H_{18}Br_2N_2O$ | 54,3 | 3,7 | 32,9 | 5,8 | 93 |
| XIIIg | $CH_2CH-CH_2$ | H | 106 | 60,2 | 4,7 | 22,2 | 8,2 | $C_{18}H_{17}BrN_2O$ | 60,5 | 4,8 | 22,4 | 7,8 | 76 |
| XIIIh | $CH_2CH-CH_2$ | Br | 215 | 47,1 | 3,2 | 39,6 | 6,3 | $C_{18}H_{16}Br_2N_2O$ | 47,4 | 3,5 | 39,5 | 6,1 | 81 |
| XIIIi | $CH_2CBr-CH_2$ | H | 164 | 47,2 | 3,5 | 39,6 | 6,3 | $C_{18}H_{16}Br_2N_2O$ | 47,7 | 3,5 | 39,5 | 6,1 | 96 |
| XIIIj | $CH_2CBr-CH_2$ | Br | 142 | 41,9 | 3,0 | 46,2 | 5,7 | $C_{18}H_{15}Br_3N_2O$ | 41,9 | 2,9 | 46,6 | 5,4 | 92 |
| XIVa | $C_2H_5$ | H | 113 | 71,9 | 6,9 |  | 10,3 | $C_{17}H_{18}N_2O_2$ | 72,3 | 6,4 |  | 9,9 | 85 |
| XIVb | $C_2H_5$ | Br | 95 | 56,3 | 4,0 | 22,6 | 7,4 | $C_{17}H_{16}BrN_2O_2$ | 56,7 | 4,4 | 22,2 | 7,7 | 89 |
| XIVc | $CH_2OH$ | H | 123 | 72,0 | 6,1 |  | 10,7 | $C_{16}H_{16}N_2O_3$ | 71,6 | 6,0 |  | 10,4 | 92 |
| XIVd | $CH_2OH$ | Br | 182 | 55,0 | 4,6 | 23,5 | 8,0 | $C_{16}H_{15}BrN_2O_3$ | 55,3 | 4,3 | 23,1 | 8,1 | 88 |
| XIVe | $CH_2COC_6H_5$ | H | 209 | 74,3 | 5,3 |  | 7,3 | $C_{23}H_{20}N_2O_3$ | 74,2 | 5,4 |  | 7,5 | 92 |
| XIVf | $CH_2C_6H_5$ | Br | 93 | 62,0 | 4,4 | 19,1 | 6,2 | $C_{22}H_{18}BrN_2O_2$ | 62,4 | 4,5 | 18,9 | 6,6 | 88 |
| XIVg | $CH_2CH-CH_2$ | H | 86 | 73,9 | 6,5 |  | 9,0 | $C_{18}H_{18}N_2O_2$ | 73,5 | 6,1 |  | 9,5 | 87 |
| XIVh | $CH_2CH-CH_2$ | Br | 91 | 57,6 | 4,7 | 21,8 | 7,1 | $C_{18}H_{17}BrN_2O_2$ | 57,9 | 4,6 | 21,4 | 7,5 | 99 |
| XIVi | $CH_2CBr-CH_2$ | H | 186 | 57,5 | 4,2 | 21,9 | 7,1 | $C_{18}H_{17}BrN_2O_2$ | 57,9 | 4,6 | 21,4 | 7,5 | 95 |
| XIVj | $CH_2CBr-CH_2$ | Br | 96 | 48,0 | 3,9 | 35,7 | 6,0 | $C_{18}H_{16}Br_2N_2O_2$ | 47,8 | 3,5 | 35,4 | 6,2 | 80 |

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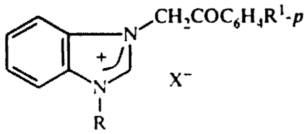
*Solvents for crystallization: aqueous DMF for III, VIII, IX, X, XII; alcohol for XIII, and aqueous alcohol for XIV.



XIII, XIV a-j

XIII X = Br. XIV X = OH

## EXPERIMENTAL

IR spectra were taken on a UR-20 instrument in Vaseline oil and PMR spectra on a Tesla BS-487 (80 MHz) instrument for $CF_3COOH$ solutions with internal standard HMDS. Chromatography was performed on $Al_2O_3$ (grade III) in chloroform.

The physicochemical parameters for the compounds prepared are given in Table 1.

**1-(2-p-Nitrophenyl-2-hydroxyethyl)benzimidazoles (IIIa-e).** A solution of benzimidazole (1.18 g, 0.01 mole) and p-nitrostyrene oxide (II, 1.65 g, 0.01 mole) in ethanol (10 ml) was heated for 10-15 min with conc. HCl (2-3 drops) at 60-80°C. The precipitated IIIa was filtered, washed with alcohol, and then with water (with 5-6 drops of conc. ammonia). Compounds IIId, e were obtained similarly by refluxing carbinols Id, e with oxirane II in alcohol for 7 h. The yields of IIId, e, obtained without addition of conc. HCl catalyst, were 56 and 40% respectively.

**Benzimidazolones (Va-d).** Thiones VIa-d (0.02 mole) and oxirane II (3.3 g, 0.02 mole) were heated with stirring on a water bath at 80-90°C for 4 h. After cooling, the melt was triturated with acetone (30 ml), filtered, and washed with acetone (20 ml). To separate Vc ($R = C_2H_5$), the reaction mixture was dissolved in chloroform (60 ml) and chromatographed on aluminium oxide. The IR spectral data and melting points of benzimidazolones Va-d agreed with those reported in the literature [10]. R, Mp (°C), yield (%) for: Va, H, 307-308, 66; Vb, $R = CH_3$, 192, 59; Vc, $C_2H_5$, 115-116, 50; Vd, $CH_2C_6H_5$, 201-202, 53. IR spectra of Va-d: 1700 (C=O), 3470-3475 $cm^{-1}$ (NH).

**Reaction of 2-Aminobenzimidazoles with p-Nitrostyrene Oxide.** A mixture of the 2-aminobenzimidazole VIIa (1.33 g, 0.01 mole) and oxide II (5 g, 0.03 mole) in butanol (10 ml) was refluxed for 4 h. After cooling, the solution was filtered to give VIIIa with IR spectrum 1665 (C=N), 3340, 3480, 3580 (−NH, −OH), 1350, 1520 $cm^{-1}$ ($NO_2$).

Reaction of amines VIIb-d (10 mmole) with oxirane II (2.5 g, 15 mmole) occurs similarly. Imine VIIIb ($R = CH_3$) or amines IXc, d were filtered off from solution, whereas imines VIIIc, d were obtained from the mother liquor by precipitation with ether. IR spectra of imines VIIIb-d: 2600-2270 (associated OH), 3345 (=NH), 1350, 1520 ($NO_2$). Amines IXc, d: 2600-2270 (OH), 3200-3250 (NH), 1350, 1520 $cm^{-1}$ ($NO_2$).

**1-(2-p-Nitrophenyl-2-hydroxyethyl)pyridinium Hydroxide (X).** A solution of pyridine (1.6 g, 0.02 mole) and oxirane II (3.3 g, 0.02 mole) in alcohol (10 ml) was heated for 10-15 min in the presence of a catalytic amount of pyridine hydrochloride or 2-3 drops of conc. HCl at 60-80°C. The precipitated X was filtered, washed with alcohol, and dried.

**1-Alkyl-3-(2-p-nitrophenyl-2-hydroxyethyl)benzimidazolium Hydroxides (XIIa-f).** A solution of the 1-alkylbenzimidazole (XIa-f, 0.01 mole) in DMF (5 ml) containing conc. HCl (2-3 drops) was heated for 5 h on a steam bath. The cooled solution was diluted with acetone and the precipitate filtered off.

**1-Alkyl-3-phenacylbenzimidazolium Bromides (XIIIa-j).** The alkylbenzimidazole (XIa-j, 15 mmole) was dissolved with heating in the minimum amount of acetone, phenacyl bromide (2.9 g, 15 mmole) or p-bromophenacyl bromide (4.1 g, 15 mmole) was added, and the product was stirred and allowed to stand overnight. The precipitate was filtered off and washed with acetone. For preparation of the salt XIIIi ($R = CH_2CBr{=}CH_2$) the acetone was removed and the residue mixed with anhydrous ether and transferred to the filter.

**1-Alkyl-3-phenacylbenzimidazolium hydroxides (XIVa-j)** were prepared by treating a solution of the bromides XIIIa-j in water with excess aqueous potassium carbonate solution. The oily precipitate of XIVa-j solidified on cooling and was filtered, and washed with water. The product was light yellow and was readily soluble in alcohol and acetone. IR spectra of XIIIa-j and XIVa-j showed a C=O absorption at 1710 $cm^{-1}$.

## REFERENCES

1. I. I. Popov, Khim. Geterotsikl. Soedin., No. 6, 781 (1996).

2. J. Rokach, Y. Girard, and J. G. Atkinson, Can. J. Chem., **51**, 3765 (1973).
3. G. Coope and W. Irwin, J. Chem. Soc. Perkin Trans. I, No. 5, 545 (1976).
4. K. Hoffman, Imidazole and Its Derivatives, New York (1963), p. 251.
5. Weygand and Hilgetag, Experimental Methods in Organic Chemistry [Russian translation], Khimiya, Moscow (1968), p. 284.
6. I. I. Popov, S. L. Boroshko, B. A. Termov, S. P. Makarov, A. M. Simonov, and B. Ya. Simkin., Khim. Geterotsikl. Soedin., No. 12, 1673 (1987).
7. A. M. Simonov and V. A. Anisimova, Khim. Geterotsikl. Soedin., No. 7, 867 (1979).
8. L. C. Einy, N. W. Berat, and F. N. Hayes, J. Am. Chem. Soc., **71**, 3498 (1949).
9. A. A. Druzhinina and P. M. Kochergin, Khim. Geterotsikl. Soedin., No. 3, 527 (1967).
10. I. S. Kashparov and A. F. Pozharskii, Khim. Geterotsikl. Soedin., No. 1, 124 (1971).