LITERATURE CITED

1. L. S. Stanishevskii, I. G. Tishchenko, and A. M. Zvonok, Vestn. Beloruss. Gos. Univ., Ser. II, No. 2, 20 (1974).
2. V. G. Dmitrieva, F. N. Mazitova, and V. K. Khairullin, Zh. Org. Khim., 13, 1508 (1977).
3. I. A. Aleksandrova, N. A. Dorofeeva, A. I. Chernova, and V. K. Khairullin, Zh. Org. Khim., 14, 1974 (1978).
4. K. D. Gutsche, Organic Reactions [Russian translation], Collective Vol. 8, Inostr. Lit., Moscow (1956), p. 469.
5. I. G. Tishchenko, L. S. Stanishevskii, A. M. Zvonok, and V. N. Sytin, Izv. Akad. Nauk BSSR, Ser. Khim., No. 3, 62 (1977).

# SYNTHESIS OF BENZIMIDAZOLE-2-CARBOXYLIC ACID AMIDES FROM o-PHENYLENEDIAMINE AND OXAMIC ACID ESTERS

P. A. Petyunin and Abdul Malek Choudry

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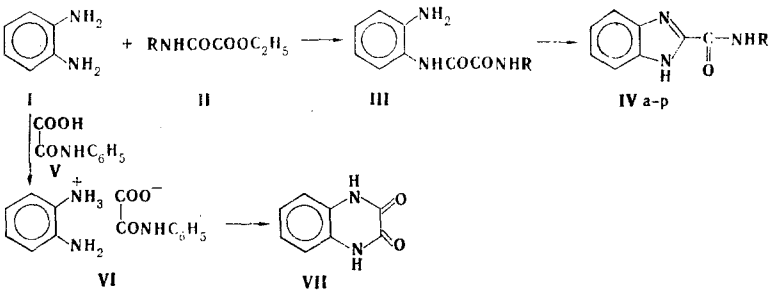
A method for the preparation of N–R amides of benzimidazole-2-carboxylic acid on the basis of the reaction between o-phenylenediamine and esters of N–R oxamic acids was developed.

Little study has been devoted to N-substituted amides of benzimidazole-2-carboxylic acid, and information regarding them is limited [1-3]. At the same time, they may be of interest as biologically active compounds.

We set out to develop a practicable method for the preparation of N–R amides (IV) of benzimidazole-2-carboxylic acid on the basis of the reaction between o-phenylenediamine I and oxamic acid esters II. This reaction is usually carried out in organic solvents [1] or in the fused state [4].

We found that amides IVa-p are formed in good (up to 90%) yields when the reaction is carried out in dimethylformamide (DMF) and that the stepwise mechanism of this transformation is described by the scheme




The possibility of the intermediate formation of amides III in the first step is in agreement with the data in [3].

Benzimidazoles IVa-p (Table 1) are crystalline substances that are soluble in aqueous alkalis; some of them are also soluble in mineral acids.

The structure of IV is confirmed by data from the IR spectra (Table 2), in which absorption bands at 1620-1650 $cm^{-1}$ (amide C=O) and absorption at 3220-3280 $cm^{-1}$, which corresponds to the stretching vibrations of the NH groups, are present. In addition, the spectra contain absorption bands that are characteristic for the benzimidazole ring [5].

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TABLE 1. Benzimidazole-2-carboxylic Acid N–R Amides

| Compound | R | mp,* °C | $R_f$ | Found, % | | | Empirical formula | Calc., % | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | | C | H | N | |
| IVa | $CH_3$ | 239—241 | 0,60 | 61,5 | 5,3 | 23,9 | $C_9H_9N_3O$ | 61,7 | 5,1 | 24,0 | 67 |
| IVb | $C_2H_5$ | 201—202 | 0,78 | 63,3 | 5,9 | 22,5 | $C_{10}H_{11}N_3O$ | 63,5 | 5,8 | 22,2 | 66 |
| IVc | $C_4H_9$ | 175—177 | 0,92 | 66,1 | 7,1 | 19,5 | $C_{12}H_{15}N_3O$ | 66,4 | 6,9 | 19,4 | 44 |
| IVd | $i$-$C_4H_9$ | 207—208 | 0,92 | 66,2 | 7,2 | 19,1 | $C_{12}H_{15}N_3O$ | 66,4 | 6,9 | 19,4 | 60 |
| IVe | $CH_2=CHCH_2$ | 215—216 | 0,87 | 65,5 | 5,6 | 20,6 | $C_{11}H_{11}N_3O$ | 65,7 | 5,5 | 20,9 | 65 |
| IVf | $C_6H_5CH_2$ | 158—159 | 0,93 | 71,6 | 5,3 | 16,7 | $C_{15}H_{13}N_3O$ | 71,7 | 5,2 | 16,7 | 71 |
| IVg | $C_6H_5CH_2CH_2$ | 190—191 | 0,91 | 72,3 | 5,8 | 15,7 | $C_{16}H_{15}N_3O$ | 72,5 | 5,7 | 15,9 | 38 |
| IVh | *cyclo*-$C_6H_{11}$ | 239—242 | 0,95 | 68,1 | 7,2 | 17,2 | $C_{14}H_{17}N_3O$ | 68,3 | 7,0 | 17,3 | 62 |
| IVi | 4-$O_2NC_6H_4CH(OH)\times$ $\times CHCH_2OH$ | 173—175 | 0,28 | 57,1 | 4,8 | 15,9 | $C_{17}H_{16}N_4O_5$ | 57,3 | 4,5 | 15,7 | 93 |
| IVj | 4-$O_2NC_6H_4CH(OH)CH_2$ | 260—263 | 0,27 | 58,6 | 4,4 | 17,0 | $C_{16}H_{14}N_4O_4$ | 58,9 | 4,3 | 17,2 | 75 |
| IVk | Bornyl | 184—185 | — | 72,6 | 7,9 | 14,2 | $C_{18}H_{23}N_3O$ | 72,7 | 7,7 | 14,1 | 42 |
| IVl | 2,6-$Cl_2C_6H_3$ | 258—260 | — | — | — | 13,9 | $C_{14}H_9Cl_2N_3O$ | — | — | 13,7 | 66 |
| IVm | 2,4,6-$(CH_3)_3C_6H_2$ | 337—340 | — | 69,9 | 6,2 | 14,9 | $C_{17}H_{17}N_3O$ | 73,1 | 6,1 | 15,0 | 72 |
| IVn | 4-$ClC_6H_4$ | 230—232 | 0,29 | — | — | 15,6 | $C_{14}H_{10}ClN_3O$ | — | — | 15,5 | 60 |
| IVo | $C_6H_5$ | 234—235 | — | — | — | — | $C_{14}H_{11}N_3O$ | — | — | — | 20 |
| IVp | 4-Antipyryl | 296—299 | — | 65,6 | 5,2 | 19,8 | $C_{19}N_{17}N_5O_2$ | 65,7 | 4,9 | 20,2 | 46 |

*The compounds were crystallized: IVa, b, f, j, m, n, p from aqueous DMF, IVc, e, g, h, l, o from aqueous ethanol, and IVi, k from aqueous $CH_3COOH$.

TABLE 2. IR Spectra of Benzimidazoles IV

| Compound | IR spectrum, $cm^{-1}$ | | |
|---|---|---|---|
| | NH | CO | benzimidazole ring |
| IVa | 3280 | 1645 | 1490, 1130, 970, 830, 725 |
| IVb | 3260 | 1630 | 1490, 1130, 980, 855, 730 |
| IVc | 3260 | 1640 | 1490, 1130, 995, 840, 725 |
| IVd | 3280 | 1640 | 1490, 1140, 995, 830, 730 |
| IVe | 3250 | 1635 | 1490, 1130, 950, 825, 730 |
| IVf | 3260 | 1640 | 1480, 1130, 945, 830, 720 |
| IVg | 3260 | 1630 | 1490, 1130, 960, 850, 720 |
| IVh | 3255 | 1620 | 1490, 1130, 950, 840, 730 |
| IVl | 3220 | 1650 | 1480, 1130, 995, 830, 740 |
| IVn | 3260 | 1650 | 1480, 1130, 985, 815, 730 |

We attempted to use oxamic acid V in addition to esters II for the cyclization. However, 2,3-dihydroxyquinoxaline VII is formed instead of benzimidazole IVo. The reaction in this case probably proceeds with anion VI rather than acid V. Similar results were obtained when we carried out the reaction in the presence of triethylamine. The reaction apparently takes place initially at the amido group of acid V, and this also determines the subsequent direction of the transformation.

No reaction takes place between N-methyloxamic acid esters and diamine I, evidently because of steric hindrance [6].

In order to expand the number of oxamic acid derivatives for the synthesis of benzimidazoles IV we used compounds with the formula $C_6H_5NHCOCONHR$, where R = H (VIII) and $CH_3$. A benzimidazole is formed only in the case of amide VIII.

The study of the effect of the substituents in the benzene ring of ester II on cyclization, particularly in the ortho and ortho' positions relative to the amide nitrogen atom, was of undoubted interest. The experiments were carried out with esters of 2,6-dichloro- and 2,4,6-trimethylphenyloxamic acids. Benzimidazoles IVl, m were obtained in both cases in up to 72% yields.

We also attempted to carry out the reaction between N-benzoyl-o-phenylenediamine IX and ester II. However, intramolecular cyclization to give 2-phenylbenzimidazole X [7] proved to be preferable to intermolecular cyclization with the participation of ester II.

## EXPERIMENTAL

The IR spectra of KBr pellets (containing 1% of the compounds) were recorded with a Specord spectrometer. Chromatography was carried out on Silufol plates in the $(CH_3)_2CO$—$CCl_4$ system (6:4). The chromatograms were developed in UV light.

Benzimidazole-2-carboxylic Acid N-Methylamide (IVa). A mixture of 3.9 g (30 mmole) of ethyl N-methyloxamate (II, R = $CH_3$), 3.24 g (30 mmole) of diamine I, and 5 ml of DMF was refluxed for 4 h, after which it was cooled and diluted with 20 ml of water. The precipitate was removed by filtration and dried in air. The yield was 3.5 g (67%).

Benzimidazoles IVb-n, p were similarly obtained (Table 2).

2,3-Dihydroxyquinoxaline (VII). A mixture of 1.65 g (10 mmole) of oxanilic acid V, 1.08 g (10 mmole) of diamine I, and 4 ml of DMF was refluxed for 3 h, after which the product was isolated as in the preceding experiment to give 0.45 g (28%) of a substance with mp 365-367°C [8] (from aqueous DMF).

Benzimidazole-2-carboxylic Acid Anilide (IVo). A mixture of 1.4 g (8.5 mmole) of amide VIII, 0.9 g (8.5 mmole) of diamine I, and 4 ml of DMF was heated for 3 h, after which it was cooled and diluted with water. The precipitate was removed by filtration and dissolved in 5% sodium hydroxide solution in the cold. The solution was filtered, and the filtrate was acidified with HCl (1:1). The precipitate was isolated and treated as indicated above to give 0.4 g (20%) of a substance with mp 234-235°C [1].

2-Phenylbenzimidazole (X). A mixture of 0.97 g (5 mmole) of ethyl oxanilate, 1.07 g (5 mmole) of IX, and 4 ml of DMF was refluxed for 4 h, after which it was cooled and diluted with water. The precipitate was removed by filtration and dried in air to give 0.5 g (51%) of a substance with mp 286-288°C [7] (from aqueous ethanol). IR spectrum: 3285 (NH); 1650 (C=N); 1545, 1480, 1130, 980, 850, 725 $cm^{-1}$ (benzimidazole ring).

## LITERATURE CITED


1. R. Salle, B. Sillion, and G. Gaudemaris, Bull. Soc. Chim. Fr., No. 10, 3368 (1966).
2. G. Holan and E. L. Samuel, J. Chem. Soc., C, No. 1, 25 (1967).
3. P. A. Bezuglyi and V. P. Chernykh, Farm. Zh., No. 2, 70 (1980).
4. P. A. Petyunin, N. N. Valyashko, and Abdul Malek Choudry, Farm. Zh., No. 5, 66 (1980).
5. G. A. Shvekhgeimer and G. A. Mikheichev, Khim. Geterotsikl. Soedin., No. 6, 820 (1974).
6. Yu. A. Naumov, A. N. Mentus, M. V. Goryacheva, and A. N. Kost, Zh. Org. Khim., 12, 2507 (1976).
7. Dictionary of Organic Compounds [Russian translation], Vol. 3, Inostr. Lit., Moscow (1949), p. 383.
8. E. S. Lane, J. Chem. Soc., 1079 (1955).