INVESTIGATION OF BENZIMIDAZOLE DERIVATIVES

XXVIII.* SYNTHESIS OF SOME 3-[2'-BENZIMIDAZOLYL]ISOXAZOLES

E. B. Tsupak, N. K. Chub,
A. M. Simonov, and N. M. Miroshnichenko

UDC 547.785.5'786.07

The hydrochlorides of the corresponding 2-benzimidazolylmethylhydroxamoyl chlorides were synthesized by the chlorination of 1-methyl-2-formylbenzimidazole oxime and its 5-methyl and 5-nitro derivatives, and 2-benzimidazolylmethylnitrolic acids were obtained by nitration of the oximes. The products of these transformations react with acetylacetone and benzoylacetone in the presence of bases to give 1',5'-substituted 3-[2-benzimidazolyl]-4-acyl-5-methylisoxazoles.

Nitrolic acids and hydroxamic acid chlorides are readily converted to nitrile N-oxides by the action of bases. The nitrile N-oxides display extremely high activity in 1,3-dipolar addition reactions. These sorts of transformations have been studied for aliphatic [2], aromatic [3-6], and several heterocyclic compounds [7-9].

Continuing the investigations we began in [10], we have synthesized substituted 2-benzimidazolylmethylnitrolic acids (IIa-d) and 2-benzimidazolylmethylhydroxamoyl chlorides (IIIa-d) and studied their reaction with acetyl- and benzoylacetones in the presence of bases. Nitrolic acids IIa-d were obtained by nitration of 2-benzimidazole aldoximes (Ia-d). Hydroxamoyl chlorides IIIa-d were synthesized by chlorination of oximes Ia-d in glacial acetic acid and were isolated as the hydrochlorides. Acetylbenzimidazolyl-2-methylhydroxamic acids are not formed under the conditions of the synthesis of IIIa-d (see [6]) because of the low solubility of the hydrochlorides of IIIa-d in glacial acetic acid.

Attempts to obtain the intermediate nitrile oxides (V), which were isolated in a number of cases (as dimers) [4], by the action of bases on the nitrolic acids (IIa-d) and hydroxamic acid chlorides (IIIa-d) did

*See [11] for communication XXVII.

TABLE 1. 3-(2-Benzimidazolyl)isoxazoles

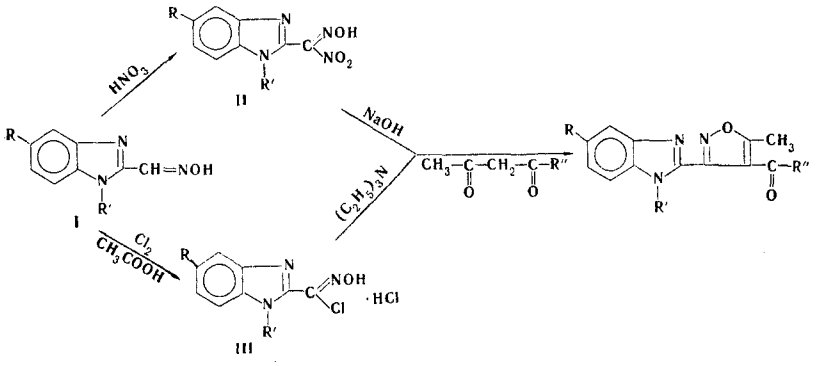
Compound	mp, °C*	Empirical formula	Found, %		Calc., %		ν_{CO}, cm^{-1}	Yield, %	
			C	H	C	H		meth. A	meth. B
IVa	169—170	$C_{13}H_{11}N_3O_2$	64,6	4,7	64,7	4,6	1670	62	64
IVb	218—219	$C_{18}H_{13}N_3O_2$	71,4	4,4	71,3	4,3	1680	50	38
IVc	107—108	$C_{14}H_{13}N_3O_2$	65,8	5,2	65,9	5,1	1690	55	62
IVd	119—121	$C_{19}H_{15}N_3O_2$	72,3	4,7	72,0	4,8	1665	44	47
IVe	131—132*	$C_{15}H_{15}N_3O_2$	66,5	5,6	66,9	5,6	1690	70	73
IVf	148—150	$C_{20}H_{17}N_3O_2$	72,1	5,2	72,5	5,2	1680	71	78
IVg	160—161	$C_{14}H_{12}N_4O_4$	56,2	4,1	56,0	4,0	1690	—†	25†
IVh	165—166	$C_{19}H_{14}N_4O_4$	62,9	4,1	62,6	3,9	1670	—†	28†

*This compound was recrystallized fron n-hexane, while the remaining compounds were recrystallized from alcohol.
†These compounds were not obtained via method A because of the low solubility of the nitrolic acid (IId) in aqueous alkali.

Rostov-on-Don State University, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 812-815, June, 1972. Original article submitted June 15, 1971.

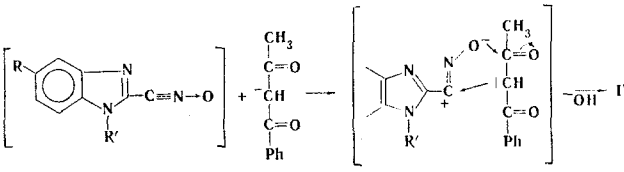
not give positive results. According to paper chromatography, the products isolated in this case are a mixture of substances that could not be identified. The nitrile oxides (V) and their hydration products – hydroxamic acids – apparently undergo subsequent transformations to give a number of complex compounds. However, it was shown that IIa-d react at room temperature in aqueous solutions with the enolates of acetylacetone and benzoylacetone (when they are present in excess amounts) to give 3-(2-benzimidazolyl)-4-acyl-5-methylisoxazoles (IVa-f). Similar results were obtained in the case of the hydroxamoyl chlorides (IIIa-d). The reaction was carried out in dimethyl sulfoxide (DMSO) in the presence of triethylamine.

It should be noted that the nature of the substituent in the 5 position of the benzimidazole ring has an appreciable effect on the yields of isoxazoles (IVa-h). Thus 5-methyl-substituted IVe and IVf were obtained in yields above 70%, while 5-nitro-substituted IVg and IVh are formed only in yields of 25-28%.



I, II, III a R=R′=H, b R=H, R′=CH_3, c R=R′=CH_3, d R=NO_2, R′=CH_3; IV a R=R′=H, R″=CH_3, b R=R′=H, R″=Ph, c R=H, R′=R″=CH_3, d R=H, R′=CH_3, R″=Ph, e R=R′=R″=CH_3, f R=R′=CH_3, R″=Ph, g R=NO_2, R′=R″=CH_3, h R=NO_2, R′=CH_3, R″=Ph

The structure of isoxazoles IVa-h corresponds to the results of elementary analysis and is confirmed by their IR spectra, in which intense bands at 1670-1690 cm^{-1} (Table 1), which are related to the CO group absorption, are observed. The structure of IVa and IVb is also confirmed by the PMR spectra. The PMR spectrum of IVa, for which only an unambiguous structure is possible because of the symmetrical character of the acetylacetone molecule, contains singlets with chemical shifts of 2.45 and 2.74 ppm relative to hexamethyldisiloxane, which correspond to the resonance of the protons of the methyl group in the 5 position and the methyl of the acetyl group in the 4 position of the isoxazole ring. Only one singlet of protons with a chemical shift of 2.4 ppm is observed in the spectrum of IVb, which can correspond only to the resonance of protons of a methyl group in the 5 position of isoxazole [11]. Thus the carbonyl carbon atom of the acetyl group rather than of the benzoyl group participates in closing of the isoxazole ring for IVb, which presupposes a reaction via the scheme



EXPERIMENTAL

The PMR spectra were recorded with a YaMR-5535 spectrometer (40 MHz) with hexamethyldisiloxane (HMDS) as the standard. The IR spectra of mineral-oil suspensions were recorded with a UR-20 spectrophotometer.

1,5-Dimethyl-2-formylbenzimidazole.* This compound [2 g (54%)] was obtained by oxidation of 5 g (0.03 mole) of 1,2,5-trimethylbenzimidazole [13] with 3.3 g (0.03 mole) of freshly sublimed selenium dioxide in 30 ml of absolute dioxane via the method in [12]. The colorless needles had mp 133-134° (from water). Found: N 16.5%. $C_{10}H_{10}N_2O$. Calculated: N 16.1%. IR spectrum, cm^{-1}: 1710 (C = O).

1,5-Dimethylbenzimidazole 2-Aldoxime (Ic). This compound [0.5 g (92%)] was obtained by the reaction of 0.5 g of 1,5-dimethyl-2-formylbenzimidazole and 0.4 g of hydroxylamine hydrochloride in aqueous

* The compound was synthesized for the first time with the participation of L. Braikova.

alcohol (2:5) in the presence of sodium acetate. The colorless prisms had mp 227-227.5° (from alcohol). Found: N 22.0%. $C_{10}H_{11}N_3O$. Calculated: N 22.2%. IR spectrum, cm^{-1}: broad band at 3100-3200 (OH), 1570 (C=N).

1-Methyl-5-nitrobenzimidazole 2-Aldoxime (Id). A solution of 0.5 g (2.4 mmole) of 1-methyl-5-nitro-2-formylbenzimidazole [12], 0.2 g (3.0 mmole) of hydroxylamine hydrochloride, and 0.25 g (3.0 mmole) of anhydrous sodium acetate in 4 ml of glacial acetic acid was refluxed for 1 h. The mixture was then diluted with water, and the crystals were removed by filtration and washed with water to give 0.46 g (80%) of yellow prisms with mp 248-248.5° (from 80% acetic acid). Found: C 49.1; H 3.9%. $C_9H_8N_4O_3$. Calculated: C 48.7; H 3.7%. IR spectrum, cm^{-1}: 3100 (OH), 1620 (C=N), 1530, 1335 (NO_2).

1-Methyl-5-nitro-2-benzimidazolylmethylnitrolic Acid (IId). A mixture of 0.5 g (2.0 mmole) of Id and 2 ml of nitric acid (sp. gr. 1.4) was heated cautiously on a water bath at 50-60° until a dark-brown solution formed. The mixture was cooled and diluted with water, and the greenish-yellow crystals were removed by filtration and washed with water to give 0.25 g (41%) of a product with mp 134° (dec.). Found: C 40.0; H 3.0%. $C_9H_7N_5O_5$. Calculated: C 40.8; H 2.7%. IR spectrum; cm^{-1}: 3100 (OH), 1555, 1340 (NO_2), 1050, 1075 ($C=NO_2^-$).

1,5-Dimethyl-2-benzimidazolylmethylnitrolic Acid (IIc). This compound [0.3 g (64%)] was obtained by nitration of 0.4 g of Ic with 2 ml of nitric acid (sp. gr. 1.4) at 50-60° as in the preparation of IId. The precipitate was treated with 3-5% sodium acetate solution to give 0.3 g (64%) of yellow needles with mp 88-89° (dec.). Found: C 52.0; H 4.6%. $C_{10}H_{10}N_4O_3$. Calculated: C 51.3; H 4.3%. IR spectrum, cm^{-1}: several peaks at 3100-3530 (OH), 1540, 1340 (NO_2).

2-Benzimidazolylmethylhydroxamoyl Chloride Hydrochloride (IIIa). A stream of chlorine was passed through a solution of 2 g of benzimidazole 2-aldoxime [14] in 20 ml of glacial acetic acid until the formation of a white precipitate ceased. The precipitate was then removed by filtration and washed with glacial acetic acid and several times with ether to give 2.85 g (quantitative) of colorless prisms with mp 204° (dec., from glacial acetic acid). Found: N 18.1%. $C_8H_6ClN_3O \cdot HCl$. Calculated: N 18.1%. IR spectrum, cm^{-1}: broad band at 3240(OH), broad band at 2600-2800 (NH, $\overset{+}{N}H$), 1630 (C=N).

1-Methyl-2-benzimidazolylmethylhydroxamoyl Chloride Hydrochloride (IIIb). This compound [1.3 g (84%)] was obtained in the same way as IIIa from 1 g of 1-methyl-2-formylbenzimidazole [12] in 10 ml of glacial acetic acid. The colorless prisms had mp 204° (dec., from glacial acetic acid). Found: C 43.7; H 3.8; Cl 28.6%. $C_9H_8ClN_3O \cdot HCl$. Calculated: C 44.0; H 3.7; Cl 28.8%. IR spectrum, cm^{-1}: 3230 (OH), broad band at 2600-2800 ($\overset{+}{N}H$), 1630 (C=N).

1,5-Dimethyl-2-benzimidazolylmethylhydroxamoyl Chloride Hydrochloride (IIIc). This compound was obtained in quantitative yield as colorless needles with mp 198° (dec., from glacial acetic acid). Found: N 16.3%. $C_{10}H_{10}ClN_3O \cdot HCl$. Calculated: N 16.2%. IR spectrum, cm^{-1}: 3300 (OH), broad band at 2600-2800 ($\overset{+}{N}H$), 1640 (C=N).

1-Methyl-5-nitro-2-benzimidazolylmethylhydroxamoyl Chloride (IIId). This compound [0.49 g (86%)] was obtained in the same way as IIIa by chlorination of 0.5 g of Id in 30 ml of glacial acetic acid. The yellow prisms had mp 194° (dec., from glacial acetic acid). Found: N 14.1%. $C_9H_7ClN_4O_3$. Calculated: N 14.0%. IR spectrum, cm^{-1}: broad band at 2700-2800 (OH), 1620 (C=N), 1535, 1340 (NO_2).

3-(2-Benzimidazolyl)-4-acetyl-5-methylisoxazole (IVa). A. A 2-g (0.01 mole) sample of 2-benzimidazolylmethylnitrolic acid [15] was added to a solution of 2 g (0.02 mole) of acetylacetone in 20 ml of 2 N sodium hydroxide, and the mixture was allowed to stand overnight at room temperature. The precipitated crystals were removed by filtration, washed with water, dried, and purified by column chromatography (aluminum oxide and chloroform). Compounds IVb-f were similarly obtained.

B. A suspension of 0.9 g (3.9 mmole) of IIIa in 5 ml of DMSO was added in portions with stirring to a mixture of 0.75 g (7.5 mmole) of acetylacetone, 1.75 g (17.5 mmole) of triethylamine, and 5 ml of DMSO. The mixture was allowed to stand overnight, and the precipitated triethylamine hydrochloride was removed by filtration. The DMSO was removed by vacuum distillation, and the residue was treated with a small amount of water to give the benzimidazolylisoxazole, which was purified by column chromatography (aluminum oxide and chloroform). Compounds IVa-h were similarly obtained.

LITERATURE CITED

1. A. F. Pozharskii, M. M. Medvedeva, É. A. Zvezdina, and A. M. Simonov, Khim. Geterotsikl. Soedin., 665 (1971).
2. C. Grundmann, Angew. Chem., 75, 450 (1963).
3. R. H. Wiley and B. J. Wakefield, J. Org. Chem., 25, 546 (1960).
4. R. Huisgen, Angew. Chem., 75, 604 (1963).
5. C. Grundmann and J. M. Dean, J. Org. Chem., 30, 2809 (1965).
6. C. Grundmann and H. D. Frommeld, J. Org. Chem., 31, 157 (1966).
7. T. Sasaki and T. Yoshioka, Bull. Chem. Soc. Japan, 40, 2604 (1967).
8. Y. Iwakura, K. Uno, S. Shiraishi, and T. Hongu, Bull. Chem. Soc. Japan, 41, 2954 (1968).
9. T. Sasaki and T. Yoshioka, Bull. Chem. Soc., Japan, 41, 3012 (1968).
10. N. K. Chub, E. B. Tsupak; and A. M. Simonov, Khim. Geterotsikl. Soedin., 1393 (1970).
11. H. Feuer and S. Markofsky, J. Org. Chem., 29, 935 (1964).
12. M. T. Le Bris and H. Wahl, Bull. Soc. Chim. France, 343 (1959).
13. G. R. Beaven, E. R. Holiday, E. A. Johnson, B. Ellis, P. Mamalis, V. Petrov, and B. Sturgeon, J. Pharm. Pharmacol., 1, 957 (1949).
14. Yu. A. Zhdanov and G. N. Dorofeenko, Zh. Obshch. Khim., 29, 2677 (1959).
15. N. K. Chub, E. B. Tsupak, and A. M. Simonov, Khim. Geterotsikl. Soedin., 127 (1970).