CHEMISTRY OF 2-HETARYLBENZIMIDAZOLES.

8.* SYNTHESIS AND PROPERTIES OF 1-METHYL-2-(5'-METHYL-2'-SELENIENYL)BENZIMIDAZOLE

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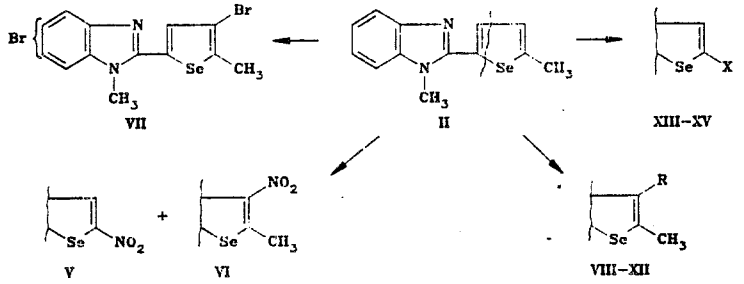
1-Methyl-2-(5'-methyl-2'-selenienyl)benzimidazole was synthesized and subjected to electrophilic-substitution reactions: nitration, bromination, sulfonation, chloromethylation, formylation, and acylation. The substituent usually enters the 4' position of the selenophene ring, but nitration with acetyl nitrate leads to a mixture of 5'-nitro and 4'-nitro derivatives. Oxidation of 2-selenienylbenzimidazole with potassium permanganate leads to the 5'-carboxy derivative, while oxidation with selenium dioxide leads to the 5'-hydroxymethyl and 5'-formyl derivatives.

In order to further study the transformations of 2-hetarylbenzimidazoles [2, 3] we obtained 2-(5'-methyl-2'-selenienyl)benzimidazole (I) by means of the Weidenhagen reaction starting from 5-methyl-2-formylselenophene and o-phenylenediamine. The product of its methylation at the NH group (II) was subjected to electrophilic-substitution and oxidation reactions.



VIII R=Br; IX R=$COCH_3$; X R=CH_2OH; XI R=CHO; XII R=SO_3H; XIII X=COOH; XIV X=CH_2OH; XV X=CHO

In contract to other 2-(5'-methyl-2'-hetaryl)benzimidazoles, in which the hetaryl group is 2-furyl (III) and 2-thienyl (IV), II under the influence of acetyl nitrate does not undergo destructive oxidation but forms a mixture of two nitro compounds. We were able to separate the mixture by column chromatography. The substance with mp 305-306°C, which was isolated in 36% yield, was the previously described [6] 1-methyl-2-(5'-nitro-2'-selenienyl)benzimidazole (V); it was also obtained by nitration of 1-methyl-2-(2'-selenienyl)benzimidazole with acetyl nitrate. The formation of V evidently proceeds via oxiation of the 5'-CH_3 group of part of II with acetyl nitrate to the 5'-carboxylic acid with its subsequent decarboxylation and incorporation of a nitro group in the freed 5' position of the selenophene ring. According to spectral data, the second compound, with mp 285-286°C, which was obtained in 45% yield, was 4'-nitro derivative VI: in addition to signals of an N-methyl group and a multiplet of aromatic protons, the PMR spectrum of VI contains a singlet at 8.2 ppm, which belongs to the 3'-H proton, as well as a singlet at 2.6 ppm of a CH_3 group.

The bromination of II in dichloroethane also proceeds differently from the bromination of analogs III and IV, which, under these conditions, form 5(6)-bromo derivatives involving the benzimidazole ring [2], while 1-methyl-2-(5'-methyl-2'-selenienyl)benzimidazole (II) is converted to 5(6),4'-dibromo derivatives VII. In the PMR spectrum of this compound the protons of the benzene ring show up in the form of a singlet at 7.4 ppm and a doublet at 7.3 ppm, while the signal of the 3'-H proton appears in the form of a singlet at 7.5 ppm. When

*See [1] for Communication 7.

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TABLE 1. 1-Methyl-2-(5'-methyl-4'-R-2'-selenienyl)benzimidazoles

Compound	T_{mp}, °C (alcohol)	IR spectrum, cm^{-1}	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
II	94—95	—	56,4	4,3	9,9	$C_{13}H_{12}N_2Se$	56,7	4,4	10,2	90
VI	285—286	1370	49,1	3,6	12,9	$C_{13}H_{11}N_3O_2Se$	48,8	3,5	13,1	45
VIII	163—164	—	43,7	3,3	8,2	$C_{13}H_{11}BrN_2Se$	44,1	3,1	7,9	64
IX	158—159	1670	57,2	4,6	9,0	$C_{15}H_{14}N_2OSe$	56,8	4,4	8,8	25
X	193—194	3240	55,3	4,3	8,8	$C_{14}H_{14}N_2OSe$	55,1	4,6	9,2	36
XI	222—223	1680	55,8	3,8	8,9	$C_{14}H_{12}N_2OSe$	55,5	4,0	9,2	72
XII	330—331	1280	44,2	3,1	8,1	$C_{13}H_{12}N_2O_3SSe$	44,0	3,4	7,9	89

the reaction is carried out in glacial acetic acid, the reactivity of the benzimidazole ring, because of protonation, proves to be reduced [4]; this leads, as in the case of III and IV, to 4'-bromo derivative VIII.

The acetylation of II was carried out at 100°C for 30 h; however, the yield of acetyl derivative IX was only 25%. In contrast to III and IV, benzoylation of II is not observed even under very severe conditions [polyphosphoric acid (PPA), 180°C], possibly because of steric hindrance.

The chloromethylation of benzimidazole II proceeds with difficulty. The reaction product, which was obtained in low yield, after treatment with alkali was isolated and identified in the form of the 4'-hydroxymethyl derivative X; a significant part of the starting compound was recovered unchanged.

Formylation via the method of Denton and Suschitzky [5] and sulfonation of II proceed smoothly and in high yields in the 4' position of the selenophene ring.

The oxidation of 1-methyl-2-(5'-methyl-2'-selenienyl)benzimidazole (II) with potassium permanganate was carried out in water at 80°C. As in the case of III and IV, as a consequence of the stabilizing effect of the benzimidazole fragment, the selenophene ring proved to be resistant to the action of this reagent. Carboxylic acid XIII (in view of its partial decarboxylation during acidification of the solution and the difficulty involved in its isolation from the reaction mass) was obtained in only 21% yield. The oxidation of the 5'-methyl group of II with selenium dioxide by refluxing in anhydrous dioxane for 10 h leads to 5'-hydroxymethyl-substituted XIV in 85% yield. The latter is converted to aldehyde XV upon more prolonged heating of the reaction mass (for another ~20 h).

We were unable to condense II with aromatic aldehydes at the CH_3' group by prolonged refluxing in acetic anhydride.

EXPERIMENTAL

The IR spectra of solutions in chloroform or suspensions in mineral oil were recorded with a UR-20 spectrometer. The PMR spectra of solutions in trifluoroacetic acid were obtained with a Tesla BS-487 spectrometer (80 MHz) with hexamethyldisiloxane (HMDS) as the internal standard.

2-(5'-Methyl-2'-selenienyl)benzimidazole (I). A mixture of 4.32 g (40 mmole) of o-phenylenediamine in 75 ml of isopropyl alcohol, 16 g (80 mmole) of copper acetate in 200 ml of water, and 6.92 g (40 mmole) of 5-methyl-2-formylselenophene was heated at 80-90°C for 2 h, after which it was cooled, and the precipitated copper salt was separated and suspended in 75 ml of dimethylformamide. Hydrogen sulfide was passed through the suspension for 1 h, after which the copper sulfide was separated, the filtrate was diluted with water, and the resulting precipitate was separated with a Büchner funnel. The yield was 2 g (77%). The colorless crystals had mp 273-274°C (from alcohol). Found: C 55.6; H 4.1; N 11.0%. $C_{12}H_{10}N_2Se$. Calculated: C 55.2; H 3.9; N 10.7%.

1-Methyl-2-(5'-methyl-2'-selenienyl)benzimidazole (II). A 2.6-g (10 mmole) sample of I was added to a solution of 2.24 g (40 mmole) of KOH in 20 ml of alcohol, after which 5.68 g (40 mmole) of methyl iodide was added dropwise, and the mixture was stirred at 20°C for 6 h. The resulting precipitate of potassium iodide was removed by filtration, and the reaction product was isolated by adding 100 ml of water. The yield was 2.46 g (90%) (Table 1).

TABLE 2. PMR Spectra of Substituted 2-Selenienyl-benzimidazoles

Compound	PMR spectrum, δ, ppm (CF_3COOH)
II	3,8 (3H, s, 3H, N—CH_3); 2,3 (3H, s, C—CH_3); 6,85 (1H, d 4′-H); 7,3 (4H, m, arom); 7,55 (1H, s, 3′-H)
VI	2,3 (3H, s, C—CH_3); 3,8 (3H, s N—CH_3); 7,3 (4H, m., arom.); 8,15 (1H, s, 3′-H)
VII	2,3 (3H, s, C—CH_3); 3,8 (3H, s, N—CH_3); 7,3 (2H, d arom.); 7,4 (1H, s, arom.); 7,5 (1H, s, 3′-H)
VIII	2,3 (3H, s, C—CH_3); 3,8 (3H, s, N—CH_3); 7,3 (4H, m, arom); 7,5 (1H, s, 3′-H)
IX	2,4 (3H, s, $COCH_3$); 2,6 (3H, s, C—CH_3); 3,8 (3H, s, N—CH_3); 7,35 (4H, m, arom); 8,1 (1H, s, 3′-H)
X	2,3 (3H, s, C—CH_3); 3,8 (3H, s, N—CH_3); 4,8 (2H, s, CH_2); 7,3 (4H, m, arom); 8,0 (1H, s, 3′-H)
XI	2,6 (3H, s, C—CH_3); 3,8 (3H, s, N—CH_3); 7,35 (4H, m, arom); 8,2 (1H, s, 3′-H); 11,8 (1H, s, SO_3H)
XII	2,7 (3H, s, C—CH_3); 3,8 (3H, s, N—CH_3); 7,3 (4H, m, arom.); 8,1 (1H, s, 3′-H); 9,6 (1H, s, CHO)

1-Methyl-2-(5′-methyl-4′-nitro-2′-selenienyl)benzimidazole (VI). A 3.3-ml sample of nitric acid (d 1.5) was added at 0°C to 7.5 g of freshly distilled acetic anhydride, after which 1.37 g (5 mmole) of II was added, and the reaction mass was stirred at 0°C for 2 h and at 20°C for 2 h. It was then diluted with 100 ml of water, and the aqueous mixture was neutralized cautiously with concentrated ammonium hydroxide to pH 7. The nitration product — a mixture of VI and V — was extracted with 50 ml of chloroform and separated by chromatography with a column packed with aluminum oxide (40 3-cm portions) by elution with chloroform to give 0.72 g of yellow crystals (Table 1).

1-Methyl-2-(5′-nitro-2′-selenienyl)benzimidazole (V). A) This compound was obtained in the synthesis of VI. The yield was 0.55 g (36%). The yellow crystals had mp 305-306°C (from alcohol).

B) A 3.3-ml sample of nitric acid (d 1.5) was added at 0°C to 7.5 g of freshly distilled acetic anhydride, after which 1.3 g (5 mmole) of 1-methyl-2-(2′-selenienyl)benzimidazole was added, and the reaction mass was stirred for 2 h at 0°C and for 2 h at 20°C. It was then diluted with 100 ml of water, and the resulting yellow crystals were removed by filtration to give 1.16 g (76%) of a product with mp 305-306°C (from alcohol). The compounds obtained by methods A and B were identical according to a mixed-melting-point determination.

1-Methyl-5(6)-bromo-2-(5′-methyl-4′-bromo-2′-selenienyl)benzimidazole (VII). A solution of 2.4 g (15 mmole) sample of bromine in 10 ml of dichloroethane was added at 80°C in the course of 10 min to a solution of 1.37 g (5 mmole) of II in 20 ml of dichloroethane. At the end of the addition the mixture was refluxed for 2 h, and the precipitated hydrobromide of VII was separated with a funnel with a stud. The base was obtained by the action on the hydrobromide of 100 ml of 10% ammonium hydroxide. The liberated reaction product was extracted with 50 ml of chloroform and chromatographed on 160 g of aluminum oxide using a column (40 × 3 cm) and elution with chloroform to give 1.36 g (63%) of a product with mp 196-197°C (from alcohol). Found: C 35.9; H 2.7; Br 36.5; N 6.4%. $C_{13}H_{10}Br_2N_2Se$. Calculated: C 36.1; H 2.3; Br 36.5; N 6.5%.

1-Methyl-2-(5′-methyl-4′-bromo-2′-selenienyl)benzimidazole (VIII). A 1.6-g (10 mmole) sample of bromine was added to a solution of 1.37 g (5 mmole) of II in 20 ml of acetic acid, after which the mixture was refluxed for 3 h. The precipitated hydrobromide of VIII was separated and converted to the base in the same way as the hydrobromide of VII (Table 1).

1-Methyl-2-(5′-methyl-4′-acetyl-2′-selenienyl)benzimidazole (IX). A mixture of 1.37 g (5 mmole) of II and 1 g (10 mmole) of acetic anhydride in 20 ml of polyphosphoric acid (PPA) was stirred at 140°C for 2 h, after which it was poured into 100 ml of water, and the aqueous mixture was neutralized cautiously with concentrated ammonium hydroxide to pH 7-8. The liberated reaction product was extracted with 50 ml of chloroform and chromatographed on 80 g of aluminum oxide using a 20 × 3 cm column and elution with chloroform (Table 1).

1-Methyl-2-(5′-methyl-4′-hydroxymethyl-2′-selenienyl)benzimidazole (X). A mixture of 1.37 g (5 mmole) of II, 1.15 g (13 mmole) of paraformaldehyde, and 10 ml of hydrochloric acid (d 1.19) was heated for 20 h at 70-80°C, after which it was cooled and neutralized cau-

tiously with 10% sodium hydroxide to pH 7.8. The reaction product was isolated in the same way as IX (Table 1).

1-Methyl-2-(5'-methyl-4'-formyl-2'-selenienyl)benzimidazole (XI). A mixture of 1.37 g (5 mmole) of II and 1.4 g (10 mmole) of urotropin in 20 g of polyphosphoric acid (PPA) was stirred at 70-80°C for 8 h, after which it was diluted with 100 ml of water, and the aqueous mixture was neutralized with concentrated ammonium hydroxide to pH 7-8. The reaction product was separated with a Büchner funnel and recrystallized (Table 1).

1-Methyl-2-(5'-methyl-4'-sulfo-2'-selenienyl)benzimidazole (XII). A mixture of 1.37 g (5 mmole) of II, 0.98 g (10 mmole) of sulfuric acid (d 1.84), and 20 g of polyphosphoric acid (PPA) was heated at 120°C for 3 h, after which it was cooled and diluted with 50 ml of water, and the precipitated sulfonic acid was removed by filtration (Table 1).

1-Methyl-2-(5'-carboxy-2'-selenienyl)benzimidazole (XIII). A suspension of 1.37 g (5 mmole) of II in 50 ml of water was stirred with 3.16 g (20 mmole) of potassium permanganate at 80°C for 1 h, after which it was cooled, and the manganese dioxide was separated. The filtrate was concentrated to half its original volume, and the concentrate was acidified with glacial acetic acid to pH 5. Acid XIII was isolated from the filtrate after it was allowed to stand in a refrigerator for 5 days. The yield was 0.32 g (21%). The colorless needles had mp 267-268°C (from water). IR spectrum: 1690 (C=O), 3740 cm^{-1} (OH). Found: C 51.6; H 3.2; N 8.9%. $C_{13}H_{10}N_2O_2Se$. Calculated: C 51.2; H 3.3; N 9.2%.

1-Methyl-2-(5'-hydroxymethyl-2'-selenienyl)benzimidazole (XIV). A 1.1-g (10 mmole) sample of freshly sublimed selenium dioxide was added gradually to a refluxing solution of 1.37 g (5 mmole) of II in 25 ml of absolute dioxane, after which refluxing was continued for 10 h. The mixture was then cooled and allowed to stand in a refrigerator for 24 h to precipitate colorless crystals, which were separated with a Büchner funnel and crystallized from alcohol. The yield of product with mp 187-188°C was 1.2 g (85%). Found: N 9.8%. $C_{13}H_{12}N_2OSe$. Calculated: N 9.6%. The compound was previously obtained by chloromethylation of 1-methyl-2-(2-selenienyl)benzimidazole with subsequent hydrolysis and had mp 187-188°C [6]. IR spectrum: 3220 cm^{-1} (OH).

1-Methyl-2-(5'-formyl-2'-selenienyl)benzimidazole (XV). A 1.1-g (10 mmole) sample of freshly sublimed selenium dioxide was added gradually to a refluxing solution of 1.37 g (5 mmole) of II in 25 ml of absolute dioxane, and the mixture was refluxed for 30 h. It was then maintained at 0-10°C for 24 h. The precipitated yellow crystals were separated with a Büchner funnel. The yield of product with mp 149-150°C (from alcohol) was 1.1 g (76%). The compound was also obtained by formylation of 1-methyl-2-(2-selenienyl)benzimidazole [6].

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