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# SYNTHESIS AND PROPERTIES OF FURAN DERIVATIVES.

## 5.* SYNTHESIS OF 2-SUBSTITUTED BENZOXAZOLES CONTAINING FURAN FRAGMENTS

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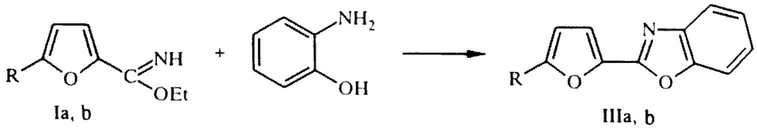
*The condensation of imidates and imidate hydrochlorides of furan acids with* o-*aminophenols gives furyl derivatives of 2-substituted benzoxazoles. Such compounds are also formed in the reaction of furan acids with* o-*aminophenol in the presence of boric acid.*

In a continuation of our work on the synthesis of furyl derivatives of azoles [2-4] and 1, 3,4-oxadiazoles [1], we now report the preparation of 2-substituted benzoxazoles containing 2-furyl or β-furylvinyl fragments.

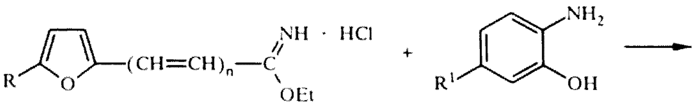
There have been only a few reports on the preparation and properties of such benzoxazoles [5-7]. On the other hand, these compounds may hold interest relative to their possible biological activity and as convenient models for studying the reactivity of bisheteroaromatic systems, in which the benzazole and π-excess rings are directly bound to each other or separated by a vinyl group [8, 9].

Imidates or salts of imidates of carboxylic acids are known to be convenient synthones in the synthesis of 2-substituted benzoxazoles [10-12]. In the present work, ethyl imidates of 2-furancarboxylic acid (Ia) and 5-methyl-2-furancarboxylic acid (Ib) as well as the hydrochloride salts of the ethyl imidates of 5-bromo-2-furancarboxylic acid (IIa), 5-nitro-2-furancarboxylic acid (IIb), and (*E*)-β-(5-R-2-furyl)acrylic acids (IIc-IIe) were used as the starting compounds in this work. The condensation of imidates Ia and Ib with *o*-aminophenol gives 2-(2-furyl)benzoxazole (IIIa) and 2-(5-methyl-2-furyl)benzoxazole (IIIb), respectively. The best yield of products IIIa and IIIb (63-67%) was achieved upon heating equimolar amounts of the reagents in dioxane at reflux for 5-6 h in the presence of 0.15-0.20 molar equivalent acetic acid.



I, III a R = H, b R = Me

Salts of imidates are known to be more reactive than pure imidates in reactions with nucleophilic reagents [10-12]. Hence, the condensation of the hydrochloride salts of imidates IIa-IIe with *o*-aminophenol and 2-amino-5-nitrophenol was carried out under milder conditions by heating equimolar amounts of the reagents in methanol for only 1-2 h. The desired 2-(5-R-2-furyl)-(IIIc-IIIe) and R-[(*E*)-β-(5-R-2-furyl)vinyl]-6-$R^1$-benzoxazoles (IIIf-IIIj) were obtained in 78-90% yield in this case (Table 1).



IIa-e

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*Communication 4, see [1].

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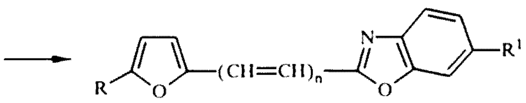

IIIc-j

IIa,d,IIIc,h R = Br; IIb,e IIId,e,i,j R = $NO_2$; IIc,IIIf,g R = H; IIIc,d,f,h,i $R^1$ = H;
IIIe,g,j $R^1$ = $NO_2$; IIa,b, IIIc=e n = 0; IIc-e , IIIf-j n = 1

Benzoxazoles IIIa, IIIf, and IIIi were also obtained in 50-56% yield by the reported method for benzoxazole synthesis by heating equimolar amounts of the corresponding furan acid, *o*-aminophenol, and boric acid in xylene.

The composition and structures of the 2-substituted benzoxazole products (IIIa-IIIj) are in good accord with the elemental analysis data and the PMR and IR spectral indices (Tables 1 and 2). Thus, the IR spectra of these compounds show strong C=N stretching bands at 1630-1610 $cm^{-1}$ for the 2-substituted benzoxazoles [13]. These spectra have strong bands at 1590-1580 and about 935 $cm^{-1}$ as well as bands at 1250 and 1020-1010 $cm^{-1}$ for asymmetric and symmetric stretching vibrations of the =C—O—C= benzoxazole fragment [11]. In addition, all the compounds show bands characteristic for 2-substituted or 2,5-disubstituted furan fragments [13]: 3175-3160 ($\nu$ CH), 1595-1560, 1390-1375 ($\nu$ ring), 1145-1130 ($\beta$ CH), 1005-995 (ring respiration bands), 995-950 ($\gamma$ CH), 890-875 and 785-770 $cm^{-1}$ ($\beta$ ring).

The furan ring proton signals in the PMR spectra of furylbenzoxazoles IIIa, IIIf, and IIIg appear as three doublets at 6.20-6.28 (3-H, $J_{35}$ = 0.8-0.9 Hz), 6.52-6.58 (4-H, $J_{34}$ = 3.2-3.4 Hz), and 7.12-7.28 ppm (5-H, $J_{45}$ = 1.8-1.9 Hz), which is characteristic for 2-substituted furans [13, 14]. The spectra of benzoxazoles IIIb-IIIe and IIIh-IIIj, which have 2,5-disubstituted furan fragments, show doublets for 3-H and 4-H at 6.34-6.50 and 6.63-6.78 ppm, respectively ($J_{34}$ = 3.2-3.7 Hz). The doublets for the vinyl group protons of IIIf-IIIj are found at 6.53-6.82 ($\alpha$-H) and 7.33-7.71 ppm ($\beta$-H). The magnitude of $J_{\alpha\beta}$ (13.5-15.0 Hz) indicates the *trans* arrangement of these protons. The assignment of the downfield signal to the $\beta$-proton relative to the furan ring was made on the basis of the data of Lukevits [14], Gracza [15], and Karakhanov [16] on the PMR spectra of $\alpha,\beta$-disubstituted vinylfurans.

Complex multiplets with integral intensity corresponding to four protons are found for the benzene rings in benzoxazoles IIIa-d, IIIf, IIIh, and IIIi. The protons of $C_{(4)}$ and $C_{(5)}$ of the benzene rings in 6-nitrobenzoxazoles IIIe, IIIg, and IIIj give two doublets of doublets at 7.18-7.30 and 7.74-7.82 ppm ($J_{45}$ = 8.4-9.0 Hz and $^4J_{57}$ = 1.8-2.2 Hz). The signal for 7-H is shifted downfield to 7.94-8.03 ppm and is seen as a quartet with $^4J_{57}$ = 1.8-2.2 Hz.

## EXPERIMENTAL

The IR spectra were taken on a Bruker IFS-48 spectrometer for KBr pellets. The PMR spectra were taken on a Bruker WR-100 SY spectrometer at 100 MHz using TMS as the internal standard. The reaction course and purity of the products were monitored by thin-layer chromatography on grade-III alumina with 10:1 benzene—methanol as the eluent. The spots were developed with iodine vapor.

Starting ethyl imidates Ia [16] and Ib [16] as well as the hydrochloride salts of ethyl imidates IIb [16], IIc [16], and IIe [17] were obtained according to reported procedures.

**Hydrochloride Salt of Ethyl Imidate of 5-Bromo-2-furancarboxylic Acid (IIa).** Dry HCl was passed through a mixture of 8.6 g (50 mmoles) 5-bromo-2-furonitrile and 2.76 g (60 mmoles) absolute ethanol in 150 ml anhydrous ether at 0°C for 2 h. The reaction mixture was then maintained at 0-5°C for 24 h. The precipitated product was filtered off, washed on the filter with anhydrous ether until neutral, and dried in vacuum over KOH to give 10.9 g (86%) IIa which decomposes at 158-159°C (from a mixture of anhydrous ether and glacial acetic acid). Found: C, 33.2; H, 3.4; N, 5.6%. Calculated for $C_7H_8BrNO_2 \cdot HCl$: C, 33.0; H, 3.5; N, 5.5%.

**Hydrochloride salt of the ethyl imidate of (*E*)-$\beta$-(5-bromo-2-furyl) acrylic acid (IId)** was obtained analogously from (*E*)-$\beta$-(5-bromo-2-furyl)acrylonitrile in 78% yield. This compound decomposes at 154-156°C (from a mixture of anhydrous ether and glacial acetic acid). Found: C, 38.4; H, 4.1; N, 5.1%. Calculated for $C_9H_{10}BrNO_2 \cdot HCl$; C, 38.5; H, 3.9; N, 5.0%.

TABLE 1. Characteristics of Products

| Compound | Found, % | | | Chemical formula | Calculated, % | | | mp, °C | $R_f$ | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|
| | C | H | N | | C | H | N | | | |
| IIIa | 71,2 | 3,6 | 7,8 | $C_{11}H_7NO_2$ | 71,3 | 3,8 | 7,6 | 88...89,5$^{*2}$ | 0,75 | 67 |
| IIIb | 72,5 | 4,6 | 6,9 | $C_{12}H_9NO_2$ | 72,4 | 4,5 | 7,0 | 97...98 | 0,67 | 63 |
| IIIc | 49,9 | 2,4 | 5,5 | $C_{11}H_6BrNO_2$ | 50,0 | 2,3 | 5,3 | 113...114,5 | 0,58 | 85 |
| IIId | 57,5 | 2,3 | 12,0 | $C_{11}H_6N_2O_4$ | 57,4 | 2,6 | 12,2 | 229...230 | 0,50 | 78 |
| IIIe | 47,8 | 2,0 | 15,4 | $C_{11}H_5N_3O_6$ | 48,0 | 1,8 | 15,3 | 242...243 | 0,60 | 90 |
| IIIf | 74,1 | 4,1 | 6,8 | $C_{13}H_9NO_2$ | 73,9 | 4,6 | 6,6 | 77...78,5 | 0,70 | 87 |
| IIIg | 60,7 | 3,0 | 11,1 | $C_{13}H_8N_2O_4$ | 60,9 | 3,1 | 10,9 | 139...140,5 | 0,68 | 80 |
| IIIh | 53,9 | 2,9 | 4,7 | $C_{13}H_8BrNO_2$ | 53,8 | 2,8 | 4,8 | 151...152 | 0,62 | 82 |
| IIIi | 61,1 | 3,2 | 10,8 | $C_{13}H_8N_2O_4$ | 60,9 | 3,1 | 10,9 | 168...169 | 0,42 | 84 |
| IIIj | 51,6 | 2,4 | 14,1 | $C_{13}H_7N_3O_6$ | 51,8 | 2,3 | 13,9 | 182...183 | 0,53 | 88 |

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*Products recrystallized from hexane (IIIa and IIIh), petroleum ether (IIIb), aqueous ethanol (IIIc, IIIh, and IIIj), and aqueous DMF (IIId, IIIe, IIIg, and IIIi).

†mp 86.5-87.5°C [6].

TABLE 2. PMR Spectral Data for Products

| Compound | Proton chemical shifts, δ, ppm, J, Hz | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | furan ring protons | | | | | | benzoxazole ring protons | other protons |
| | 3-H(1H) | 4-H(1H) | 5-H(1H) | $J_{35}$ | $J_{34}$ | $J_{45}$ | | |
| IIIa | 6,28 d.d | 6,52 d.d | 7,12 d.d | 0,9 | 3,2 | 1,8 | 7,35...7,62 (4H, m) | – |
| IIIb | 6,34 d | 6,63 d | – | – | 3,3 | – | 7,42...7,90 (4H, m) | 2,18 (3H, s, 5-Me) |
| IIIc | 6,50 d | 6,74 d | – | – | 3,5 | – | 7,53...7,83 (4H, m) | – |
| IIId | 6,42 d | 6,75 d | – | – | 3,7 | – | 7,37...7,72 (4H, m) | – |
| IIIe | 6,38 d | 6,70 d | – | – | 3,6 | – | 7,18 (1H, d.d, 4-H), $J_{45}$ = 9,0, $^4J_{57}$ = 1,8), 7,74 (1H, d.d, 5-H), 8,03 (1H, q, 7-H) | – |
| IIIf | 6,24 d.d | 6,58 d.d | 7,28 d.d | 0,8 | 3,4 | 1,9 | 7,48...7,81 (4H, m) | 6,74 (1H, d, α-CH=, $J\alpha\beta$ = 15,0), 7,40 (1H, d, β-CH=) |
| IIIg | 6,20 d.d | 6,55 d.d | 7,20 d.d | 0,8 | 3,3 | 1,9 | 7,30 (1H, d.d, 4-H, $J_{45}$ = 8,4, $^4J_{57}$ = 2,2), 7,82 (1H, d.d, 5-H), 7,94 (1H, q, 7-H | 6,76 (1H, d, α-CH=, $J\alpha\beta$ = 14,6), 7,55 (1H, d, β-CH=) |
| IIIh | 6,38 d | 6,78 d | – | – | 3,2 | – | 7,56...7,87 (4H, m) | 6,53 (1H, d, α-CH=, $J\alpha\beta$ = 14,0), 7,33 (1H, d, β-CH=) |
| IIIi | 6,48 d | 6,73 d | – | – | 3,3 | – | 7,33...7,59 (4H, m) | 6,82 (1H, d, α-CH=, $J\alpha\beta$ = 13,5), 7,71 (1H, d, β-CH=) |
| IIIj | 6,45 d | 6,68 d | – | – | 3,5 | – | 7,24 (1H, d.d, 4-H, $J_{45}$ = 8,7, $^4J_{57}$ = 2,0), 7,80 (1H, d.d, 5-H), 7,98 (1H, q, 7-H) | 6,80 (1H, d, α-CH=, $J\alpha\beta$ = 13,8), 7,64 (1H, d, β-CH=) |

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*The spectra for IIIa, IIIc, IIIf and IIIh taken in $CD_3OD$, for IIId, IIIe, IIIg and IIIj in DMSO-$d_6$.

**2-(2-Furyl)benzoxazole (IIIa).** A mixture of 2.08 g (15 mmoles) ethyl imidate Ia, 1.64 g (15 mmoles) *o*-aminophenol, and 0.18 g (3 mmoles) acetic acid in 50 ml dioxane was heated at reflux with stirring for 6 h. The reaction mixture was cooled to 20°C and poured into 20 ml cold water. The solution was brought to pH 7.0-7.5 by adding aqueous ammonia. The precipitate of IIIa was filtered off, washed on the filter with water, and dried.

2-(5-Methyl-2-furyl)benzoxazole IIIb was synthesized analogously from imidate Ib.

**2-(2-Bromo-2-furyl)benzoxazole (IIIc).** A mixture of 3.05 g (12 mmoles) hydrochloride salt of imidate IIa and 1.31 g (12 mmoles) in 50 ml absolute methanol was heated at reflux with stirring for 2 h. The reaction mixture was cooled to 20°C and poured into 150 ml cold water. The precipitate of IIIc was filtered off, washed on the filter with water, and dried.

Benzoxazoles IIId-IIIj were synthesized analogously from the hydrochloride salts of imidates IIb-IIe and *o*-aminophenol or 2-amino-5-nitrophenol.

**2-[(*E*)-β-(2-Furyl)vinyl]benzoxazole (IIIf).** A mixture of 1.4 g (30 mmoles) (*E*)-β-(2-furyl)acrylic acid, 3.27 g (30 mmoles) *o*-aminophenol, and 1.8 g (30 mmoles) boric acid in 100 ml xylene was heated at reflux with stirring for 24 h in an apparatus equipped with a Dean—Stark trap. The reaction mixture was cooled to 20°C and filtered. The filtrate was evaporated at reduced pressure and the residue was crystallized from hexane to give 3.55 g (56%) benzoxazole IIIf.

Benzoxazole IIIa was synthesized in 50% yield by this method from 2-furancarboxylic acid, while 2-[(*E*)-β-(5-nitro-2-furyl)vinyl]benzoxazole IIIi was similarly obtained in 53% yield from (*E*)-β-(5-nitro-2-furyl)acrylic acid.

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