SYNTHESIS AND STRUCTURE OF DERIVATIVES OF 7-AMINOBENZO[b]THIOPHENE

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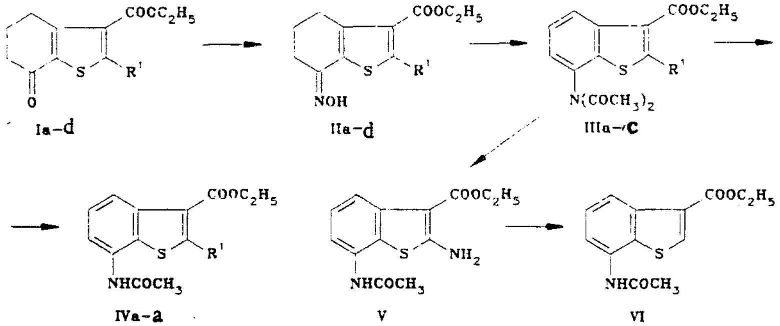
UDC 547.736.07:543.422

Oximes of 2-acylamino-3-ethoxycarbonyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophenes have been prepared. A method for the synthesis of derivatives of 7-aminobenzo[b]thiophene is proposed and the hydrolysis of the compounds prepared has been studied.

Derivatives of 7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene (Ia-d) [1] readily form oximes IIa-d in 50-64% yield. In the IR spectra of oximes IIa-d broad absorption bands are observed in the 3200 cm^{-1} region, evidently due to OH and NH groups participating in the formation of hydrogen bonds. Aromatization of the oximes IIa-c by the action of pyridine, acetyl chloride and acetic anhydride leads to the 7-diacetylaminobenzo[b]thiophenes (IIIa-c). The structure of the compounds prepared was proved by PMR and IR spectroscopy. In the PMR spectrum of the compound IIIa the following signals were observed in the aromatic proton region: 4-H, 8.35 (d, J_{45} = 7.5 Hz), 5-H, 7.52 (t, $J_{45} = J_{56}$ = 7.5 Hz), 6-H, 7.12 ppm (d, J_{56} = 7.5 Hz). To establish the positions of the monoacetylamino- and diacetylamino-groups comparative IR spectra of compound IIIa were run in concentrated and dilute solution in CCl_4. The absence of any shift in the NH band (3240 cm^{-1}) for 4 and 0.02% solutions of IIIa proves that intramolecular hydrogen bonding is present. Hence, the monoacetylamino group is situated at position 2 and is bonded by intramolecular hydrogen bonding with the CO of the ester grouping and the diacetylamino group is at position 7. The acid and alkaline hydrolysis of compounds IIIa-c was studied. The 2,7-bis-acetylamino derivatives IVa, c were isolated by action of dilute acetic acid on benzo[b]thiophenes IIIa, c. 7-Acetylaminobenzo[b]thiophene IVb was prepared by alkaline hydrolysis of compound IIIb. In the IR spectrum of the benzo[b]thiophene IVa, run in concentrated and dilute CCl_4 solution, a band at 3240 cm^{-1}, characteristic of an NH group bonded by intramolecular hydrogen bonds, was observed together with a band due to free NH at 3420 cm^{-1}. Such spectra of derivative IVa are indicative of the hydrolysis of one of the acetyl groups of the diacetylamino substituent at position 7.



I-IV a $R'=NHCOCH_3$; b $R'=NHCOC_6H_5$; c $R'=NHCOC_2H_5$; I-II d $R'=H$

Alkaline hydrolysis of compound IIIa leads to the amino derivative V. In the IR spectrum of compound V, run as a mull in Nujol, NH_2 bands were observed at 3280 and 3400 cm^{-1} and the band due to NH at 3240 cm^{-1} was retained. To prove the position of the amino group, deamination was carried out by the diazo-method. The PMR spectrum of compound VI thus obtained, besides signals for 4-H, 5-H, and 6-H protons at 8.40 (d, J_{45} = 7.5 Hz), 7.49 (5, $J_{45} = J_{56}$ = 7.5 Hz), and 7.70 (d, J_{56} = 7.5 Hz), respectively, there was a singlet 2-H proton signal at 8.54 ppm.

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*Deceased.

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TABLE 1. Characteristics of Compounds Prepared

Compound	mp, °C*	Found, %				Empirical formula	Calc., %				Yield, %
		C	H	N	S		C	H	N	S	
IIb	227—228	60,5	5,2	7,8	9,1	$C_{18}H_{18}N_2O_4S$	60,3	5,1	7,8	8,9	47,4
IIc	219—220	53,9	6,0	9,0	10,7	$C_{14}H_{18}N_2O_4S$	54.2	5,8	9,0	10,3	64,5
IId	143—144	55,4	5,7	6,3	13,5	$C_{11}H_{13}NO_3S$	55,2	5,5	5,9	13,4	51,3
IIIb	234—235	62,4	4,6	6,7	7,5	$C_{22}H_{20}N_2O_5S$	62,2	4,7	6,6	7,5	61,3
IIIc	199—200	57,0	4,9	7,1	8,4	$C_{18}H_{20}N_2O_5S$	57,4	5,3	7,4	8,5	39,6
IVc	211—212	57,6	5,6	8,3	9,5	$C_{16}H_{18}N_2O_4S$	57,5	5,4	8,4	9,6	66,0

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*Compound IIb was recrystallized from 2:1 methanol—dioxane; IId from 80% aqueous EtOH; IIIb, c and IVc from dioxane.

EXPERIMENTAL

PMR spectra were run on a Varian XL-200 instrument; TMS was used as reference standard. A Perkin-Elmer 599 spectrophotometer was used for the infrared spectra; samples were examined as Nujol mulls or in CCl_4 solution. The molecular weight of the compounds prepared was determined by mass spectrometry on a Varian MAT-112 instrument with direct introduction of the sample into the ion source, The ionization energy was 70 eV.

Characteristics of the compounds prepared are set out in Table 1.

Oxime of 2-Acetylamino-3-ethoxycarbonyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene (IIa). To a solution of 14 g (50 mmole) compound Ia in 100 ml dry pyridine was added 4.2 g (60 mmole) hydroxylamine hydrochloride. The reaction mixture was kept at 20°C for 48 h. It was poured into water and the precipitate filtered off and recrystallized from 2:1 methanol—dioxane. Yield 9.8 g (55.2%), mp 226-227°C. IR spectrum, cm^{-1}: 1675 (CO), 3200 (OH). Found, %: C 52.6, H 5.4, N 9.2, S 10.8; M^+ 296. $C_{13}H_{16}N_2O_4S$. Calculated, %: C 52.7, H 5.4, N 9.4, S 10.8; M 296.

2-Acetylamino-7-diacetylamino-3-ethoxycarbonylbenzo[b]thiophene (IIIa). To a suspension of 2.96 g (10 mmole) compound IIa in 6 ml acetic anhydride and 0.8 ml (10 mmole) dry pyridine was added a mixture of 0.9 ml (12 mmole) acetyl chloride and 4 ml acetic anhydride. The reaction mixture was boiled for 1 h, cooled, and the precipitated solid filtered off and washed with alcohol. Yield 1.81 g (50.0%), mp 181.5-182.5°C (1:1 dioxane alcohol). IR spectrum, cm^{-1}: 1670, 1690, 1710 (CO); 3240 (NH). PMR spectrum, ppm (in $CDCl_3$): 12.0 (str. s, NH), 8.35 (d, J = 7.5 Hz, 4-H), 7.52 (t, J_{45} = J_{56} = 7.5 Hz, 5-H), 7.12 (d, J_{56} = 7.5 Hz, 6-H), 1.52, 4.51 (t, q. $COOC_2H_5$), 2.33, 2.35 (s, $NHCOCH_3$, s, 6-H, $N(COCH_3)_2$). Found, %: C 56.3, H 5.2, N 7.8, S 9.3; M^+ 362. $C_{17}H_{18}N_2O_5S$. Calculated, %: C 56.3, H 5.0, N 7.7, S 8.8; M 362.

2,7-Diacetylamino-3-ethoxycarbonylbenzo[b]thiophene (IVa). A reaction mixture comprising 7 g (195 mmole) compound IIIa, 56 ml acetic acid, and 14 ml water was heated to boiling for 2 h, cooled, and the precipitate filtered off and washed with methanol. Yield 5.8 g (93.8%), mp 241-242°C (dioxane). IR spectrum, cm^{-1}: 1660, 1700 (CO), 3240 (NH). Found, %: C 56.5, H 5.0, N 8.4, S 9.8; M^+ 320. $C_{15}H_{16}N_2O_4S$. Calculated, %: C 56.2, H 5.0, N 8.7, S 10.0; M 320.

7-Acetylamino-2-benzoylamino-3-ethoxycarbonylbenzo[b]thiophene (IVb). To a suspension of 2 g (47 mmole) compound IIIc in 5 ml dioxan and 10 ml alcohol was added a solution of 0.5 g (12.5 mmole) NaOH in 3 ml water and the mixture stirred for 1 1/2 h at 20°C and then filter The filtrate was poured into water and the precipitated solid filtered off. Yield 0.82 g (45.5%, mp 258-259°C (from dioxane). IR spectrum, cm^{-1}: 1660 (CO), 3240 (NH). Found, %: C 62.9, H 4.8, N. 7.5, S 8.3; M^+ 382. $C_{20}H_{18}N_2O_4S$. Calculated, %: C 62.8, H 4.7, N 7.3, S 8.4; M 382.

2-Amino-7-acetylamino-3-ethoxycarbonylbenzo[b]thiophene (V). To a suspension of 18 g (50 mmole) compound IIIa in 30 ml dioxan and 50 ml methanol was added a solution of 5 g (125 mmole) NaOH in 15 ml water and the mixture stirred for 30 min. It was then diluted with water and the precipitated solid filtered off. Yield 11.4 g (82.5%), mp 222-223°C (from EtOH). IR spectrum, cm^{-1}: 1630, 1670 (CO); 3240 (NH); 3280, 3400 (NH_2). Found, %: C 56.0, H 5.0, N 10.3, S 11.5; M^+ 278. $C_{13}H_{14}N_2O_3S$. Calculated, %: C 56.1, H 5.1, N 10.1, S 11.5; M 278.

7-Acetylamino-3-ethoxycarbonylbenzo[b]thiophene (VI). To a suspension of 3 g (11 mmole) compound V in 60 ml dioxane, 40 ml EtOH and 9 ml concentrated HCl, cooled to −10°C, was added a solution of 2 g (29 mmole) sodium nitrite in 6 ml water, maintaining the reaction mixture at −10°C and holding it as this temperature for a further 20 min. The diazo solution was then added to a solution of 0.05 g copper acetate in 25 ml EtOH and the mixture held at 70°C for 30 min and then poured into water. The solution was extracted with $CHCl_3$, the chloroform evaporated, alcohol added to the residue and the solid filtered off. Yield 1 g (35.2%), mp 194-195°C (from EtOH). IR spectrum, cm^{-1}: 1645, 1710 (CO); 3240 (NH). PMR spectrum (in acetone-d_6), ppm: 9.26 (str. s, NH), 8.55 (s, 2-CH), 8.40 (d, J_{45} = 7.5 Hz, 4-CH), 7.70 (str. d, J_{45} = 7.5 Hz, 6-H), 7.49 (t, J_{45} = J_{56} = 7.5 Hz, 5-H), 4.39, 1.70 (t, d, $COOCH_2CH_3$), 2.20 (str. s, $COCH_3$). Found, %: C 59.2, H 5.0, N 5.2, S 12.3; M^+ 263. $C_{13}H_{13}NO_3S$. Calculated, %: C 59.3, H 5.0, N 5.3, S 12.2; M 263.

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^{13}C AND ^{15}N NMR SPECTRA OF 2,3-SUBSTITUTED 2H-AZIRINES

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UDC 547.717:543.422.25

The ^{13}C and ^{15}N NMR spectra of a series of 2,3-substituted 2H-azirines have been studied. The ^{15}N chemical shift for the nitrogen in the azirine ring is found at much higher field than in acyclic imines with a considerable electronic effect for the substituents on the double bond. Cooperative steric and electronic effects associated with substituents on the unsaturated carbon atom of the ring were found to influence the shielding of the ^{13}C and ^{15}N nuclei. Reaction constants have been calculated for 2-alkyl(aryl)-3-phenylazirines. It has been shown that the azirine ring has a powerful −I effect (when compared with the phenyl ring) that exceeds the analogous value for the cyano group.

The ^{13}C and ^{15}N NMR spectra of a series of 2,3-substituted 2H-azirines have been examined in order to study the factors influencing ^{13}C and ^{15}N nuclear shielding in 2H-azirines and the effect of the azirine ring on adjacent bonds.

The ^{13}C and ^{15}N NMR spectral parameters are given in Tables 1 and 2. In the literature [1, 2] only the ^{13}C spectra of II and III have been reported and our results are in good agreement. Assignment of ^{13}C signals were carried out using long range $^{13}C-^{1}H$ spin-spin coupling constants as described in [2].

The ^{15}N signal for the nitrogen of the azirine ring was shifted to high field of the cyclic analogues of azirines — the imines [3, 4]. This is apparently due to steric strain in the three membered ring. Analogous shifts have been reported [5] for aziridines when compared with acyclic amines. High field shifts for the azirines (~40-50 ppm) were larger than for the aziridines (~35-45 ppm) [5]. This is possibly connected with the higher ring strain at the nitrogen atom in the azirines than the aziridines. ^{15}N chemical shifts (CS) depend significantly on the properties of the substituents on the double bond, the basic influence on this shift being the mesomeric effect. This is a consequence of the correlation of ^{15}N CS with the reaction constants for the 3-substituents. The ^{15}N resonance was shifted to higher field with increasing donor ability of this substituent (COOEt < Ph < NH_2) and is in agreement with observations on imines [3, 4]. The effect of the C_2 substituent on the ^{15}N shift was also observed. Notable symbate shifts for both ^{15}N and C_3 resonances were observed

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0009-3122/86/2209-0953$12.50