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SYNTHESIS AND STRUCTURE OF DERIVATIVES OF 7-OXO-4,5,6,7-TETRAHYDROBENZO[b]-THIOPHENE AND 7-HYDROXYBENZO[b]THIOPHENE

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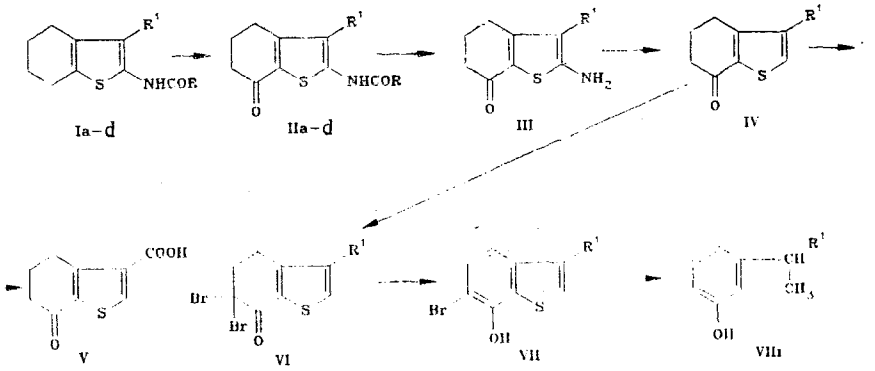
The oxidation of 2-acylamino-3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thiophenes gave the corresponding 7-oxotetrahydrobenzo[b]thiophenes and some of the transformations of these compounds were studied. These compounds were used for the synthesis of 3-ethoxycarbonyl-6-bromo-7-hydroxybenzo[b]thiophene. The structures of the compounds prepared were established by chemical and spectral methods.

α-Amino derivatives of heterocyclic compounds often display an enhanced tendency to undergo oxidation, thereby giving valuable oxo and hydroxy compounds [1]. We studied the potassium dichromate oxidation of 2-acylamino-3-ethoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thiophenes Ia-d [2, 3] in acetic acid, which leads to the corresponding 7-oxotetrahydrobenzo[b]thiophenes IIa-d. A subsequent series of transformations (see Scheme) permits preparation not only of various derivatives of 7-oxotetrahydrobenzo[b]thiophenes and 3-ethoxycarbonyl-6-bromo-7-hydroxybenzo[b]thiophene (VII), but also phenol VIII by desulfurization of VII. This final step facilitated the proof of the structures of all the compounds synthesized.



I, II a R=CH_3; b R=H; c R=CH_2Cl; d R=C_6H_5; I—IV, VI—VIII R^1=$COOC_2H_5$

The PMR spectrum of Ia has signals for methylene groups at positions 5 and 6 as a complex multiplet centered at 1.78 ppm, while the signals for the methylene groups at positions 4 and 7 appear as triplets at 2.75 and 2.64 ppm, respectively. The assignment of the two latter signals was made by comparison with the spectrum of 2-acetylamino-4,5,6,7-tetrahydrobenzo-[b]thiophene (IX) [3], which does not contain an ethoxycarbonyl group at C-3. The only signal shifted downfield by 0.26 ppm in going from IX to Ia was assigned to the CH_2 group at C-4. The PMR spectrum of the oxidized product IIa was signals for three methylene groups: two triplets (at 2.57 and 3.07 ppm) and a quintet (at 2.16 ppm). This multiplicity is possible only if the carbonyl group is at C-4 or at C-7. Selection of these two positions by comparison of

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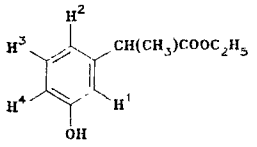
TABLE 1. Derivatives of 2-Acylamino-3-ethoxycarbonyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene (IIb-d)

Compound	mp, °C*	Found, %				Chemical formula	Calculated, %				Yield, %
		C	H	N	S		C	H	N	S	
IIb	191—192	53,7	4,9	5,2	11,8	$C_{12}H_{13}NO_4S$	53,9	4,9	5,2	12,0	52,1
IIc	158—159	49,5	4,6	4,3	9,9	$C_{13}H_{14}ClNO_4S$	49,5	4,5	4,4	10,1	50,9
IId	250—251	63,0	4,8	4,0	9,1	$C_{18}H_{17}NO_4S$	63,0	5,0	4,0	9,3	39,7

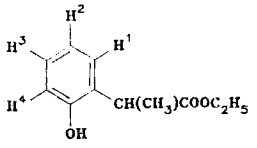
*IIb and IIc were crystallized from 5:1 methanol—dioxane, while IId was crystallized from dioxane.

the PMR spectra of Ia and IIa is impossible due to the slight difference in the chemical shifts of the methylene groups at C-4 and C-7 in the spectrum of Ia.

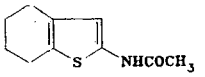
An unequivocal conclusion concerning the structure of IIa-d was obtained in a spectroscopic study of VIII. Depending on the position of the carbonyl group in IIa-d (at C-7 or C-4), phenol VIII may have either structure VIIIa or VIIIb.



VIIIa



VIIIb



IX

The signal of only one proton in phenol VIIIa may be split by two ortho couplings with protons at C-6 and C-4, while the signals of two protons at C-4 and C-5 should be split by the same constants in phenol VIIIb. The actual spectrum shows only one signal split by two ortho couplings at 7.10 ppm (J^1 = 8.2, J^2 = 7.8, J^3 = 0.3 Hz). Apparently, such a signal may belong only to proton 5-H in VIIIa. Proton 6-H has a signal at 6.82 ppm (octet, J_{56} = 8.2, J_{26} = 2.4, J_{64} = 1 Hz). The signals of the two remaining aromatic protons in the monoresonance spectrum have more complex multiplicity due to long-range spin—spin couling with a substituent proton. This signal is found at 3.56 ppm and appears as a quartet, each component of which is split into doublets with J ≅ 0.6 Hz. The double resonance spectrum with suppression of the coupling of this proton has simplified multiplicity for the aromatic protons indicated above. This multiplicity permitted the following assignments: 4-H, 6.87 (octet, J_{45} = 7.8, J_{64} = 1, J_{24} = 1.6 Hz) and 2-H, 7.05 ppm (octet, J_{42} = 1.6, J_{26} = 2.4, J_{25} = 0.3 Hz). We should note that the existence of long-range allylic coupling for proton 4-H permits distinction of the signals for 4-H and 6-H and provides additional support with two aromatic protons (4-H and 2-H).

Thus, our study of VIII demonstrates that the oxo and hydroxy groups in derivatives II (a-d)-VII are at C-7.

EXPERIMENTAL

The PMR spectra were taken on a Varian XL-200 spectrometer with TMS as internal standard. The IR spectra were taken on a Perkin-Elmer 599 spectrophotometer. The molecular masses of the compounds synthesized were found using a Varian MAT-112 mass spectrometer with direct sample introduction into the ion source. The electron ionization energy was 70 eV.

2-Acetylamino-3-ethoxycarbonyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene (IIa). A solution of 200 g potassium dichromate in 500 ml water at 60-70°C was added with stirring to a solution of 120 g (0.45 mole) Ia in 1 liter acetic acid heated to 60°C, maintaining the temperature of the reaction mixture at 65-80°C. After addition of the potassium dichromate solu-

tion, the reaction mixture was slowly cooled to 20°C and maintained for 2 h. Water was added. The precipitate was filtered off and recrystallized from 1:1 methanol–dioxane to yield 82 g (64.9%) IIa, mp 188-189°C. IR spectrum: 1660, 1690 (CO), 3235 cm^{-1} (NH). Found: C, 55.5; H, 5.5; N, 5.0; S 11.6%; M^+ 281. Calculated for $C_{13}H_{15}NO_4S$: C, 55.5; H 5.4; N, 5.0; S, 11.4%; M 281.

The characteristics of IIb-d are given in Table 1.

2-Amino-3-ethoxycarbonyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene (III). A. A sample of sodium methylate prepared from 1.25 g (0.5 mole) sodium and 12.5 ml methanol was added to a suspension of 15 g (0.35 mole) acylamine IIa in 80 ml methanol. The reaction mass was maintained for 1 h at 20°C. The precipitate was filtered off and washed with methanol to give 11 g (83%) amine III, mp 208-209°C (from 1:1 dioxane–methanol). IR spectrum: 1630, 1680 (CO), 3180-3380 cm^{-1} (NH_2). Found: C, 54.8; H,5.1; N, 5.7; S, 13.6% M^+ 239. Calculated for $C_{11}H_{13}NO_3S$: C, 55.2; H, 5.4; N, 5.8; S, 13.4%; M 239.

B. A solution of 5.6 g (0.1 mole) KOH in 110 ml methanol was added to a suspension of 21 g (0.075 mole) acylamine IIa in 210 ml methanol. The reaction mass was maintained for 1 h at 20°C. The precipitate was filtered off and washed with methanol to yield 12.6 g (67%) amine III, mp 208-209°C (from 1:1 dioxane–methanol). Samples of III obtained from amide IIa by method B and from amides IIb-d by methods A and B does not give a depressed mixed melting points with a sample of III obtained from IIa by method A and have identical IR spectra.

3-Ethoxycarbonyl-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene (IV). A solution of 56.7 g (0.72 mole) sodium nitrile in 150 ml water was ddded to a suspension of 97 g (0.4 mole) amine III in 360 ml dioxane and 283 ml conc. HCl cooled to −10°C, maintaining the temperature of the reaction mass from −7° to −10°C. After addition, the reaction mass was maintained for an additional 20 min at this temperature. Then the diazo solution obtained was added to a solution of 1.54 g copper acetate in 790 ml ethanol and the reaction mixture was maintained for 30 min at 70°C, poured into water, and extracted with chloroform. The chloroform was distilled off and the residue was distilled at 185-190°C (11 mm) to yield 55.2 g (60.7%) ester IV, mp 62-63°C (from hexane). IR spectrum: 1670, 1715 cm^{-1} (CO). PMR spectrum ($CDCl_3$, ppm): 1.39 T (CH_3, J = 7 Hz), 2.20 q (2H), 2.63 t (2H), 3.19 t (2H), 4.35 q (CH_2, J = Hz), 8.39 s (1H). Found: C, 58.6; H, 5.3; S, 13.6%; M^+ 224. Calculated for $C_{11}H_{12}O_3S$: C, 58.9; H, 5.4; S, 14.3%; M 224.

7-Oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylic Acid (V). A reaction mixture consisting of 4.48 g (0.02 mole) ester IV, 1.6 g (0.04 mole) NaOH and 20 ml ethanol was heated at reflux for 20 min, poured into ice water, acidified with hydrochloric acid, the precipitate was filtered off and recrystallized from methanol to yield 1.8 g (45.9%) V, mp 287-288°C. IR spectrum: 1640, 1720 (CO), 3040 cm^{-1} (OH). Found: C, 54.8; H, 4.1; S, 16.3%. Calculated for $C_9H_8O_3S$: C, 55.1; H, 4.1; S, 16.3%.

3-Ethoxycarbonyl-6,6-dibromo-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene (VI). A solution of 5.25 ml (0.1 mole) bromine in 50 ml chloroform was gradually added to a solution of 11.2 g (0.05 mole) ester IV in 150 ml chloroform containing a catalytic amount of benzoyl peroxide and heated at reflux. The reaction mass was heated at reflux for an additional 45 min, cooled and washed with water. The chloroform was distilled off and the residue was crystallized from 3:1 hexane–benzene to yield 18 g (93.7%) dibromide VI, mp 101-102°C. PMR spectrum ($CDCl_3$, ppm): 1.4 t (CH_3, J = 7 Hz), 3.12 t (2H), 3.32 t (2H), 4.36 q (CH_2, J = 7 Hz), 8.50 s (1H). Found: C, 34.8; H, 2.6; Br, 41.5%; M^+ 380 (^{79}Br). Calculated for $C_{11}H_{10}Br_2O_3S$: C, 34.6; H, 2.6; Br, 41.8%; M 380 (^{79}Br).

3-Ethoxycarbonyl-6-bromo-7-hydroxybenzo[b]thiophene (VII). A reaction mixture consisting of 11.46 g (0.03 mole) dibromide VI, 7.38 g (0.09 mole) fused sodium acetate and 75 ml acetic acid was heated at reflux for 7 h, poured into water, and extracted with chloroform. The chloroform was distilled off and the residue was distilled at 212-214°C (10 mm) to give 3.7 g (42.7%) VII, mp 97-97.5°C (hexane). IR spectrum: 1700 (CO), 3200-3500 cm^{-1} (OH). PMR spectrum ($CDCl_3$, ppm): 1.43 t (CH_3, J = 7 Hz), 4.42 q (CH_2, J = 7 Hz), 7.53 d (1H, J = 8.7 Hz), 8.05 d (1H, J = 8.7 Hz), 8.36 S (1H). Found: C, 43.8; H 3.0; Br, 26.5; S, 10.3%; M^+ 300 (^{79}Br). Calculated for $C_{11}H_9BrO_3S$: C, 43.9; H, 3.0; Br, 26.5; S, 10.6%; M 300 (^{79}Br).

Ethyl Ester of α-(3-Hydroxyphenyl)propionic Acid (VIII). A reaction mixture consisting of 15 g (0.05 mole) VII, 75 g W7 Raney nickel [4] and 330 ml 50% aqueous ethanol was heated at reflux for 2 h and filtered. The mother liquid was evaporated in vacuum. The oily residue was dissolved in benzene. The benzene solution was purified with activated charcoal and

the benzene was distilled off. The oily residue was dissolved in ether. The ethereal solution was washed with water, purified with activated charcoal, and dried over magnesium sulfate. The ether was distilled off to give 6.5 g (67.3%) phenol VIII as an oily liquid without impurities as indicated by thin-layer chromatography on Silufol plate with 20:1 chloroform–ethanol as eluent, R_f 0.68. IR spectrum: 1660 (CO), 3400 cm^{-1} (OH). PMR spectrum (C_6D_6, ppm): 0.88 t (CH_3, J = 7 Hz), 1.42 d (CH_3, J = 7 Hz), 3.56 oct (1H, J^1 = 7 Hz, J^2 = 0.6 Hz), 3.90 m (CH_2). Found: C, 67.9; H, 7.2%; M^+ 194. Calculated for $C_{11}H_{14}O_3$: C, 68.0; H, 7.3%; M 194.

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MONOESTERS OF TETRATHIAFULVALENE-2,6(7)-DICARBOXYLIC ACID AND THEIR USE IN THE PREPARATION OF TETRATHIAFULVALENECARBOXYLIC ACID

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Monoesters of tetrathiafulvalene-2,6(7)-dicarboxylic acid were synthesized. Decarboxylation of these esters with subsequent hydrolysis gave tetrathiafulvalenecarboxylic acid. Pure mono- and diesters of tetrathiafulvalenedicarboxylic acids were isolated but their assignment to the 2,6- and 2,7-series requires further study.

Three carboxylic acids are known among the strong tetrathiafulvalene derivative electron donors: tetrathiafulvalenetetracarboxylic acid (I) [1], tetrathiafulvalene-2,6(7)-dicarboxylic acid (II) [2], and tetrathiafulvalenecarboxylic acid (III) [3]. Special interest lies in the not readily available monoacid III which contains an active functional group which permits various reactions while at the same time it is a strong electron donor [3]. Several good methods are known for the preparation of acids I and II [1, 2, 4, 5]. Thus, we found it useful to develop a synthesis for acid III from the more available dicarboxylic acid II.

The direct conversion of II to III, as observed in the case of the conversion of I to II [2], is impossible since monocarboxylic acid III decarboxylates much more readily than acid II [6]. Thus, we protected one carboxylic acid function as an ester with subsequent decarboxylation and hydrolysis.

Monoesters of dicarboxylic acid II have not been reported. Alkylation of II using alkyl bromides and iodides according to Shaw et al. [7] leads to a mixture of monoester IV (∿30%) and diester V (15-25%). In addition, we encounter <5% products of the decarboxylation of acids III and IV (tetrathiafulvene and alkoxycarbonyltetrathiafulvalene VI) and the recovery of about 40% of starting acid II (Table 1).

Monoesters IVa-d decarboxylate above 160°C, for example, in refluxing diglyme, to give VIa-d in 70-90% yield: these products may be used to obtain acid III [8].

The spectral data for esters VIa-d which are reported for the first time in this communication are summarized along with the data for the known ester of tetrathiafulvalenecarboxylic acid [3] given for comparison (Table 2).

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