ALKYL- AND ARYLAMINATION OF 3-HYDROXY-4-CARBETHOXY-5-METHYLTHIOPHENE

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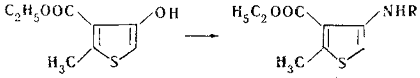
N-Alkylaminothiophene derivatives were obtained by the reaction of 3-hydroxy-4-carbethoxy-5-methylthiophene with alkylammonium acetates, while N-arylaminothiophene derivatives were obtained by the reaction of the same thiophene derivative with aromatic amines in the presence of catalytic amounts of iodine.

Alkylaminothiophenes are comparatively hard to obtain and are unstable [1]. There are no data on arylaminophenes in the literature. We have studied the reaction of 3-hydroxy-4-carbethoxy-5-methylthiophene [2] with alkylammonium acetates. While 3-amino-4-carbethoxy-5-methylthiophene or a dithienylamine derivative [2,3] are formed by the action of ammonium acetate on 3-hydroxy-4-carbethoxy-5-methylthiophene, depending on the reaction conditions, the reaction with alkylammonium acetates proceeds unambiguously and leads to the formation of high yields of substituted alkylaminothiophenes (I-III). The thiophenes obtained in this study are stable compounds; this may be explained by the presence of an electronegative substituent in the thiophene ring. We have synthesized arylaminothiophenes (IV-VI) for the first time in 69-86% yields by condensation of 3-hydroxy-4-carbethoxy-5-methylthiophene with aromatic amines in the presence of catalytic amounts of iodine [4].



An N-acetyl derivative was obtained by acetylation of II with acetyl chloride; this was hydrolyzed without isolation to 3-(N-acetyl)-butylamino-5-methylthiophene-4-carboxylic acid (VII).

The structure of the compounds obtained were confirmed by IR, UV, and NMR spectroscopy. An intense absorption at 3420-3360 cm^{-1} was observed in the IR spectra of I-VI and corresponds to the valence vibrations of the NH group. Acetylation of the latter leads to the disappearance of this absorption and to the appearance of a new band at 1615 cm^{-1} (RCONH). The absorption at 3120 cm^{-1} in the spectra of both the starting 3-hydroxy-4-carbethoxy-5-methylthiophene and the I-VI is due to the valence vibrations of the α-CH group, which was previously noted in other cases [5-7]. The vibrational frequency of the carbonyl group of I-VI, as in derivatives of 2-amino-3-carbethoxythiophenes [8], is lowered to 1700-1680 cm^{-1}, which can be explained by the presence of a hydrogen bond between the carbonyl and amino groups. An absorption characteristic for the thiophene ring is present at ~790 cm^{-1} in the IR spectra of all of the compounds studied and corresponds to the vibrational frequencies of thiophene and its derivatives [7].

Depending on the character of the radical attached to the carbon atom, the UV spectra of the compounds we synthesized differ from the UV spectra of unsubstituted aminothiophenes. Two peaks of high intensity are observed at 230 and 315 nm [8] in the UV spectra of the aminocarbethoxythiophenes. The introduction of an alkyl substituent on the amino group leads to a bathochromic shift of the absorption band at 315-345 nm (log ε 3.32), while no definite changes were observed in the position of the maximum at 230 nm. Replacement of the hydrogen of the amino group by an aryl residue (IV-VI) causes a bathochromic shift in

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TABLE 1. N-Substituted 3-Amino-4-carbethoxy-5-methylthiophene

Compound	R	Mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
				C	H	N	S	C	H	N	S	
I	CH_3	37—38	$C_9H_{13}NO_2S$	54,45 54,23	6,70 6,47	7,12 7,26	16,12 16,36	54,24	6,78	7,03	16,09	86
II	n-C_4H_9	*	$C_{12}H_{19}NO_2S$	59,69 59,79	7,76 7,76	6,05 6,06	13,12 13,44	59,72	7,93	5,80	13,29	69
III	CH_2—C_6H_5	25—26	$C_{15}H_{17}NO_2S$	65,62 65,82	6,25 6,34	4,97 5,21	11,64 11,60	65,43	6,22	5,09	11,64	69
IV	C_6H_5	54—55	$C_{14}H_{15}NO_2S$	64,39 64,05	5,60 5,71	5,29 5,48	12,43 12,69	64,33	5,78	5,36	12,27	83
V	p-$CH_3C_6H_4$	83,5—84	$C_{15}H_{17}NO_2S$	65,03 65,02	6,19 6,09	4,97 5,00	11,82 11,78	65,43	6,22	5,09	11,64	81
VI	p-$CH_3OC_6H_4$	90—90,5	$C_{15}H_{17}NO_3S$	61,80 61,49	5,72 5,60	5,03 4,95	10,82 11,10	61,83	5,88	4,80	11,00	87

*Bp 133-134°C (1 mm).

the bands at both 230 nm and 315 nm and gives rise to a new absorption maximum. The first two peaks are of about equal intensity and are found at 250 and 283 nm (log ε 4.17 and 4.21), while the third is at 355 nm (log ε 3.35).

The NMR spectra of arylaminophenes IV and VI contain one singlet at 6 ppm, which can be ascribed to the proton in the α position of the thiophene ring, and a weak signal from the NH proton with a chemical shift of 8.2 ppm. The signals of the amine protons in the spectra of aminocarbethoxythiophenes that are not substituted at nitrogen are shifted to stronger field (δ 7.02-6 ppm) [9].

EXPERIMENTAL

3-Alkylamino-4-carbethoxy-5-methylthiophenes (I-III). A mixture of 0.025 mole of 3-hydroxy-4-carbethoxy-5-methylthiophene and 0.5 mole of alkylammonium acetate was heated with stirring at 120-130 deg C for 10 min. The reaction solution was then poured into 100 ml of ice water, and the resulting precipitate was filtered and washed on the filter with water. When the alkylaminothiophene derivative formed was an oil, it was extracted with ether. The ether solution was then washed with water and dried with magnesium sulfate. The solvent was removed, and the residue was distilled in vacuo.

3-Arylamino-4-carbethoxy-5-methylthiophenes (IV-VI). A mixture of 0.025 mole of 3-hydroxy-4-carbethoxy-5-methylthiophene, 0.5 mole of aromatic amine, and 0.015 g of iodine crystals was heated for 3 h at 180-190 deg. The reaction mixture was then cooled to room temperature and poured with stirring into 40 ml of ice-cooled 10% hydrochloric acid. The resulting precipitate was filtered and washed with water.

Data on aminothiophenes I-VI are presented in Table 1.

3-(N-Acetyl)-butylamino-5-methylthiophene-4-carboxylic Acid (VII). A mixture of 1.6 g (0.006 mole) of II, 1.6 ml of dioxane, and 3.2 ml (0.045 mole) of acetyl chloride was refluxed for 20 min. The reaction solution was then poured into ice water, and the resulting oil was extracted with ether. The ether solution was washed with water, dried with magnesium sulfate, and the solvent was removed by distillation. The residue was refluxed for 30 min with alcoholic alkali prepared from 0.5 g (0.012 mole) of sodium hydroxide and 10 ml of ethanol. The resulting solution was diluted with three volumes of water and acidified with acetic acid. The precipitate was filtered and washed with water to give 1.3 g (79%) of VII with mp 154-155 deg (from methanol). Found, %: C 56.54, 56.37; H 6.58, 6.86; N 5.75, 5.80; S 12.62, 12.74. $C_{12}H_{17}NO_3S$. Calculated %: C 56.45; H 6.71; N 5.49; S 12.55.

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