SYNTHESIS OF DERIVATIVES OF 2-AMINO-3-ETHOXYCARBONYLTHIOPHENE

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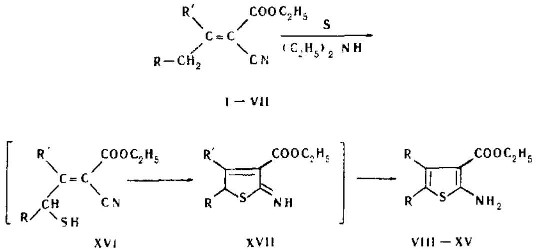
A number of alkylidene esters are synthesized from the corresponding ketones and cyanoacetic ester, and treatment of the esters with sulfur in the presence of a catalytic amount of diethylamine gives 2-amino-3-ethoxycarbonylthiophene derivatives.

One of our papers [1] describes the synthesis of some 2-amino-3-ethoxycarbonylthiophene derivatives by the Gewald method [2]. Continuing these researches, we found that alkylidenecyanoacetic esters (I–VI) prepared by a known method [3] from aromatic ketones are readily converted by reaction with sulfur in the presence of a catalytic amount of diethylamine, into 2-amino-3-ethoxycarbonyl-4-arylthiophenes* (VIII–XIII).

Furthermore, 2-amino-3-ethoxycarbonyl-4-methyl-5-acetoxyethylthiophene (XIV) is obtained from acetopropyl acetate via the alkylidene derivative VII.

Reaction of I–VII with elemental sulfur evidently first results in formation of mercapto derivatives XVI, cyclizing to aminothiophenes VIII–XV via the imines XVII which are tautomers of the latter. Secondary amines catalyze this process.



Formation of 2-amino-3-ethoxycarbonyl derivatives of pyrrole [4] and furan [5] proceeds similarly.

The UV spectra of the 2-amino-3-ethoxycarbonylthiophene derivatives obtained exhibit two absorption maxima, one characteristic of thiophene derivatives and having λ_{max} at about 230 mμ [6], with a heightened absorption intensity (lg ε 4.3–4.48 instead of 3.9), and the other in the 300 mμ region, and of somewhat lower intensity. Evidently the observed bathochromic effect is due to the presence of functional groups conjugated with the thiophene ring, and interacting between themselves. The IR spectra of all the compounds investigated are found to contain absorption bands characteristic of the thiophene ring, at 785 cm^{-1} (medium) and 1410 cm^{-1} (strong) [7].

EXPERIMENTAL

Preparation of alkylidene esters (I-VII). A mixture of 0.25 mole ketone, 28.3 g (0.25 mole) cyanoacetic ester, 3.8 g NH$_4$OAc, 6 g glacial AcOH, and 50 ml benzene was refluxed under a Dean and Stark device until water ceased to separate. The reaction products were washed with water, the benzene distilled off, and the residue vacuum-distilled (Table 1).

Synthesis of 2-amino-3-ethoxycarbonylthiophene derivatives (VIII-XIV). 0.16 mole alkylidene ester, 5.1 g (0.16 g at) finely ground S, 35 ml EtOH, and 6 ml Et$_2$NH were stirred together until the solid sulfur had dissolved, the homogeneous solution heated for 20 min on a water-bath, and left to cool, then the crystals formed were filtered off (Table 2).

2-Amino-3-ethoxycarbonyl-4-(2', 5'-dimethoxyphenyl)thiophene (XV). A mixture of 46.6 g (0.26 mole) 2, 5-dimethoxyacetophenone, 28.3 g (0.25 mole) cyanoacetic ester, 3.85 g NH$_4$OAc, 6 g glacial AcOH, and 50 ml benzene was refluxed under a Dean and Stark device, for 6 hr. The reaction products were cooled, washed with water, and the solvent vacuum-distilled off on a water-bath. 6.4 g (0.2 g at) S, 40 ml EtOH, and 8 ml Et$_2$NH were added, and reaction effected under the conditions previously described, to give 66 g XV (82.8%), mp 100–101° (ex acetone). Found: C 58.52; 58.57; H 5.56; 5.90; N 4.42; 4.39; S 10.29; 10.21%. Calculated for $C_{15}H_{17}NO_4S$: C 58.61; H 5.57; N 4.56; S 10.43%.

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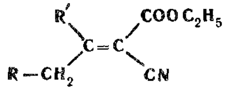
*2-Amino-3-ethoxycarbonyl-4-(2', 5'-dimethoxyphenyl)thiophene (XV) is obtained without isolating the alkylidene ester.

Table 1



Alkylidene Esters

Compound	R	R′	Amount of starting ketone g (mole)	Bp, °C (pressure, mm)	n_D^{20}	Formula	Found, %			Calculated, %			Yield, %
							C	H	N	C	H	N	
I	H	p-$CH_3C_6H_5$	40.2 (0.3)	161—164 (4)	1.5522	$C_{14}H_{15}NO_2$	72.88 73.09	6.34 6.44	5.83 5.94	73.34	6.59	6.11	55.6
II	H	2′,5′-$(CH_3)_2C_6H_3$	37 (0.25)	160—163 (5)	1.5370	$C_{15}H_{17}NO_2$	74.47 73.90	7.10 6.85	5.77 5.43	74.05	7.04	5.76	43.5
III	H	2′,4′-$(CH_3)_2C_6H_3$	37 (0.25)	160—161 (4)	1.5360	$C_{15}H_{17}NO_2$	73.55 73.89	6.57 6.80	6.08 6.03	74.05	7.04	5.76	46.4
IV	H	p-$OCH_3C_6H_4$	40 (0.26)	183—189 (4)	1.6723	$C_{14}H_{15}NO_3$	68.75 69.20	5.96 6.20	5.99 6.02	68.55	6.16	5.71	46.7
V	H	3′,4′-$(OCH_3)_2C_6H_3$	45.6 (0.25)	*	—	$C_{15}H_{17}NO_4$	65.83 65.58	6.32 6.26	5.24 5.28	65.44	6.22	5.09	35.7
VI	H	2′,4′-$(OCH_3)_2C_6H_3$	45.6 (0.25)	**	—	$C_{15}H_{17}NO_4$	65.64 65.83	6.23 6.22	5.06 5.21	65.44	6.22	5.09	42.9
VII	CH_2—CH_2—$OCOCH_3$	CH_3	36 (0.25)	162 (4)	1.4732	$C_{12}H_{17}NO_4$	60.36 60.35	7.00 6.96	6.08 6.01	60.23	7.16	5.85	75.8

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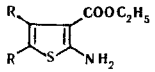
*Mp 118.5–119° (ex MeOH)

**Mp 105–105.5° (ex MeOH)

Table 2



2-Amino-3-ethoxycarbonylthiophene Derivatives

Compound	R	R′	Starting material g (mole)	Mp, °C (solvent)	Formula	Found, %				Calculated, %				Yield, %
						C	H	N	S	C	H	N	S	
VIII	H	p-$CH_3C_6H_4$	I 37 (0.16)	104—105 (MeOH)	$C_{14}H_{15}NO_2S$	64.34 64.04	5.82 5.70	5.16 5.29	12.60 12.39	64.34	5.79	5.36	12.27	77.8
IX	H	2′,5′-$(CH_3)_2C_6H_3$	II 25.1 (0.1)	84.5—85.5 (MeOH)	$C_{15}H_{17}NO_2S$	65.46 65.68	6.43 6.47	4.95 4.95	11.18 11.45	65.42	6.22	5.09	11.64	21.5
X	H	2′,4′-$(CH_3)_2C_6H_3$	III 25.4 (0.1)	81—82 (MeOH)	$C_{15}H_{17}NO_2S$	64.90 64.91	6.45 6.10	5.04 4.98	11.81 11.78	65.42	6.22	5.09	11.64	72
XI	H	p-$OCH_3C_6H_4$	IV 12.2 (0.05)	75.5—76 (75% MeOH)	$C_{14}H_{15}NO_3S$	60.91 60.92	5.52 5.31	5.35 5.17	11.63 11.69	60.63	5.45	5.05	11.56	68.8
XII	H	3′,4′-$(OCH_3)_2C_6H_3$	V 15.5 (0.05)	143—144 (MeOH)	$C_{15}H_{17}NO_4S$	58.20 58.50	5.33 5.55	4.69 4.71	10.27 10.60	58.61	5.57	4.56	10.43	93
XIII	H	2′,4′-$(OCH_3)_2C_6H_3$	VI 15.5 (0.056)	95—96 (MeOH)	$C_{15}H_{17}NO_4S$	59.07 59.11	5.70 5.58	4.26 4.41	10.58 10.30	58.61	5.57	4.56	10.43	60.6
XIV	$CH_2—CH_2—OCOCH_3$	CH_3	VII 23.9 (0.1)	64—65 (MeOH)	$C_{12}H_{17}NO_4S$	52.94 53.39	5.99 6.25	5.46 5.27	11.57 11.69	53.11	6.32	5.16	11.81	77.1