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SYNTHESIS OF DERIVATIVES OF 2-AMINOTHIOPHENE AND OF THIENOXAZINE

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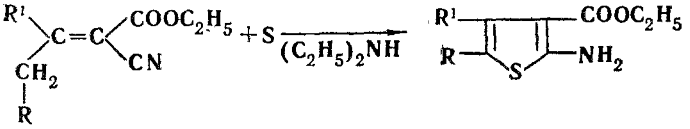
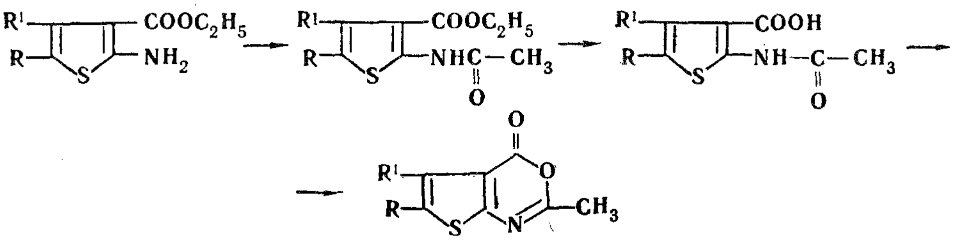
2-Amino-3-ethoxycarbonylthiophenes are synthesized by condensing alkylidenecyanoacetic esters with sulfur, and converted to a series of 2-aminothiophene derivatives. 4-Oxothienooxazine derivatives are synthesized by reaction of 2-acetylaminothiophene-3-carboxylic acid with acetic anhydride.

In one of our papers [1], it was shown that reaction of enamines with cyanoacetic ester and sulfur gives 2-amino-3-ethoxycarbonylthiophene derivatives. In the present paper, other aminothiophenes (I-III) prepared from methylethyl ketone, acetophenone, and acetothienone, are enamines which are not readily accessible by the method of [2].



I R=R'=CH$_3$
II R=H; R'=C$_6$H$_6$
III R=H; R'=C$_4$H$_3$S

A number of N-acyl derivatives (IV-IX) are synthesized by acetylating substituted 2-aminothiophenes with acetyl chloride, and hydrolysis of these gives 2-acetylaminothiophene-3-carboxylic acids (X-XIII). Treatment of acids X-XIII, and of 2-acetylamino-4-thienylthiophene-3-carboxylic acid (XIV) (which it has not been possible to isolate pure) with acetic anhydride, gives the thienoxazine derivatives XV-XIX.



IV R=R'=CH$_3$
V R=H, R'=C$_6$H$_5$
VI R=H, R'=C$_4$H$_3$S
VII R=C$_2$H$_5$, R'=H
VIII R=COOC$_2$H$_5$, R'=CH$_3$
IX R, R'=(CH$_2$)$_4$

X R=R'=CH$_3$
XI R=H, R'=C$_6$H$_5$
XII R=C$_2$H$_5$, R'=H
XIII R, R'=(CH$_2$)$_4$

XV R=R'=CH$_3$
XVI R=H, R'=C$_6$H$_5$
XVII R=C$_2$H$_5$, R'=H
XVIII R, R'=(CH$_2$)$_4$
XIX R=H, R'=C$_4$H$_3$S

Experimental

2-Amino-3-ethoxycarbonyl-4, 5-dimethylthiophene (I). The following were mixed: 76 g (0.45 mole) isobutylidenecyanoacetic ester, 14.6 g (0.45 g at) finely-ground sulfur, 35 ml EtOH, and 10 ml diethylamine. The mixture was stirred at room temperature, when heat was evolved, the sulfur dissolved gradually, and a homogeneous solution was formed, which was heated for 5 min on a water bath, then allowed to cool. The crystals which formed were separated off. Yield of I 49.2 g (54.5%), mp 85-86° (ex MeOH). Found: C 53.82, 53.90; H 6.28, 6.52; N 7.28, 6.99; S 15.90, 15.81%. Calculated for $C_9H_{13}NO_2S$: C 54.26; H 6.57; N 7.03; S 16.09%.

2-Amino-3-ethoxycarbonyl-4-phenylthiophene (II). The reaction was carried out as above, using 6.5 g (0.03 mole) phenylethylidenecyanoacetic ester, 1 g (0.03 g at) S, 5 ml EtOH, and 2 ml Et_2NH. Yield of II 6 g (80%), mp 93-94°C (ex MeOH). Found: C 62.75, 63.23; H 5.28, 5.32; N 5.64, 5.80; S 13.02, 12.94%. Calculated for $C_{13}H_{13}NO_2S$: C 63.13; H 5.29; N 5.66; S 12.96%.

2-Amino-3-ethoxycarbonyl-4-thienylthiophene (III). The reaction was carried out as above, using 49.3 g (0.4 mole) thienylethylidenecyanoacetic ester, 8 g (0.25 g at) S, 30 ml EtOH, and 20 ml Et_2NH. Yield of III 20.7 g (33%), mp 77-78°C (ex MeOH). Found: C 52.65, 52.49; H 4.61, 4.40; N 5.76, 5.65; S 25.14, 24.98%. Calculated

Table 1

2-Acetylamino-3-ethoxycarbonylthiophene Derivatives

Starting material g(mole)	Dioxane, ml; AcOCl, ml (mole)	Reaction product	Mp (ex MeOH)	Formula	Found, %		Calculated, %		Yield, %
					N	S	N	S	
II, 12,3 (0.05)	10; 14 (0.2)	2-Acetylamino-3-ethoxycarbonyl-4-phenylthiophene (V)	90—91	$C_{15}H_{15}NO_3S$	4.90 4.81	10.97 11.20	4.84	11.08	90.3
III, 7,6 (0.03)	7; 8.5 (1.2)	2-Acetylamino-3-ethoxycarbonyl-4-thienylthiophene(VI)	72—73	$C_{13}H_{13}NO_3S_2$	—	21.32 21.57	—	21.71	99
2-Amino-3-ethoxycarbonyl-5-ethylthiophene 6.9 (0.034)	7; 14 (0.2)	2-Acetylamino-3-ethoxycarbonyl-5-ethylthiophene (VII)	54—55	$C_{11}H_{15}NO_3S$	6.04 5.94	13.42 13.19	5.80	13.28	90
2-Amino-3, 5-diethoxycarbonyl-4-methylthiophene 8 (0.03)	10; 8.5 (1.2)	2-Acetylamino-3, 5-diethoxycarbonyl-4-methylthiophene (VIII)	126—127	$C_{13}H_{17}NO_5S$	4.97 5.06	10.91 11.13	4.67	10.71	75.4
2-Amino-3-ethoxycarbonyl-4, 5, 6, 7-tetrahydrothionaphthene 1(0.004)	1; 2 (0.03)	2-Acetylamino-3-ethoxycarbonyl-4, 5, 6, 7-tetrahydrothionaphthene (IX)	120—121[1]	—	—	—	—	—	84

Table 2

2-Acetylaminothiophene-3-Carboxylic Acid Derivatives

Starting material, (g mole)	NaOH g (mole)	50% MeOH, g	Reaction product	T. Mp °C	Formula	Found, %		Calculated, %		Yield, %
						N	S	N	S	
V, 10.5 (0.036)	2.9 (0.07)	50	2-Acetylamino-4-phenylthiophene-3-carboxylic acid (XI)	223—224	$C_{13}H_{10}NO_3S$	5.32 5.54	12.35 12.46	5.38	12.33	66.6
VII, 5.2 (0.021)	1.8 (0.045)	20	2-Acetylamino-5-ethylithiophene-3-carboxylic acid (XII)	174—175	$C_9H_{11}NO_3S$	6.82 6.66	14.66 14.86	6.56	15.03	87.3
IX, 11.6 (0.043)	1.9 (0.047)	100	2-Acetylamino-4,5,6,7-tetrahydrothionaphthene-3-carboxylic acid (XIII)	244—245	$C_{11}H_{13}NO_3S$	6.35 6.20	13.15 13.41	5.85	13.40	89

for $C_{11}H_{11}NO_2S_2$: C 52.15; H 4.37; N 5.52; S 25.31%.

2-Acetylamino-3-ethoxycarbonyl-4, 5-dimethylthiophene (IV). 20 ml (0.28 mole) AcOCl was added to a solution of 10 g (0.05 mole) aminothiophene I in 15 ml dioxane. Heat was evolved, and HCl began to be evolved. To complete the reaction, the solution formed was refluxed for 15 min and then poured into cold water. The crystals of IV which formed were separated off and dried in a vacuum-desiccator. Yield of IV 12 g (99.3%), mp 96–97° C (ex

MeOH). Found: N 5.91, 6.03; S 13.37, 13.39%. Calculated for $C_{11}H_{15}NO_3S$: N 5.80; S 13.28%.

The other 2-acetylaminothiophenes (V-IX) were obtained similarly.

Table 3

4-Oxothienoxazine Derivatives

Starting material, g, (mole)	Ac_2O, ml (mole)	Reaction product	Mp °C	Formula,	Found, %		Calculated, %		Yield, %
					N	S	N	S	
XI, 1.9 (0.007)	8 (0.086)	2-Methyl-4-oxo-5-phenylthienoxazine (XVI)	175—176	$C_{13}H_9NO_2S$	5.63 5.68	12.93 13.02	5.75	13.18	99
XII, 2.5 (0.011)	8 (0.086)	2-Methyl-4-oxo-6-ethylthienooxazine (XVII)	47—48	$C_9H_9NO_2S$	6.95 7.13	16.24 16.38	7.17	16.42	87.5
XIII, 4.1 (0.017)	20 (0.215)	2-Methyl-4-oxo-4,5,6,7-tetrahydrothionaphtheneoxazine (XVIII)	131—132	$C_{11}H_{11}NO_2S$	6.51 6.54	14.96 14.68	6.33	14.49	60.5
XIV, 2 (0.009)	8 (0.086)	2-Methyl-4-oxo-5-thienylthienoxazine (XIX)	149—150	$C_{11}H_7NO_2S_2$	5.73 5.71	25.23 25.57	5.61	25.72	61

2-Acetylamino-4, 5-dimethylthiophene-3-carboxylic acid (X). 7.2 g (0.03 mole) thiophene derivative IV was added to a solution of 2.4 g (0.06 mole) NaOH in 30 ml 50% MeOH, the resultant solution refluxed for 30 min, diluted for 3 vols of water, and filtered. The filtrate was cooled with ice, and acidified with concentrated HCl (to congo red). Yield of X 5 g (78.5%), mp 205-206° (ex MeOH). Found: C 6.91, 6.88; S 14.78, 15.07%. Calculated for $C_9H_{11}NO_3S$: N 6.56; S 15.03%.

Other derivatives of thiophene carboxylic acids XI-XIII were prepared similarly.

2, 5, 6-Trimethyl-4-oxothienoxazine (XV). A solution of 1.7 g (0.008 mole) acid X in 5 ml (0.054 mole) Ac_2O was refluxed for 1 hr, the crystals which formed on cooling were separated off, washed with 5 ml petrol ether, and dried. Yield of XV 1.4 g (90%) mp 104-105°C (ex petrol ether). Found: N 7.12, 7.20; S 16.07, 15.99%. Calculated for $C_9H_9NO_2S$: N 7.17; S 16.42%.

Other thienoxazine derivatives XVI-XIX, were obtained similarly (Table 3).

REFERENCES

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