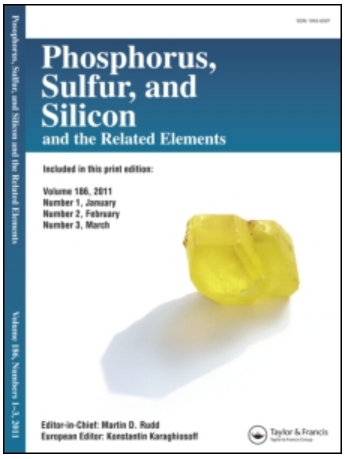

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REACTION OF THIOPHENE DICARBOXALDEHYDES WITH *p*-AMINOACETOPHENONE: A NEW SYNTHESIS OF THIENOPYRROLE DERIVATIVES

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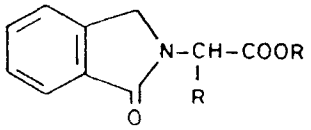
The thiophene 3,4- and 2,3-dicarboxaldehydes react with *p*-aminoacetophenone in xylene to give *N*-(4-acetyl phenyl)-5,6-dihydro-4-oxo-4H-thieno[3,4-c] and [2,3-c]pyrroles. On the reaction of thiophene 2,3-dicarboxaldehyde in the presence of 2-mercaptoethanol, *N*-(4-acetyl phenyl)-2-thioalkylthieno[2,3-c]pyrrole and *N*-(4-acetyl phenyl)-2,5-dithioalkylthieno-[2,3-c]pyrrole are obtained, and characterized by ^{1}H nmr and mass spectroscopy.

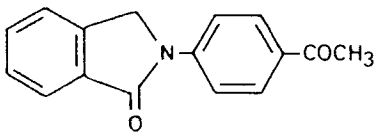
Key words: Thienopyrrole, NMR, mass spectra, heterocycles.

In continuation of our interest in the reactions of five membered-heterocyclic vicinal dicarboxaldehydes,[1–5] we report the reactions of 3,4- and 2,3-thiophenedicarboxaldehydes with *p*-aminoacetophenone.

It is well known that the isoindoline derivatives (**A**) and (**B**) have potent anti-inflammatory and analgesic activities.[6–8]



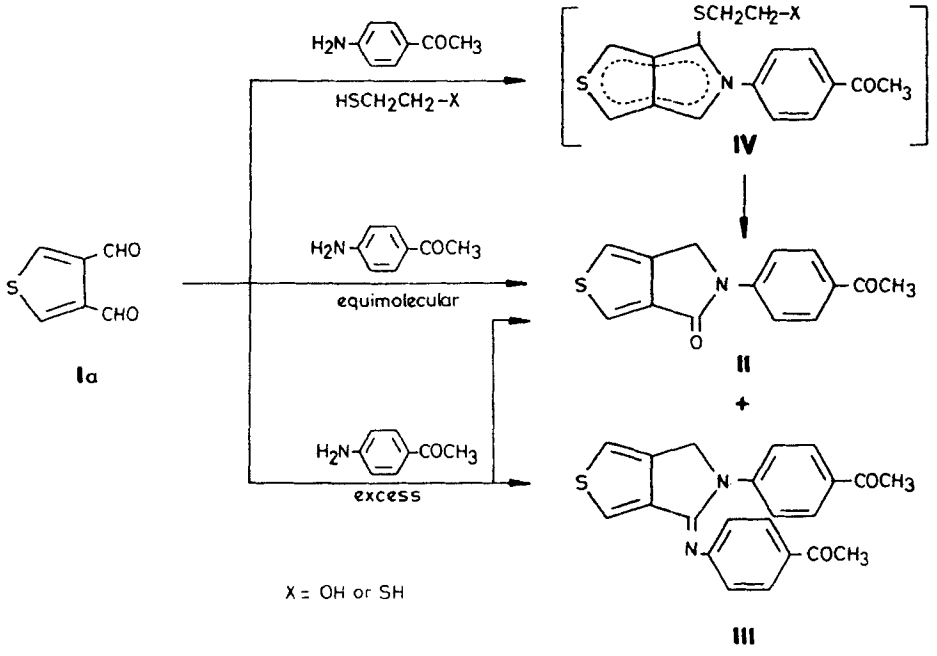
(A)



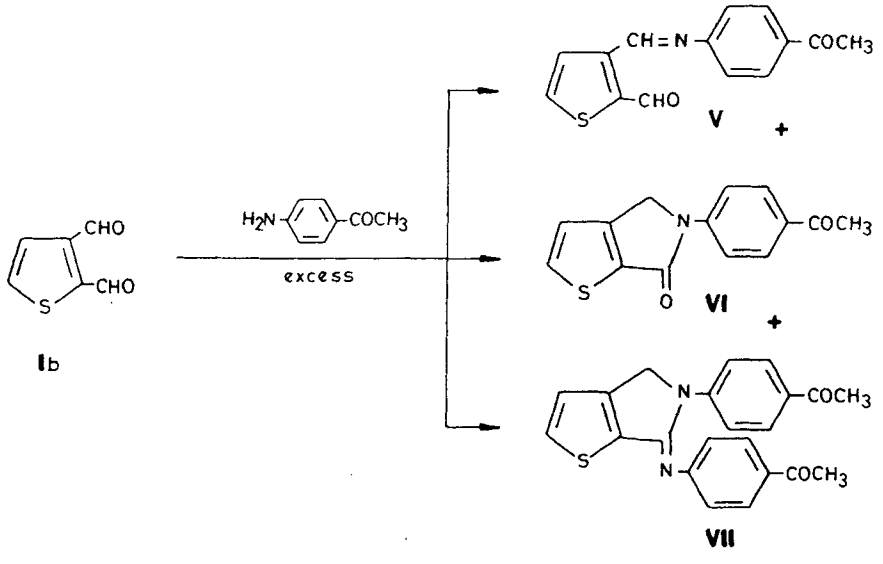
(B)

The reaction of (**Ia**) with equimolar quantities of *p*-aminoacetophenone in a large amount of anhydrous xylene gave *N*-(4-acetyl phenyl)-5,6-dihydro-4-oxo-4H-thieno[3,4-c]pyrrole (**II**) in low yield (17%). In the presence of excess of amine, two products were isolated; compound **II** in 23% yield and diadduct **III** in 14% yield.

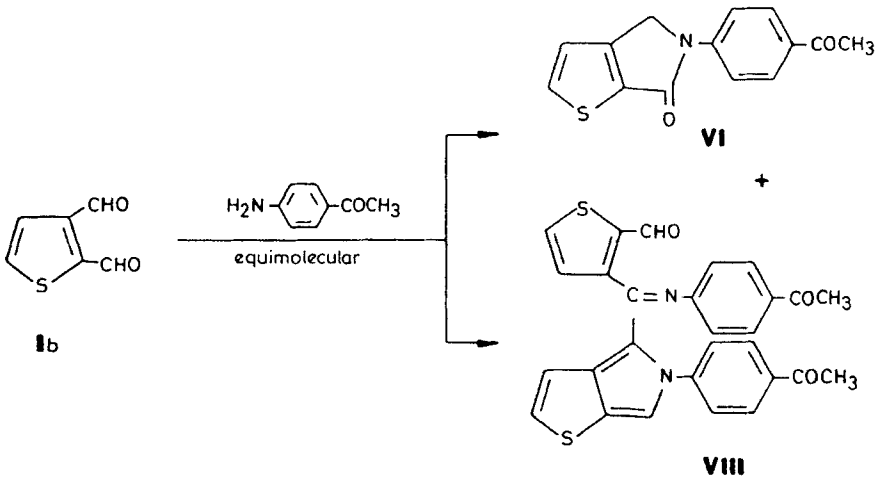
By carrying out the reaction in the presence of 2-mercaptoethanol or 1,2-ethandithiol in ethyl alcohol, only compound **II** was formed through intermediate **IV**, because the formation of thienopyrrole would be mechanistically impossible.



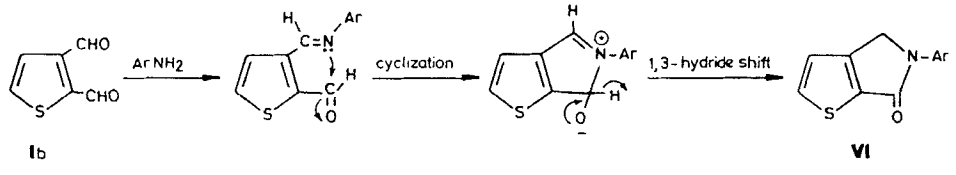
The reaction of **Ib** with excess of *p*-aminoacetophenone in refluxing xylene, three products **V**, **VI** and **VII** were isolated in yields of 8%, 22% and 17%. The first to elute from a silica gel column was the monocondensed product **V**, the second was *N*-(4-acetyl phenyl)-5,6-dihydro-6-oxo-4H-thieno[2,3-c]pyrrole (**VI**), and the third was the diadduct **VII**.



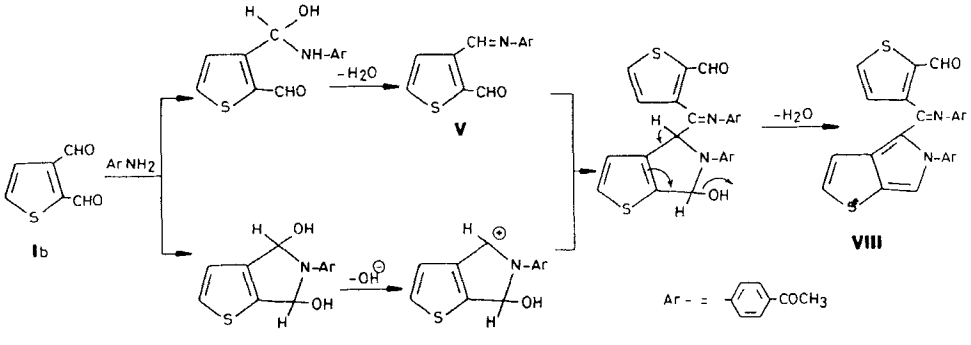
By carrying out the reaction for a long time and in the presence of equimolar quantities of amine, compound **VI** and the colored high melting compound **VIII**, were formed in 16% and 60% yields.



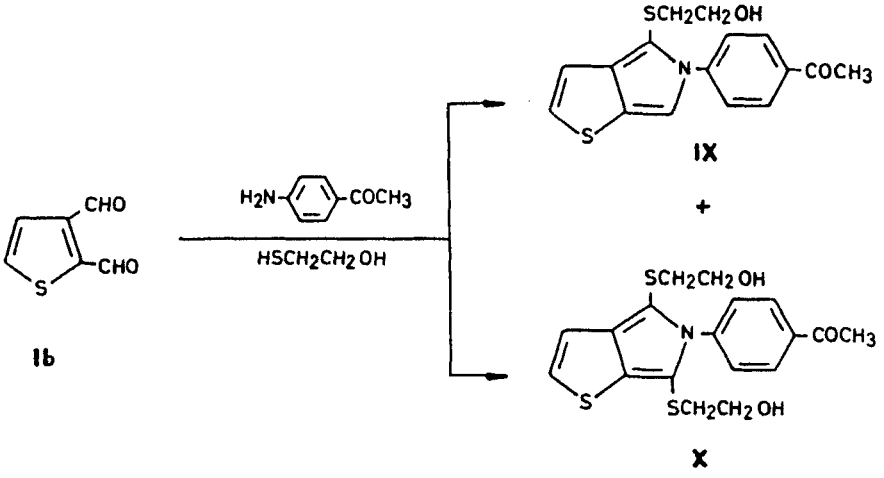
A possible reaction scheme starts with the condensation of the amine with the formyl group in position 3 followed by cyclization via a 1,3-hydride shift to give compound **VI**.



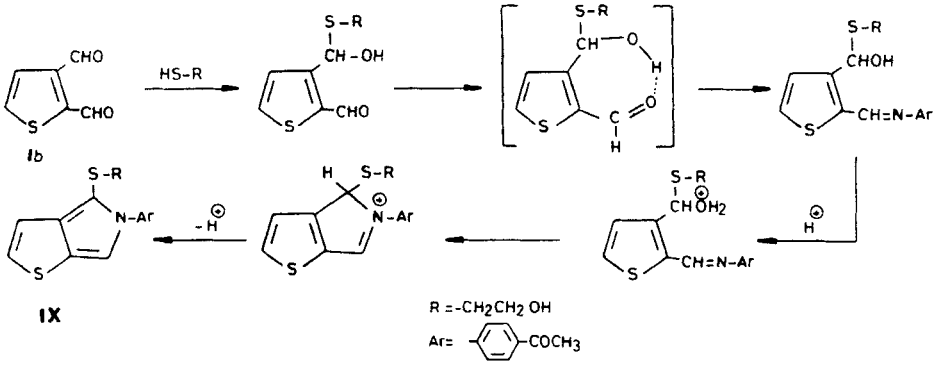
The formation of compound (**VIII**) may be obtained through the dehydration of the thienopyrrolidene intermediate as proposed by the following scheme.



By carrying out the reaction in the presence of 2-mercaptoethanol in ethyl alcohol, the *N*-(4-acetyl phenyl)-2-thioethanol thieno[2,3-c]pyrrole (**IX**) and *N*-(4-acetyl phenyl)-2,5-dithioethanol thieno[2,3-c]pyrrole (**X**) were formed in 54% and 14% yields.



The following mechanism[10] was proposed for the formation of compound **IX**.



It is worthy to mention that, compounds **IX** and **X** are the five-membered heterocyclic analogs of the adducts formed by the fluorogenic reaction of *o*-phthaldehyde/2-mercaptoethanol which is used for the detection of picomole quantities of amino acids, peptides and proteins.[11-15] Application of the fluorogenic reactions of these amino compounds is in progress.

EXPERIMENTAL

The thiophene 3,4- and 2,3-dicarboxaldehydes were prepared according to previously reported methods.[16-18] Infra-red spectra were recorded on a Beckman IR-4 using KBr wafers. ^{1}H nmr spectra were recorded on a Joel-90 MHz spectrometer in $CDCl_3$ using TMS as the internal standard. Mass spectra were obtained on a Finnigan 3000 spectrometer (70 eV; 90°C). The melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Microanalyses were performed at the National Center of Scientific Research (CNRS), Central Service of Microanalysis, France.

The usual work-up consisted of diluting the reaction mixture with water followed by extraction with methylene chloride, drying over magnesium sulphate, and evaporation of the solvent under reduced pressure. The compounds thus prepared were purified by column chromatography using silica gel 60 (Merk). The experimental results are reported in Table I, and the spectral data are reported in Table II.

TABLE I

Experimental data of the prepared compounds

Compd.	Procd.	Time (min.)	Eluent	Yield %	Solvent	M.P. °C	Mol. Formula (Mol. Weight).		Analyses % C	H	N	S
II	A	30	E - H (3:1)	17	B - H (1:1)	160-161	$C_{14}H_{11}NO_2S$ (257.31)	Calcd.	65.35	4.31	5.44	12.46
								Found	65.44	4.40	5.39	12.64
III	B	60	E - H (3:1)	14	B - H (1:1)	123-125	$C_{22}H_{18}N_2O_2S$ (374.45)	Calcd.	70.59	4.82	7.49	8.56
								Found	70.78	4.56	7.41	8.27
V	B	120	E - H (3:1)	8	B - H (1:1)	192-193	$C_{14}H_{11}NO_2S$ (257.31)	Calcd.	65.35	4.31	5.44	12.46
								Found	65.39	4.57	5.47	12.69
VI	B	120	E - H (1:1)	22	B - H (2:1)	112-114	$C_{14}H_{11}NO_2S$ (257.31)	Calcd.	65.35	4.31	5.44	12.46
								Found	65.57	4.56	5.32	12.73
VII	A	120	E - H (2:1)	16	B - H (3:1)	173	$C_{22}H_{18}N_2O_2S$ (374.45)	Calcd.	70.59	4.82	7.49	8.56
								Found	70.83	4.59	7.68	8.31
VIII	A	120	E - H (2:1)	60	T - H (3:1)	284-285	$C_{28}H_{20}N_2O_3S_2$ (496.60)	Calcd.	67.74	4.04	5.64	12.90
								Found	67.54	3.94	5.35	12.68
IX	C	30	B - H (2:1)	54	B - H (3:1)	128-130	$C_{16}H_{15}NO_2S_2$ (317.43)	Calcd.	60.54	4.76	4.41	20.20
								Found	60.39	4.81	4.47	19.94
X	C	30	B - H (2:1)	14	B - H (3:1)	164	$C_{18}H_{19}NO_3S_3$ (393.53)	Calcd.	54.96	4.83	3.56	24.43
								Found	54.62	4.72	3.62	24.55

B = Benzene; E = Ether; H = Hexane; T = Toluene.

TABLE II

Spectroscopic data of the prepared compounds

Compd.	I.R. data cm^{-1}	^1H nmr data in δ ppm	Mass spectral data
II	1666($COCH_3$).	2.64(3H,s,CH_3);4.70(2H,s,CH_2);7.65-6.90(4H,m,phenyl);7.42(1H,s,β-thienyl);7.28(1H,s,α-thienyl).	M^+257(39 %); m/e = 214(100 %); 212(31 %); 139(42 %); 124(59%)
III	1698,1692($COCH_3$);1638(C=N).	2.64,2.66(3H & 3H,s,2CH_3); 4.74 (2H,s,CH_2);6.85 - 6.90(4H & 4H,m,2 phenyl); 7.48(1H,s,β-thienyl);7.32 (1H,s,α-thienyl).	M^+374(19 %); m/e = 331(100 %); 329(27 %); 288(57 %); 241(67%); 108(21 %).
V	1675(CHO);1665($COCH_3$); 1625(CH=N).	2.60(3H,s,CH_3);7.73(2H,dd,phenyl); 8.00(2H,d,phenyl);8.95(1H,s,HC=N-); 7.23(1H,s,β-thienyl);7.26(1H,s,α-thienyl);10.42(1H,s,CHO).	M^+257(44 %); m/e = 228(37 %); 214(100 %); 212(24 %).
VI	1695(C=O);1660($COCH_3$).	2.58(3H,s,CH_3);7.89(2H,dd,phenyl); 8.00(2H,s,phenyl);4.82(2H,s,CH_2); 7.11(1H,d,β-thienyl);7.73(1H,d,α-thienyl).	M^+257(42 %); m/e = 214(100 %); 212(28 %); 139(21 %).
VII	1672,1660($COCH_3$);1642(C=N).	2.68,2.72(3H & 3H,s,2CH_3);7.20-8.40 (4H & 4H,m,2phenyl);7.40(1H,d, α-thienyl);7.11(1H,d,β-thienyl).	M^+374(27 %); m/e = 331(100 %); 288(41 %); 241(37 %); 108(29%)
VIII	1692(CHO);1669,1661($COCH_3$).	2.64,2.68(3H & 3H,s,2CH_3); 7.20-8.10 (4H & 4H,m, 2phenyl);7.28-7.34(2H, d,β-thienyl);7.10-7.14(2H,d,α-thienyl);8.90(1H,s,C=C-N-);10.50 (1H,s,CHO).	M^+496(17 %); m/e = 467(37 %); 453(100 %); 451(23 %); 410(59 %);363(33 %).
IX	1662($COCH_3$).	1.73(1H,t,OH);2.56(2H,t,S-CH_2); 2.64(3H,s,CH_3);3.40(2H,q,O-CH_2); 7.11(1H,d,β-thienyl);7.01(1H,d,α-thienyl);7.16(1H,s, C=C-N-); 7.55(2H,dd,phenyl);8.08(2H,dd, phenyl).	M^+317(21 %); m/e = 316(67 %); 274(51 %);240(100 %); 184 (54 %).
X	1668($COCH_3$).	1.65(1H & 1H,m,2OH);2.56(2H,t,S-CH_2);2.61(2H,t,S-CH_2);2.67(3H,s, CH_3);3.47(2H & 2H,m,2 O-CH_2);7.14 (1H,d,β-thienyl),7.03(1H,d,α-thienyl);7.42(2H,dd,phenyl);8.13 (2H,dd,phenyl).	M^+393(19 %);392(32 %); 391 (49 %);375(31 %); 350(100 %); 348(47 %);260(61 %);239(27%).

Procedure: A Compound **Ia** or **b**, 700 mg (0.005 mole) and *p*-aminoacetophenone 675 mg (0.005 mole) in boiling 250 ml of anhydrous xylene.

Procedure: B Compound **Ia** or **b**, 700 mg (0.005 mole) and *p*-aminoacetophenone 2.0 gm (0.015 mole) in boiling 250 ml of anhydrous xylene.

Procedure: C Compound **Ia** or **b**, 700 mg (0.005 mole), 2-mercaptoethanol or 1,2-ethandithiol (0.01 mole) and *p*-aminoacetophenone 700 mg (0.005 mole) in 250 ml of absolute ethyl alcohol at 0°C.

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