

# Reactions of 2-thienylacetic acid with anhydrides of dicarboxylic acids and aromatic aldehydes under the Perkin synthesis conditions

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Condensations of 2-thienylacetic acid with phthalic and 4-azaphthalic anhydride have been carried out under conditions of the Gabriel modification of the Perkin synthesis. The phthalides and 4-azaphthalides prepared were rearranged to give 1,3-indandione derivatives. Condensations of 2-thienylacetic acid with benzaldehyde, 3-chlorobenzaldehyde, 4-chlorobenzaldehyde, 2-thiophenecarbaldehyde, and cinnamaldehyde are also described. The structure of the products is proved by IR and  $^1\text{H}$  NMR spectra.

Проведены конденсации 2-тиенилуксусной кислоты с фталевым и 4-азафталевым ангидридами в условиях Габриэлевой модификации синтеза Перкина. Полученные фталиды и 4-азафталиды перегруппировывались с образованием производных 1,3-индандиона. Описаны также конденсации 2-тиенилуксусной кислоты с бензальдегидом, 3-хлорбензальдегидом, 4-хлорбензальдегидом, 2-тиофенкарбальдегидом и циннамальдегидом. Структура полученных продуктов доказана с помощью методов ИК- и  $^1\text{H}$  ЯМР-спектроскопии.

2-Thienylacetic acid has been used in the synthesis of cephalosporins and penicillins as a reagent with an active methylene group. Therefore, the studies dealing with this compound where reactivity of its methylene group is evaluated are topical. We have chosen the Perkin synthesis and its Gabriel modification as a study basis, because there has been no experience yet with the behaviour of 2-thienylacetic acid under conditions of the reaction in question. Of the great number of carbonyl compounds, we focused our attention to two anhydrides of dicarboxylic acids — phthalanhydride and 4-azaphthalanhydride — with which we have had experience and many published results from our previous work.

2-Thienylacetic acid can be compared with its two analogues phenylacetic acid and 2-furylacetic acid. The chemistry of aldol syntheses with phenylacetic acid has

copious documentary material to compare with and we have published our results of the condensation reaction of 2-furylacetic acid with phthalanhydride [1].

On the basis of experimental results, we conclude that 2-thienylacetic acid is less stable than phenylacetic acid (e.g. the former decarboxylates more easily) since successful experiments have been done with phenylacetic acid at about 260 °C [2] without decomposition. On the other hand, according to our observation, the reaction mixture containing 2-thienylacetic acid turns brown quickly at temperatures higher than 200 °C and mostly oily dark-brown products are formed. The optimal reaction temperature for this reaction is 180–195 °C. The thermal instability of 2-thienylacetic acid resembles that of 2-furylacetic acid. As follows from the paper [1], the highest yields of 3-(2-furylmethylene)phthalide were 40 % at 150–160 °C and at higher temperature they decreased sharply. Though the condensations with 2-thienylacetic acid are carried out at lower temperatures than those with phenylacetic acid, the yields are approximately the same (60–80 %) with both acids.

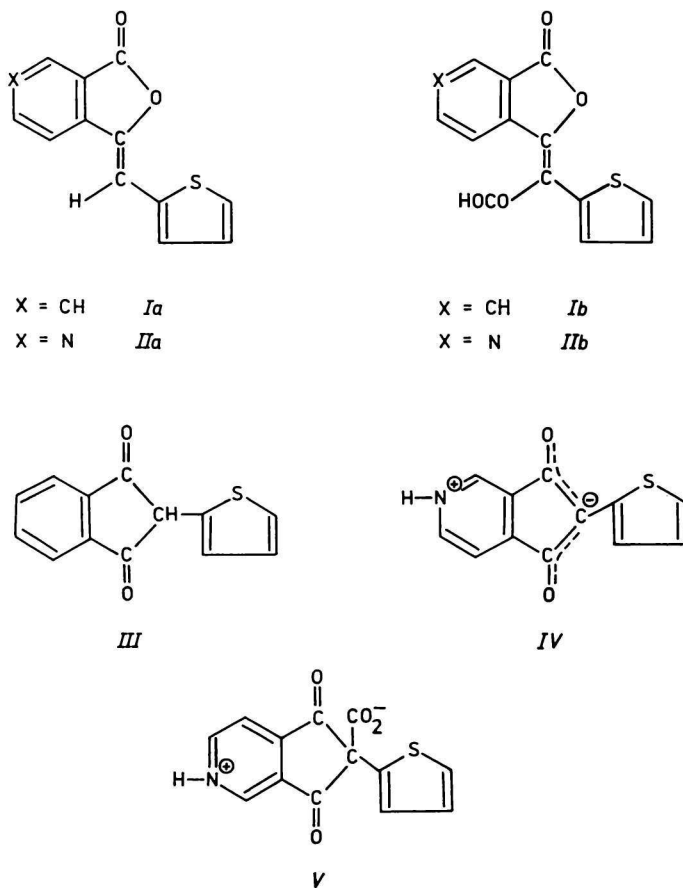
The lower temperature of the reaction is also advantageous for the synthesis of the thienyl derivative of 6-azaphthalide because, as can be seen from papers [3, 4], 4-azaphthalanhydride gives the best yields at 190–205 °C.

The reaction of phthalanhydride with 2-thienylacetic acid (Method A) afforded 3-(2-thienylmethylene)phthalide (*Ia*) and also 3-phthalidylidene-2-thienylacetic acid (*Ib*) (Method B). Both these phthalide derivatives undergo a rearrangement reaction with sodium methoxide to give 2-(2-thienyl)-1,3-indandione (*III*). The reaction is accompanied by decarboxylation of the acid *Ib* (Scheme 1). Reaction of 4-azaphthalanhydride with 2-thienylacetic acid (Method B) gave analogous products 3-(2-thienylmethylene)-6-azaphthalide (*IIa*) and 6-aza-3-phthalidylidene-2-thienylacetic acid (*Iib*).

Only one carbonyl group of 4-azaphthalanhydride reacts with 2-thienylacetic acid similarly as with substituted phenylacetic acids [2]. On the basis of analogy with the substituted phenylacetic acids, we assume that the structural isomers *IIa* and *Iib* are formed, i.e. that 2-thienylacetic acid reacts with the carbonyl group in position 1 of 4-azaphthalanhydride. We assign the geometric isomerism *E* to both the phthalides *Ia*, *IIa* and the acids *Ib*, *Iib* since the *E*-isomers are energetically favourable and have been proved for benzalphthalide.

Rearrangement of *IIa* leads to 2-(2-thienyl)-5-aza-1,3-indandione (*IV*). This compound, like 2-phenyl-5-aza-1,3-indandione [4], possesses a betaine structure. This conclusion is supported by infrared spectrum of the compound. The absorption bands corresponding to the symmetric and asymmetric stretching C=O vibrations were found at 1620 cm<sup>-1</sup> and 1570 cm<sup>-1</sup>, respectively, indicating a delocalized anion of β-dicarbonyl group. A broader band of stretching N—H vibration at 3240 cm<sup>-1</sup> is also consistent with the betaine structure of *IV*.

The compound *Iib* does not decarboxylate during its rearrangement when



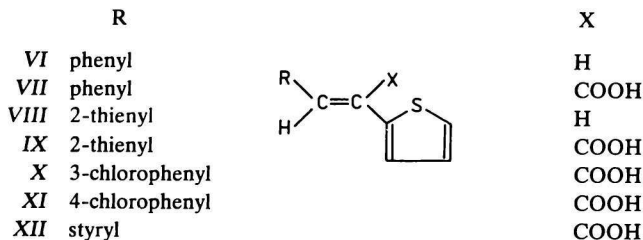
Scheme 1

treated with sodium methoxide in methanol and hence an inner salt of 5-aza-1,3-dioxo-2-(2-thienyl)-2-indancarboxylic acid (V) is formed. Infrared spectrum of this compound contains a strong band at  $1602 \text{ cm}^{-1}$  which can be assigned to the carboxylate anion and a band at  $3300 \text{ cm}^{-1}$ , corresponding to the stretching N—H vibration. The bands of symmetric and asymmetric vibrations of the group  $\text{CO—CR}_2\text{—CO}$  are at relatively high frequencies ( $1705 \text{ cm}^{-1}$  and  $1780 \text{ cm}^{-1}$ ) in accordance with previous findings [4] for such a grouping.

It should be noted that the compound *IIb* also possesses a betaine structure. Two bands can be found in the region of  $\text{C=O}$  stretching frequencies. We assign the first one at  $1775 \text{ cm}^{-1}$  to the phthalidic  $\text{C=O}$  group and the other at  $1622 \text{ cm}^{-1}$  to the carboxylate anion. The band corresponding to the stretching N—H vibration is at  $3300 \text{ cm}^{-1}$ .

2-Aryl-1,3-indandiones are known to be prepared also by sodium methoxide-catalyzed condensation of phthalide and aromatic aldehydes [5]. We used this procedure to prepare 2-(2-thienyl)-1,3-indandione (*III*). We obtained this product in 50 % yield.

Besides the two anhydrides mentioned, we used also aromatic aldehydes as carbonyl components in the reaction with 2-thienylacetic acid under conditions of the Perkin synthesis. The best yields were achieved at 150–170 °C, the products being both stilbene analogues and corresponding acids (Scheme 2).



Scheme 2

Under conditions described in Experimental, only one geometric isomer is formed (*E*) and the products decarboxylate only partly at the reaction temperatures used.

## Experimental

Infrared spectra (nujol suspensions) were recorded with a Specord 75 IR spectrophotometer in the region of 400–4000 cm<sup>-1</sup>; polystyrene foil was used for calibration.

<sup>1</sup>H NMR spectra were measured on a Tesla BS 487 A apparatus at 80 MHz; saturated solutions in deuterated dimethyl sulfoxide with hexamethyldisiloxane as internal standard were used.

### Method A

#### 3-(2-Thienylmethylene)phthalide (*Ia*)

A mixture of sublimated phthalanhydride (3.0 g; 20 mmol), 2-thienylacetic acid (1.5 g; 10 mmol), and freshly melted potassium acetate (0.5 g) was stirred at  $\theta = 190$  °C for 2 h with removal of reaction water. After cooling, water (50 cm<sup>3</sup>) and sodium hydrogen carbonate (1.0 g) was added. The solid was filtered off, dried and crystallized from benzene. The yield (calculated on 2-thienylacetic acid) 65 %, m.p. = 117–118 °C.

For C<sub>13</sub>H<sub>8</sub>O<sub>2</sub>S (*M<sub>r</sub>* = 228) *w<sub>i</sub>*(calculated): 68.40 % C, 3.53 % H, 14.05 % S; *w<sub>i</sub>*(found): 68.32 % C, 3.69 % H, 13.89 % S. <sup>1</sup>H NMR ( $\delta$ /ppm): 7.23 (1H, s), 7.02–8.07 (7H, m). IR spectra ( $\tilde{\nu}$ /cm<sup>-1</sup>): 1773  $\nu$ (C=O), 1633  $\nu$ (C=C), 1600  $\nu_{\text{arom}}$ (C=C).

*Method B*

**3-(2-Thienylmethylene)phthalide (Ia)**  
**3-Phthalidyldiene-2-thienylacetic acid (Ib)**

A mixture of sublimated phthalanhydride (2.25 g; 15 mmol), potassium carbonate (0.3 g) and 2-thienylacetic acid (1.5 g; 10 mmol) in acetonitrile (30 cm<sup>3</sup>) was stirred at  $\theta = 100^\circ\text{C}$  for 2 h. After cooling to  $\theta = 25^\circ\text{C}$ , the mixture was stirred for 12 h, poured in water (100 cm<sup>3</sup>) and precipitated raw product was triturated in a saturated sodium hydrogen carbonate solution. Insoluble portion was separated, dried and crystallized from benzene to give 3-(2-thienylmethylene)phthalide in 30% yield, m.p. = 117–118  $^\circ\text{C}$ . The filtrate was acidified to pH = 2.0 with hydrochloric acid. After 1 h, yellowish precipitate was filtered off and crystallized from ethanol. The yield was 50% (calculated on 2-thienylacetic acid), m.p. = 195  $^\circ\text{C}$ .

For C<sub>14</sub>H<sub>8</sub>O<sub>4</sub>S ( $M_r$  = 272)  $w_i$ (calculated): 61.76% C, 2.96% H, 11.78% S;  $w_i$ (found): 61.92% C, 2.90% H, 11.91% S. <sup>1</sup>H NMR ( $\delta$ ,/ppm): 7.05–7.35 (3H, m), 7.75–8.05 (4H, m). IR spectra ( $\tilde{\nu}$ /cm<sup>-1</sup>): 1720, 1754  $\nu$ (C=O); 1667, 1627, 1600  $\nu$ (C=C); 1028  $\nu$ (C—O—C), 1330  $\nu_{as}$ (C—O—C).

**3-(2-Thienylmethylene)-6-azaphthalide (IIa)**

**Method A.** The yield 54%, m.p. = 169–170  $^\circ\text{C}$ .

For C<sub>13</sub>H<sub>7</sub>NO<sub>2</sub>S ( $M_r$  = 229)  $w_i$ (calculated): 62.87% C, 3.08% H, 13.98% S, 6.11% N;  $w_i$ (found): 62.94% C, 3.19% H, 13.95% S, 6.26% N. IR spectra ( $\tilde{\nu}$ /cm<sup>-1</sup>): 1766  $\nu$ (C=O); 1641, 1600  $\nu$ (C=C), 956  $\nu$ (C—O—C).

**3-(2-Thienylmethylene)-6-azaphthalide (IIa)**  
**6-Aza-3-phthalidyldiene-2-thienylacetic acid (IIb)**

**Method B.** The yield of IIa 30%, m.p. = 169–170  $^\circ\text{C}$ ; the yield of IIb 37%, m.p. = 175–177  $^\circ\text{C}$  (decomposition).

For C<sub>13</sub>H<sub>7</sub>O<sub>4</sub>NS ( $M_r$  = 273)  $w_i$ (calculated): 57.14% C, 2.58% H, 11.73% S, 5.13% N;  $w_i$ (found): 57.10% C, 2.48% H, 11.79% S, 5.02% N. <sup>1</sup>H NMR ( $\delta$ ,/ppm): 7.10–7.25 (1H, q), 7.47–7.55 (1H, d), 7.73 (1H, s), 7.82–7.87 (1H, d), 8.22–8.30 (1H, d), 8.90–8.97 (1H, d), 9.30 (1H, s). IR spectra ( $\tilde{\nu}$ /cm<sup>-1</sup>): 1775, 1622  $\nu$ (C=O), 1590  $\nu$ (C=C), 3300  $\nu$ (N—H), 980  $\nu$ (C—O—C).

**2-(2-Thienyl)-1,3-indandione (III)**

Ia or Ib (5 mmol) was added to 0.1% solution of sodium methoxide in methanol (30 cm<sup>3</sup>) at  $\theta = 60^\circ\text{C}$  during 10 min. The mixture was heated for 15 min under reflux. Three fourth parts of the solvent were removed under reduced pressure, 1% hydrochloric acid (40 cm<sup>3</sup>) was added and the mixture was stirred for 30 min. The precipitate was filtered off, washed with water, dried and crystallized from benzene. The yield was 80%, m.p. = 148–149  $^\circ\text{C}$ .

Table 1

Characterization of the synthesized 1-R-2-X-2-thienylethylenes

Compound	R	X	Formula	$M_r$	$w_i(\text{calc.})/\%$ $w_i(\text{found})/\%$				Yield %	M.p. °C
					C	H	S	Cl		
VI	Phenyl	H	$\text{C}_{12}\text{H}_{10}\text{S}$	198	77.37	5.41	17.21		15	107—110
					77.12	5.48	17.01			
VII	Phenyl	COOH	$\text{C}_{13}\text{H}_{10}\text{O}_2\text{S}$	230	67.80	4.38	13.92		45	169—170
					67.77	4.39	13.97			
VIII	2-Thienyl	H	$\text{C}_{10}\text{H}_8\text{S}_2$	192	62.46	4.19	33.36		18	129—131
					62.54	3.86	33.48			
IX	2-Thienyl	COOH	$\text{C}_{11}\text{H}_8\text{O}_2\text{S}_2$	236	55.91	3.41	27.14		40	245—246
					56.22	3.44	26.88			
X	3-Chlorophenyl	COOH	$\text{C}_{13}\text{H}_9\text{OClS}$	265	58.76	3.79	12.07	13.34	68	147—149
					58.96	3.48	12.14	13.39		
XI	4-Chlorophenyl	COOH	$\text{C}_{13}\text{H}_9\text{OClS}$	265	58.76	3.79	12.07	13.34	65	190—192
					59.01	3.61	12.02	13.36		
XII	Styryl	COOH	$\text{C}_{15}\text{H}_{12}\text{O}_2\text{S}$	256	70.29	4.71	12.51		50	203—205
					70.00	4.82	12.71			

Table 2

Spectral data of the compounds VI—XII

Compound	IR $\tilde{\nu}/\text{cm}^{-1}$				$^1\text{H}$ NMR $\delta_r/\text{ppm}$
	$\nu(\text{C}=\text{O})$	$\nu(\text{C}=\text{C})$	$\nu(\text{C}-\text{S})$	$\nu(\text{C}-\text{O})$	
VI		1672	692	—	6.75—7.55 (m)
VII	1678	1660	685		7.80 (1H, s), 6.80—7.42 (8H, m)
VIII		1660	695	1278	6.87—7.68 (m)
IX	1674	1656	698	1278	8.01 (1H, s), 6.88—7.68 (6H, m)
X	1668	1654	700	1278	7.75 (1H, s), 6.82—7.62 (7H, m)
XI	1680	1645	700	1266	
XII	1670	1650	690	1278	
		1625			

For  $C_{13}H_8O_2S$  ( $M_r = 228$ )  $w_i$ (calculated): 68.40% C, 3.53% H, 14.05% S;  $w_i$ (found): 68.58% C, 3.59% H, 13.78% S.  $^1H$  NMR ( $\delta$ /ppm): 7.03 (1H, s), 7.15—7.75 (7H, m). IR spectra ( $\tilde{\nu}/cm^{-1}$ ): 1639, 1650  $\nu(C=O)$ , 1567  $\nu_{arom}(C=C)$ .

### 2-(2-Thienyl)-5-aza-1,3-indandione (IV)

The same procedure as for III, using IIa (5 mmol). The yield 60%, m.p. = 140 °C (decomposition).

For  $C_{12}H_7O_2NS$  ( $M_r = 228$ )  $w_i$ (calculated): 62.87% C, 3.08% H, 13.98% S, 6.11% N;  $w_i$ (found): 62.58% C, 3.19% H, 13.90% S, 6.19% N. IR spectra ( $\tilde{\nu}/cm^{-1}$ ): 1620, 1570  $\nu(C=O)$ , 1533  $\nu(C=C)$ , 3240  $\nu(N-H)$ .

### 5-Aza-1,3-dioxo-2-(2-thienyl)-2-indancarboxylic acid (V)

The same procedure as for III, using IIb. The yield 54%, m.p. = 140 °C (decomposition).

For  $C_{13}H_7NO_4S$  ( $M_r = 273$ )  $w_i$ (calculated): 57.14% C, 2.58% H, 11.73% S, 5.13% N;  $w_i$ (found): 57.19% C, 2.49% H, 11.52% S, 5.64% N. IR spectra ( $\tilde{\nu}/cm^{-1}$ ): 1780  $\nu(C=O)$ , 1705  $\nu_{as}(C=O)$ , 1602  $\nu_{as}(C=O)$ , 1405  $\nu_s(C=O)$ , 1620  $\nu(C=C)$ , 3300  $\nu(N-H)$ .

### Substituted (2-thienyl)ethylenes VI—XII

A mixture of 2-thienylacetic acid (10 mmol), corresponding aldehyde (15 mmol), and potassium acetate (0.3 g) in acetonitrile (10 cm<sup>3</sup>) was stirred at  $\theta = 150$  °C for 2 h and then at  $\theta = 20$  °C for 10 h. Finely crashed ice (100 cm<sup>3</sup>) was added to the mixture. The raw product was separated, washed with water and 5% aqueous sodium hydrogen sulfite solution. A sodium hydrogen carbonate solution was added to the organic portion and the mixture was stirred for 2 h. The solid was separated and crystallized from diethyl ether or benzene. Acidifying of the filtrate afforded acids, which were crystallized from ethanol. The yields, analytical data, melting points, and spectral data of the compounds VI—XII are listed in Tables 1 and 2.

### References

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