FUNCTIONAL DERIVATIVES OF THIOPHENE

XIII.* SYNTHESIS OF ACYL DERIVATIVES OF SUBSTITUTED β-THIENYLHYDRAZINE

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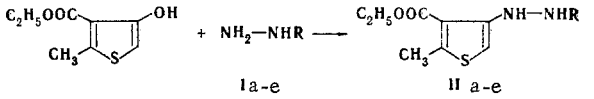
Acyl derivatives of substituted β-thienylhydrazines were obtained by reaction of 2-methyl-3-carbethoxy-4-hydroxythiophene with acyl hydrazines. Hydrolysis of the products gave a thienylhydrazine derivative and its hydrochloride.

Thienylhydrazine derivatives with a free ortho position are of considerable interest in the synthesis of thienopyrroles by the Fischer method. An attempt to obtain a substituted thienylhydrazine from 2-methyl-3-carbethoxy-4-hydroxythiophene led to hydrazinolysis of the thiophene ring [2].

We have found that completely stable† acyl derivatives of β-thienylhydrazine (IIa-e) are formed in high yields in the reaction of 2-methyl-3-carbethoxy-4-hydroxythiophene with acylhydrazines (Ia-e).



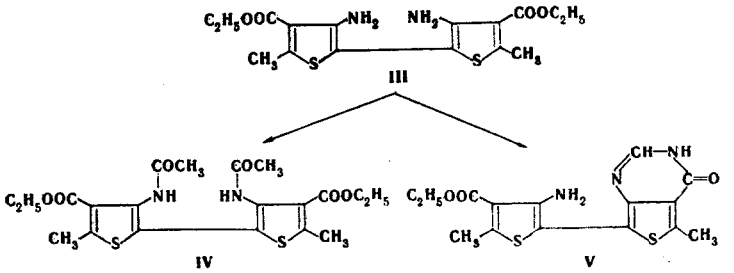
Ia-e IIa-e

IIa R=CHO; b R=COCH$_3$; c R=COC$_6$H$_5$; d R=CONH$_2$; e R=CSNH$_2$

Excess acylhydrazine has a substantial effect on the yields of acylthienylhydrazines IIa, b. A twofold excess of Ia, b insures a 20% yield of IIa, b. The use of a 10-20-fold excess of Ia, b raises the yields of IIa, b to 60-70%. A twofold excess of acylhydrazines Ic-e is sufficient for the formation of IIc-e.

The synthesis of IIa, b is accompanied by the formation of a side product – 3,3'-diamino-4-4'-dicarbethoxy-5,5'-dimethyl-2,2'-dithienyl (III).

3,3'-Diacetamido-4,4'-dicarbethoxy-5,5'-dimethyl-2,2'-dithienyl (IV) was obtained by acylation of III with acetyl chloride, whereas 4-oxo-3,4-dihydro-5-methyl-6-(2'-methyl-3'-carbethoxy-4'-amino-5'-thienyl)thieno[3,4-d]pyrimidine (V) was obtained by heating III in formamide. The unusual character of the



III

IV V

*See [1] for communication XI.

†A communication regarding the synthesis of an unsubstituted β-thienylhydrazine recently appeared. The product is unstable and was obtained in only 24% yield [3].

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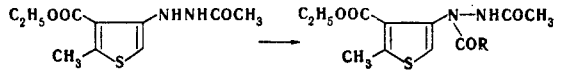
TABLE 1. PMR Spectra (Chemical Shifts, δ, ppm)

Compound	$CH_3(C_2H_5)$	$CH_2(C_2H_5)$	2-CH_3	5-H	NH	CHO	$COCH_3$	α-N-$COCH_3$	C_6H_5	NH_2
IIa	1,37 t	4,35q	2,57s	6,01s	7,57 s	8,18 s	—	—	—	—
	1,38 t	4,36q	2,58s	6,03s	7,82s	8,38 s				
IIb	1,33 t	4,30q	2,59s	5,85s	7,58 d	—	1,96s	—	—	—
	1,37 t	4,35q	2,64s	5,90s	7,80 d		2,07s			
VIa	1,37 t	4,32q	2,65s	7,30s	7,46 s	—	1,98s	1,90s	—	—
	1,38 t	4,33q	2,71 s		8,12 s		2,17s	1,98s		
IIc	1,37 t	4,32q	2,60 s	6,03s	8,00d	—	—	—	7,39m	—
					8,25d				7,87m	
IId	1,37 t	4,34q	2,64s	6,12s	—	—	—	—	—	—
IIe	1,37 t	4,33q	2,65s	6,16s	7,80s	—	—	—	—	3,40 s
					7,30s					

of the formation of V is explained by the fact that this compound is extremely difficult to dissolve, and it therefore immediately precipitates and is removed from the reaction sphere. The molecular weights of III and V were determined by mass spectrometry.

The acylation of IIb with acetyl chloride and p-chlorobenzoyl chloride gives diacyl derivatives VIa, b.



IIb VIa, b

VI a R = $COCH_3$; VI b R = p-ClC_6H_4CO

2-Methyl-3-carbethoxy-4-thienylhydrazine hydrochloride (VII) was obtained by hydrolysis of IIe with an alcohol solution of hydrochloric acid. The free base is unstable and decomposes in a few hours.

The structure of IIa-e was confirmed by the IR and PMR spectra. Doubling of the signals of the proton-containing groups of the molecules (intensity ratios of 2:1, 2:1, and 1:1, respectively) is observed in the PMR spectra of IIa, b and VIa (see Table 1). An increase in the temperature leads to merging of the double signals, and doubling of the signals is again observed when the compounds are cooled to room temperature. The observed phenomena are probably caused by amide isomerism, i.e., by the presence of two equilibrium states formed by rotation of the R—C(=O)— group about the amide C–N bond [4]. An indication in favor of this is the greatest difference in the chemical shifts of the formyl protons ($\Delta\delta$ = 0.2 ppm) as compared with the other groups ($\Delta\delta$ = 0.1 ppm) in the two isomers of IIa and, correspondingly, of the acetyl protons in IIb and VIa. Doubling of the signals vanishes in deuterodimethyl sulfoxide solution because of steric hindrance arising as a result of the formation of complexes of the substance with the solvent. The absence of doubling of the signals in IIc, d can be explained by the donor properties of the phenyl and amino groups, which lower the energy barrier to rotation. Cooling of solutions of these compounds to – 60° does not lead to doubling of the signals.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The UV spectra of alcohols solutions of the compounds were recorded with a Hitachi EPS-3 spectrophotometer. The PMR spectra of deuterochloroform solutions of the compounds were recorded with a JEOL JNM-4H-100 spectrometer (100 MHZ with hexamethyldisiloxane as the internal standard. The mass spectra were recorded with an LKB-9000 mass spectrometer at an ionizing voltage of 70 eV, a cathode emission current of 60 μA, and an ion source temperature of 250-270°.

Acyl Derivatives of β-Thienylhydrazine (IIa-e). A) A 0.01-mole sample of 2-methyl-3-carbethoxy-4-hydroxythiophene was added to a solution of acylhydrazine Ia-c in glacial acetic acid (0.1 mole of Ia and 6 ml of acid were used for the synthesis of IIa, 0.2 mole of Ib and 12 ml of acid were used for the synthesis of IIb, and 0.02 mole of Ic and 4 ml of acid were used for the synthesis of IIc. The reaction mixture was then stirred at 90-100° for 10 min, after which it was poured over ice, and the resulting precipitate was removed by filtration.

B) A 0.01-mole sample of 2-methyl-3-carbethoxy-4-hydroxythiophene was added to a solution of the acylhydrazine derivative in glacial acetic acid (0.02 mole of Id and 25 ml of acid were used for the synthe-

sis of IId, and 0.02 mole of Ie and 6 ml of acid were used for the synthesis of IIe). The reaction mixture was then refluxed for 1.5 h, after which it was poured over ice, and the resulting precipitate was removed by filtration.

3,3'-Diamino-4,4'-dicarbethoxy-5,5'-dimethyl-2,2'-dithienyl (III). The mother liquor remaining after recrystallization of IIa, b was evaporated to give III with mp 144-145° (from dioxane) in 15% yield. IR spectrum: 1660, 1680 (C=O); 3320, 3410 cm^{-1} (NH_2). UV spectrum, λ_{max}, nm (log ε): 222 (4.55), 254 (4.42), and 350 (3.90). Found: C 52.1; H 5.5; N 7.6; S 17.1%; M 368. $C_{16}H_{20}N_2O_4S_2$. Calculated: C 52.1; H 5.4; N 7.6; S 17.4%; M 368, 484.

3,3'-Diacetamido-4,4'-dicarbethoxy-5,5'-dimethyl-2,2'-dithienyl (IV). A solution of 1.8 g (5 mmole) of III and 5 ml (70 mmole) of acetyl chloride in 20 ml of dry dioxane was heated at 100° for 30 min, after which the mixture was cooled, and the resulting precipitate was removed by filtration to give 1.6 g (73%) of IV with mp 270-271° [from dimethylformamide (DMF)]. IR spectrum: 1670, 1710 cm^{-1} (C=O); 3240 cm^{-1} Found: C 52.8; H 5.6; N 6.2; S 14.1%. $C_{20}H_{24}N_2O_6S_2$. Calculated: C 53.1; H 5.3; N 6.2; S 14.2%.

4-Oxo-3,4-dihydro-5-methyl-6-(2'-methyl-3'-carbethoxy-4'-amino-5'-thienyl)thieno[3,4-d]pyrimidine (V). A solution of 1.8 g (5 mmole) of III in 70 ml of formamide was refluxed for 1.5 h, after which it was cooled, and the resulting precipitate was removed by filtration to give 1.6 g (100%) of V with mp 244-245° (dec., from DMF). IR spectrum: 935 (pyrimidine ring) and 1670 cm^{-1} (C=O). Found: C 51.3; H 4.4; N 12.2; S 18.1%; M 349. $C_{15}H_{15}N_3O_3S_2$. Calculated: C 51.5; H 4.3; N 12.0; S 18.3%; M 349.446.

1,1-Diacetyl-2-(2'-methyl-3'-carbethoxy-4'-thienyl)hydrazine (VIa). A solution of 2.4 g (0.01 mole) of IIb and 3 ml of acetyl chloride in 15 ml of dioxane was heated at 100° for 1 h, after which the solvent was removed by distillation, and the residue was diluted with ether. The resulting precipitate was removed by filtration to give 2.1 g (74%) of VIa with mp 128-129° (from benzene-petroleum ether). IR spectrum: 1660, 1700 (C=O); 3130 (CH); 3260 cm^{-1} (NH). Found: C 51.0; H 5.4, N 10.0; S 11.3%. $C_{12}H_{26}N_2O_4S$. Calculated: C 50.7; H 5.7; N 9.9; S 11.3%.

1-Acetyl-2-(p-chlorobenzoyl)-2-(2'-methyl-3'-carbethoxy-4-thienyl)hydrazine (VIb). This compound was obtained as in the preceding experiment from 2.4 g (0.01 mole) of IIb and 1.8 g (0.01 mole) of p-chlorobenzoyl chloride in 15 ml of dry dioxane. The yield of VIb, with mp 129.5-130.5° (from aqueous methanol), was 2.2 g (60%). IR spectrum: 1650, 1700 (C=O); 3120 (CH); 3260 cm^{-1} (NH). Found: C 53.4; H 4.4; Cl 9.5; N 7.4; S 8.5%. $C_{17}H_{17}ClN_2O_4S$. Calculated: C 53.6; H 4.5; Cl 9.3; N 7.4; S 8.4%.

1-(2'-Methyl-3'-carbethoxy-4'-thienyl)hydrazine Hydrochloride (VII). A solution of 3.6 g (0.015 mole) of IIb in 36 ml of methanol and 3.3 ml (0.45 mole) of concentrated hydrochloric acid was refluxed for 1 h, after which the solvent was removed by distillation. The residue was dissolved in alcohol, and VII was precipitated by the addition of ether to give 1.8 g (50%) of a product with mp 160-161° (from methanol). Found: C 40;4; H 5.5; Cl 15.3; N 11.8; S 13.4%. $C_8H_{13}ClN_2O_2S$. Calculated: C 40.6; H 5.5; Cl 15.0; N 11.8; S 13.5%. 1-(2'-Methyl-3'-carbethoxy-4'-thienyl)hydrazine was obtained by alkalization of an aqueous solution of the hydrochloride and had bp 142-143° (1 mm) and mp 55-56° (from petroleum ether). IR spectrum: 1680 (C=O); 3120 (CH); 3170, 3290 (NH); 3400 cm^{-1} (NH_2). Found: C 47.8; H 5.9; N 14.1; S 16.3%. $C_8H_{12}N_2O_2S$. Calculated: C 48.0; H 6.0; N 14.0; S 16.0%.

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