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Synthesis of 4-(2-Thienyl)pyrimidine Derivatives. Studies on Heterocyclic Chemistry. VI[1]

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4-(2-Thienyl)pyrimidines are little studied.[2,3] In connection with other programmes some of their derivatives (IX, X, XI, XII) were prepared from the corresponding β-diketones having a thiophene ring and guanidine or urea.

The Wolff-Kishner reduction of 2-isovalerylthiophene (I) gave 2-isoamylthiophene (II) in better yield of 77% than the reported Clemmensen procedure of 32% yield.[4] Reduction of I with lithium aluminum hydride afforded an alcohol III, which was obtained in a pure state only by its acetylation to IV and subsequent hydrolysis to III, because repeated fractional distillations of the crude reaction product could not give an analytically pure sample.

1) Part V. T. Nishiwaki, T. Kitamura, and A. Nakano, *Tetrahedron*, **26**, 453 (1970).

2) S. Gronowitz and J. Röe, *Acta. Chem. Scand.*, **19**, 1741 (1965).

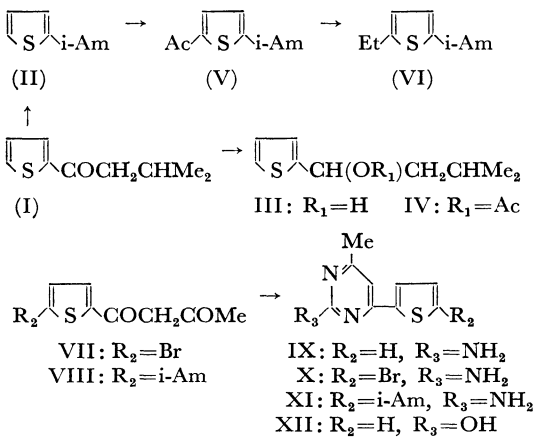
3) H. Bredereck, R. Gompper, and H. Herlinger, *Chem. Ber.*, **91**, 2832 (1958).

4) W. Steinkopf and I. Schubart, *Ann.*, **424**, 1 (1920).

Table 1. NMR spectra of 4-(2-thienyl)pyrimidines IX, X, XI, XII[a,b]

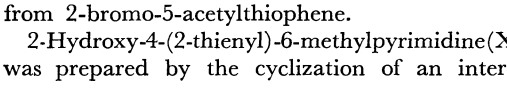
Compound	Chemical Shifts (τ values, J (Hz))			
	Pyrimidine	Thiophene		
	C_5–H	C_3–H	C_4–H	C_5–H
IX	3.06	2.22 (dd, J_{34}=4.5) (J_{35}=1.5)	2.87 (dd, J_{45}=5.3) (J_{34}=4.5)	2.36 (dd, J_{45}=5.3) (J_{35}=1.5)
X	3.00	2.30 (d, J_{34}=4.2)	2.71 (d, J_{34}=4.2)	
XI	3.14[c]	2.40 (d, J_{34}=4.2)	3.14[c]	
XII	3.18	1.97 (dd, J_{34}=4.2) (J_{35}=1.5)	2.65 (dd, J_{34}=4.2) (J_{45}=5.4)	2.08 (dd, J_{45}=5.4) (J_{35}=1.5)

a) The spectra were determined in dimethyl sulfoxide or its d_6-analogue at room temperature or at 60°C (for XII).
b) dd, double doublet.
c) Broad peak due to overlapping.



Friedel-Crafts reaction of II with acetic acid in the presence of polyphosphoric acid produced 2-isoamyl-5-acetylthiophene (V), from which a β-diketone VIII was derived. The structure of V was verified by NMR spectrum,[5] which showed in carbon tetrachloride two β-protons of thiophene ring at τ 3.22 (dd, J=4.0 Hz and J=1.0 Hz,*1 C_3–H) and τ 2.52 (d, J=4.0 Hz, C_4–H). An additional support is provided by reduction of V to 2-isoamyl-5-ethylthiophene (VI), the NMR spectrum of which exhibited in carbon tetrachloride only one signal at τ 3.60 corresponding to two β-protons. A β-diketone VII was similarly derived from 2-bromo-5-acetylthiophene.

2-Hydroxy-4-(2-thienyl)-6-methylpyrimidine(XII) was prepared by the cyclization of an intermediate uramido compound which has two possible structures, XIII and XIV.



The structures of the pyrimidines (IX—XII) were characterized by NMR spectra in the aromatic region as shown in Table 1.

Experimental

Melting points were determined on a Yanagimoto hot stage and uncorrected. NMR spectra were taken at 60 MHz with a JNM-3H-60 spectrometer with TMS as an internal standard.

2-Isoamylthiophene (II). 2-Isovalerylthiophene[4] (I) (29.9 g, 0.18 mol), hydrazine hydrate (80%) (34 m*l*, 0.70 mol), and ethylene glycol (400 m*l*) were stirred at 120—130°C for 2 hr. After cooling the mixture to 50°C, a solution of potassium hydroxide (30.0 g) in ethylene glycol (100 m*l*) was added at once to this mixture. The mixture was heated at 130—140°C for 1 hr with stirring, left overnight and distilled at atmospheric pressure up to 220°C. The distillate was extracted with ether and the extracts were washed with water, 2N hydrochloric acid, and water successively, dried (Na_2SO_4), and distilled to give II, 21.2 g (77%), bp 56—57°C/2 mmHg, n_D^{20} 1.4951, (lit,[4] bp 72—77°C/11 mmHg). (Found: C, 70.0; H, 9.0; S, 21.0%).

Reduction of 2-Isovalerylthiophene (I) with Lithium Alminum Hydride. A solution of the ketone (I) (13.4 g, 0.08 mol) in anhydrous ether (40 m*l*) was slowly added to a suspension of lithium aluminum hydride (6.0 g, 0.16 mol) in anhydrous ether (200 m*l*). The mixture was refluxed for 3 hr and worked-up in the usual manner to afford an oil, the gas chromatogram of which showed the presence of at least five components. This oil was heated with a mixture of acetic anhydride (11.5 g) and anhydrous sodium acetate (1.5 g) at 100°C for 2 hr and poured into water. Ether extraction and distillation afforded an acetate (IV), 10.1 g (60%), bp 69—70°C/0.4 mmHg, $\nu_{C=O}^{Neat}$ 1745 cm^{-1}.

Found: C, 62.5; H, 7.8; S, 15.8%. Calcd for $C_{11}H_{16}O_2S$: C, 62.2; H, 7.6; S, 15.1%.

This acetate (9.8 g, 0.05 mol) was refluxed with potassium hydroxide (3.1 g) in ethanol (30 m*l*) for 2 hr. The mixture was poured into water and extracted with ether. Distillation of the dried (Na_2SO_4) extracts gave an alcohol (III), 5.4 g (68%), bp 71—72°C/0.8

*1 Coupling with the side chain.

5) R. White, "Physical Method in Heterocyclic Chemistry," Vol. 2 ed. by A. R. Katritzky, Academic Press, New York, (1964), p. 103.

mmHg, n_D^{20} 1.5168, ν_{OH}^{Neat} 3280 cm^{-1}.

Found: C, 63.5; H, 8.5; S, 18.6%. Calcd for $C_9H_{14}OS$: C, 63.5; H, 8.3; S, 18.8%.

2-Isoamyl-5-acetylthiophene (V). A mixture of polyphosphoric acid (200 g), acetic acid (33.3 g) and 2-isoamylthiophene (II) (30.0 g, 0.19 mol) was stirred at 80—85°C for 1 hr and the mixture was poured into water and extracted with ether. The etheral extracts were dried (Na_2SO_4) and distilled at 89—92°C/0.2 mmHg to give a compound (V), 31.5 g (83%), n_D^{20} 1.5277, $\nu_{C=O}^{Neat}$ 1660 cm^{-1}.

Found: C, 67.2; H, 8.5; S, 16.4%. Calcd for $C_{11}H_{16}OS$: C, 67.3; H, 8.2; S, 16.3%.

The 2,4-dinitrophenylhydrazone, mp 170—171°C (from benzene-ligroin), (Found: C, 53.9; H, 5.3; S, 8.4%. Calcd for $C_{17}H_{20}N_4O_4S$: C, 54.2; H, 5.4; S, 8.5 %). The semicarbazone, mp 215—216°C (from methanol), (Found: C, 56.9; H, 7.85; N, 16.14%. Calcd for $C_{12}H_{19}N_3OS$: C, 56.9; H, 7.6; N, 16.6%).

2-Isoamyl-5-ethylthiophene (VI). A mixture of the ketone (V) (10.0 g, 0.05 mol), diethylene glycol (150 m*l*), and hydrazine hydrate (80%) (10 m*l*, 0.26 mol) was heated at 120°C for 2 hr. After cooling to 50°C, a solution of potassium hydroxide (10.0 g) in diethylene glycol (50 m*l*) was added to this mixture at once and heated at 140°C for 1 hr. The mixture was distilled up to 230°C and the distillate was treated as before to give VI, 8.0 g (86%), bp 58—60°C/0.6 mmHg, n_D^{20} 1.4930.

Found: C, 72.1; H, 10.0%. Calcd for $C_{11}H_{18}S$: C, 72.5; H, 9.95%.

2-Isoamyl-5-thenoylacetone (VIII). A solution of V (9.8 g) in ethyl acetate (15.0 g) was added to a suspension of powdered sodium (1.3 g) in anhydrous ether (70 m*l*). The mixture was refluxed for 2 hr with stirring. The sodium salt was filtered off, dissolved in water and extracted with ether. The aqueous solution was acidified and extracted with ether. The dried (Na_2SO_4) extracts afforded the β-diketone by distillation at 102—106°C/0.2 mmHg, 2.6 g (22%), n_D^{20} 1.5676.

Found: C, 65.9; H, 7.7%. Calcd for $C_{13}H_{18}O_2S$: C, 65.5; H, 7.6%.

2-Bromo-5-thenoylacetone (VII). This was prepared similarly from 2-bromo-5-acetylthiophene in 38% yield after recrystallization from methanol, mp 132—133°C.

Found: C, 38.8; H, 2.85%. Calcd for $C_8H_7BrO_2S$: C, 38.9; H, 2.85%.

2-Amino-4-(5-isoamyl-2-thienyl)-6-methylpyrimidine (XI). The β-diketone (VIII) (1.7 g) and guanidine carbonate (0.8 g) were melted at 140—150°C for 1 hr. After cooling, the mixture was washed with water and insoluble product (1.6 g, 84%) was recrystallized twice from *n*-heptane as pale yellow needles, mp 126°C.

Found: C, 64.2; H, 7.3%. Calcd for $C_{14}H_{19}N_3S$: C, 64.3; H, 7.3%.

2-Amino-4-(2-thienyl)-6-methylpyrimidine (IX). This compound was obtained from 2-thenoylacetone and guanidine carbonate in 79% yield and recrystallized from ethanol, mp 173—174°C.

Found: C, 56.4; H, 5.0%. Calcd for $C_9H_9N_3S$: C, 56.5; H, 4.75%.

2-Amino-4-(5-bromo-2-thienyl)-6-methylpyrimidine (X). This compound was prepared from VII and guanidine carbonate in 90% yield and recrystallized from acetone, mp 200—201°C.

Found: C, 40.2; H, 3.0%. Calcd for $C_9H_8BrN_3S$: C, 40.0; H, 3.0%.

2-Hydroxy-4-(2-thienyl)-6-methylpyrimidine (XII). A mixture of 2-thenoylacetone (8.4 g), urea (3.00 g), anhydrous ethanol (50 m*l*), and hydrochloric acid (0.5 m*l*) was left for 40 hr at room temperature with occasional shaking. Homogeneous solution resulted after a few hours and then pale yellow soild began to precipitate. Two recrystallizations from ethanol gave an uramido compound, 5.39 g (51%), as pale yellow plates, mp 192—194°C (decomp.).

Found: C, 51.5; H, 5.0; N, 13.2; S, 15.1%. Calcd for $C_9H_{10}N_2O_2S$: C, 51.4; H, 4.8; N, 13.3; S, 15.25%.

This compound (1.18 g) was heated with potassium hydroxide (0.5 g) in water (10 m*l*) until a clear solution had resulted. After cooling, the solution was acidified and precipitates (0.90 g, 84%) were recrystallized from water as colourless needles, mp 280—282°C (decomp).

Found: C, 56.3; H, 4.0; N, 14.2; S, 16.7%. Calcd for $C_9H_8N_2OS$: C, 56.2; H, 4.2; N, 14.6; S, 16.7%.