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原 著

Formation of 5,5-dimethyl-7-(2-thienyl)-2,4,5,6-tetrahydro-(3H)-1,2-diazepin-3-one, a byproduct, in the Wolff-Kishner reduction of 3,3-dimethyl-4-(2-thienyl)butanoic acid

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Abstract

The Wolff-Kishner reduction of 3,3-dimethyl-4-(2-thienyl)butanoic acid by Huang-Minlon's procedure gave 5,5-dimethyl-7-(2-thienyl)-2,4,5,6-tetrahydro-(3H)-1,2-diazepin-3-one along with the desired 3,3-dimethyl-5-(2-thienyl)pentanoic acid. This 1,2-diazepine derivative was found to produce by ring cyclization of hydrazone of 3,3-dimethyl-4-(2-thienyl)butanoic acid. This method was applied to the preparation of 1,2-diazepin-3-one derivatives by the action of hydrazine on 3,3-dimethyl-5-keto acids. These 1,2-diazepine derivatives are considered pharmacologically as very interesting drugs.

keywords : wolff-kishner reduction, diazepine, psychotroic activity, thiophen, ring cyclization

3,3-ジメチル-4-(2-チエニル)ブタン酸のWolff-Kishner還元による副産物としての5,5-ジメチル-7-(2-チエニル)-2,4,5,6-テトラヒドロ-(3H)-1,2-ジアゼピン-3-オンの生成

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要　旨

Huang-Minlon の方法による 3,3- ジメチル -4-(2- チエニル) ブタン酸の Wolff-Kishner 還元から期待した 3,3- ジメチル -5-(2- チエニル) ペンタン酸の他に 5,5- ジメチル -7-(2- チエニル)-2,4,5,6- テトラヒドロ -(3H)-1,2- ジアゼピン -3- オンを得た。この 1,2 － ジアゼピン誘導体は、3,3- ジメチル -4-(2- チエニル) ブタン酸のヒドラゾンの環化により生成することが分かった。この方法は 3,3- ジメチル -5- ケト酸にヒドラジンを作用させる 1,2 － ジアゼピン -3- オン誘導体の合成に応用できる。このような 1,2- ジアゼピン誘導体は薬理学

的に非常に興味深い薬と考えられている。

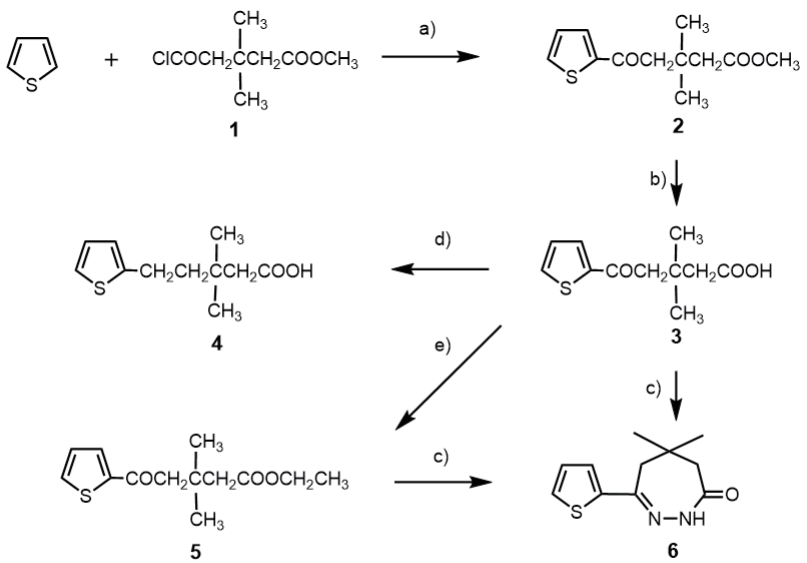
キーワード：wolff-kishner 還元、ジアゼピン、向精神活性、チオフェン、環化反応

In connection with metabolic studies of fatty acids, the author reported the preparation of 3,3,12,12-tetramethyltetradecanoic acid (TMTD) by the Kolbe electrolysis[1]. This TMTD, neopentyl type carboxylic acid, is very resistant to general ß-oxidation in organisms, and considered as a sort of non-oxidizable fatty acids. In an attempt to synthesize ^{14}C-TMTD, the synthetic method using thiophene as a carbon chain-extender was examined along with the pathway shown in Chart 1.

After the modified Wolff-Kishner reduction process[2] of 3,3-dimethyl-4-(2-thienyl) butanoic acid with 85% hydrazine hydrate, an unknown substance was isolated as chloroform-soluble fraction in the separation procedure of the desired compound, 3,3-dimethyl-5-(2-thienyl)pentanoic acid **(4)**. This paper describes the identification of 5,5-dimethyl-7-(2-thienyl)-2,4,5,6-tetrahydro(3H)-1,2- diazepin-3-one **(6)**, obtained as a new byproduct.

Results and Discussion

3,3-Dimethyl-4-(2-thienyl)butanoic acid **(2)**, a starting material, was first prepared by the modified known method[3-5]. Compound **(2)** was synthesized by Buu-Hoi et al.[6], by $AlCl_3$-catalysed Friedel-Crafts acylation of thiophen with 3,3-dimethylglutaric anhydride. Wolff-Kishner reduction of the keto acid **(3)** by Huang-Minlon's procedure furnished colorless 3,3-dimethyl-5-(2-thienyl)pentanoic acid **(4)** with mp 56 − 57 ℃ after recrystallization from a mixture of acetone and petroleum-ether (bp 36.5 − 53.5 ℃). This melting point is different from mp 48 ℃ reported by Buu-Hoi et al., although the reason of this discrepancy is unknown. During the isolation of this acid **(4)** alkali-insoluble and chloroform-soluble crystals were obtained in a small amount and melted at 193 − 194 ℃ . The high melting point (mp 201 − 204 ℃), a low solubility in general organic solvents and IR spectral data (1630 cm^{-1}) of this product suggested the presence of the acid amide group in the cyclized molecule. Next, for clarification of the chemical structure of the above anticipated compound, reaction of 3,3-dimethyl-4-(2-thienyl)butanoic acid **(3)** with 80% hydrazine hydrate was performed to give colorless crystals. The data of Mass, NMR, IR, UV spectra of this colorless product supported positively the chemical structure of **(6)**. These data were identical to those of the isolated product with mp 193 − 194 ℃ , undepressed on admixture with a synthetic specimen. It is well known that the *gem*-dimethyl group in this case facilitates ring cyclization.[7] While a mixture of ethyl 3,3-dimethyl-4-(2-thienyl)butanoate **(5)** and 80% hydrazine hydrate gave the same compound **(6)**, but the ring cyclization reaction proceeded very slowly under the same condition as the use of free acid **(3)**.



Reagents and conditions: a) $SnCl_4$; b) 10%KOH-EtOH; c) NH_2NH_2; d) NH_2NH_2-KOH; e) EtOH

Chart 1. Synthetic Pathways of 5,5-Dimethyl-1,2-Diazepin-3-one (**6**)

For the preparation of 2-methylated derivative of **(6)** the use of monomethylhydrazine instead of 80% hydrazine hydrate failed to give any crystalline compound under the above-mentioned reaction condition. This result was consistent with that of Rosen and Popp.[8] Reaction of 3,3-dimethyl-5-aroyl fatty acids with 80% hydrazine hydrate give the desired 1,2-diazepin-3-one derivatives. At present the synthesis of some 5,5-dimethyl-7-(2-aryl)-2,4,5,6-tetrahydro-(3H)-1,2-diazepin-3-one derivatives is in progress for the pharmacological screening of these compounds. The feature of the chemistry of 1,2-diazepines is their facility for ring *trans*-formation reactions under thermal, photochemical, acidic and basic conditions.[9-12] Our reported 1,2-diazepine compounds are very interesting from the point of psychotropic and analgesic activity[13] as well as its chemistry. Pharmacological and biochemical studies are in progress using this unique compound **(6)** and its some analogs.

Experimental

All chemicals were of the highest grade commercially available. Melting points were determined without correction on a Yanagimoto apparatus. IR spectra were recorded on a JASCO A-100 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on JEOL JNM-GX 300. Chemical Shifts are given in δ values (ppm) with tetramethylsilane as an internal standard and coupling constants *(J)* are given in Hz. Low-resolution mass spectra were obtained with a JEOL HX110A mass spectrometer. Elemental analysis (CHN) was performed on a Yanaco CHN Corder MT-3.

3,3-Dimethyl-4-(2-thienyl)butanoic Acid (3) Anhydrous stannic chloride (25 mL) was

added slowly in 50 min to a stirred solution of freshly distilled thiophene (18 mL) and 4-carbomethoxy-3,3-dimethylbutyryl chloride (1) (28.2 g) in dry benzene (155 mL), during which time reaction vessel was cooled in an ice-salt bath. After being stirred at room temperature for further 1 h, the mixture in red color was poured on ice (150 g) and c-HCl (110 mL), and the mixture was extracted with benzene, petroleum ether and ether. The combined organic layer (about 500 mL) was washed with dilute $NaHCO_3$ solution, water and dried over $CaCl_2$. After removal of the organic solvent crude oil (38 g) was subjected to distillation to give colorless oil (bp 159 − 162℃, 32.1 g) **(2)** which on standing became rapidly pale yellow in color. *Anal.* Calcd. for $C_{12}H_{16}O_3S$: C, 60.01; H, 6.72. Found: C, 60.17; H, 7.01. This methyl ester **(2)** (32 g) was hydrolysed with 10% KOH-EtOH solution (200 mL) for 4 h on a steam bath.

Ether-soluble acidic fraction (22.6 g, free acid) was obtained after acidification by HCl of the hydrolysed alkaline mixture. Colorless 3,3-dimethyl-4-(2-thienyl)butanoic acid **(3)** melted at 76 − 76.5℃ after recrystallization from acetone. Following mass peaks, m/z 226 (M^+, 20.5) and 126 (base peak, 100.0) were obtained by E.I. mass spectrometry. *Anal.* Calcd. for $C_{11}H_{14}O_3S$: C, 58.40; H, 6.24. Found: C, 58.71; H, 6.18. The oxime of **(3)** was obtained in the usual method and melted at 128 − 130℃ after recrystallization from acetone. *Anal.* Calcd for $C_{11}H_{14}O_3N_2S$: C, 54.76; H, 6.27; N, 5.81. Found: C, 54.57; H, 6.21; N, 5.45.

3,3-Dimethyl-5-(2-thienyl)pentanoic Acid (4)　According to the Huang-Minlon's procedure, the keto acid **(3)** (22.6 g) was dissolved in a mixture of 85% aqueous hydrazine hydrate (40 ml) and alkaline-diethylene glycol (DEG) solution (5.6 g KOH in 100 mL), and refluxed for 16 h, then KOH (28 g) and DEG (100 mL) was added to the reaction mixture, and water as well as excess hydrazine was removed by distillation. The temperature of the content rose gradually up to 180℃, with distillate (about 40 mL), when the mixture was heated under reflux for an additional 28 h. After cooling, the mixture was poured into cold water, acidified with c-HCl, extracted with chloroform, the chloroform layer was treated with saturated $NaHCO_3$. The biocarbonate-soluble fraction was acidified with c-HCl and extracted with ether. The ether extract (about 200 mL) was dried over Na_2SO_4 and then ether was removed to obtain 14.5 g of crystals.

A part (1.2 g) of crude acid **(4)** was subjected to silicic acid column chromatography (silicic acid : 20 g, 2.5 cm in diameter × 6.9 cm long) and colorless crystals were obtained from chloroform eluates. The crystals were recrystallized from a mixture of petroleum-ether (b.p. 36.5 - 53.5℃) and acetone to give colorless crystals, **(4)** mp 56 – 57℃. *Anal.* Calcd. for $C_{11}H_{16}O_2S$: C, 62.24; H, 7.60. Found. C, 62.45; H, 7.85. The above alkali-insoluble fraction (chloroform layer) gave pale yellow crystals after removal of chloroform. Crystals were recrystallized from acetone and then chloroform to give 2.7 g of colorless needles which melted at 193–l94℃. In order to clarify the chemical structure of this product the next experiment was carried out.

5,5-Dimethyl-7-(2-thienyl)-2,4,5,6-tetrahydro-(3H)-1,2-diazepin-3-one (6)

The keto acid **(3)** (0.85 g) in a small amount of ethanol was reacted with 80%

hydrazine hydrate (0.4 mL) for 4 h under reflux to obtain the corresponding hydrazone. Crude crystals were recrystallized twice from ethanol to give pale yellow crystals, mp 195 – 198 ℃. Colorless crystals were obtained by further recrystallization from ethanol and showed mp 201 – 204 ℃. UV λ_{max} (EtOH): 221, 263, 315 nm. Its mass spectrum showed the following peaks: m/z 126 (base peak, 100) and 222 (M^+, 13), respectively. The IR (KBr, cm^{-1}) spectrum also showed the typical absorption at 1630 (CO-NH), suggesting the presence of the amide moiety in the molecule. ^{1}H-NMR (DMSO-d_6) δ : 1.08 (6H, s), 2.05 (2H, s), 2.69 (2H, s), 7.14 (1H, dd, *J*=3.7, 5.0 Hz, H-4), 7.60 (1H, dd, *J*=0.8, 3.7 Hz, H-3), 7.67 (1H, dd, *J*=0.8, 5.0 Hz, H-5), 10.41 (1H, s). ^{13}C-NMR (DMSO-d_6) δ : 29.1, 40.3, 40.8, 47,3, 127.8, 129.1, 129.8, 142.2, 170.5. *Anal.* Calcd. for $C_{11}H_{14}N_2OS$: C, 59.45; H, 6.35; N, 12.60. Found. C, 59.51; H, 6.40; N, 12.47.

Based on the spectral data and elemental analysis, the chemical structure of this compound was found to be 5,5-dimethyl-7-(2-thienyl)-2,4,5,6-tetrahydro-(3H)-1,2-diazepin-3-one (**6**) resulted by dehydration between the amino group of once formed hydrazone and the calboxyl group of the above-mentioned 3,3-dimethylated fatty acid.

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