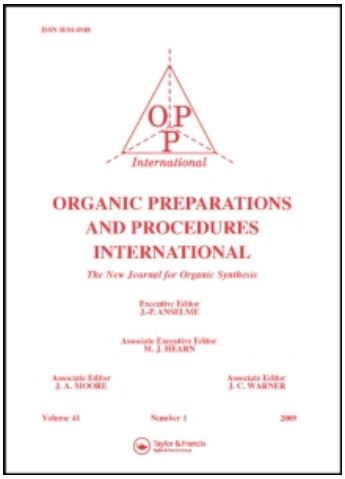

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SYNTHESIS OF 4-HYDROXY-4-(2-THIENYL)PENTAMIDE

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SYNTHESIS OF 4-HYDROXY-4-(2-THIENYL)PENTAMIDE†

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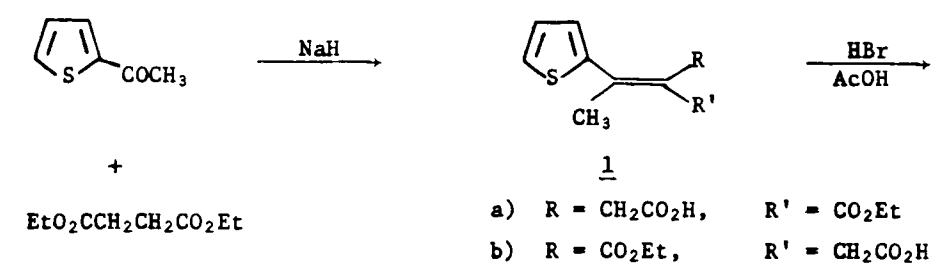
4-Hydroxy-4-phenylpentamide[1] and structurally related compounds as well as alkyl substituted γ-butyrolactones[2] exhibit anticonvulsant activity. This paper describes two different routes to 4-hydroxy-4-(2-thienyl)pentamide 4 and the synthesis of the interesting γ-butyrolactones 2a and 2b.

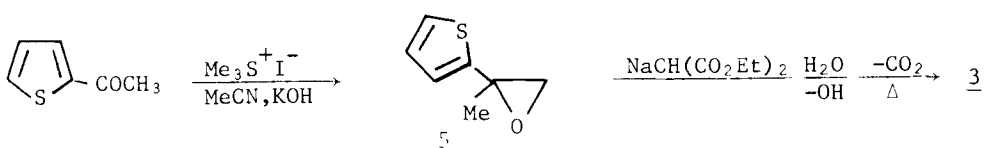
The first approach involved a Stobbe condensation of 2-acetylthiophene with ethyl succinate, which afforded in a 75% yield the isomeric mixture



of E-3-carbethoxy-4-(2-thienyl)-3-pentenoic acid 1a and its corresponding Z-isomer 1b. While the Z isomer crystallized, the E-isomer remained as an oil. Further purification of both isomers by column chromatography afforded pure Z and E-isomers in 27% and 26% yield respectively. The assignment

of their structures was based mainly on their spectral ^1H nmr data. Thus Z-isomer exhibits the ester ethyl group shifted to high field due to diamagnetic currents in the thiophene ring. The methyl group on the double bond in E-isomer is shifted low field due to carbonyl ester deshielding. Treatment of the isomeric (E-Z) mixture with hydrobromic acid in acetic acid (38% v/v) gave a mixture of three products. Separation by hplc afforded the expected butyrolactone 3 in 18% yield together with the stereoisomeric carbethoxylactones 2a and 2b, in 12% and 10% yield, respectively. Once again, the stereochemistry of the diasteroisomeric pair, 2a and 2b was assigned on the basis of their ^1H nmr spectra. In the *cis*-compound 2a the γ-methyl group is more drastically affected by anisotropic effects from the carbethoxy group than in the corresponding *trans*-isomer 2b. This effect can be evaluated by comparison with the related compound 3, where the carbethoxy group is absent. Finally, lactone 3 was converted into amide 5 (87%) by treatment with ammonia under pressure; the overall yield of 5 was 11%.

In order to improve the overall yield, an alternative route using 2-acetylthiophene as starting material and γ-butyrolactone as a key intermediate was explored. Several methods for the synthesis of γ-butyrolactones starting from epoxides[3] have been described. One of the most versatile methods for the conversion of aldehydes and ketones into epoxides using dimethylsulfonium methylides[4] has been modified so as to not require anhydrous conditions reported[5]. Treatment 2-acetylthiophene with the sodium salt diethyl malonate, followed by cyclization of the ring-opened intermediate, hydrolysis and decarboxylation in one-pot gave butyrolactone 3 in 57% yield.



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The γ-hydroxyamide 4 obtained as described above proceeded in a 39% over-

all yield. Compound 4 has been submitted for testing[6] to the Antiepileptic Drug Development (ADD) Program of the National Institute of Health, USA.

EXPERIMENTAL SECTION

Melting points were determined on a Fisher-Jones apparatus and are uncorrected. The ir spectra were recorded on a Perkin Elmer 283 B Spectrophotometer using either potassium bromide mulls or neat liquids between sodium chloride plates. The ^{1}H nmr spectra were obtained on a Varian FT-80 instrument with TMS as internal standard. Mass spectra were recorded with a Hewlett Packard 5985 B spectrometer with gc/ms system; compounds were introduced through the direct insertion probe. The hplc was performed using a Varian 8500 liquid chromatograph; a refractive index detector and a Varian A-25 recorder were employed. Samples were separated on a Micropack Si-10 column; the eluent was hexane-ethyl acetate (8:2), at 200 ml/hr. Elemental analyses were performed by Dr. F. Pasher's Laboratory, Bonn, West Germany.

(E,Z) 3-Carbethoxy-4-(2-thienyl)-3-pentenoic acid, 1a and 1b.- Into 500 ml round bottom flask with two ground joints, fitted with condenser, drying tube, addition funnel and magnetic stirrer, was placed a suspension of 4.8 g (0.2 mol) of sodium hydride (as 50% suspension in oil) in 120 ml of dry benzene. A mixture of 12.62 g (0.1 mol) of 2-acetylthiophene, 34.8 g (0.2 mol) of diethyl succinate and 120 ml of dry benzene was added dropwise and the contents stirred at room temperature for 3 hrs. After this period, the reaction mixture was cooled in an ice-water bath and methanol (2 ml) was added to destroy sodium hydride. After acidification with hydrochloric acid, the solvent was removed under reduced pressure and the mixture was diluted with water (200 ml) and extracted with ether (3 x 150 ml). The organic layer was extracted with a 5% solution of potassium hydroxide (3 x 60 ml). After acidification, the aqueous layer was extracted with ether, and the combined organic layers were dried over anhydrous sodium sulfate and evaporated to dryness to afford 19.0 g (75%) of an oily product which is the E,Z-mixture of the Stobbe condensation products. This oily product was used without separation.

Separation of the E and Z Isomers.- The oily product described above crystallized partially on standing overnight. The solid was collected, washed with hexane, passed through a silica gel column and eluted with an 8:2 mixture of ethyl acetate-hexane; the solid obtained after evaporation was recrystallized from ethyl acetate and identified as Z-3-carbethoxy-4-(2-thienyl)-3-pentenoic acid (1b), (6.96 g, 27%), mp. 93-95°; IR (KBr): 3300-2500, 3070, 1705, 1626, 1520, 1425, 1380, 1240, 925 cm^{-1}; ^1H nmr ($CDCl_3$): δ 0.95 (3H, t, J = 7 Hz), 2.18 (3H, s), 3.50 (2H, s), 3.95 (2H, q, J = 7 Hz), 6.90 (2H, m), 7.20 (1H, m), 7.75 (1H, broad); Ms (m/z, relative intensities): 254 (8,M^+), 210 (30), 209 (15), 181 (40), 165 (11), 164 (42), 137 (18), 136 (100), 135 (79), 91 (45).

Anal. Calcd. for $C_{12}H_{14}O_4S$: C, 56.68; H, 5.55; S, 12.61

Found : C, 56.53; H, 5.50; S, 12.66

The filtrate, composed mainly by the E-isomer was then purified by column chromatography (silica gel, using an 8:2 mixture of ethyl acetate:hexane as eluent) and then preparative tlc to give 6.52 g (26%) of the pure E-isomer as an oil: IR(film):3300-2500, 3060, 1710, 1610, 1365, 1280, 1190, 920 cm^{-1}: ^1H nmr ($CDCl_3$): δ 1.30 (3H, t, J = 7 Hz), 2.46 (3H, s), 3.50 (2H, s), 4.25 (2H, q, J = 7 Hz), 6.95 (2H, m), 7.25 (1H, m), 8.50 (1H, broad); Ms (m/z relative intensities) 254 (8,M^+), 210 (28), 209 (13), 181 (28), 165 (11), 164 (47), 137 (26), 136 (100), 135 (80), 91 (25).

Anal. Calcd. for $C_{12}H_{14}O_4S$: C, 56.68; H, 5.55; S, 12.61

Found : C, 56.63; H, 5.68; S, 12.57

Reaction of 1 with Hydrobromic Acid.- In a 250 ml round bottom flask equipped with a condenser and magnetic stirrer were mixed 12.5 g (0.049 mol) of the isomeric mixture of acids 1a and 1b, 50.0 ml of glacial acetic acid, 38.0 ml of a hydrobromic acid in acetic acid 38% (v/v), 11.0 ml of water and heated at 50° for 1.5 hrs. After this period, the reaction mixture was

cooled to room temperature and diluted with 50.0 ml of water and extracted with ether (3 x 75 ml). The ethereal extract was washed with a 5% solution of potassium carbonate (3 x 50 ml) and water until neutral, dried over anhydrous sodium sulfate and the solvent evaporated to dryness. The residual brownish oil was passed through a column of silica gel (70-230 mesh) eluted with a 8:2 hexane-ethyl acetate mixture to give 5.13 g of an oily product. A mixture of three products with very similar rf value was detected by tlc. Separation of such mixture was performed by hplc, using 8:2 hexane-ethyl acetate as eluent. The compounds were characterized as follows.

3-(2-Thienyl)-γ-valerolactone (3), IR ($CHCl_3$): 2980, 2915, 1782, 1425, 1380, 1260, 710 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.82 (3H, s), 2.60 (4H, m), 6.90 (6H, m), 7.20 (1H, m); Ms (m/z relative intensities): 182 (44, M^+), 167 (77), 139 (17), 127 (61), 123 (35), 111 (100), 97 (10), 43 (38).

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.32; H, 5.53; S, 17.59

Found : C, 59.35; H, 5.65; S, 17.72

"cis" Carbethoxy lactone (2b), IR ($CHCl_3$): 2915, 2840, 1785, 1730, 1455, 1410, 1370, 1235, 1215, 1180, 1155, 700 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.33 (3H, t, J = 7 Hz), 1.75 (3H, s), 2.74 (1H, dd, J = 18 Hz, J = 9 Hz), 3.10 (1H, dd, J = 18 Hz, J = 7 Hz), 3.62 (1H, dd, J= 9 Hz, J = 7 Hz), 4.25 (2H, q, J = 7 Hz), 7.0 (2H, m), 7.25 (1H, m); Ms (m/z relative intensities): 254 (20, M^+), 181 (3), 166 (6), 128 (43), 127 (42), 111 (100), 100 (38), 55 (49), 43 (20).

Anal. Calcd. for $C_{12}H_{14}O_4S$: C, 56.68; H, 5.55; S, 12.61

Found : C, 56.75; H, 5.68; S, 12.69

"trans" Carbethoxy Lactone (2a), IR ($CHCl_3$) : 2990, 2940, 1795, 1740, 1450, 1420, 1370, 1220, 1152, 1182, 710 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.14 (3H, t, J = 7 Hz), 2.04 (3H, s), 2.71 (1H, dd, J = 17 Hz, J = 8 Hz), 3.20 (1H, dd, J = 17 Hz, J = 9 Hz), 3.50 (1H, dd, J = 8 Hz, J = 9 Hz), 3.95 (2H, q, J = 7

Hz), 6.90 (2H, m), 7.20 (1H, m); Ms (m/z relative intensities): 254 (14, M^+), 181 (4), 166 (4), 128 (99), 127 (100), 111 (99), 100 (98), 55 (93), 43 (63).

Anal. Calcd. for $C_{12}H_{14}O_4S$: C, 56.68; H, 5.55; S, 12.61

Found : C, 56.57; H, 5.72; S, 12.57

4-Hydroxy-4-(2-thienyl)pentamide (4).- A high pressure hydrogenation vessel was charged with 1.0 g (0.0055 mol) of lactone 3 and 35 ml of liquid ammonia and heated at 35° for 5.0 hrs (the pressure reached at this temperature was 13.6 atm). After this reaction period, the excess of ammonia was evaporated. The solid residue was crystallized from chloroform-hexane affording 0.95 g (87%) of 4, mp. 59-61°; IR ($CHCl_3$): 3700-3100, 3530, 3415, 2965, 2930, 1680, 1590, 1410 cm^{-1}; ^1H nmr (DMSO D_6): δ 1.65 (3H, s), 2.25 (4H, m), 4.15 (1H, broad), 5.55 (2H, broad), 6.90 (2H, m), 7.20 (1H, m); Ms (m/z relative intensities): 199 (5, M^+), 184 (60), 183 (10), 181 (3), 127 (81), 111 (29), 73 (71), 44 (26), 43 (100).

Anal. Calcd. for $C_9H_{13}O_2NS$: C, 54.25; H, 6.58; N, 7.03; S, 16.09

Found : C, 54.11; H, 6.63; N, 7.12; S, 16.15

Preparation of 2-Methyl-2-(2-thienyl)oxirane (5).- In a 250 ml round bottom flask fitted with a condenser and magnetic stirrer, were placed 5.0 g (0.039 mol) of 2-acetylthiophene, 8.9 g (0.043 mol) of trimethylsulfonium iodide, 6.7 g (0.119 mol) of potassium hydroxide, 0.178 g (0.009 mol) of water and 90 ml of acetonitrile under a nitrogen atmosphere. The reaction mixture was stirred vigorously and heated at 60° for 20 hrs. After this period, the reaction mixture was cooled at room temperature and the solid was collected and washed with 15 ml of acetonitrile. The filtrate was concentrated under reduced pressure at room temperature to give an oil (4.95 g, 95% yield) which was used for the next reaction without further purification. An analytical sample was obtained by distillation of the crude

product; however, appreciable decomposition was observed. IR (film): 3132, 2981, 1667, 1439, 1270, 1220, 1067, 981, 907, 825 cm^{-1}; ^1H nmr ($CDCl_3$) : δ 1.73 (3H, s), 2.98 (2H, s), 6.95 (2H, m), 7.13 (1H, m); Ms (m/z relative intensities): 140 (M^+, 2), 125 (5), 124 (3), 83 (7), 57 (100).

Anal. Calcd. for C_7H_8OS : C, 59.97; H, 5.75; S, 22.87

Found : C, 59.79; H, 5.86; S, 22.96

Preparation of 3-(2-Thienyl)-γ-valerolactone (3).- In a three necked 250 ml flask fitted with a condenser, drying tube, addition funnel, septum and magnetic stirrer, were placed 30.0 ml of absolute ethanol and 1.43 g (0.62 mol) of sodium wire. To this solution of sodium ethoxide was added dropwise 9.97 g (0.062 mol) of freshly distilled ethyl malonate and the mixture stirred for 10 min. After this time, 4.89 g (0.062 mol) of 5 was added *via* a hypodermic syringe and the reaction mixture heated at 80° for 5 hrs. After cooling to room temperature, a solution of 3.13 g of potassium hydroxide in 12 ml of water was added and the reaction mixture heated under reflux for 5 hrs. Then, ethanol was removed under reduced pressure, the residue was cooled in an ice-water bath and sulfuric acid (4.94 g in 10 g of ice) was carefully added with stirring at rt for 5 hrs. The product was extracted with ether (3 x 50 ml). The ethereal phase was dried over sodium sulfate and the ether evaporated. The brownish-yellow oily residue was decarboxylated by heating without solvent at 145-150° in an oil bath until evolution of carbon dioxide ceased. The residue was distilled under reduced pressure to afford 3.96 g (57%) of lactone 3, bp. 140-145°/1 mm Hg.

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