Synthesis and Spectral Properties of 6*H*-2,7,7-Trimethyl-7,8-dihydrofuro[3,2-*c*]azepines

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The preparation of novel 7,8-Dihydrofuro[3,2-*c*]azepines is described. The structure of all products was corroborated by ir, ^{1}H-nmr and mass spectrometry.

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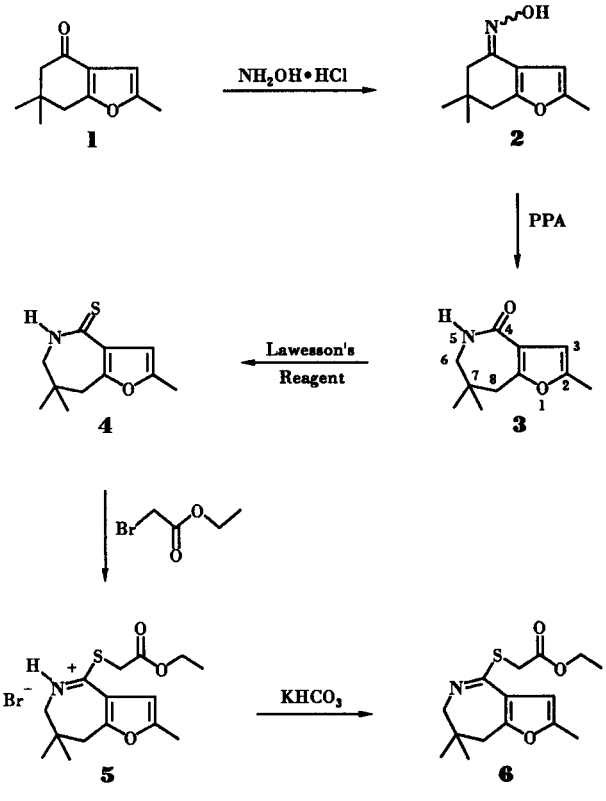
There has been little interest in the synthesis of furo[3,2-*c*]azepines over the past decade in spite of the fact that they represent a series of compounds of medicinal interest, mainly as tranquilizing agents [3]. Thus there are only two patents on the preparation of this type of compounds [3,4]. As a part of program directed towards the synthesis and spectral property determination of heterocyclic derivatives with possible pharmacological activity, we describe in this report the synthesis of compounds **3**, **4**, **5**, and **6** (Scheme 1).

Scheme 1



In a typical procedure tetrahydrobenzofuran-4-one **1** [5], hydroxylamine hydrochloride and sodium hydroxide were refluxed in ethanol on a steam bath to give a colourless mixture of oximes **2** (*syn*/*anti*). The structure of this mixture followed from spectroscopic data; of particular note a one-proton singlet at δ 6.65 in the ^{1}H-nmr spectrum of **2** could be assigned to the 3-furan-proton of the *syn*-oxime [6] while the 3-furan proton of the *anti*-oxime gives rise a signal at δ 6.12. The presence of ions at m/z 193 [M$^+$, 100% relative abundance], 177 and 163 in the mass spectrum of **2** was consistent with its structure.

The oxime mixture **2** was converted to the furoazepin-4-one **3** by heating in the presence of polyphosphoric acid in 98% yield [7]. In agreement with the suggested structure the ir spectra (chloroform) of compound **3** exhibited a strong amide carbonyl band at 1650 cm^{-1}. Its ^{1}H-nmr spectrum showed a singlet at δ 1.07 for the methyl protons of C-7 as well one singlet of the methyl protons joined to C-2 at δ 2.22. Two two-proton signal at δ 2.72 (singlet) and δ 3.05 (doublet, J = 6 Hz) were assigned to the methylene protons joined to C-8 and C-6. The mass spectrum of the compound showed the molecular ion at m/z 193 (100% relative abundance) and its fragmentation is in accordance with the assigned structure.

Treatment of furazepin-4-one **3** with Lawesson's reagent [8] in refluxing toluene afforded **4**. The infrared spectrum of compound **4** displayed absorptions at 3398 and 1565 cm^{-1} which were assigned to -NH- and -C=S stretching, respectively. In the ^{1}H-nmr spectra of derivative **4** the presence of a down-field one-proton broad signal at δ 8.85, which exchanges with deuterium oxide, was consistent with the presence of an thioamide group; other one-proton singlet at δ 6.56 was assigned to the methine proton joined to C-3. Two-proton signal at δ 3.15 (doublet, J = 6 Hz) and δ 2.72 (singlet) were assigned to the methylene protons joined to C-6 and C-8. The mass spectrum of the compound showed the molecular ion at m/z 209 (100% relative abundance).

The reaction of furazepine-4-thione **4** with ethyl bromoacetate in methylene chloride at room temperature [9] gave the hydrobromide **5** as a yellow solid. Spectroscopic evidence was consistent with the structure of **5**. In the infrared spectra the appearance of absorption bands at 1736

and 1593 cm^{-1} indicated the incorporation of a thiomethylcarboxyethyl group into the furazepine framework. It was confirmed with the ^{1}H-nmr spectra of **5** which showed the characteristic signals for this group, a two-proton singlet at δ 4.87 (-S-CH_2-CO), a quartet at δ 4.25 (J = 8 Hz) and a triplet at δ 1.32 (J = 8 Hz) for the methylene and methyl protons of the ethyl moiety. Further evidence concerning the structure of the hydrobromide **5** has been derived from the mass spectrum which confirmed the presence of the hydrobromide moiety in the molecule [10].

When hydrobromide **5** was treated in methylene chloride with a saturated solution of potassium hydrogen carbonate at 0° for 10 minutes **6** was obtained as a yellow oil in 98% yield. The appearance of an carbonyl absorption band at 1738 cm^{-1} and the absence of an -NH band at 3350 cm^{-1} was consistent with the suggested structure. Further evidence concerning the structure of the furazepine **6** has been derived from its mass spectral data. While compound **5** yields an ion at m/z 80, 82 (HBr^+, 20% relative abundance), the mass spectrum of **6** was lacking this ion completely. In the ^{1}H-nmr spectrum of **6** the peak arising from the hydrogen joined to C-3 appeared as a singlet at δ 6.13, one quartet at δ 4.18 (J = 8 Hz) and one triplet at δ 1.28 (J = 8 Hz) were assigned to the protons of the ethyl moiety whereas a singlet at δ 3.78 was assigned to the methylene protons bonded to carbon joined the sulfur atom.

Further investigation on the synthesis of novel compounds from furazepin-4-one **3** are presently being carried out.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Nicolet FT-55X spectrophotometer. The ^{1}H-nmr spectra were recorded on a Varian FT-80 spectrometer operating at 80 MHz, in deuteriochloroform solution containing tetramethylsilane as the internal standard with chemical shifts (δ) expressed downfield from TMS. Mass spectra were obtained with a Hewlett Packard 59854-A quadrupole mass spectrometer.

Compound **1** has been prepared following a reported procedure [5]. The structure of **1** was supported by ir, ^{1}H-nmr and mass spectral data which are similar to those reported.

Synthesis of 2,6,6-Trimethyl-4-oxo-4,5,6-tetrahydrobenzofuran Oximes (*syn*/*anti*), **2**.

To a solution of **1** (0.318 g, 1.78 x 10^{-3} mole) dissolved in 2 ml of ethanol was added a solution of 0.62 g (9 x 10^{-3} mole) of hydroxylamine hydrochloride dissolved in 10 ml of 5*M* sodium hydroxide and the mixture was stirred on a steam-bath for 30 minutes, the resulting solution was diluted with methylene chloride (30 ml) and washed with water (2 x 10 ml), dried over anhydrous sodium sulfate and concentrated (rotatory evaporator) to afford 0.344 g (98%) of **2** as a colourless oil; ir (chloroform): ν 3590-3200 (-N-OH), 1645 (C=N) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.09 (bs, 12H, $(CH_3)_2$C), 2.25 (bs, 8H, 5- and 7-H), 2.55 (bs, 6H, 2-CH_3), 6.05 (bs, 3H, 3-H (*anti*), NOH *syn-anti*, deuterium oxide-exchangeable), 6.65 (s, 1H, 3-H *syn*); ms: m/z 193 (M^+), 177 (15), 163 (10), 134 (74), 120 (68).

Synthesis of 6*H*-2,7,7-Trimethyl-4,5,7,8-tetrahydrofuro[3,2-*c*]azepin-4-one, **3**.

To a mixture of phosphorus pentoxide (40 g, 2.8 x 10^{-1} mole) and phosphoric acid (20 g, 2 x 10^{-1} mole) was added 3.44 g (1.78 x 10^{-3} mole) of **2** and the mixture was mechanically stirred at 120-130° for 30 minutes. The reaction mixture was treated with ice-water, neutralized with sodium carbonate and extracted with methylene chloride (6 x 25 ml); the combined organic extracts were washed with water (2 x 40 ml) and dried (sodium sulfate). Removal of the solvent under reduced pressure followed by recrystallization from ethyl acetate gave 0.275 g (80%) of **3** mp 199-201°; ir (chloroform): ν 3420 (NH), 1650 (amide CO) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.07 (s, 6H, $(CH_3)_2$C) 2.22 (s, 3H, 2-CH_3), 2.72 (s, 2H, 8-H), 3.05 (d, J = 6 Hz, 2H, 6-H), 6.3 (bs, 2H, 3-H and -NH, deuterium oxide-exchangeable); ms: m/z 193 (M^+), 149 (85), 122 (40), 43 (50).

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.32; H, 7.80.

Synthesis of 6*H*-2,7,7-Trimethyl-4,5,7,8-tetrahydrofuro[3,2-*c*]azepin-4-thione, **4**.

A solution of 0.65 g (3.2 x 10^{-3} mole) of furoazepin-4-one, **3**, and 0.65 g (1 x 10^{-3} mole) of Lawesson's reagent in 50 ml of toluene was heated at reflux for two hours. Evaporation of toluene *in vacuo* gave an oily residue. The residue was separated by column chromatography (silica gel-methylene chloride) to give 0.69 g (98%) of **4**, mp 193-194°; ir (chloroform): ν 3400 (NH), 1565 (C=S) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.05 (s, 6H, $(CH_3)_2$C), 2.2 (s, 3H, 2-CH_3), 2.72 (s, 2H, 8-H), 3.15 (d, J = 6 Hz, 6-H), 6.56 (s, 1H, 3-H), 8.85 (bs, 1H, NH, deuterium oxide-exchangeable); ms: m/z 209 (M^+, 100), 194 (74), 138 (45), 43 (40).

Anal. Calcd. for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22. Found: C, 63.10; H, 7.20.

Synthesis of 6*H*-2,7,7-Trimethyl-4-(2-carboxyethyl-1-thioxaethanyl)-7,8-dihydrofuro[3,2-*c*]azepine Hydrobromide, **5**.

A solution of 0.1 g (4.7 x 10^{-4} mole) of furoazepin-4-thione, **4**, and 0.08 g (4.8 x 10^{-4} mole) of ethyl bromoacetate in 10 m. of methylene chloride was stirred, under a nitrogen atmosphere and in the dark, for two hours at room temperature. Evaporation of the methylene chloride *in vacuo* gave a light yellow solid, which was recrystallized from ethyl acetate to give 0.176 g (98%) of **5**, mp 145-147°; ir (chloroform): 3000-2900 (NH^+), 1736 (ester CO), 1593, 1557 (N=C-S) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.17 (s, 6H, $(CH_3)_2$C), 1.32 (t, J = 8 Hz, 3H, OCH_2-CH_3), 2.3 (s, 3H, 2-CH_3), 2.92 (s, 2H, 8-H), 3.73 (d, J = 6 Hz, 2H, 6-H, simplified with deuterium oxide), 4.25 (q, J = 8 Hz, 2H, OCH_2-CH_3), 4.87 (s, 2H, S-CH_2), 6.37 (s, 1H, 3-H), 11.0 (bs, 1H, NH, deuterium oxide-exchangeable); ms: m/z 375 (M^+), 295 [M-HBr, (45)], 222 (76), 208 (47), 179 (45), 120 (100), 80/82 (17).

Synthesis of 6*H*-2,7,7-Trimethyl-4-(2-carboxyethyl-1-thioxaethanyl)-7,8-dihydrofuro[3,2-*c*]azepine, **6**.

A solution of 0.185 g (4.7 x 10^{-4} mole) of hydrobromide **5** dissolved in 10 ml of methylene chloride was cooled to 0°. The hydrobromide **5** was neutralized by adding 15 ml of a saturated solution of potassium hydrogen carbonate in water. After the ad-

dition the solution was stirred at 0° for 10 minutes. The methylene chloride layer was separated and the aqueous layer was extracted with methylene chloride (3 x 10 ml); the latter solution was added to the methylene chloride layer previously obtained and dried (sodium sulfate) and evaporated to yield 0.135 g of a yellow oil (95%), which easily decomposed (it should be keep in the dark and under a nitrogen atmosphere); ir (neat): ν 1738 (ester CO), 1623 (C=N), 1579 (C=C) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 0.97 (s, 6H, $(CH_3)_2C$), 1.28 (t, J = 8 Hz, 3H, OCH_2CH_3), 2.23 (s, 3H, 2-CH_3), 2.7 (s, 2H, 8-H), 3.57 (s, 2H, 6-H), 3.78 (s, 2H, S-CH_2), 4.18 (q, J = 8 Hz, 2H, OCH_2-CH_3), 6.13 (s, 1H, 3-H); ms: m/z 295 ($M^{\cdot+}$, 42), 222 (52), 179 (48), 134 (30), 120 (100), 43 (62).

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