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SYNTHESIS OF 2-ANILINO-7-HYDROXY-6H-1,3,4-THIADIAZEPINS BY THE REACTION OF 1-ACYL-2-PHENYLACETYLENES WITH 4-PHENYLTHIOSEMICARBAZIDES

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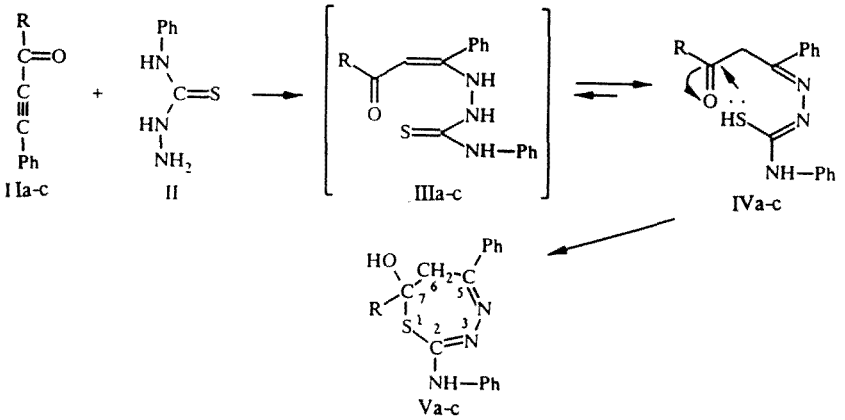
2-Anilino-7-hydroxy-7-methyl(phenyl, thienyl-2)-6H-1,3,4-thiadiazepins have been obtained in good yield by the reaction of 4-phenylthiosemicarbazides with 1-acyl-2-phenylacetylenes using glacial acetic acid as condensing agent.

The reaction of dimethyl acetylenedicarboxylate with thiosemicarbazides and 1-substituted thiosemicarbazides is known to give 2-hydrazino-5-methoxycarbonylmethylene-1,3-thiazolin-4-ones [1] and the reaction with 4-substituted thiosemicarbazides is known to give 3-amino-2-imino-6-methoxycarbonyl-1,3-thiazin-4-ones [2]. 2-Acylmethyl-5-imino-3-phenyl-4H-1,3,4-thiadiazoles [3] were obtained from the reaction of terminal acylacetylenes with 1-phenylthiosemicarbazides in methanol at 20°C, while with 4-methyl- and 4-phenylthiosemicarbazides of acylacetaldehyde thiosemicarbazones, 1,1-bis(acylvinyl)thiosemicarbazides and 5-phenylamino-3-acylvinyl-2-acylmethyl-1,3,4-thiadiazepins were obtained, depending on the reaction conditions [4].

2-Amino-7-hydroxy-5,7-substituted-1,3,4-thiadiazepins [5] were obtained in 71-75% yield from the reactions of 1-phenyl- and 1-(thienyl-2)-benzoylacetylene with thiosemicarbazides.

We have established that the reaction of 1-acyl-2-phenylacetylenes with 4-phenylthiosemicarbazide in methanol at 20°C in the presence of glacial acetic acid gave 2-anilino-7-hydroxy-7-methyl(phenyl, thienyl-2)-6H-1,3,4-thiadiazepins Va-Vc in 72-86% yield.

The first step in the process is evidently the addition of the primary amino group of the 4-phenylthiosemicarbazide II to the triple bond of the acetylenes Ia-Ic to give the intermediates IIIa-IIIc which rapidly isomerize to the more stable intermediates IVa-IVc. Under our reaction conditions, the latter cyclize intramolecularly to give the substituted 1,3,4-thiadiazepins Va-Vc.



I, III–V a R = Me, b R = Ph, c R = thienyl-2

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The IR spectra of compounds Va-Vc contain absorptions at 708-712 (C–S), 1522-1540 (C=N), and 3502-3515 and 3370-3385 cm^{-1} (NH_2). The presence of broad bands for associated OH groups in the 3240-3258 cm^{-1} suggest the presence of intramolecular hydrogen bonds of the OH...H type. Decreasing the concentration of compound Va in chloroform to $5 \cdot 10^{-4}$ mole·dm^{-3} did not cause a decrease in the relative intensity of the OH band which indicated the absence of intermolecular association [5].

EXPERIMENTAL

IR spectra were recorded with a UR-75 spectrometer as KBr discs or chloroform solutions, ^{13}C NMR spectra were recorded on an FX-90 Q machine (22.49 MHz) in $CDCl_3$ of DMSO-D_6 with TMS as internal standard. UV spectra of ethanol solutions were obtained with a Carl Zeiss Specord M-40. Mass spectra were recorded on MX-1303 mass spectrometers with direct inlet into the ion source (ionizing voltage 30 eV).

2-Anilino-7-hydroxy-7-methyl-5-phenyl-6H-1,3,4-thiadiazepin (Va). Glacial acetic acid (2 cm^3) was added to a vigorously stirred solution of 1-phenyl-2-acetylacetylene (0.72 g, 5 mmole) and 4-phenylthiosemicarbazide (0.84 g, 5 mmole) in dry methanol (40 cm^3) and the mixture was stirred for 1 h at 20°C. The solution was cooled to 0°C, the residue was filtered off and washed many times with cold water on the filter, then with cold methanol and was dried in vacuum to give light yellow crystals (1.12 g, 72% based on the initial ketone), mp 107-108°C, soluble in DMSO, DMF, ethanol, acetone and chloroform, but insoluble in water and ether. IR spectrum: 3260, 3342, 1605 and 1573 cm^{-1}. ^{13}C NMR spectrum (DMSO-D_6): 173.31 (C-5), 152.62 (C-2), 137.72, 128.43, 126.20, 125.48 (C_6H_5NH), 131.06, 130.53, 128.89, 126.78 (phenyl on C-5), 152.62 (C-2), 94.87 (C-7), 48.88 (C-6), 27.69 ppm (CH_3). Found (%): C 65.70, H 5.50, N 13.48, S 10.31. Calc. for $C_{17}H_{17}N_3OS$ (%): C 65.59, H 5.46, N 13.50, S 10.29.

2-Anilino-7-hydroxy-5,7-diphenyl-6H-1,3,4-thiadiazepin (Vb) was prepared analogously to Va from 1-benzoyl-2-phenylacetylene (1.03 g, 5 mmole) and 4-phenylthiosemicarbazide (0.84 g, 5 mmole). Yield 1.62 g (86%), white crystals, mp 166-167°C. IR spectrum: 3340, 3240, 1593, 1573 cm^{-1}. ^{13}C NMR spectrum ($CDCl_3$): 173.57 (C-5), 152.30 (C-2), 137.74, 124.92, 128.70, 126.03 (C_6H_5NH), 131.7, 130.45, 128.96, 128.70 (phenyl on C-5), 144.37, 127.92, 126.88, 124.08 (phenyl on C-7), 96.05 (C-7), 51.50 ppm (CH_3). UV spectrum, λ_{max} (log ε): 322 (4.46), 225 nm (4.35). Mass spectrum, *m/z*: 373 (M^+), 280, 254, 220, 135, 105, 93, 77. Found (%): C 70.74, H 5.05, N 10.94, S 8.65. Calc. for $C_{22}H_{19}N_3OS$ (%): C 70.79, H 5.09, N 11.26, S 8.58.

2-Anilino-7-hydroxy-7-(thienyl-2)-5-phenyl-6H-1,3,4-thiadiazepin (Vc), was prepared analogously to Va from 1-phenyl-2-thienoylacetylene (Ic) (1.06 g, 5 mmole) and 4-phenylthiosemicarbazide (0.84 g, 5 mmole). Yield 1.54 g (81%). Light yellow crystals, mp 170-171°C. IR spectrum: 3340, 3245, 1595, 1573 cm^{-1}. UV spectrum, λ_{max} (log ε): 314 (4.38), 244 (4.14) 225 nm (4.23). Mass spectrum, *m/z*: 379 (M^+), 286, 254, 226, 135, 111, 93, 83, 77. Found (%): C 63.23, H 4.45, N 11.07, S 16.75. Calc. for $C_{20}H_{17}N_3OS_2$ (%): C 63.32, H 4.48, N 11.08, S 16.88.

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