Synthesis and Spectral Properties of 6*H*-1-(2-, 3- and 4-*R*-Phenyl)-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4-ones

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The preparation of novel 4,5,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4-ones is described. The structure of all the products was corroborated by ir, mass spectrometry and ^{1}H and ^{13}C-nmr.

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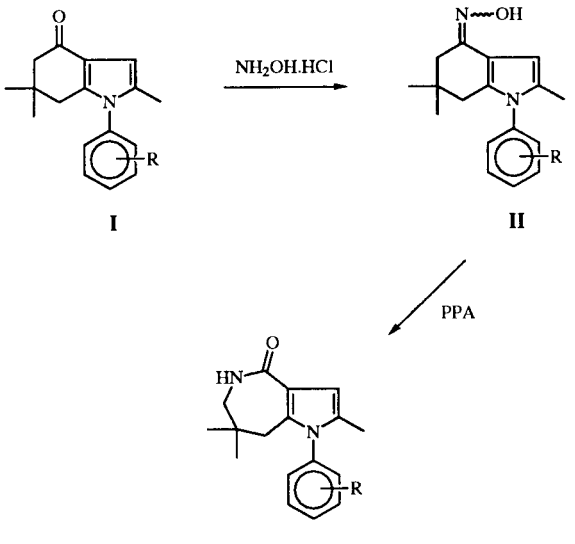
In continuation of our interest in using 1,3-dicarbonylic compounds in organic synthesis [3] we have recently described a general synthesis of furo[3,2-*c*]-azepines starting from dimedone [4]. In this work, we report the extension of this synthetic strategy to a synthesis of *N*-arylpyrrolo[3,2-*c*]azepin-4-ones **IIIa-f** (Scheme 1).

Scheme 1



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a	H	**d**	*p*-Br
b	*p*-CH_3	**e**	*o*-Cl
c	*p*-OCH_3	**f**	*m*-Cl

Compounds **Ia-f** have been prepared following a reported procedure [5]. The structures of these compounds were supported by ir, ^{1}H and ^{13}C-nmr and mass spectral data that were similar to those reported.

In a typical procedure tetrahydroindol-4-ones **Ia-f** [6], hydroxylamine hydrochloride and sodium hydroxide were refluxed in ethanol on a steam bath to give a colorless mixture of oximes **IIa-f** (*syn*/*anti*). The structure of this mixture followed from spectroscopic data; of particular note a one-proton signal at δ 6.83-6.71 in the ^{1}H-nmr spectrum of **IIa-f** could be assigned to the 3-pyrrolo-proton of the *syn* oximes [7] while the 3-pyrrole-proton of the *anti*-oximes gives rise to a signal at δ 6.25-6.19. The presence of the molecular ions and m/z (M^+-16) and (M^+-30) fragments in the mass spectrum of compounds **IIa-f** was consistent with their structures.

The oximes mixture **IIa-f** were converted to the pyrrolo[3,2-*c*]azepin-4-ones **IIIa-f** by heating in the presence of polyphosphoric acid in 40-55% yield [8]. In agreement with the suggested structure the ir spectra (chloroform) of all the compounds **IIIa-f** exhibited strong amide carbonyl band at 1650-1640 cm^{-1}. Its ^{1}H-nmr spectrum showed a singlet at δ 0.97 for the methyl protons of C-7 as well as one singlet of the methyl protons joined to C-2 at δ 1.96. Two two-proton signals at δ 2.32 (singlet) and δ 3.03 (doublet, J = 6 Hz) were assigned to the methylene protons joined to C-8 and C-6. The remaining aromatic protons in compounds **IIIa-f** appeared at δ 7.66-7.10. The ^{13}C nmr spectrum showed 14 signals and DEPT experiment indicated that two of them correspond to CH_3, two to CH_2, three to CH and seven to Cq. ^{1}H-^{13}C correlation (HETCOR) allowed us the identification of nine signals: δ 12.6 (CH_3-C2), 26.7 (2xCH_3-C7), 35.2 (C7), 40.4 (C8), 52.9 (C6), 108.0 (C3), 130.0 and 132.7 (aromatic carbons) and 169.9 (C=O, amide), the remaining signals correspond to quaternary carbons. The mass spectrum of the compounds showed their molecular ions and its fragmentation is according to the assigned structures.

Further investigation on the synthesis of novel compounds from tetrahydroindol-4-ones **1** are presently being carried out.

Table 1

Physical, Analytical and Spectral Data for Compounds **II**

Compound No.	R	Mp °C	Yield %	Spectral Data
a	H	186-190	95	ir (chloroform): 3588 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.45-7.17 (5H), 6.81 (H-3, *syn*), 6.24 (H-3, *anti*), 2.58 (H-5, *anti*), 2.27 (CH_3-C2, *syn*), 2.25 (H-5, *syn*), 2.24 (H-7), 2.05 (CH_3-C2, *anti*), 1.02 (2 x CH_3-C6, *anti*), 1.0 (2 x CH_3-C 6, *syn*); ms: M^+ at m/z 268.1563.
b	*p*-Me	220-225	90	ir (chloroform): 3588 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.24-7.05 (4H), 6.78 (H-3, *syn*), 6.19 (H-3, *anti*), 2.56 (H-5, *anti*), 2.40 (CH_3-Ar), 2.24 (CH_3-C2, *syn*, H-7), 2.23 (H-5, *syn*), 2.03 (CH_3-C2, *anti*), 1.0 (2 x CH_3-C6, *anti*), 0.98 (2 x CH_3-C6, *syn*); ms: M^+ at m/z 282.1563.
c	*p*-OMe	212-213	97	ir (chloroform): 3588 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.10-6.97 (4H), 6.71 (H-3, *syn*), 6.23 (H-3, *anti*), 3.81 (CH_3O-Ar), 2.59 (H-5, *anti*), 2.28 (H-5, *syn*), 2.26 (CH_3-C2, *syn*, H-7), 2.05 (CH_3-C2, *anti*), 1.02 (2 x CH_3-C6, *anti*), 1.0 (2 x CH_3-C6, *syn*); ms: M^+ at m/z 298.1681.
d	*p*-Br	208-210	94	ir (chloroform): 3588 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.62-7.08 (4H), 6.83 (H-3, *syn*), 6.25 (H-3, *anti*), 2.58 (H-5, *anti*), 2.28 (CH_3-C2, *syn*), 2.25 (H-5, *syn*), 2.24 (H-7), 2.06 (CH_3-C2, *anti*), 1.03 (2 x CH_3-C6, *anti*), 1.01 (2 x CH_3-C6, *syn*); ms: M^+ at m/z 364.0680.
e	*o*-Cl	195-197	90	ir (chloroform): 3588 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.40-7.20 (4H), 6.81 (H-3, *syn*), 6.22 (H-3, *anti*), 2.58 (H-5, *anti*), 2.29 (CH_3-C2, *syn*), 2.27 (H-5, *syn*), 2.26 (H-7), 2.06 (CH_3-C2, *anti*), 1.05 (2 x CH_3-C6, *anti*), 1.02 (2 x CH_3-C6, *syn*); ms: M^+ at m/z 302.1185.
f	*o*-Cl	175-180	94	ir (chloroform): 3588 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.54-7.25 (4H), 6.83 (H-3, *syn*), 6.23 (H-3, *anti*), 2.61 (H-5, *anti*), 2.26 (CH_3-C2, *syn*), 2.21 (H-5, *syn*), 2.12 (H-7), 1.96 (CH_3-C2, *anti*), 1.02 (2 x CH_3-C6, *anti*), 0.99 (2 x CH_3-C6, *syn*); ms: M^+ at m/z 302.1180.

Table 2

Physical, Analytical and Spectral Data for Compounds **III**

Compound No.	R	Mp °C	Yield %	Analysis C	Analysis H	Spectral Data
a	-H	237-238	47	76.09 (76.14)	7.51 (7.49)	ir (chloroform): 1631 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.49-7.19 (5H, Ar), 6.46 (H-3), 5.98 (-NH), 3.0 (H-6), 2.33 (H-8), 1.96 (CH_3-C2), 0.96 (2 x CH_3-C7); ms: M^+ at m/z 268.
b	*p*-Me	250-251	45	76.56 (76.60)	7.85 (7.84)	ir (chloroform): 1629 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.28-7.04 (4H, Ar), 6.44 (H-3), 5.90 (-NH), 3.0 (H-6), 2.44 (CH_3-Ar), 2.32 (H-8), 1.95 (CH_3-C2), 0.96 (2 x CH_3-C7); ms: M^+ at m/z 282.
c	*p*-OMe	230-231	55	72.46 (72.49)	7.43 (7.42)	ir (chloroform): 1628 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.1-7.0 (4H, Ar), 6.44 (H-3), 6.0 (-NH), 3.88 (CH_3O-Ar), 3.0 (H-6), 2.32 (H-8), 1.95 (CH_3-C2), 0.96 (2 x CH_3-C7); ms: M^+ at m/z 298.
d	*p*-Br	247-248	52	58.80 (58.85)	5.51 (5.51)	ir (chloroform): 1631 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.65-7.07 (4H, Ar), 6.46 (H-3), 6.32 (-NH), 3.0 (H-6), 2.32 (H-8), 1.96 (CH_3-C2), 0.97 (2 x CH_3-C7); ms: M^+ at m/z 364.
e	*o*-Cl	221-223	47	67.43 (67.50)	6.32 (6.30)	ir (chloroform): 1628 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.42-7.18 (4H, Ar), 6.43 (H-3), 6.0 (-NH), 2.99 (H-6), 2.29 (H-8), 1.94 (CH_3-C2), 1.94 (2 x CH_3-C2), 0.94 (2 x CH_3-C7); ms: M^+ at m/z 302.
f	*m*-Cl	169-170	45	67.43 (67.49)	6.32 (6.29)	ir (chloroform) 1630 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.47-7.23 (4H, Ar), 6.45 (H-3), 6.34 (-NH) 3.0 (H-6), 2.33 (H-8), 1.95 (CH_3-C2), 0.96 (2 x CH_3-C7); ms: M^+ at m/z 302.

EXPERIMENTAL

Melting points were determined in a Fisher-Jones melting point apparatus and are uncorrected. The ir spectra were determined in Perkin-Elmer 283-B and Nicolet FT-5SX spectrometer. The ^{1}H nmr and ^{13}C nmr were determined in Varian Gemini 200 and Varian-VXR-300S spectrometers in deuteriochloroform solution containing tetramethylsilane as the internal standard with chemical shifts (δ) expressed downfield from TMS. Column chromatography was carried out on Merck silica gel 60F-254. Mass spectra were obtained with a Jeol SX-100 mass spectrometer.

Compounds **Ia-f** have been prepared following a reported procedure [5]. The structures of compounds **Ia-f** were supported by ir, ^{1}H-nmr and mass spectral data which are similar to those reported.

Synthesis of 1-(4-*R*-Phenyl)-2.6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindole Oximes (*syn/anti*), **Ia-f**.

General Procedure (R = Br).

To a solution of **Id** (0.1 g, 1.26 x 10^{-3} mole) dissolved in 50 ml of ethanol was added a solution of 0.13 g (5.5 x 10^{-3} mole) of hydroxylamine hydrochloride dissolved in 30 ml of 5 *M* sodium hydroxide and the mixture was stirred on a steam-bath for two hours. Removal of the solvent under reduced pressure gave an amorphous solid that was separated

by column chromatography (silica gel, hexane-ethyl acetate 6:4) to give 0.084 g (94%) of **IId** mp 208-210°. The physical, analytical and spectral data for synthesized compounds **IIa-f** are recorded on Table 1.

Synthesis of 6*H*-1-(2-, 3- and 4-*R*-Phenyl)-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4-ones, **IIIa-f**.

General Procedure (R = Br).

To a mixture of phosphorus pentoxide (0.1 g, 7 x 10^{-4} mole) and phosphoric acid (1 ml) was added 0.1 g (3 x 10^{-4} mole) of **IId** and the mixture was mechanically stirred at 80-100° for 2 hours. The mixture was treated with ice-water, neutralized with sodium carbonate and extracted with methylene chloride (3 x 5 ml); the combined organic extracts were washed with water (2 x 10 ml) and dried (sodium sulfate). Removal of the solvent under reduced pressure gave an amorphous solid that was separated by column chromatography (silica gel, hexane-ethyl acetate 6:4) to give 0.052 g (52%) of **IIId** mp 247-248°. The physical, analytical and spectral data for synthesized compounds **IIIa-f** are recorded in Table 2.

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REFERENCES AND FOOTNOTES

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