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LETTERS TO THE EDITOR

Unusual Carbocyclization in Three-Component Reaction Involving Acetylacetone, Primary Amines, and Aromatic Aldehydes

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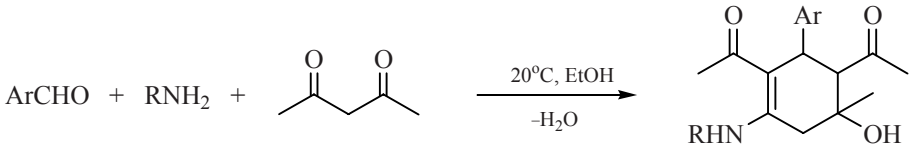
Over 100 years ago Hantzsch discovered an effective synthetic route to dihydropyridine derivatives by reaction of aldehydes with ethyl acetoacetate in the presence of ammonia [1]. Later Scholtz [2] and then Phillips [3] carried out similar reaction with acetylacetone. With primary amines the Hantzsch heterocyclization proceeds with the formation of N-substituted dihydropyridines [4]. In spite of numerous investigations in this field [5], reaction of primary amines with acetylacetone in the presence of aldehydes were not reported.

Experiments carried by us showed that this reaction in alcohol at 20°C does not result in dihydropyridines, but carbocyclization proceeds to give 5-*N*-R-amino-3-aryl-2,4-diacetyl-1-methyl-4-cyclohexen-1-ols **IVa–IVe**.



Ia, Ib **IIa–IIe** **III** **IVa–IVe**

IVa: Ar = *p*-$O_2NC_6H_4$, R = CH_2CH_2OH; **IVb**: Ar = Ph, R = CH_2CH_2OH; **IVc**: Ar = Ph, R = $CH_2CH_2CH_2OH$; **IVd**: Ar = Ph, R = Bn, **IVe**, Ar = Ph, R = Cy.

Structure of compounds **IVa–IVe** was determined by the ^1H and ^{13}C NMR spectroscopy. COSY, NOESY, HMQC and DEPT methods were used to assign signals in the spectra and also to establish conformational features of compound obtained. From the spectra follows that in all compounds the substituents at 2- and 3-positions are equatorially oriented as was demonstrated by the spin-spin coupling constant value (10 Hz) between 2- and 3-protons. Methyl group at C-1 also occupies the equatorial position. Diaxial position of 2- and 3-protons is seen in the NOESY spectra from the absence of NOE between these protons. In this case the methyl group at C-1 has a week NOE with proton at C-2 attesting that this group is equatorially oriented. The most strong NOE was observed between *ortho*-protons of 3-phenyl and 3-H and 2-H, 2-Ac and 3-H and 4-Ac and 2-H.

5-*N*-(2-Hydroxyethyl)amino-2,4-diacetyl-1-methyl-3-*p*-nitrophenyl-4-cyclohexen-1-ol (IVa). To a solution of 3.02 g (0.02 mol) of **Ia** in 10 ml of anhydrous ethanol were added 1.22 g (0.02 mol) of **IIa**

and 4 g (0.04 mol) of acetylacetone **III,** and this mixture was kept at room temperature for 2–3 days. Crystals precipitated were filtered off, washed with small amounts of anhydrous ether. Yield 4.3 g (57%), mp 160°C (from ethanol). IR spectrum, ν, cm^{-1} : 1600 (C=C), 1720 (C=O), 3100–3200 (OH), 3300–3400 (NH). ^{1}H NMR spectrum, δ, ppm (DMSO-d_6/CCl_4, 1:3) (signals assignment was made on the based NOESY and DEPT spectra): 1.19 s (3H, 1-CH_3), 1.53 s (3H, 4-Ac), 2.00 s (3H, 2-Ac), 2.52 d (1H, ^2J 17.3 Hz) and 2.61 d (1H, ^2J 17.3 Hz, 6-CH_2), 2.60 d (1H, ^3J 10.0 Hz, 2-CH), 3.34 m (2H, NCH_2), 3.61 q (2H, ^3J 5.5 Hz, OCH_2), 4.35 s (1H, 1-OH), 4.37 d (1H, ^3J 10.0 Hz, 3-CH), 4.66 t (1H, ^3J 5.5 Hz, CH_2OH), 7.35 m (2H, 2,6-H_{Ar}), 8.09 m (2H, 3,5-H_{Ar}), 11.54 t (1H, ^3J 5.6 Hz, NH). ^{13}C NMR spectrum, δ_C, ppm (DMSO-d_6): 27.91 (1-CH_3), 28.44 (CH_3, 2-Ac), 31.55 (CH_3, 4-Ac), 40.33 (C-6), 43.27 (C-3), 44.41 (NCH_2), 60.14 (OCH_2), 64.95 (C-2), 67.13 (C-1), 101.82 (C_{ipso}), 123.12 (2C, C_{ortho}), 128.60 (2C, C_{metha}), 145.57 (C-4), 155.23 (C_{para}), 159.06 (C-5), 193.65 (CO, 4-Ac), 209.35 (CO, 2-Ac).

5-*N*-(2-Hydroxyethyl)amino-2,4-diacetyl-1-methyl-3-phenyl-4-cyclohexen-1-ol (IVb) was prepared similarly from 2.12 g (0.02 mol) of **Ib**, 1.22 g (0.02 mol) of **IIb** and 4 g (0.04 mol) of **III** in 10 ml of absolute ethanol. Yield 3.37 g (51%), mp 156–157°C (from ethanol) [6, 7]. IR spectrum, ν, cm^{-1}: 1600 (C=C), 1720 (C=O), 3100–3200 (OH), 3300–3400 (NH). ^{1}H NMR spectrum, δ, ppm (DMSO-d_6/CCl_4, 1:3): 1.17 s (3H, 1-CH_3), 1.53 s (3H, 4-Ac), 1.86 s (3H, 2-Ac), 2.45 d (1H, ^2J 17.4 Hz) and 2.58 d (1H, ^2J 17.4 Hz, 6-CH_2), 2.61 d (1H, ^3J 10.0 Hz, 2-CH), 3.30 d. q (1H, ^2J 13.3 Hz, ^3J 6.0 Hz) and 3.34 d. q (1H, ^2J 13.3 Hz, ^3J 6.0 Hz, NCH_2), 3.60 t. d (2H, ^3J 6.0 Hz, ^3J 5.2 Hz, OCH_2), 4.10 s (1H, 1-OH), 4.12 d (1H, ^3J 10.0 Hz, 3-CH), 4.63 t (1H, ^3J 5.2 Hz, CH_2OH), 7.06–7.13 m (3H) and 7.21 m (2H, Ph), 11.44 t (1H, ^3J 5.7 Hz, NH).

5-*N*-(2-Hydroxypropyl)amino-2,4-diacetyl-1-methyl-3-phenyl-4-cyclohexen-1-ol (IVc) was prepared similarly from 1.06 g (0.01 mol) of **Ib**, 0.75 g (0.01 mol) of **IIc** and 2 g (0.02 mol) of **III** in 5 ml of absolute ethanol. Yield 1.79 g (52%), mp 155°C (from ethanol). IR spectrum, ν, cm^{-1}: 1580 (C=C), 1690 (C=O), 3100–3200 (OH), 3360 (NH). ^{1}H NMR spectrum, δ, ppm (DMSO-d_6/CCl_4, 1:3): 1.17 s (3H, 1-CH_3), 1.52 s (3H, 4-Ac), 1.86 s (3H, 2-Ac), 1.75 m (2H, CH_2), 2.45 d (1H, ^2J 17.4 Hz) and 2.60 d (1H, ^2J 17.4 Hz, 6-CH_2), 2.61 d (1H, ^3J 10.0 Hz, 2-CH), 3.34 m (2H, NCH_2), 3.55 t (2H, ^3J 5.9 Hz, OCH_2), 4.07 br (1H, 1-OH), 4.11 d (1H, ^3J 10.0 Hz, 3-CH), 4.24 br (1H, CH_2OH), 7.05–7.13 m (3H) and 7.21 m (2H, Ph), 11.43 t (1H, ^3J 5.8 Hz, NH).^{13}C NMR spectrum, δ_C, ppm (DMSO-d_6): 27.89 (1-CH_3), 28.43 (CH_3, 2-Ac), 32.00 (CH_3, 4-Ac), 32.65 (CH_2), 40.05 (C-6), 43.56 (C-3), 38.55 (NCH_2), 57.58 (OCH_2), 64.71 (C-2), 67.23 (C-1), 102.49 (C_{ipso}), 125.33 (C_{para}), 127.30 (2C) and 127.87 (2C, C_{ortho} and C_{metha}), 146.78 (C-4), 158.27 (C-5), 194.23 (CO, 4-Ac), 210.89 (CO, 2-Ac).

5-*N*-Benzylamino-2,4-diacetyl-1-methyl-3-phenyl-4-cyclohexen-1-ol (IVd) was prepared similarly from 2.12 g (0.02 mol) **Ib**, 2.14 g (0.02 mol) **IId** and 4 g (0.04 mol) of **III** in 10 ml of absolute ethanol. Yield 2.71 g (36%), mp 167°C (from ethanol) [8]. IR spectrum, ν, cm^{-1}: 1580 (C=C), 1690 (C=O), 3100–3200 (OH), 3360 (NH). ^{1}H NMR spectrum, δ, ppm (DMSO-d_6/CCl_4, 1:3): 1.13 s (3H, 1-CH_3), 1.57 s (3H, 4-Ac), 1.84 s (3H, 2-Ac), 2.42 d (1H, ^2J 17.4 Hz) and 2.59 d (1H, ^2J 17.4 Hz, 6-CH_2), 2.63 d (1H, ^3J 10.0 Hz, 2-CH), 4.08 br (1H, 1-OH), 4.14 d (1H, ^3J 10.0 Hz, 3-CH), 4.49 d. d (1H, ^2J 15.7 Hz, ^3J 5.9 Hz) and 4.52 d. d (1H, ^2J 15.7 Hz, ^3J 5.9 Hz, NCH_2), 7.07–7.15 m (3H), 7.20–7.29 m (3H) and 7.31–7.39 m (4H, 2Ph), 11.72 t (1H, ^3J 5.9 Hz, NH). ^{13}C NMR spectrum, δ_C, ppm (DMSO-d_6): 27.80 (1-CH_3), 28.50 (CH_3, 2-Ac), 32.18 (CH_3, 4-Ac), 38.93 (C-6), 43.63 (C-3), 45.50 (NCH_2), 64.43 (C-2), 67.23 (C-1), 103.36 (C_{ipso}), 125.33 (C_{para}), 126.42 (2C) and 128.09 (2C, C_{ortho} and C_{metha}, Bn), 126.57 (C_{para}, Bn), 127.27 (2C) and 127.91 (2C, C_{ortho} and C_{metha}), 138.25 (C_{ipso}, Bn), 146.47 (C-4), 157.69 (C-5), 195.12 (CO, 4-Ac), 210.93 (CO, 2-Ac).

5-*N*-Cyclohexylamino-2,4-diacetyl-1-methyl-3-phenyl-4-cyclohexen-1-ol (IVe) was prepared similarly from 1.06 g (0.01 mol) of **Ib**, 1 g (0.01 mol) of **IIe** and 2 g (0.02 mol) of **III** in 5 ml of absolute ethanol. Yield 1.28 g (34.8%), mp 152–153°C (from ethanol). IR spectrum, ν, cm^{-1}: 1600 (C=C), 1690 (C=O), 3300 (NH). ^{1}H NMR spectrum, δ, ppm (DMSO-d_6/CCl_4, 1:3): 1.16 s (3H, 1-CH_3), 1.19–1.49 m (5H), 1.52 s (3H, 4-Ac), 1.54–1.68 m (1H), 1.71–1.96 m (4H), 1.85 s (3H, 2-Ac), 2.44 d (1H, ^2J 17.2 Hz) and 2.56 d (1H, ^2J 17.2 Hz, 6-CH_2), 2.60 d (1H, ^3J 10.0 Hz, 2-CH), 3.44 m (1H, CHN), 4.06 s (1H, 1-OH), 4.10 d (1H, ^3J 10.0 Hz, 3-CH), 7.01–7.25 m (5H, Ph), 11.58 d (1H, ^3J 8.5 Hz, NH).

The IR spectra were measured on a Specord 75 IR instrument (mineral oil). The NMR spectra were recorded on a Varian Mercury-300 spectrometer (300 MHz), internal reference TMS.

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