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Synthesis of Substituted 5-*N*-(R)Amino-4-cyclohexyl-1-ols by the Reaction of Secondary Enaminones of β-Dicarbonyl Compounds with Chalcones

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Abstract—Reaction of secondary enaminones of acetylacetone or acetoacetic ester with chalcones at room temperature, is shown to lead to 5-*N*-(R)amino-4-cyclohexen-1-ols, distinctly to the reaction of the related primary derivatives leading to 1,4-dihydropyridines. Tertiary enaminones of identical structure are found not reacting with chalcones under the similar conditions. The reasons for the difference in the behavior of primary, secondary and tertiary enaminones in the reaction with chalcones are discussed.

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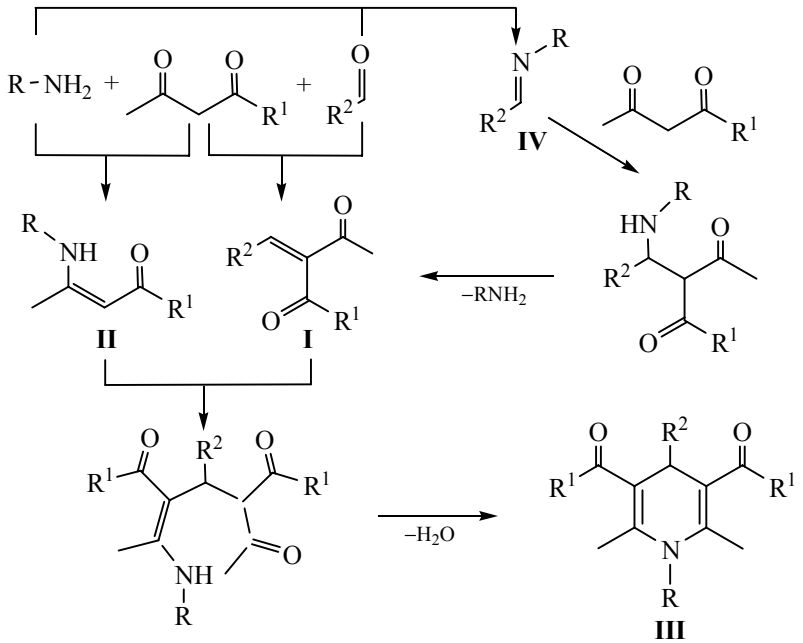
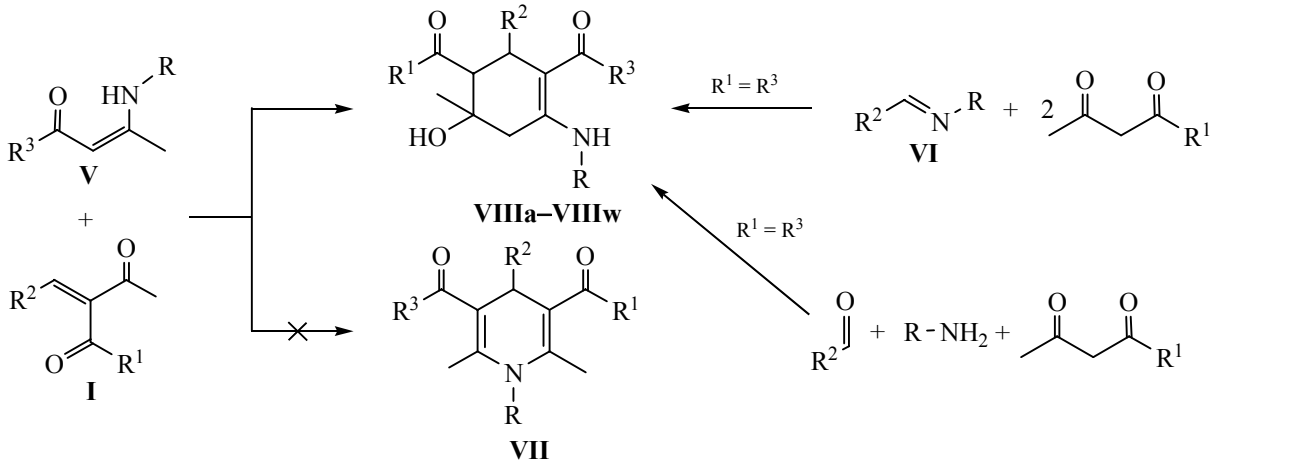
As is known, for the formation of substituted 1,4-dihydropyridines **III** in the Hantzsch synthesis (R=H) [1] is generally accepted a mechanism that includes initial formation of α,β-unsaturated dicarbonyl compound **I** (chalcone) and enaminone **II**, then their addition, heterocyclization and water cleavage [2]. Among the evidences supporting such course of the Hantzsch reaction is considered the fact that the reaction of preliminary obtained chalcone **I** with enaminone **II** also leads to the formation of 1,4-dihydropyridines [3].

It is easy to see that under the conditions of the Hantzsch reaction the intermediate imine **IV** can also be a source of chalcone [4]. For the first time the possibility of formation of the imine in the Hantzsch



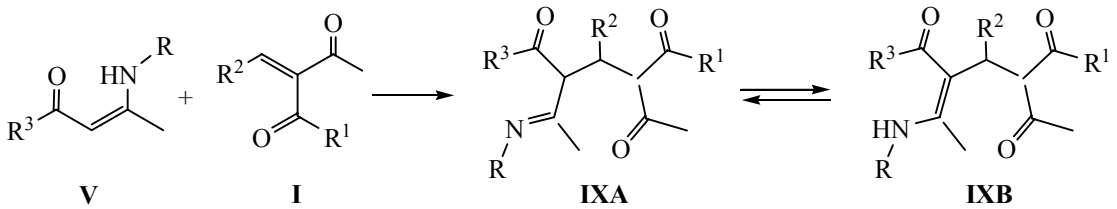
reaction was expressed in [4]. It was shown that arylamines and related Schiff bases under the conditions of the Hantzsch reaction afford the 1,4-dihydropyridine derivatives **III** (R = Ar).

The picture changes dramatically when in the Hantzsch reaction and its modified versions are used primary aminoalcohols. Recently, we have shown on several examples that in the reaction of chalcone **I** with either acetoacetic ester or acetylacetone enaminones **V** obtained from primary aminoalcohols [5] or in the reaction of imines **VI** of the same aminoalcohol with acetylacetone [6], as well as in the three-component reaction of aldehyde, aminoalcohol and β-dicarbonyl compound [7, 8] in alcohol at room temperature instead of the expected N-substituted 1,4-dihydropyridines **VII** (heterocyclization) are formed the corresponding derivatives of 5-*N*-(ω-hydroxy)alkylamino-4-cyclohexen-1-ol **VIII** (carbocyclization).



To realize the reason for this difference, we investigated in detail in the present study the reaction of chalcone **I** with enaminones **V**. The experiments showed that the direction of carbocyclization is of general nature (see the table, **VIIIa–VIIIp**). In order to ascertain whether the carbocyclization is caused by the presence of the hydroxyl group in the enaminones **V** [R = $(CH_2)_nOH$], it was replaced by a methoxy group. It turned out that the direction of the reaction does not change (see the table, **VIIIq–VIIIs**). Consequently, the different behavior of the enaminones **II** and **V** is a consequence of the fact that the hydrogen atom in the enaminones **II** (R = H) is replaced by an alkyl group. Based on the foregoing, we involved in this reaction the enaminones **V** with a N-alkyl group. Experiments showed that in this case occurs carbocyclization (see the table, **VIIIt–VIIIw**).

Comparing the data obtained by us using primary amines in two-component (enamine–chalcone, imine–β-dicarbonyl compounds or tri-component (alkylamine–aldehyde–β-dicarbonyl compound) syntheses of the aminocyclohexenol derivatives with the data obtained in the syntheses of the derivatives of 1,4-dihydropyridines using ammonia, one can see that structure of the intermediates that in one case lead to aminocyclohexenols, while in other to 1,4-dihydropyridines**,** is the same, because both these reactions proceed via the formation of enaminone and chalcone.

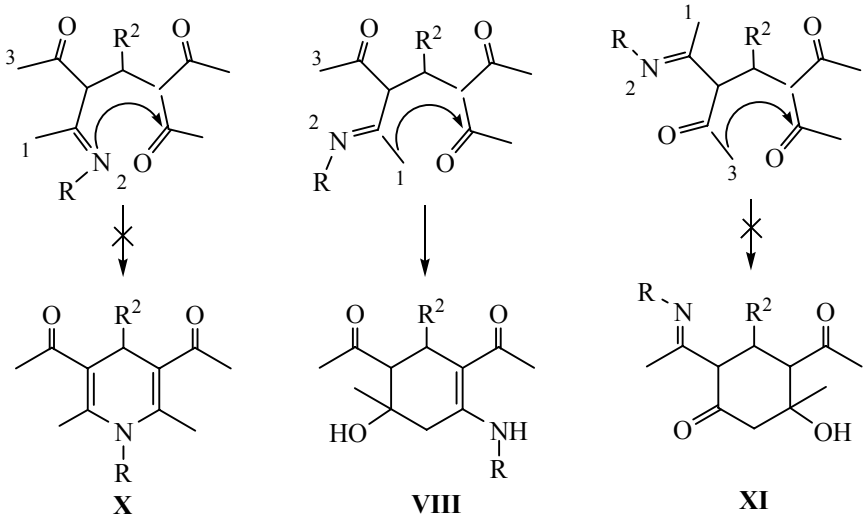


Yields and melting points of 5-*N*-(R)-amino-4-cyclohexene-1-ols

Comp. no.	R	R^1	R^2	R^3	Yield, %	mp, °C
VIIIa	$(CH_2)_3OH$	OEt	Ph	OEt	53	96 [7]
VIIIb	$(CH_2)_2OH$	OEt	$4\text{-}ClC_6H_4$	OEt	35.5	95–96
VIIIc	$(CH_2)_2OH$	OEt	2-Furyl	OEt	20	78
VIIId	$(CH_2)_3OH$	OEt	2-Furyl	OEt	41	95
VIIIe	$(CH_2)_3OH$	OEt	$4\text{-}NO_2C_6H_4$	OEt	48	120
VIIIf	$(CH_2)_3OH$	Me	Ph	OEt	52.3	109
VIIIg	$(CH_2)_2OH$	Me	$4\text{-}NO_2C_6H_4$	OEt	46.8	158 [8]
VIIIh	$(CH_2)_2OH$	Me	2-Furyl	OEt	46	145
VIIIi	$(CH_2)_3OH$	Me	Ph	Me	73.9	155 [6]
VIIIj	$(CH_2)_2OH$	Me	$4\text{-}NO_2C_6H_4$	Me	54.3	160 [8]
VIIIk	$C(CH_3)_2CH_2OH$	Me	Ph	Me	51	178
VIIIl	$(CH_2)_2OH$	Me	2-(3,4,5-Trichlorothienyl)	Me	45.5	161
VIIIm	$(CH_2)_2OH$	OEt	Ph	Me	41.5	115–116
VIIIn	$(CH_2)_2OH$	OEt	$4\text{-}ClC_6H_4$	Me	27.8	116
VIIIo	$(CH_2)_2OH$	OEt	$4\text{-}NO_2C_6H_4$	Me	41	135 [8]
VIIIp	$(CH_2)_2OH$	OEt	2-Furyl	Me	45.5	123
VIIIq	$(CH_2)_3OMe$	Me	Ph	Me	64.2	107
VIIIr	$(CH_2)_3OMe$	Me	$4\text{-}ClC_6H_4$	Me	43.3	130
VIIIs	$(CH_2)_3OMe$	OEt	$4\text{-}ClC_6H_4$	Me	28.3	111–112
VIIIt	Cy	Me	Ph	Me	45	145 [8]
VIIIu	Bn	Me	Ph	Me	63.6	165–166 [9]
VIIIv	Bn	OEt	Ph	OEt	36.7	74–75
VIIIw	Bn	Me	2-Furyl	Me	68	156

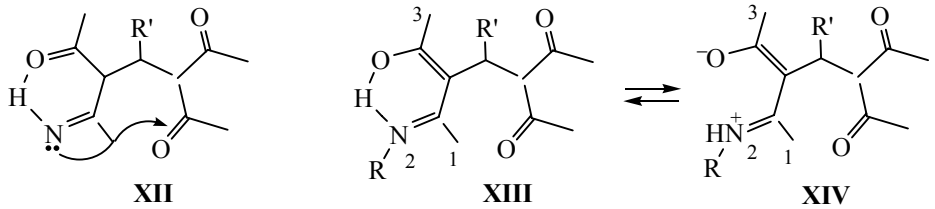
The question naturally arises, what is the cause of the either regioselective cyclization (carbocyclization involving the methyl group at the C=N bond) or heterocyclization involving the nitrogen atom of the intermediate compound **IX**. In our view, firstly, both heterocyclization and carbocyclization proceed with the participation of the imine tautomeric form **IXA** only of intermediate **IX**, as the enamine tautomeric form **IXB** being a vinylog of amide will have lower nucleophilicity compared to the imine. In addition, we showed in a separate experiment that the tertiary enaminones which can not form imine, did not react under similar conditions. Secondly, this difference is not due to different nucleophilicity of nitrogen atom, since otherwise the heterocyclization involving N-alkylimino group theoretically would be more likely.

To understand the reason for the different behavior of nitrogen in primary and secondary enaminones, we supposed that in the intermediate compound, in the case when $R^1 = R^3 = CH_3$, there are three nucleophilic centers [two methyl groups (1, 3) and a nitrogen atom (2)], the reactivity of two of them (2 and 3) is somehow inhibited, or vice versa, some factors contribute to increased reactivity of the methyl group (1) associated with the C=N double bond.



X **VIII** **XI**

Such an assumption is quite reasonable, because otherwise would have to react the theoretically more reactive centers 2 or 3, to form **X** or **XI**, respectively. A factor affecting the reactivity of CH_3 group may be the formation of intramolecular hydrogen bond in the intermediate **IX**. In the case of ammonia the hydrogen bond apparently involves the hydrogen atom of NH group (**XII**), while in the case of N-substituted analogs the nitrogen atom as shown by **XIII**, so that the reactivity of methyl group 1 in the zwitter-ion **XIV** [9] is enhanced, while of the remaining two (2 and 3), on the contrary, is diminished.



XII **XIII** **XIV**

At this stage there is only one evidence of the existence of an intramolecular hydrogen bond in the intermediate: is the formation of aminocyclohexenols (according to NMR COSY, NOESY, HMQC and DEPT spectra) as a single stereoisomer.

EXPERIMENTAL

^{1}H NMR spectra of the synthesized compounds were recorded on a Varian Mercury-300 instrument at a frequency 300 MHz, at 303 K in DMSO-d_6. Chemical shifts are given relative to internal TMS. IR spectra were recorded on a Specord 75 IR instrument from the samples with vaseline oil, mass spectra on a MX-1321 device with a direct inlet of the sample into the ion source.

A general procedure for reacting enamnones V with chalcone I. A solution of enaminone **V** and chalcone **I** in absolute ethanol at a molar ratio 1:1 was kept at room temperature until the end of dropping crystals (1–10 days). Precipitated crystals were filtered off, washed with absolute ether and recrystallized from absolute ethanol. Attempted isolation of any compound from the viscous mass remained after removing the solvent, failed.

3-(*p*-Chlorophenyl)-5-*N*-(2-hydroxyethyl)amino-2,4-diethoxycarbonyl-1-methyl-4-cyclohexen-1-ol (VIIIb). IR spectrum, ν, cm^{-1} : 3400–3200 (OH, NH), 1720 (COO), 1640, 1580, 710 (C=C–C=O and Ar). ^{1}H NMR spectrum, δ, ppm: 0.73 t (3H, Me, 4-CO_2Et, J = 7.1 Hz), 1.07 t (3H, Me, 2-CO_2Et, J = 7.1 Hz), 1.20 s (3H, 1-CH_3), 2.32 d (2-CH, J = 10.8 Hz), 2.45 d (1H, J = 17.2 Hz) and 2.56 d (1H, 6-CH_2, J = 17.2 Hz), 3.18–3.37 m (2H, NCH_2), 3.52–3.59 m (2H, CH_2OH), 3.62 d.q (1H, J = 7.1, 10.7 Hz) and 3.75 d.q (1H, CH_2CH_3, 4-CO_2Et, J = 7.1, 10.7 Hz), 3.88–4.01 m (2H, CH_2CH_3, 2-CO_2Et), 4.02 s (1H, 1-OH), 4.04 g (1H, 3-CH, J = 10.4 Hz), 4.60 br (1H, CH_2OH), 7.01–7.15 m (4H, 4-ClC_6H_4), 9.04 t (1H, NH, J = 5.6 Hz).

3-(α-Furyl)-5-*N*-(2-hydroxyethyl)amino-2,4-diethoxycarbnyl-1-methyl-4-cyclohexen-1-ol (VIIIc). IR spectrum, ν, cm^{-1}: 3400–3200 (OH, NH), 1730 (COO), 1650, 1580, 710 (C=C–C=O), 1450 (Fu). ^1H NMR spectrum, δ, ppm: 0.94 t (3H, Me, 4-CO_2Et, J = 7.1 Hz), 1.18 t (3H, Me, 2-CO_2Et, J = 7.1 Hz), 1.19 s (3H, 1-CH_3), 2.36 d (1H, J = 17.0 Hz) and 2.58 d (1H, 6-CH_2, J = 16.9 Hz), 2.59 d (1H, 2-CH, J = 9.2 Hz), 3.18–3.37 m (2H, NCH_2), 3.57 q (2H, $C\underline{H}_2OH$, J = 5.4 Hz), 3.76 q.d (1H, J = 7.1, 10.7 Hz) and 3.92 q.d (1H, CH_2CH_3, 4-CO_2Et, J = 7.1, 10.7 Hz), 4.04 s (1H, 1-OH), 4.05 q (2H , $C\underline{H}_2CH_3$, 2-CO_2Et, J = 7.1 Hz), 4.21 d (1H, 3-CH, J = 9.1 Hz), 4.56 t (1H, $CH_2O\underline{H}$, J = 5.1 Hz), 5.79 d.t (1H, 3'-H, J = 3.7, 0.9 Hz) and 6.15 d.d (1H, 4'-H, J = 1.8, 3.1 Hz) and 7.20 d.d (1H, 5'-H, α-Fu, J = 0.7, 1.8 Hz), 9.10 t (1H, NH, J = 5.6 Hz).

3-(α-Furyl)-5-*N*-(3-hydroxypropyl)amino-2,4-diethoxycarbnyl-1-methyl-4-cyclohexen-1-ol (VIIId). IR spectrum, ν, cm^{-1}: 3400–3200 (OH, NH), 1720 (COO), 1640, 1580, 710 (C=C–C=O), 1450 (Fu). ^1H NMR spectrum, δ, ppm: 0.94 t (3H, Me, 4-CO_2Et, J = 7.1 Hz), 1.18 t (3H, Me, 2-CO_2Et, J = 7.1 Hz), 1.19 s (3H, 1-CH_3), 1.71 quintet (2H, $CH_2CH_2CH_2$, J = 6.6 Hz), 2.37 d (1H, J = 17.1 Hz) and 2.59 d (1H, 6-CH_2, J = 17.0 Hz), 2.59 d (1H 2-CH, J = 9.2 Hz), 3.20-3.39 m (2H, NCH_2), 3.53 q (2H, $C\underline{H}_2OH$, J = 5.4 Hz), 3.76 d.q (1H, J = 10.7, 7.1 Hz) and 3.92 d.q (1H, $C\underline{H}_2CH_3$, 4-CO_2Et, J = 10.7, 7.1 Hz), 4.03 s (1H, 1-OH), 4.06 q (2H, $C\underline{H}_2CH_3$, 2-CO_2Et, J = 7.1 Hz), 4.19 d (1H, 3-CH, J = 9.1 Hz), 4.22 t (1H, $CH_2O\underline{H}$, J = 5.0 Hz), 5.78 d.t (1H, 3'-H, J = 3.3, 0.7 Hz) and 6.15 d.d (1H, 4'-H, J = 3.2, 1.9 Hz), and 7.20 d.d (1H, 5'-H, α-Fu, J = 1.9, 0.8 Hz), 8.99 t (1H, NH, J = 5.6 Hz).

3-(*p*-Nitrophenyl)-5-*N*-(3-hydroxypropyl)amino-2,4-diethoxycarbnyl-1-methyl-4-cyclohexen-1-ol (VIIIe). IR spectrum, ν, cm^{-1}: 3430 (OH), 3290 (NH), 1730 (COO), 1630, 1590, 1520, 860, 840 (C=C–C=O and Ar). ^1H NMR spectrum, δ, ppm: 0.71 t (3H, Me, 4-CO_2Et, J = 7.1 Hz), 1.07 t (3H, Me, 2-CO_2Et, J = 7.1 Hz), 1.23 s (3H, 1-CH_3), 1.73 quintet (2H, $CH_2C\underline{H}_2CH_2$, J = 6.5 Hz), 2.36 d (1H, 2-CH, J = 11.0 Hz), 2.51 d (1H, J = 17.2 Hz) and 2.63 d (1H, 6-CH_2, J = 17.4 Hz), 3.33 d.q (2H, NCH_2, J = 12.9, 6.1 Hz), 3.55 d.d (2H, $C\underline{H}_2OH$, J = 11.1, 5.9 Hz), 3.58–3.77 m (2H, $C\underline{H}_2CH_3$, 4-CO_2Et), 3.85–4.05 m (2H, $C\underline{H}_2CH_3$, 2-CO_2Et), 4.14 s (1H, 1-OH), 4.21 d (1H, 3-CH, J = 11.0 Hz), 4.26 t (1H, $CH_2O\underline{H}$, J = 5.0 Hz), 7.28–7.34 m (2H) and 7.98–8.05 m (2H, 4-NO_2 C_6H_4), 9.04 t (1H, NH, J = 5.5 Hz).

3-Phenyl-5-*N*-(3-hydroxypropyl)amino-2-acetyl-4-ethoxycarbonyl-1-methyl-4-cyclohexen-1-ol (VIIIf). IR spectrum, ν, cm^{-1}: 3400–3320 (OH, NH), 1690 (C=O), 1630, 1570, 780, 690 (C=C–C=O and Ph). ^1H NMR spectrum, δ, ppm: 0.66 t (3H, Me, 4-CO_2Et, J = 7.1 Hz), 1.17 s (3H, 1-CH_3) 1.73 quintet (2H, $CH_2C\underline{H}_2CH_2$, J = 6.6 Hz), 1.81 s (3H, 2-Ac), 2.42 d (1H, J = 17.5 Hz) and 2.56 d (1H, 6-CH_2, J = 17.5 Hz), 2.58 d (1H, 2-CH, J = 10.6 Hz), 3.20–3.42 m (2H, NCH_2), 3.54 t (J = 5.8 Hz, 2H, $C\underline{H}_2OH$), 3.53–3.79 m (2H, $OC\underline{H}_2CH_3$), 3.95 d (1H, 3-CH, J = 11.1 Hz), 4.01 br.s (1H, 1-OH), 4.13–4.32 br.s (1H, $CH_2O\underline{H}$), 6.99–7.21 m (5H, Ph), 8.92 t (1H, NH, J = 5.6 Hz).

3-(α-Furyl)-5-*N*-(2-hydroxyethyl)amino-2-acetyl-4-ethoxycarbonyl-1-methyl-4-cyclohexen-1-ol (VIIIh). IR spectrum, ν, cm^{-1} : 3400–3220 (OH, NH), 1710 (C=O), 1650, 1580 (C=C–C=O), 1400 (Fu). ^1H NMR spectrum, δ, ppm: 0.94 t (3H, Me, 4-CO_2Et, J = 7.1 Hz), 1.14 s (3H, 1-CH_3), 2.7 s (3H, 2-Ac) , 2.35 d (1H, J = 17.2 Hz) and 2.52 d (1H, 6-CH_2, J = 17.2 Hz), 2.73 d (1H, 2-CH, J = 8.7 Hz), 3.20–3.34 m (2H, NCH_2), 3.57 q (2H, $C\underline{H}_2OH$, J = 5.5 Hz), 3.77 q.d (1H, J = 7.1, 10.7 Hz) and 3.92 q.d (1H, $OC\underline{H}_2CH_3$, J = 7.1, 10.7 Hz), 4.14 d (1H, 3-CH, J = 8.8 Hz), 4.25 s (1H, 1-OH), 4.57 t (1H, $CH_2O\underline{H}$, J = 5.1 Hz), 5.79 t.d (1H, 3'-H, J = 0.6, 3.1 Hz) and 6.11 d.d (1H, 4'-H, J = 1.8, 3.1 Hz), and 7.22 d.d (1H, 5'-H, α-Fu, J = 0.9, 1.8 Hz), 9.09 t (J = 5.6 Hz, 1H, NH).

3-Phenyl-5-*N*-(1,1-dimethyl-2-hydroxyethyl)amino-2,4-diacetyl-1-methyl-4-cyclohexene-1-ol (VIIIk). IR spectrum, ν, cm^{-1}: 3290 (OH), 3200 (NH), 1680 (C=O), 1590, 1510 (C=C–C=O), 760, 690 (Ph). ^1H NMR spectrum, δ, ppm: 1.08 s (3H, 1-CH_3), 1.24 s (3H) and 1.32 s (3H, $(CH_3)_2C$), 1.67 c (3H, 4-Ac) , 1.77 d (1H, J = 13.4 Hz) and 1.89 d (1-H, 6-CH_2, J = 13.3 Hz), 1.91 s (3H, 2-Ac), 2.74 d (1H, 2-CH, J = 10.8 Hz), 3.22 d (1H, J = 8.1 Hz) and 3.59 d (1H, $C\underline{H}_2OH$, J = 8.1 Hz), 3.33 d.d (1H, $CH_2O\underline{H}$, J = 17.8, 7.0 Hz), 3.38 d (1H, 3-CH, J = 10.9 Hz), 4.06 s (1H, 1-OH), 6.86 s (1H, NH), 7.11–7.28 m (5H, Ph).

3-(1,2,3-Trichloro)thienyl-5-*N*-(2-hydroxyethyl)-amino-2,4-diacetyl-1-methyl-4-cyclohexen-1-ol (VIIIl). IR spectrum, ν, cm^{-1}: 3400–3200 (OH, NH), 1690 (C=O), 1580, 1540 (C=C–C=O). ^1H NMR spectrum, δ, ppm: 1.25 s (3H, 1-CH_3), 1.80 s (3H, 4-Ac), 2.24 s (3H, 2-Ac), 2.41 d (1H, J = 16.8 Hz) and 2.62 d (1H, 6-CH_2, J = 16.8 Hz), 2.78 d (2-CH, J = 6.7 Hz), 3.25–3.43 m (2H, CH_2N), 3.59 q (2H, $C\underline{H}_2OH$, J = 5.4 Hz),

4.55 d (1H, 3-CH, J = 6.7 Hz), 4.58 s (1H, 1-OH), 4.69 t (1H, $CH_2O\underline{H}$, J = 5.0 Hz), 11.59 t (1H, NH, J = 5.6 Hz) . Mass spectrum, *m/e*: 439, 441 $[M]^+$.

3-Phenyl-5-*N*-(2-hydroxyethyl)amino-2-ethoxycarbonyl-4-acetyl-1-methyl-4-cyclohexen-1-ol (VIIIo). IR spectrum, ν, cm^{-1}: 3320 (OH), 3150 (NH), 1720 (COO), 1580, 1510, 750, 700 (C=C-C=O and Ph). ^{1}H NMR spectrum, δ, ppm: 1.07 t (3H, Me, 2-CO_2Et, J = 7.1 Hz), 1.20 s (3H, 1-CH_3), 1.53 s (3H, 4-Ac) , 2.36 d (1H, 2-CH, J = 10.3 Hz), 2.45 d (1H, J = 17.3 Hz) and 2.63 d (1H, 6-CH_2, J = 17.4 Hz), 3.24–3.39 m (2H, NCH_2), 3.60 q (2H, $C\underline{H}_2OH$, J = 5.5 Hz), 3.98 q.d (2H, $OC\underline{H}_2CH_3$, J = 7.1, 1.3 Hz), 4.4 s (1H, 1-OH), 4.20 d (1H, 3-CH, J = 10.2 Hz), 4.62 t (1H, $CH_2O\underline{H}$, J = 5.2 Hz), 7.05–7.12 m (3H) and 7.14–7.22 m (2H, Ph), 11.42 t (1H, NH, J = 5.6 Hz).

3-(p-Chlorophenyl)-5-*N*-(2-hydroxyethyl)amino-2-ethoxycarbonyl-4-acetyl-1-methyl-4-cyclohexen-1-ol (VIIIn). IR spectrum, ν, cm^{-1} : 3400–3200 (OH, NH), 1720 (COO), 1590, 1530, 860, 810 (C=C–C=O and Ar). ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, Me, 2-CO_2Et, J = 7.1 Hz), 1.20 s (3H, 1-CH_3), 1.54 s (3H, 4-Ac) , 2.32 d (1H, 2-CH, J = 10.3 Hz), 2.46 d (1H, J = 17.1 Hz) and 2.62 d (1H, 6-CH_2, J = 17.4 Hz), 3.23–3.41 m (2H, NCH_2), 3.59 d.d (2H, $C\underline{H}_2OH$, J = 5.1, 9.8 Hz), 3.93–4.06 m (2H, $OC\underline{H}_2CH_3$), 4.11 br.s (1H, 1-OH), 4.21 d (1H 3-CH, J = 10.3 Hz), 4.61 t (1H, $CH_2O\underline{H}$, J = 5.2 Hz), 7.06–7.21 m (4H, 4-ClC_6H_4), 11.43 t (1H, NH, J = 5.7 Hz).

3-(α-Furyl)-5-*N*-(2-hydroxyethyl)amino-2-ethoxycarbonyl-4-acetyl-1-methyl-4-cyclohexene-1-ol (VIIIp). IR spectrum, ν, cm^{-1}: 3400–3340 (OH), 3120 (NH), 1720 (COO), 1590, 1530 (C=C–C=O), 1450 (Fu). ^{1}H NMR spectrum, δ, ppm: 1.21 t (3H, Me, 2-CO_2Et, J = 7.1 Hz), 1.22 s (3H, 1-CH_3), 1.76 s (3H, 4-Ac) , 2.36 d (1H, J = 16.7 Hz) and 2.63 d (1H, 6-CH_2, J = 16.8 Hz), 2.68 d (1H, 2-CH, J = 7.6 Hz), 3.24-3.40 m (2H, NCH_2), 3.58 t (2H, $C\underline{H}_2OH$, J = 5.5 Hz), 4.09 q (2H, $OC\underline{H}_2CH_3$, J = 7.1 Hz), 4.19 br.s (1H, 1-OH), 4.33 d (1H, 3-CH, J = 7.6 Hz), 4.65 br.s (1H, CH_2OH), 5.88 d.t (1H, 3'- H, J = 3.5, 0.9 Hz) and 6.20 d.d (1H, 4'-H, J = 3.2, 1.8 Hz), and 7.29 d.d (1H, 5'-H, α-Fu, J = 1.9, 0.9 Hz), 11.49 t (1H, NH, J = 5.8 Hz).

3-Phenyl-5-*N*-(3-methoxypropyl)amino-2,4-diacetyl-1-methyl-4-cyclohexen-1-ol (VIIIq). IR spectrum, ν, cm^{-1}: 3400–3200 (OH, NH), 1700 (C=O), 1590, 1540, 750, 710 (C=C–C=O and Ar), 1190–1110 (COC). ^{1}H NMR spectrum, δ, ppm: 1.15 s (3H, 1-CH_3), 1.52 s (3H, 4-Ac), 1.81 d.d (2H, $CH_2C\underline{H}_2CH_2$, J = 12.2, 6.1 Hz), 1.86 s (3H, 2-Ac), 2.42 d (1H, J = 17.4 Hz) and 2.55 d (1H, 6-CH_2, J = 17.4 Hz), 2.60 d (1H, 2-CH, J = 10.2 Hz), 3.31 s (3H, MeO), 3.31 d.q (2H, NCH_2, J = 13.2, 6.5 Hz), 3.44 t (2H, CH_2O, J = 6.0 Hz), br.s 3.90–4.26 (1H, 1-OH), 4.10 d (1H, 3-CH, J = 10.0 Hz), 7.00–7.27 m (5H, Ph), 11.43 t (1H, NH, J = 5.6 Hz).

3-(*p*-Chlorophenyl)-5-*N*-(3-methoxypropyl)amino-2,4-diacetyl-1-methyl-4-cyclohexen-1-ol (VIIIr). IR spectrum, ν, cm^{-1}: 3400–3150 (OH, NH), 1700 (C=O), 1590, 1540, 860, 810 (C=C–C=O and Ar), 1200, 1100 (COC). ^{1}H NMR spectrum, δ, ppm : 1.16 s (3H, 1-CH_3), 1.53 s (3H, 4-Ac), 1.77–1.88 m (2H, $CH_2C\underline{H}_2CH_2$), 1.92 s (3H, 2-Ac), 2.43 d (1H, J = 17.2 Hz) and 2.56 d (1H, 6-CH_2, J = 17.4 Hz), 2.54 d (1H, 2-CH, J = 10.0 Hz), 3.21–3.39 m (2H, NCH_2), 3.32 s (3H, MeO), 3.44 t (2H, CH_2O, J = 6.0 Hz), 4.00–4.30 br.s (1H, 1-OH), 4.13 d (1H, 3-CH, J = 10.0 Hz), 7.03–7.08 m (2H) and 7.16–7.22 m (2H, 4-ClC_6H_4), 11.45 t (1H, NH, J = 5.6 Hz).

3-(*p*-Chlorophenyl)-5-*N*-(3-methoxypropyl)amino-2-ethoxycarbonyl-4-acetyl-1-methyl-4-cyclohexen-1-ol (VIIIs). IR spectrum, ν, cm^{-1}: 3400–3200 (OH, NH), 1720 (COO), 1590, 1540, 860, 810 (C=C–C=O and Ar), 1190, 1110 (COC). ^{1}H NMR , δ, ppm: 1.10 t (3H, Me, 2-CO_2Et, J = 7.1 Hz), 1.19 s (3H, 1-CH_3), 1.52 s (3H, 4-Ac), 1.76–1.87 m (2H, $CH_2C\underline{H}_2CH_2$), 2.31 d (1H, 2-CH, J = 10.4 Hz), 2.44 d (1H, J = 17.1 Hz) and 2.59 d (1H, 6-CH_2, J = 17.4 Hz), 3.31 s (3H, MeO), 3.31 d.t.d (2H, NCH_2, J = 16.5, 9.4, 6.9 Hz), 3.43 t (2H, CH_2O, J = 5.9 Hz), 3.98 q.d.d (2H, $OC\underline{H}_2CH_3$, J = 14.1, 9.0, 5.3 Hz), 4.06–4.25 br.s (1H, 1-OH), 4.19 d (1H, 3-CH, J = 10.3 Hz), 7.02–7.12 m (2H) and 7.13–7.22 m (2H, 4-ClC_6H_4), 11.42 t (1H, NH, J = 5.5 Hz).

3-Phenyl-5-*N*-benzylamino-2,4-diethoxycarbnyl-1-methyl-4-cyclohexen-1-ol (VIIIv). IR spectrum, ν, cm^{-1}: 3350–3200 (OH, NH), 1720 (COO), 1690, 750, 710 (C=C–C=O and Ar); ^{1}H NMR spectrum, δ, ppm: 0.67 t (3H, CH_3, 2-CO_2Et J = 7.1 Hz), 0.87 t (CH_3, 4-CO_2Et, J = 7.1 Hz), 1.17 s (3H, 1-CH_3), 2.35 d (1H, 2-CH, J = 10.7 Hz), 2.38 d (J = 17.3 Hz , 1H) and 2.58 d (1H, 6-CH_2, J = 17.2 Hz), 3.61 d.q (1H, J = 10.8, 7.1 Hz) and 3.75 d.q (1H, CH_2, 4-CO_2Et, J = 10.8, 7.1 Hz,), 3.89 s (1H, 1-OH), 3.93 d.d (2H, CH_2, 2-CO_2Et, J = 14.3, 7.2 Hz), 4.05 d (1H, 3-CH, J = 10.8 Hz), 4.44–4.50 m (2H, NCH_2), 6.99–7.40 m (10H, 2Ph), 9.28 t (1H, NH, J = 6.0 Hz).

3-(α-Furyl)-5-*N*-benzylamino-2,4-diacetyl-1-methyl-

4-cyclohexen-1-ol (VIIIw). IR spectrum, ν, cm^{-1}: 3400–3150 (OH, NH), 1710 (C=O), 1590, 790, 710 (C=C–C=O and Ar), 1460 (Fu). ^1H NMR spectrum, δ, ppm: 1.13 s (3H, 1-CH_3), 1.78 s (3H, 4-Ac), 2.14 s (3H, 2-Ac), 2.35 d (1H, J = 16.9 Hz) and 2.55 d (1H, 6-CH_2, J = 17.0 Hz), 2.86 d (1H, 2-CH, J = 7.4 Hz), 4.25 d (1H, 3-CH, J = 7.5 Hz), 4.37 s (1H, 1-OH), 4.49 d (2H, CH_2N, J = 5.9 Hz), 5.91 t.d (1H, 3'-H, J = 0.8, 3.5 Hz) and 6.23 d.d (1H, 4'-H, J = 1.8, 3.2 Hz) and 7.21–7.38 m (6H, 5'-H, α-Fu and the 5H, Ph), 11.76 t (1H, NH, J = 5.9 Hz).

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