Chemistry of Heterocyclic Compounds, Vol. 43, No. 1, 2007

RECYCLIZATION OF 1,4-DIHYDROPYRIDINE DERIVATIVES IN ACIDIC MEDIUM

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The recyclization of 1,4-dihydropyridines in aqueous-alcoholic hydrochloric acid medium proceeds with cleavage of a C-N bond and pyridine ring opening. Cyclohexenone derivatives are formed as a result of the subsequent intramolecular crotonic condensation of the acyclic intermediate. The leaving carbonyl substituents depart simultaneously with recyclization, depending on the acidity of the reaction medium.

Keywords: 1,4-dihydropyridines, cyclohex-2-enones, recyclization, hydrolysis of enamines, elimination of carbonyl substituents.

The recyclization of dihydropyridines (DHP) in acidic medium, leading to the formation of cyclohexenone derivatives, has been recommended [1] for obtaining these difficultly available compounds, and is frequently used in the organic synthesis, although yields of them did not exceed 30%. 1,5-Diketones are intermediates of 1,4-DHP transformation and can be also the target products [2-4]. The conversion of certain readily available ethyl 4-phenyl-1,4-dihydropyridine-3,5-dicarboxylates into derivatives of cyclohex-2-enones by the action of hydrochloric acid in aqueous alcoholic medium has been described previously [5].

In the present work the recyclization of 1,4-DHP with differing substituents in positions 3 and 5 has been studied. The character of the 3- and 5-substituents of DHP has a strong influence on the DHP ring opening ability, on the tendency towards elimination of these functions under recyclization conditions, and also on the formation of cyclohexenone regioisomers.

Ring opening of dihydropyridines in acidic medium takes place as the hydrolysis of enamines comprising three separate stages: 1) protonation of the enamine, leading to an immonium ion; 2) addition of water forming a hydroxy amine; 3) elimination of amine.

It is generally accepted that in acidic medium the rate limiting step is elimination of amine [6]. Hydrolysis is preceded by the equilibrium protonation stage (equilibrium of enamine – immonium ion), which depends on the acidity of the medium and the basicity of the enamine.

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* Dedicated to Prof. Dr. E. Lukevics on the occasion of his 70th birthday.
To respected scientist and dependable friend. The instant in which we live is the most significant. Nobody is able to stop the moment, and risks only to make a mark.

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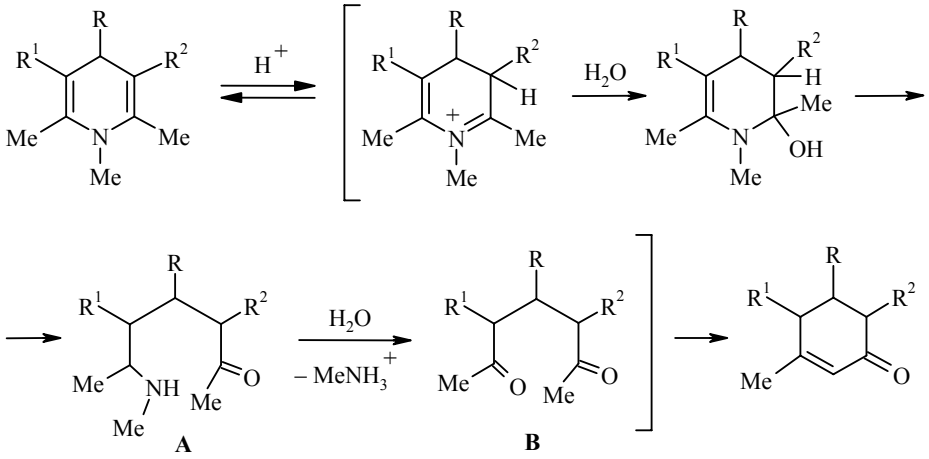
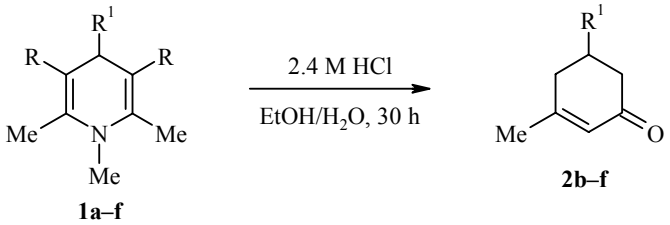


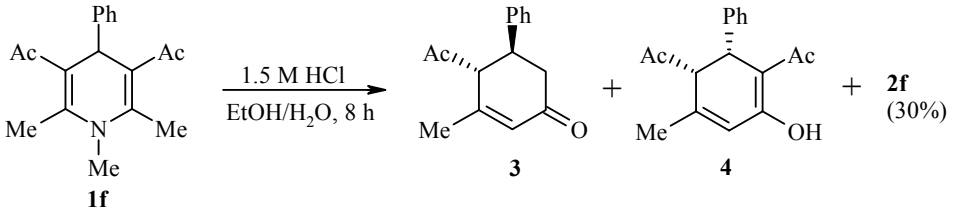
The hydrolysis of DHP enamine fragment includes a cleavage of the N-$C_{(2)}$ bond and subsequent elimination of amine from the resulting acyclic intermediate **A** leading to the pentane-2,6-dione derivative **B**. The latter affords the cyclohexenone derivative upon intramolecular condensation of the terminal methyl group with a carbonyl function.

In strongly acidic medium (2.4 M HCl) recyclization of 1,4-DHP **1a-f** resulted in the formation of cyclohexenones **2b-f** in 54-84% yield. Under the reaction conditions elimination of both carbonyl functions of the DHP occurs, consequently the same cyclohexenone **2b** is formed either from DHP **1a** or **1b**.

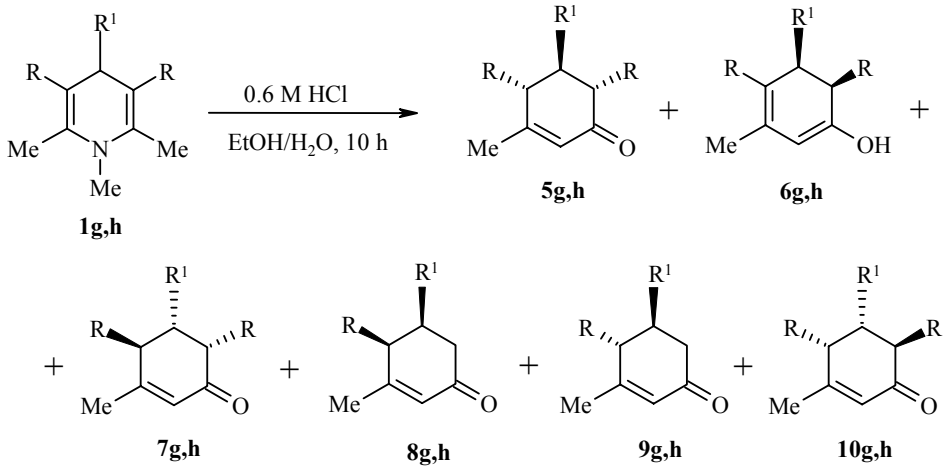


1 a, f R = Ac, **b–e** R = COOEt; **1a, b, 2 b** R^1 = Me;
1, **2 c** R^1 = Et, **d** R^1 = Pr, **e** R^1 = *i*-Pr, **f** R^1 = Ph

If DHP **1f** is subjected to hydrolysis under the action of acid of a lower concentration the acetyl derivatives **3** and **4** are formed together with cyclohexenone **2f**.



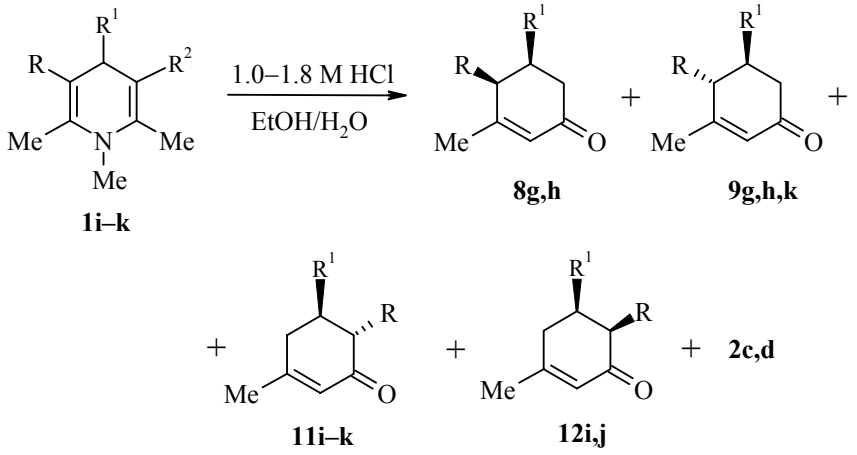
The ester group of a 1,4-DHP is comparatively stable under mild reaction conditions and a complex mixture of recyclization products is isolated from the reaction mixture of DHP **1g,h** acidic hydrolysis.



1g,h **5g,h** **6g,h** **7g,h** **8g,h** **9g,h** **10g,h**

1, **5–10** R = COOEt, **g** R^1 = Et, **h** R^1 = Pr

The acetyl substituent proved to be the more labile on cleavage of the unsymmetrical DHP ($R \neq R^2$) in a medium of 1.0-1.8 M HCl in aqueous alcoholic solution. The recyclization of ethyl 5-acetyl-1,4-dihydropyridine-3-carboxylates **1i,j** resulted in formation of regio- and stereoisomeric esters of cyclohexenonecarboxylic acids **8g,h, 9g,h, 11i,j**, and **12i,j** in addition to alkylcyclohexenes **2c,d**.



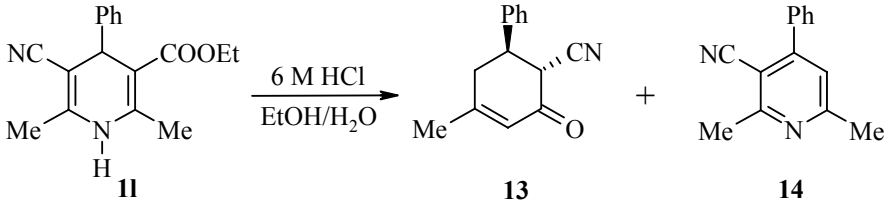
1i–k **8g,h** **9g,h,k** **11i–k** **12i,j**

1 i–k R = COOEt; **i** R^1 = Et, **j** R^1 = Pr, **k** R^1 = Ph; **i–k** R^2 = Ac;
8g, **9g**, **11i**, **12i** R = COOEt, R^1 = Et; **8h**, **9h**, **11j**, **12j** R =COOEt, R^1 = Pr;
9k, **11k** R = COOEt, R^1 = Ph

The occurrence of different cyclohexenone regioisomers is caused by the ability of both terminal methyl groups of the intermediate **B** ($R \neq R^1$) to recyclization, and the formation of different diastereomers of these isomers depends on the proton attack to the DHP ring: whether from the side of the 4-substituent or from the opposite one.

In contrast to the above compounds **1i,j**, the acidic recyclization of DHP **1k** proceeds with the formation of only two regioisomers **9k** and **11k**.

On recyclizing DHP **1l** in strongly acidic medium, apart from cyanocyclohexenone **13,** pyridine **14** was isolated as a side product. In the course of recyclization the COOEt group is subject to elimination exclusively. It has therefore been established that the DHP substituents at positions 3 and/or 5 can be arranged in the series Ac > COOEt > CN in tendency to be split off.



1l **13** **14**

The structures of all obtained compounds were established by NMR spectroscopy. The interaction observed in the gHMBC spectrum of the H-4 proton with the C=C carbon atoms of cyclohexenone **3**, (chemical shifts 156.5 and 129.1 ppm respectively) and the CO group of the acetyl function (207.9 ppm) demonstrate that the Ac substituent is located at the C-4 atom of cyclohexenone **3**. The coupling constant $J_{4,5}$ = 8.9 Hz indicates a *trans* disposition of these protons.

The NOESY spectrum of compound **3** showed an intramolecular Overhauser effect between proton H-4 (3.76 ppm) and one of the protons at C-6 (2.66 ppm) that is possible only if these protons are disposed axially, and the acetyl group equatorially. This is feasible only in the case when both bulky substituents (Ac and Ph) are situated equatorially.

In the ^{1}H NMR spectrum of 1,5-diacetyl-2-hydroxy-4-methyl-6-phenylcyclohexa-1,3-diene (**4**) the signal of the acetyl group located at the C-1 atom is shifted upfield than the signal of the other C=O group (1.94 and 2.27 ppm). In the ^{13}C NMR spectrum of enol **4** no signal is attributable to CO group (in ketone **3** the corresponding signal is at 194.0 ppm). At the same time the signal present at 180 ppm corresponds to hydroxyl-bearing olefinic carbon, which also confirms the structure of diene **4**. The coupling constant $J_{5,6}$ = 1.1 Hz indicates the *cis* disposition of the 5-$COCH_3$ and 6-C_6H_5 substituents.

The structures of compounds **5g,h** and **10g,h** (Table 1) were established by comparison of their NMR spectra with the spectra of the known diastereomers of 4,6-dimethoxycarbonyl-3-methyl-5-phenyl-cyclohex-2-enones [7].

Chromatography of the mixture of products obtained on hydrolysis of DHP **1i,j** gave individual regioisomers, each of which was a mixture of two diastereomers **8, 9** and **11, 12**. Assignment of these compounds to the series of derivatives of 2-oxocyclohex-3-ene- and 4-oxocyclohex-2-enecarboxylic acids was made by analysis of NMR spectra (Table 2). Interaction of the ring proton with the ester group, observed in the gHMBC spectra of all four isomers, enables to recognize the signal of H-1 correctly. Interaction of the cyclohexenone proton H-1 with a carbon atom of the C=C bond (**8, 9**), or with the carbon atom of the 2-C=O group (**11, 12**) enables the regioisomers to be identified. The coupling constants of the H-1 and H-6 protons J = 10.9 and J = 5.4 Hz confirmed a *trans* (**11**) or *cis* (**12**) position of the ester group and the alkyl substituent of the isomers. Diastereomers **8** and **9** also differ in the spatial disposition of the 1-COOEt and 6-alkyl substituents. The spectral characteristics of compounds **8g** and **9g** are in agreement with the data of [8], where they are described as an unresolvable mixture of isomers.

The *trans* disposition of the 1- and 6-substituents in cyclohexenone **13** was also established by ^{1}H NMR.

For comparing the reactivity of the various DHP the rate constants of ring opening were determined in a medium of 50% aqueous ethanolic hydrochloric acid. The acidity of reaction medium was characterized with Hammett function according to [9].

TABLE 1. ^{1}H NMR Spectra of the Synthesized Compounds **5-7**, **10**

Compound	Chemical shifts, δ, ppm. (SSCC, *J*, Hz)*			
	H-1	H-2	H-3	H-5
5g	3.19 (d, *J* = 11.6)	3.07-3.19 (m)	2.93 (d, *J* = 8.5)	5.87 (m)
6g	2.83 (d, *J* = 0.9)	3.47 (dt, *J* = 0.9, *J* = 7.5)	—	5.97 (m)
7g	3.78 (s)	2.54 (m)	3.13 (d, *J* = 11.3)	6.01 (m)
10g	3.76 (d, *J* = 13.0)	2.57 (m)	3.43 (d, *J* = 5.0)	6.01 (m)
5h	3.13 (d, *J* = 11.6)	3.06-3.13(m)	2.77 (d, *J* = 8.0)	5.79 (m)
6h	2.72 (s)	3.50 (t, *J* = 7.6)	—	5.91 (m)
7h	3.71 (s)	2.60 (m)	3.13 (d, *J* = 11.3)	5.93 (m)
10h	3.70 (d, *J* = 13.2)	2.62 (m)	3.35 (d, *J* = 5.1)	5.95 (s)

*The spectra of compounds were recorded in C_6D_6 at 600 MHz (**5h-7h**); $CDCl_3$ at 400 MHz (**10h**); C_6D_6 at 400 MHz (**5g-7g**); $CDCl_3$ at 200 MHz (**10g**, **7g**).

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds **8h**, **9h**, **11i,j**, **12i,j**

Compound	Chemical shifts, δ, ppm (SSCC, *J*, Hz)*			
	H-1	H-3	5-CH_2	H-6, m
11i	2.93 (d, *J* = 12.1)	5.75 (m)	0.57-1.44 (1H, m); 1.69 (dd, *J* = 5.3, *J* = 18.0)	2.24
12i	3.46 (d, *J* = 4.9)	5.91 (m)	0.57-1.44 (1H, m); 1.69 (d.d, *J* = 5.3, *J* = 18.0)	2.24
8h	3.08 (d, *J* = 6.3)	5.95 (m)	2.12 (1H, dd, *J* = 8.5, *J* = 16.4); 2.62 (1H, dd, *J* = 4.7, *J* = 16.4)	2.45
9h	3.21 (d, *J* = 5.1)	5.94 (m)	2.31 (1H, dd, *J* = 4.4, *J* = 16.4); 2.59 (1H, dd, *J* = 3.2, *J* = 16.4)	2.27
11j	3.00 (d, *J* = 10.9)	5.82 (s)	2.00 (1H, dd, *J* = 11.0, *J* = 18.0); 2.36-2.42 (1H, m)	2.36-2.42
12j	3.29 (d, *J* = 5.4)	5.82 (s)	2.12 (1H, dd, *J* = 5.0, *J* = 18.0); 2.36-2.42 (1H, m)	2.19

*Spectra of compounds were obtained in C_6D_6 at 200 MHz (**11i**, **12i**) and $CDCl_3$ at 600 MHz (**11j**, **12j**, **8h**, **9h**).

The measurements showed that for ring opening of N-unsubstituted DHP a substantially higher acidity of the reaction medium is required than for hydrolysis of N-substituted 1,4-DHP (Fig. 1). 3- and 5-Substituents of the starting DHP have a significant effect on the DHP ring opening: the acidity of the medium required for hydrolysis grows in the series of substituents Ac < COOEt < CN.

Introduction at the nitrogen atom of a substituent (4-$MeOC_6H_4$) more electron-donating than Me has an insignificant effect on the rate of DHP ring opening.

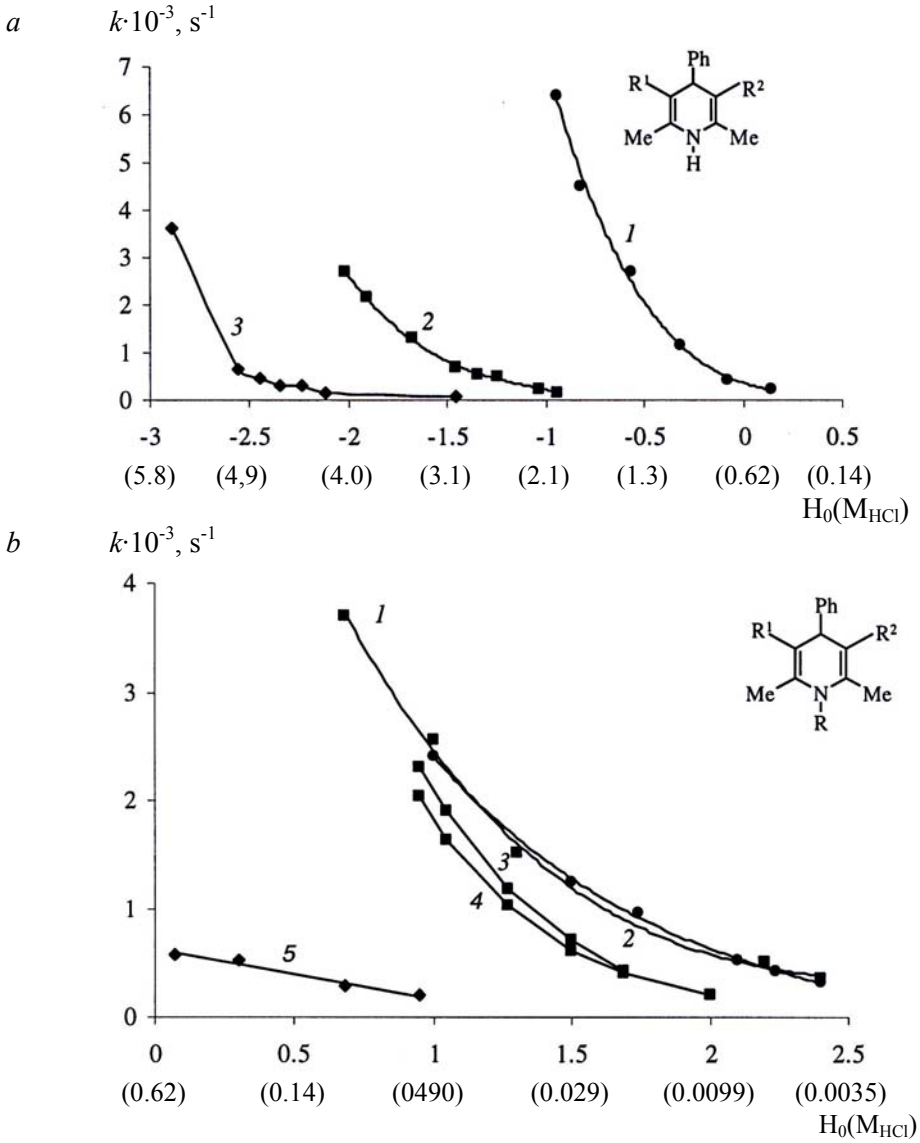


Fig. 1. The rate dependence of dihydropyridine ring opening on the acidity of medium:
a: 1 – $R^1 = R^2$ = Ac; *2* – $R^1 = R^2$ = COOEt; *3* – **1l**; *b: 1* – R = Me, $R^1 = R^2$ = COOEt; *2* – **1f**;
3 – R = Ph, $R^1 = R^2$ = COOEt; *4* – R = 4-MeOPh, $R^1 = R^2$ = COOEt; *5* – R =Me, R^1 = CN, R^2 = COOEt

EXPERIMENTAL

The ^1H, ^{13}C, gHMBC, and (H, H)-NOESY NMR spectra were recorded on Varian Mercury 200, Varian Mercury 400, and Varian-Inova 600 spectrometers (signals were referred to TMS). The IR spectra were taken on a IR Prestige 21 spectrometer in KBr discs. The mass spectra were obtained on a HP 6890 GCMS spectrometer, ionization energy 70 eV. The UV spectra were recorded on a Specord UV-VIS spectrometer.

The previously unknown 1,4-DHP **1i,j** were synthesized by the method of [10]. N-Alkylation was carried out analogously to [11].

Recyclization of 1,4-Dihydropyridines 1a-f under the Action of 2.4 M HCl (general procedure). A solution of 1,4-DHP **1** (3 mmol) and conc. HCl (4.4 ml: 46 mmol) in 80% ethanol (15 ml) was refluxed for 30 h, then cooled to room temperature, diluted with water (20 ml), and extracted with CH_2Cl_2 (4×25 ml). The combined extracts were dried and evaporated in vacuum. The yellow oil obtained was chromatographed (hexane – *t*-butyl methyl ether (TBME), 2 : 1, silica gel) and 5-alkyl-3-methylcyclohexenones **2** were isolated.

The previously known dicyclohexenones **2b,e,f**, obtained after recyclization in yields of 54 (from **1a**) or 74 (from **1b**), 83, and 68% respectively, corresponded in all characteristics with the data of [12-14].

5-Ethyl-3-methylcyclohex-2-enone (2c). Yield 0.33 g (79%). IR spectrum, ν, cm^{-1}: 1667 (C=O). ^{1}H NMR spectrum (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.93 (3H, t, *J* = 7.3, $CH_2C\underline{H}_3$); 1.41 (2H, m, $C\underline{H}_2CH_3$); 1.93-2.12 (6H, m, 3-CH_3, 4-CH_2, 5-CH); 2.24-2.52 (2H, m, 6-CH_2); 5,87 (1H, m, 2-CH). Mass spectrum, *m/z*, (I_{rel}, %): 138 (20) $[M]^+$, 110 (3), 82 (100), 77 (2.4), 67 (3.8), 54 (9.6), 43 (2.4), 39 (9.6).

3-Methyl-5-propylcyclohex-2-enone (2d). Yield 0.38 g (84%). Bp 60°C (1.2 mbar). IR spectrum, ν, cm^{-1}: 1669 (C=O). ^{1}H NMR spectrum (200 MHz, $CDCl_3$), δ, ppm: 0.91 (3H, m, 5-$(CH_2)_2C\underline{H}_3$); 1.35 (4H, m, 5-$(C\underline{H}_2)_2CH_3$); 1.92-2.51 (8H, m, 3-CH_3, 4-CH_2, 5-CH, 6-CH_2); 5.86 (1H, m, 2-CH). Mass spectrum, *m/z* (I_{rel}, %): 152 (9) $[M]^+$, 109 (13), 82 (100), 77 (2.9), 67 (3.4), 54 (8.7), 43 (5.8), 39 (8.7).

Recyclization of 3,5-Diacetyl-1,2,6-trimethyl-4-phenyl-1,4-dihydropyridine (1f). Conc. HCl (8.0 ml, 84.8 mmol) was added to a solution of the 1,4-DHP (4.0 g, 14 mmol) in 80% ethanol (47 ml) and the mixture refluxed for 8 h. The reaction mixture, after treatment analogous to that given above, was chromatographed (hexane–TBME–MeOH, 10 : 2 : 1, Silasorb). Two fractions were collected. The first fraction, consisting of cyclohexenone **2f** and cyclohexadiene **4**, was chromatographed once more (toluene–TBME, 5 : 1, Silasorb) and ketone **2f** (0.79 g: 30%) and hydroxy product **4** (0.07 g, 2%) were isolated. From the second fraction cyclohexenone **3** (0.57 g: 18%) was isolated.

4-Acetyl-3-methyl-5-phenylcyclohex-2-enone (3). Mp 92-95°C. IR spectrum, ν, cm^{-1}: 1661 (C=O), 1701 (C=O). ^{1}H NMR spectrum (600 MHz, C_6D_6), δ, ppm (*J*, Hz): 1.36, (3H, s, 3-CH_3); 1.44 (3H, s, $COCH_3$); 2.30 (1H, dd, *J* = 11.8, *J* = 16.4, CH_2); 2.51 (1H, dd, *J* = 4.4, *J* = 16.4, CH_2); 3.10 (1H, d, *J* = 8.9, 4-CH); 3.19 (1H, m, 5-CH); 6.00 (1H, m, 2-CH); 6.85 (2H, dd, *J* = 1.4, *J* = 6.9, *o*-CH); 7.02 (1H, tt, *J* = 1.4, *J* = 7.3, *p*-CH); 7.06 (2H, m, *m*-CH). ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ, ppm: 22.6 (3-CH_3); 31.4 ($CO\underline{C}H_3$); 42.6 (6-CH_2); 44.0 (5-CH); 60.7 (4-CH); 127.2 (2', 6'-CH); 127.4 (4'-CH); 129.0 (3', 5'-CH); 129.1 (2-CH); 140.9 (1'-CH); 156.5 (3-C); 197.1 (1-C=O); 207.9 ($\underline{C}OCH_3$). Found, %: C 78.66; H 7.08. $C_{15}H_{16}O_2$. Calculated, %: C 78.92; H 7.06.

1,5-Diacetyl-2-hydroxy-4-methyl-6-phenylcyclohexa-1,3-diene (4). ^{1}H NMR spectrum (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.86 (3H, d, *J* = 1.3, 4-CH_3); 1.94 (3H, s, 5-$COCH_3$); 2.27 (3H, s, 1-$COCH_3$); 3.20 (1H, d, *J* = 1.1, H-5); 4.27 (1H, d, *J* = 1.1, H-6); 6.19 (1H, m, H-3). ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ, ppm: 22.5 (4-CH_3); 24.5 (1-$CO\underline{C}H_3$); 28.0 (5-$CO\underline{C}H_3$); 41.8 (5-CH); 62.9 (6-CH); 104.2 (C-1); 125.2 (3-CH); 127.0 (4'-CH); 127.1 (2', 6'-CH); 128.8 (3', 5'-CH); 142.4 (C-1'); 149.2 (C-4); 180.4 (C-2); 191.0 (1-CO); 204.8 (5-CO). Mass spectrum, *m/z* (I_{rel}, %): 270 (19) $[M]^+$ (19), 252 (5) $[M-18]^+$, 227 (65), 209 (16), 185 (27), 135 (9), 77 (10), 43 (100).

Recyclization of Dihydropyridines 1i-k in Hydrochloric Acid Solution. Recyclization of DHP **1j** in 1.0 M HCl and **1i** in 1.8 M HCl was carried out as indicated above for 4 h. The reaction mixture was diluted with water, extracted with CH_2Cl_2, the solvent distilled off, and the residue fractionated in vacuum. From pyridine **1i** (9.2 g: 34 mmol) ketone **2c** (0.47 g: 31%) was obtained of bp 56-58°C (1.8 mbar). Further fraction collected at 92-93°C (0.8 mbar) was a mixture of monoesters **8g, 9g, 11i**, and **12i** (3.0 g, yield 40%, ratio 2 : 1 : 10 : 2.5). From dihydropyridine **1j** (11.3 g, 40 mmol) ketone **2d** (0.80 g: 12%) was obtained of bp 60°C (1.2 mbar). An intermediate fraction collected at 80-100°C (1.2 mbar) consisted of ketone **2d** and a mixture of monoesters **8h, 9h, 11j,** and **12j** (0.42 g). The fraction of bp 105-111 °C (1.2 mbar) was a mixture of monoesters **8h, 9h, 11j**, and **12j** (4.1 g, 41%, ratio 3 : 2 : 11 : 3). The pairs of diastereomers **8g,h, 9g,h, 11i,j**, and **12i,j** were resolved chromatographically (hexane–TBME–MeOH, 125 : 25 : 1, Silasorb).

The reaction mixture obtained on recyclizing DHP **1k** (1.0 g: 3.2 mmol) in 1.4 M HCl was resolved chromatographically (hexane–TBME–MeOH, 5 : 2 : 1, Silasorb) after work up. Ketone **1f** (0.17 g: 28%), pure ester **11k** (0.16 g: 21%), and a mixture of regioisomers **11k** and **9k** (0.05 g: 10%, ratio 1 : 1) were obtained.

Ethyl Esters of 4-Methyl-2-oxo-6-propylcyclohex-3-enecarboxylic Acids 12j and 11j. ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ, ppm: isomer **12j**, 13.8 ($(CH_2)_2\underline{C}H_3$); 14.0 ($OCH_2\underline{C}H_3$); 19.6 ($CH_2\underline{C}H_2CH_3$); 24.3 (4-CH_3); 34.5-36.7 (C-5, C-6, $\underline{C}H_2CH_2CH_3$); 55.6 (C-1); 60.70 ($O\underline{C}H_2CH_3$); 125.0 (C-3); 161.8 (C-4); 168.3 (2-C=O); 194.2 (1-C=O); isomer **11j**, 13.9 ($(CH_2)_2\underline{C}H_3$); 14.0 ($OCH_2\underline{C}H_3$); 19.1 ($CH_2\underline{C}H_2CH_3$); 24.2 (4-CH_3); 34.5-36.7 (C-5, C-6, $\underline{C}H_2CH_2CH_3$); 59.3 (C-1); 60.8 ($O\underline{C}H_2CH_3$); 125.3 (C-3); 163.8 (C-4); 170.25 (C-2); 194.3 (COOEt).

Ethyl Ester of 2-Methyl-4-oxo-6-propylcyclohex-2-enecarboxylic Acid (8h). IR spectrum, ν, cm^{-1}: 1674 (C=O), 1730 (C=O). ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ, ppm: 13.9 ($(CH_2)_2\underline{C}H_3$); 14.0 ($OCH_2\underline{C}H_3$); 19.7 ($CH_2\underline{C}H_2CH_3$); 23.0 (2-CH_3); 35.9 ($\underline{C}H_2CH_2CH_3$); 37.3 (C-5); 40.3 (C-6); 52.8 (C-1); 61.3 ($O\underline{C}H_2CH_3$); 128.1 (C-3); 155.8 (C-2); 171.9 (4-C=O); 198.2 (1-C=O).

Ethyl Ester of 2-Methyl-4-oxo-6-phenylcyclohex-2-enecarboxylic Acid (9k). Mp 45.5-46.5°C. ^{1}H NMR spectrum (200 MHz, C_6D_6), δ, ppm (*J*, Hz): 0.62 (3H, t, *J* = 1.4, $OCH_2C\underline{H}_3$); 1.52 (3H, t, *J* = 1.3, 2-CH_3); 2.23 (1H, dd, *J* = 16.4, *J* = 12.3, H-5); 2.53 (1H, dd, *J* = 16.4, *J* = 4.3, H-5); 3.15 (1H, d, *J* = 9.7, H-1); 3.43 (1H, m, H-6); 3.65 (2H, m, $OC\underline{H}_2CH_3$); 5.93 (1H, m, H-3); 6.84-7.08 (5H, m, C_6H_5). Found, %: C 74.10; H 7.04. $C_{16}H_{18}O_3$. Calculated, %: C 74.40; H 7.02.

The ethyl ester of 4-methyl-2-oxo-6-phenylcyclohex-3-enecarboxylic acid (**11k**) corresponded in all characteristics with the literature data of [15].

Recyclization of Dihydropyridines 1g,h under the Action of 0.6 M HCl. The requisite amount of conc. HCl was added to a solution of 1,4-DHP **1g,h** in 80% ethanol and the obtained mixture was refluxed for 10 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The solvent was evaporated, and the residue, a yellow oil, was resolved chromatographically (hexane–TBME–MeOH, 10 : 4 : 1, Silica gel) into fractions.

The first fraction, containing diesters **5-7**, was chromatographed once again (toluene–TBME, 5 : 1, Silasorb) and a mixture of the indicated esters was obtained. The second fraction was a mixture of monoesters **8, 9**, and diester **10**. The third fraction, consisting of diester **10** with contaminating monoesters **8** and **9,** was chromatographed again (toluene–TBME, 5, 1, Silasorb) and diester **10** was isolated as a pure product. The yield and ratio of diesters, obtained on recyclization of both DHP **1g** and **1h** was the same – 34% and **5** : **6** : **7**, 1 : 1 : 0.2. The ratio of products isolated from the second fraction on recyclization of DHP **1g** was **8g** : **9g** : **10g**, 4 : 1 : 5, yield was 26%. Yield of diester **10g** was 6%.

As with the recyclization of DHP **1h** the ratio of products in the second fraction **8h** : **9h** : **10h** was 4 : 20 : 5, 22% yield. Yield of diester **10h** from the third fraction was 8%.

Diethyl Esters of 2-Ethyl-4-methyl-6-oxocyclohex-4-ene-1,3-dicarboxylic Acids 5g and 7g. ^{13}C NMR spectrum (100 MHz, C_6D_6), δ, ppm: isomer **5g**, 7.0 ($CH_2\underline{C}H_3$); 19.9 (4-CH_3); 22.3 ($\underline{C}H_2CH_3$); 38.5 (2-CH); 48.4 (3-CH); 54.7 (1-CH); 58.2-58.7 (1-$OCH_2\underline{C}H_3$, 3-$OCH_2\underline{C}H_3$); 125.5 (5-CH); 126.3-127.8 (1-$O\underline{C}H_2CH_3$, 3-$O\underline{C}H_2CH_3$); 153.8 (C-4); 167.5 (1-C=O); 169.2 (3-C=O); 190.4 (6-C=O); isomer **7g**, 9.5 ($CH_2\underline{C}H_3$); 19.8 (4-CH_3); 22.8 ($\underline{C}H_2CH_3$); 39.8 (2-CH); 49.5 (3-CH); 52.3 (1-CH); 58.2-58.7 (1-$OCH_2\underline{C}H_3$, 3-$OCH_2\underline{C}H_3$); 125.2 (5-CH); 126.3-127.8 (1-$O\underline{C}H_2CH_3$, 3-$O\underline{C}H_2CH_3$); 155.2 (C-4); 166.4 (1-C=O); 167.5 (3-C=O); 189.6 (6-C=O).

Diethyl Ester of 2-Ethyl-6-hydroxy-4-methylcyclohexa-3,5-diene-1,3-dicarboxylic Acid (6g). ^{13}C NMR spectrum (100 MHz, C_6D_6), δ, ppm: 9.2 ($CH_2\underline{C}H_3$); 21.8 (4-CH_3); 24.9 ($\underline{C}H_2CH_3$); 47.4 (1-CH); 34.4 (2-CH); 58.2-58.7 (1-$OCH_2\underline{C}H_3$, 3-$OCH_2\underline{C}H_3$); 94.4 (3-CH); 119.2 (5-CH); 126.3-127.8 (1-$O\underline{C}H_2CH_3$, 3-$O\underline{C}H_2CH_3$); 142.9 (C-4); 164.7 (1-C=O); 169.2 (3-C=O); 170.7 (6-COH).

Recyclization of Dihydropyridine 1l under the Action of 6 M HCl. A solution of 1,4-dihydropyridine **1l** (1.2 g: 4.2 mmol) and conc. HCl (22 ml) in ethanol (15 ml) was refluxed for 7.5 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The solvent was evaporated and the residue, a yellow oil, was

separated chromatographically (CH_2Cl_2–EtOAc, 30 : 1, Silica gel) into two fractions. The first fraction contained cyclohexenecarbonitrile **13** and the second pyridine **14**.

4-Methyl-2-oxo-6-phenylcyclohex-3-enecarbonitrile (13). Yield 0.17 g (20%). Mp 129-130°C. IR spectrum, ν, cm^{-1}: 2249 (C≡N), 1670 (C=O). ^1H NMR spectrum (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 2.05 (3H, s, 4-CH_3); 2.55-2.73 (2H, m, 4-CH_2); 3.41-3.59 (1H, m, H-6); 3.74 (1H, d, *J* = 13.0, H-1); 6.08 (1H, m, H-3); 7.24-7.47 (5H, m, C_6H_5). Found, %: C 79.60; H 6.42; N 6.35. $C_{14}H_{13}NO$. Calculated, %: C 79.59; H 6.20; N 6.63.

2,6-Dimethyl-4-phenylnicotinic Acid Nitrile (14) (23% yield) corresponded in all respects with the literature data of [16].

Rate Constants (*k*) Determination of 1,4-DHP ring opening in Acidic Medium. Acid (1 ml), prepared from conc. HCl and water so as to provide the required concentration of HCl in the reaction medium, was added to a boiling solution (50 ml) of the 1,4-DHP (4.10^{-3} M) in 50% ethanol. The solution was boiled and samples of 1.5 ml were taken directly after adding the acid and at intervals of 1, 2-5 min, or 5, 10, 15 min depending on the rate of hydrolysis of the 1,4-DHP. Each sample was diluted with ethanol up to 25 ml and the concentration of 1,4-DHP was determined by measuring the UV absorption at the maximum characteristic of each 1,4-DHP.

The work was carried out with the financial support of the European Social Fund.

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