# SYNTHESIS OF DECAHYDROPHENANTHRIDINE-1,7-DIONE AND HEXAHYDROISOQUINOL-8-ONE DERIVATIVES IN THE REACTION OF 2-ACETYL-2-CYCLOHEXENE-1-ONES WITH CONJUGATED ENAMINOCARBONYL COMPOUNDS

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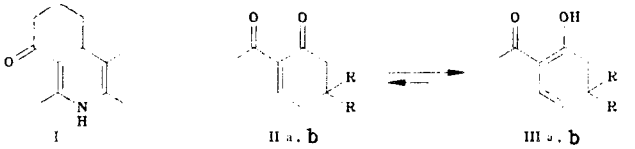
Derivatives of decahydrophenanthridine-1,7-dione were obtained by the reaction of 2-acetyl-2-cyclohexen-1-ones with enamines of cyclic β-diketones (dihydroresorcinol, dimedone). Derivatives of hexahydroisoquinol-8-one having electron-acceptor substituents at the 4-position were obtained by the reaction of 2-acetyl-5,5-dimethyl-2-cyclohexen-1-one with acyclic enaminocarbonyl compounds. The reaction mechanism is discussed.

In the present work, the synthesis of decahydrophenanthridine-1,7-dione and hexahydroisoquinol-8-one derivatives which contain a 1,4-dihydropyridine ring is described. These compounds belong to a new type of hydrogenated, nitrogen-containing heterocyclic system (I) and are of interest as potential physiologically active compounds, and also as convenient models for studying the problems of s-cis-s-trans-isomerism of 3,5-dialkanoyl-1,4-dihydropyridines, since they contain a β-aminovinylcarbonyl fragment, in which the keto group is present in a s-cis-configuration with respect to the double bond.




II, III a R=H; b R=CH$_3$

The synthesis of the condensed heterosystem of type I has been carried out by the reaction of 2-acetyl-2-cyclohexen-1-ones with enaminocarbonyl compounds.

The synthesis of the starting acetylcyclohexenones IIa, b was described in [1-3]. The most convenient method for their preparation is by the hydrogenolysis of 2-acetyl-3-chloro-2-cyclohexene-1-ones [4] by the action of zinc, activated by silver acetate [5]. It was shown [1] that the cross-conjugated endiones II are unstable compounds and readily isomerize into a keto-dienol form III, existing as such virtually without change under normal conditions. However, from the previously effected [3] high yield 1,4-addition reaction of the cyclic β-diketone enolates to ketodienols III, it can be concluded that the tautomeric keto-enol transformation II ⇄ III is reversible, and enamino derivatives of β-dicarbonyl compounds can be added to them.

The reaction of enamino-ketone IVa with endione IIa ⇄ IIIa proceeds even at a temperature of −10°C with the formation of four reaction products. The structure of dienamino-diketone Xa was ascribed to one of them. In the IR spectrum of this compound there are absorption bands of enamino-ketonic (1485, 1600, 1635, 1678 cm$^{-1}$) groups. The UV spectrum contains a long-wave absorption maximum at 405 nm, which is characteristic for systems containing a β-acyl-1,4-dihydropyridine fragment [6].

The two other compounds have identical composition and molecular weight and similar spectral characteristics, wherefrom their isomeric character can be assumed. Analysis of the UV and IR spectra, and also of the $^1$H and $^{13}$C NMR spectra makes it possible to ascribe the structure of α-hydroxytetrahydropyridine VIIa to these compounds. In particular, there

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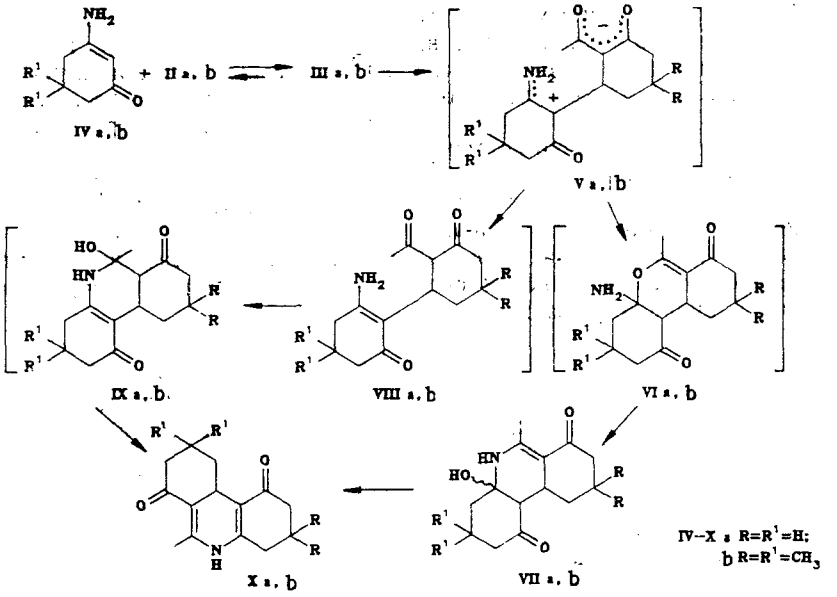
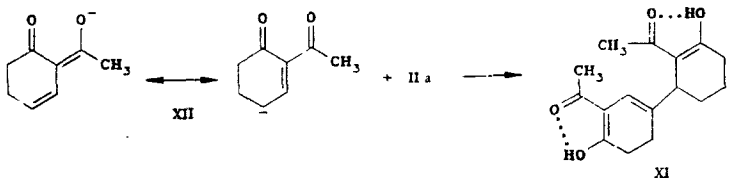
is a maximum at 300 nm appearing in the UV spectra, corresponding to the absorption of the enamino-ketone grouping. In the $^{13}C$ NMR spectra, all the signals can be assigned in accordance with structure VIIa (see the experimental part). The yield of the first of the isomers is 62%, and that of the second is 7%, while the first converts into the second isomer on heating in benzene in the presence of pyrrolidine.

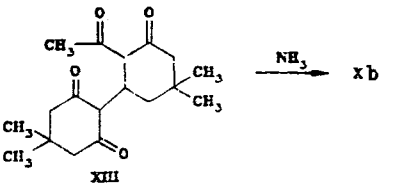



Since the chemical shifts and the character of the proton signals in the $^1H$ NMR spectra at the $C_{(10a)}$ and $C_{(10b)}$ atoms practically coincide, it can be concluded that the stereoisomers differ in the configuration of the hydroxy group at the $C_{(4a)}$ atom, and are thus stereoisomers with cis- and trans-coupling of the rings. A cis-configuration can be ascribed to the first isomer (A), since it converts into the second on heating in the presence of a base. The trans-configuration of ring coupling is ascribed to the second isomer (B), as the more stable one. When heated in toluene in the presence of p-toluenesulfonic acid, the two isomers convert into dienamino-diketone Xa. In consideration of the literature data on the investigation of the reaction mechanism of enamines with α,β-unsaturated carbonyl compounds [7], the course of the reaction can be represented as follows. The initial attack by the enamino-ketone IVa on the electrophilic center of endione IIa leads to the formation of a bipolar ion Va, which can react by two paths: either with the formation of a dihydropyran ring of VIa, or by proton transfer resulting in enamino-triketone VIIIa.

It is also not to be excluded that the formation of the dihydropyran derivative VIa takes place by a synchronous Diels-Alder type reaction, which occurs, as known [8], with α,β-unsaturated ketones and aldehydes reacting with electron-donor dienophiles, also including enamines. The unstable pyran VIa may rearrange into the hydroxy derivative VIIa, dehydration of which gives the dienamino-diketone Xa. By the second path, Xa is formed from the enamino-triketone VIIIa via the intermediate hydroxyaminodiketone IXa.

As well as the above discussed products of the reaction of enamino-ketone and endione, a dimer of the latter was isolated from the reaction mixture, to which the structure XI was ascribed on the basis of the analysis of data obtained by physicochemical methods. In particular, there is a molecular ion (m/z 276) in its mass spectrum, in the $^1H$ NMR spectrum there are two signals of hydroxylic protons of the cis-β-keto-enolic fragments at 14.88 and 15.50 ppm, signals of the allyl (3.28 ppm) olefinic (5.80 ppm) protons and of two acetyl groups (2.02 and 2.08 ppm). The same compound is obtained from the transformation of the endione IIa in the $CH_3ONa/CH_3OH$ system. The formation of the bicyclic compounds XI clearly takes place as a result of a Michael addition of the enolate-anion XII to a molecule present in an endione form:

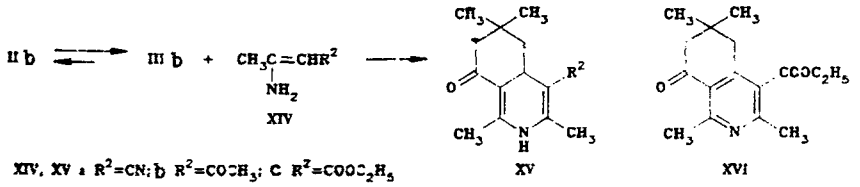




XIII

The reaction of dimedone enamine IVb and endione IIb ⇄ IIIb leads to dienamino-diketone Xb. The intermediate compounds and by-products could not be isolated in this case. It is possible that the reaction proceeds via the formation of intermediate compounds VIIIb and IXb. The structure of the tricyclic product Xb was also confirmed by an alternate synthesis from tetraketone XIII. The bicyclic adduct XIII was obtained by addition of dimedone to 2-acetylcyclohexadienone (IIb ⇄ IIIb) [3].

To obtain a series of derivatives of the new hydrogenated isoquinoline system containing 1,4-dihydropyridine ring with a known s-cis-fixed β-aminovinylcarbonyl fragment, we studied the reaction of 2-acetyl-5,5-dimethyl-2-cyclohexene-1-one (IIb) with acyclic enaminocarbonyl components XIV. Heating the reagents in methanol gave compounds to which structure XV was ascribed on the basis of the spectral and elemental analysis data.



XIV, XV a $R^2$=CN; b $R^2$=$COCH_3$; c $R^2$=$COOC_2H_5$

The character of the change in the value of the bathochromic shift of the long-wave maximum in the electronic absorption spectra of compounds XV depending on the β-substituent $R^2$ is the same as in the case of monocyclic 1,4-dihydropyridines [6]: CN (377 nm) < $COOC_2H_5$ (398 nm), < $COCH_3$ (412 nm).

In the IR spectra of compounds XV there are absorption bands in the stretching vibrations region of the double bonds and the NH groups, which belong to the enaminocarbonyl and enaminonitrile fragments of XV (Table 1).

In the $^1H$ NMR spectra the absorption of protons of all the structural fragments of isoquinolones XV was observed (Table 1). Most characteristic is the presence of a signal of a methine proton in the γ-position of the 1,4-dihydropyridine ring in the form of a doublet of doublets in the 3.49...3.80 ppm region, depending on the nature of the β-substituent, and also a signal of the NH group protons in the form of a singlet in weak fields in the 6.0... 8.0 ppm region (see Table 1).

From the products of the reaction of endione IIb and ethyl β-aminocrotonate XIVc, a pyridine derivative XVI was isolated in low yield, the formation of which can be explained by the ready oxidizability of isoquinolone XVc. The formation of the pyridine derivatives in the reaction of enamino-ketones with α,β-unsaturated ketones has also been previously mentioned in [8].

The method of synthesis that we have developed is an original modification of the Hantzsch reaction, which for the first time enables the transition from cyclic 1,3-diketones and enaminocarbonyl compounds to derivatives of isoquinolone and phenanthridine series with a 1,4-dihydropyridine fragment, which, unlike the corresponding hydrogenated quinolones and acridinediones [9, 10], are not compounds which are readily available by known methods.

It should be noted that the endione system of compounds (II) has a markedly higher reactivity with respect to nucleophilic reagents than the enone system. In particular, acetylcylohexenones II readily enter the reaction with dimedone [3], while 1-acetyl-cyclohexene does not react with it under the same conditions. It is known from the literature data [11] that the introduction of an electron-acceptor substituent in the α-position of an α,β-unsaturated carbonyl compound increases its reactivity, which is probably due to an increase in the positive charge at the electrophilic center [12]. This indicates that the endione system of type II has considerable potential for syntheses. In particular, by including endiones IIa,b in the reaction with cyclic β-diketones [3] and β-ketolactones [13], new types of polycyclic heterocyclic systems can be obtained.

TABLE 1. Spectral Characteristics of Compounds XVa-c

| Compound | UV spectrum, $\lambda_{max}$, nm (log ε) | IR spectrum, $cm^{-1}$ | $^1H$ NMR spectrum ($CDCl_3$), δ, ppm |
|---|---|---|---|
| XVa | 246 (4.09), 377 (3.75) | 1588, 1610, 1657, 1670, 1684, 2200, 3220, 3280 | 0.93 and 1.00 (two s, 6H, 6-$(CH_3)_2$); 2.13 (s, 2H, 7-$CH_2$); 2.00 and 2.16 (s, 3H and 3H, 1,3-2$CH_3$); 1.98 and 1.62 (d.d and t, 1H and 1H, J = 12.2; 4.5 and 12.2 Hz, 5-$CH_2$); 3.49 (d.d, 1H, J = 12.2 and 4.5 Hz, $C_{(4a)}H$); 8.00 (br.s, 1H, NH). |
| XVb | 254 (4.01), 285 (3.75), 412 (3.82) | 1595, 1618, 1635, 1690, 3320 | 0.94 and 1.04 (two s, 6H, 6-$(CH_3)_2$; 2.17 (s, 2H, 7-$CH_2$); 2.02, 2.18 and 2.23 (three s, 9H, 1,3-2$CH_3$ and $COCH_3$); 1.66 and 1.49 (two d.d, 2H; J = 12.5; 4.5; 12.0 and 12.5 Hz; 5-$CH_2$); 3.80 (d.d, 1H, J = 12.0 and 4.6 Hz, $C_{(4a)}H$); 5.9 (br.s, 1H, NH). |
| XVc | 246 (4,09), 263 (3.65), 398 (3.79) | 1582, 1670, 1695, 1727, 3280 | 0.93 and 1.02 (two s, 6H, 6-$(CH_3)_2$); 2.24 and 2.11 (q (AB), 1H and 1H, J = 15.1 Hz, 7-$CH_2$); 2.17 and 2.13 (two s, 6H, 1,3-2$CH_3$); 1.28 (t, 3H, J = 6.7 Hz, $CH_2CH_3$); 1.93 and 1.41 (d.d and t, 1H and 1H. J = 4.0; 12.0 and 12.0 Hz, 5-$CH_2$); 3.73 (d.d, 1H, J = 12.0 and 4.0 Hz, $C_{(4a)}H$); 3.9...4.2 (m, 2H, $OCH_2$); 5.43 (br. s, 1H, NH) |

## EXPERIMENTAL

The IR spectra were recorded on PE-580B and UR-20 spectrophotometers (in mineral oil), the UV spectra on a Specord UV-vis spectrometer (in ethanol) and the NMR spectra on Bruker WH-90 and WH-360 spectrometers. The mass spectra were run on the AEI MS-50 and Varian MAT-311 spectrometers at an energy of ionizing electrons of 70 eV. The course of the reaction was monitored by TLC on Silufol UV-254 plates in a chloroform–hexane–acetone (9:7:2) solvent system. The results of the elemental analysis for C, H, N matched the calculated values.

The spectral characteristics of the synthesized compounds are given in Table 1.

Reaction of 3-Amino-2-cyclohexene-1-one (IVa) with 2-Acetyl-2-cyclohexen-1-one (IIa ⇄ IIIa). A mixture of compounds obtained after the reduction of 4 g of 3-chloro-2-acetyl-2-cyclohexen-1-one [3] was dissolved in 20 ml of methanol, 1,3 g of enamino-ketone IVa was added, and the mixture was allowed to stand for 24 h at −10°C. The solvent was evaporated under vacuum, and the residue was partitioned on a chromatographic column (silica gel L 100/400), using an ether-hexane (1:2, 1:1, 2:1) mixture as eluent. The following compounds were obtained:

6-Methyl-1,2,3,4,5,7,8,9,10,10a-decahydrophenanthridine-1,7-dione (Xa) (0.09 g; 3%), mp 225-228°C (from ether). UV spectrum (in methanol), $\lambda_{max}$ (log ε): 206 (3.65), 245 (3.88), 252 (3.90), 272 (3.60), 405 nm (3.70). Compound Xa was also obtained by boiling 0.04 g of compound VIIa (isomer A) in 20 ml of toluene in the presence of p-toluenesulfonic acid for 30 min, followed by cooling. Yield, 0.03 g (81%).

6-Methyl-4a-hydroxy-1,2,3,4,4a,5,7,8,9,10,10a,10b-dodecaphenanthridine-1,7-dione (VIIa $C_{14}H_{19}NO_3$, isomer A) (1.81 g; 62%), mp 170-172 C (from ether). $^1H$ NMR spectrum ($CDCl_3$): 2.35 (s, 3H, 6-$CH_3$), 2.55 (s, 1H, $C_{(10b)}$ H), 3.91 (m, 1H, $C_{(10a)}$ H), 4.46 (br.s, NH), 4.95 (br.s, OH), 1.1-2.3 ppm (m, 12H, 6$CH_2$). $^{13}C$ NMR spectrum ($CD_3OD$): 210.29 ($C_{(1)}$), 194.35 ($C_{(7)}$), 164.55 ($C_{(6)}$), 108.14 ($C_{(4a)}$), 83.14 ($C_{(6a)}$), 56.84 ($C_{(10b)}$), 37.23 ($C_{(2)}$), 36.78 ($C_{(8)}$), 32.35 ($C_{(10a)}$), 31.40 (6-$CH_3$), 28.61, 26.34, 23.04, 20.30 ($C_{(3)}$, $C_{(4)}$, $C_{(9)}$, $C_{(10)}$). Mass spectrum (m/z): 249 ($M^+$), 231 $(M - H_2O)^+$. The hydrochloride, mp 150-170°C (from methanol) was obtained by passing hydrogen chloride through a solution of compound VIIa in methanol.

6-Methyl-4a-hydroxy-1,2,3,4,4a,5,7,8,9,10,10a,10b-dodecaphenanthridine-1,7-dione (VIIa, isomer B), (0.20 g; 7%), mp 213-215°C (from ether). IR spectrum ($CHCl_3$): 1225, 1390, 1485, 1580, 1612, 1690, 2950, 3000, 3430 $cm^{-1}$. $^1H$ NMR spectrum ($CDCl_3$): 2.17 (s, 3H, 6-$CH_3$), 2.56 (s, 1H, $C_{(10b)}$ H), 3.86 (br.s, 1H, $C_{(10a)}$H), 5.16 (br. s, 1H, NH), 6.03 (br.s, 1H, OH) 1.1-2.4 ppm (m, 12H, 6-$CH_2$). Mass spectrum (m/z): 249 ($M^+$), 231 $(M - H_2O)^+$.

2-Acetyl-4-(2'-acetyl-1'-hydroxy-2-cyclohexenyl)1,3-cyclohexadien-1-ol (XI, $C_{16}H_{20}O_4$), (0.11 g; 4%), mp 130-132°C (from ether), IR spectrum (KBr): 1410, 1610, 2600, 3400 $cm^{-1}$.

$^1$H NMR spectrum ($CDCl_3$): 1.70 (m, 4H, 2-$CH_2$), 2.02 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.2-2.6 (m, 6H, 3-$CH_2$), 3.28 (s, 1H, $C_{(3)}H$), $W_{1/2}$ = 10 Hz, 5.80 (s, 1H, $C_{(3)}H$), 14.88 and 15.50 (two s, 1H, OH). Mass spectrum (m/z): 276 ($M^+$).

3,3,6,9,9-Pentamethyl-1,2,3,4,5,7,8,9,10,10a-decahydrophenanthridine-1,7-dione (Xb). A mixture of compounds obtained by reduction of 2 g of 3-chloro-5,5-dimethyl-2-acetyl-2-cyclohexen-1-one [3] and 0.5 g of enamino ketone IVb was allowed to stand for 3 days at room temperature in 30 ml of ethanol. It was then boiled for 1 h, the solvent was evaporated under vacuum, and the residue was chromatographed on a column as described in the preceding experiment. Yield, 0.77 g (75%) of compound Xb, the characteristics of which corresponded to a compound synthesized from tetraketone XIII by the action on it of ammonia [3].

Isomerization of VIIa (A) to VIIa (B). A solution of 0.2 g of isomer VIIa (A) and 0.5 g of pyrrolidine in 40 ml of toluene was boiled for 1 h 30 min. The mixture was cooled to room temperature, the crystals that separated out were filtered off and washed with 2 ml of ether. Yield, 0.12 g (60%) of isomer VIIa (B).

1,3,6,6-Tetramethyl-4-cyano-2,4a,5,6,7,8-hexahydroisoquinol-8-one (XVa, $C_{14}H_{18}N_2O$). A mixture of 50 ml of methanol, 3.3 g (20 mmoles) of dienonol IIb (IIIb) obtained according to the method in [3], and 1.6 g (20 mmoles) of β-aminocrotonitrile XIVa was boiled for 3 h. The mixture was filtered off, the filtrate was evaporated, and the residue was dissolved in 50 ml of ethanol. The solution was concentrated to 20-25 ml volume, and chromatographed in four portions on 220 × 280 mm preparative glass plates on a nonstationary layer of silica gel L 40/100 in a chloroform-hexane-acetone (9:7:2) system. yellow-colored strips were collected from the plates and eluted with 120 ml of ethanol. The eluates were filtered, evaporated, and the residue was treated with ether. Yellow crystals were obtained, mp 135-137°C (from ethanol). Yield, 0.9 g (20%). Mass spectrum (m/z): 230 ($M^+$).

1,3,6,6-Tetramethyl-4-acetyl-2,4a,5,6,7,8-hexahydroisoquinol-8-one (XVb, $C_{15}H_{21}NO_2$). In a similar manner, from 3.3 g (20 mmoles) of dienonol IIb (IIIb) and 2.0 g (20 mmoles) of acetylacetone imine XIVb, 1.23 g (25%) of yellow crystals of compound XVb were obtained, mp 123-124°C (from ethanol). Mass spectrum (m/z): 247 ($M^+$).

1,3,6,6-Tetramethyl-4-carbethoxy-2,4a,5,6,7,8-hexahydroisoquinol-8-one (XVc, $C_{16}H_{23}NO_3$) and 1,3,6,6-Tetramethyl-4-carbethoxy-5,6,7,8-tetrahydroisoquinol-8-one (XVI , $C_{16}H_{23}NO_3$). In a similar manner, from 3.3 g (20 mmoles) of dienonol IIb (IIIb) and 2.6 g (20 mmoles) of ethyl β-aminocrotonate XIVb, 3.95 g (72%) of compound XVc was obtained, mp 105-107°C (from ethanol). Mass spectrum (m/z) 277 ($M^+$). In addition, 0.17 g (3%) of compound XVI, mp 78-82°C (from ether) was also isolated. Mass spectrum (m/z): 275 ($M^+$).

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