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# N-3-OXOALKYLAMIDES AND -THIOAMIDES IN SYNTHESIS OF HETEROCYCLIC COMPOUNDS. 4.* SYNTHESIS OF HYDROGENATED DERIVATIVES OF QUINOLINE AND ISOQUINOLINE BASED ON N-3-OXOALKYLAMIDES

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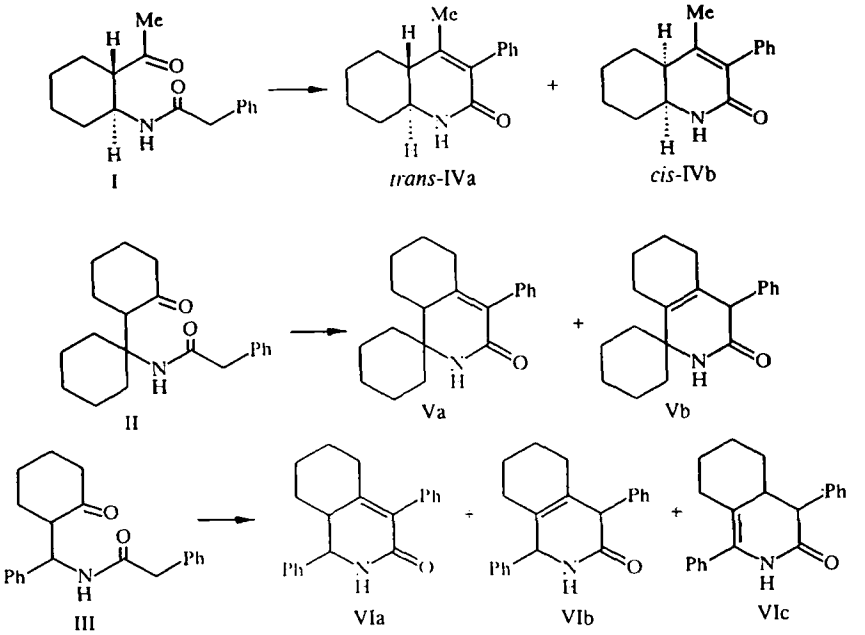
*Hydrogenated derivatives of quinoline and isoquinoline were obtained by cyclization of N-3-oxoalkylamides with bases.*

N-(3-Oxoalkyl)-substituted arylacetamides are cyclized into 3-aryl-5,6-dihydropyridin-2(1H)-ones with bases with high yields, and their dehydrogenation yields 3-aryl-2-pyridones [2, 3]. The possibility of synthesizing 3-aryl-5,6-dihydropyridin-2(1H)-ones annelated with carbocycles has not been investigated. Analogs of N-3-oxoalkylamides containing cyclohexane fragments were prepared for this purpose: compound I by acylation of the corresponding aminoketone, compounds II and III by the reaction of 1,3-chloroketones with nitriles in the presence of $SnCl_4$ by the methods in [2, 4].

The studies showed that *trans*-N-(2-acetylcyclohexyl)phenylacetamide (I) is cyclized into an equilibrium mixture of *cis*- and *trans*-isomers of 4*a*,5,6,7,8,8*a*-hexahydroquinolin-2(1H)-one (IVa, b) in a 10% solution of KOH in ethyl alcohol at the boiling point, and compounds II and III are cyclized into a mixture of hydrogenated derivatives of isoquinolin-3(2H)-one Va, b and VIa-c, which differ due to the position of the double bond in the heterocycle.




*See [1] for Communication 3.

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TABLE 1. Properties of the Synthesized Compounds

| Compound | Empirical formula | Found, %/ Calculated, % | | mp, °C | IR spectrum, $\nu$, $cm^{-1}$ | | | Reaction time, h | Yield, % |
|---|---|---|---|---|---|---|---|---|---|
| | | C | H | | NH | CO | CONH | | |
| I | $C_{16}H_{21}NO_2$ | 74,07 / 74,10 | 7,94 / 8,16 | 136...137*[3] | 3410 | 1710 | 1680 | —*[7] | 40 |
| II | $C_{20}H_{27}NO_2$ | 76,75 / 76,65 | 8,84 / 8,68 | 118...119*[4] | 3420 | 1710 | 1670 | —*[7] | 23 |
| III* | $C_{21}H_{23}NO_2$ | 78,77 / 78,47 | 7,03 / 7,21 | 152...153*[4] | 3420 | 1710 | 1680 | —*[7] | 20 |
| IV* | $C_{16}H_{19}NO$ | 79,86 / 79,63 | 7,99 / 7,94 | 159...160*[5] | 3400 | — | 1655 | 1 | 84 |
| Va, b | $C_{20}H_{25}NO$ | 81,66 / 81,31 | 8,48 / 8,53 | 207...208*[6] | 3395 | — | 1660 | 0,75 | 91 |
| VIa-c | $C_{21}H_{21}NO$ | 83,51 / 83,13 | 7,14 / 6,98 | 123...125*[4] | 3385 | — | 1670 | 2 | 87 |
| VIII | $C_{18}H_{17}NO$ | 82,13 / 82,10 | 6,52 / 6,51 | 175...177*[6] | 3400 | — | 1690 | 2 | 29 |
| XI | $C_{16}H_{13}NO$ | 81,60 / 81,68 | 5,63 / 5,57 | 255...256*[4] | 3385 | — | 1655 | 2 | 36 |
| XII | $C_{21}H_{19}NO$ | 83,59 / 83,69 | 6,35 / 6,35 | 212...213*[6] | 3380 | — | 1645 | 2 | 57 |

*Mixture of *erythro*- and *threo*-isomers.

*[2]Mixture of *cis*- and *trans*-isomers.

*[3]From heptane.

*[4]Benzene–hexane.

*[5]Hexane.

*[6]Ethanol.

*[7]See [2, 4].

For α-β-unsaturated carboxylate ions, ethers, and ketones, equilibrium between both unsaturated forms is essentially a function of the position and nature of the substituents in the propylene fragment [5, 6]. The possibility of isomerization of 5,6-dihydropyridin-2(1H)-ones into 3,6-dihydropyridin-2(1H)-ones was also mentioned in [7]. The exocyclic position of the double bond with respect to the carbocycle in compounds Va and VIa evidently strains the bicyclic system so that the structures become less stable than in alkyl-substituted 5,6-dihydropyridin-2(1H)-ones [2], which shifts the equilibrium toward β,γ-unsaturated cyclic lactones V and VIb. The presence of a mobile hydrogen atom in position 6 of the heterocycle makes isomerization of compound VIb into VIc possible.

To study the possibility of isomerization of 3-aryl-5,6-dihydropyridin-2(1H)-ones [2, 3] with bases, 4-methyl-3,6-diphenyl-5,6-dihydropyridin-2(1H)-one (VII) was heated in a 0.7% solution of KOH in DMSO. After 2 h, 4-methyl-3,6-diphenyl-3,4-dihydropyridin-2(1H)-one (VIII) and 4-methyl-3,6-diphenylpyridin-2(1H)-one were separated from the reaction mixture with yields of 29 and 24%, respectively.

3,4-Dihydropyridin-2(1H)-one VII is oxidized into pyridone IX by atmospheric oxygen and this perhaps includes the stage of formation of dianion X, as reported in [8].

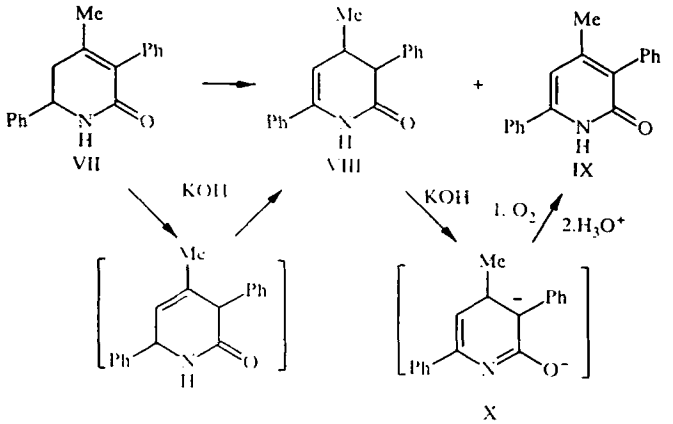

TABLE 2. NMR Spectra of the Synthesized Compounds

| Compound | Chemical shifts (δ, ppm) and SSCC, Hz |
|---|---|
| I | 7.35...7.19 (5H, m, Ph); 5.28 (1H, br. d, $^3J_{HNH}$ = 8.8, NH); 4.00 (1H, m, $^3J_{ac}$ = 4.0, $^3J_{aa}$ = $^3J_{ac}$ = 11.0, $^3J_{HNH}$ = 8.8, CHNH); 3.50 (2H, s, $CH_2Ph$); 2.23 (1H, m, $^3J_{ac}$ = 4.0, $^3J_{aa}$ = $^3J_{ac}$ = 11.0, CHCO); 2.07 (3H, s, $CH_3$); 1.97...1.08 (8H, m, $(-CH_2-)_4$) |
| II | 7.24 (5H, m, Ph); 5.39 (1H, br. s, NH); 3.42 (2H, s, $CH_2Ph$); 3.22 (1H, d. d, $^3J_{aa}$ = 15.0, $^3J_{ac}$ = 6.0, CHCO); 2.10...1.20 (18H, m, $(-CH_2-)_4$, $(-CH_2-)_5$) |
| III* | 7.38...7.14 (10H, m, 2Ph); 6.82 and 6.86 (1H, br. s, NH); 5.19 and 5.16 (1H, d, $^3J_{NCH,Ha}$ = 12.3 and d, $^3J_{NCH,Ha}$ = 10.2, CHN); 3.54 and 3.58 (2H, s, $CH_2Ph$); 2.86 and 2.94 (1H, m, $^3J_{NCH,Ha}$ = $^3J_{aa}$ = 12.3, $^3J_{ac}$ = 6.0 and m $^3J_{NCH,Ha}$ = $^3J_{aa}$ = 10.2, $^3J_{ac}$ = 4.7, CHCO); 2.33...1.43 (8H, m, $(-CH_2-)_4$) |
| IVa*2 | 7.33...7.07 (5H, m, Ph); 5.88 (1H, br. s, NH); 3.18 (1H, m, $^3J_{aa}$ = $^3J_{aa}$ = 11.0, $^3J_{ac}$ = 4.0, 8a-H); 2.20 (1H, m, $^3J_{aa}$ = $^3J_{aa}$ = 11.0, $^3J_{ac}$ = 4.0, 4a-H); 1.67 (3H, s, $CH_3$); 2.06...1.15 (8H, m, $(-CH_2-)_4$) |
| IVb*2 | 7.33...7.07 (5H, m, Ph); 5.58 (1H, br. s, NH); 3.78 (1H, m, 8a-H); 2.02 (1H, m, 4a-H); 1.63 (3H, s, $CH_3$), 2.06...1.15 (8H, m, $(-CH_2-)_4$) |
| Va*3 | 7.37...7.18 (5H, m, Ph); 6.57(1H, br. s NH); 2.45 (1H, d. d $^3J_{aa}$ = 12.0, $^3J_{ac}$ = 4.0, 8a-H); 2.30...1.27 (18H, m, $(-CH_2-)_4$, $(-CH_2-)_5$) |
| Vb*3 | 7.37...7.18 (5H, m, Ph); 6.50(1H, br. s, NH); 3.98 (1H, s, CHPh); 2.30...1.27 (18H, m, $(-CH_2-)_4$, $(-CH_2-)_5$) |
| VIa*4 | 7.40...7.19 (10H, m, 1-Ph, 4-Ph); 6.18 (1H, s, NH); 4.85 (1H, br. s, 1-H); 2.54 (1H, m, 8a-H); 1.86...1.25 (8H, m, $(-CH_2-)_4$) |
| VIb*4 | 7.40...7.19 (10H, m, 1-Ph, 4-Ph); 5.98 (1H, s, NH); 4.98 (1H, br. s, 1-H); 3.96 (1H, m, 4-H), 1.86...1.25 (8H, m, $(-CH_2-)_4$) |
| VIc*4 | 7.40...7.19 (10H, m, 2Ph); 5.57 (1H, s, NH); 4.34 (1H, d, $^3J_{aa}$ = 11.1, 4-H); 2.58 (1H, m, 4a-H); 1.86...1.25 (8H, m, $(-CH_2-)_4$) |
| VIII | 7.50...7.34 (10H, m, 2Ph); 5.42 (1H, d.d, $^3J_{4,5}$ = 3.8, $^4J_{HNH}$ = 1.8, 5-H); 3.45 (1H, d, $^3J_{3,4}$ = 9.8, 3-H); 2.94 (1H, m, $^3J_{4,5}$ = 3.8, $^3J_{H,CH3}$ = 7.0, $^3J_{3,4}$ = 9.8, 4-H); 1.12 (3H, d, $^3J_{H,CH3}$ = 7.0, 4-$CH_3$) |
| XI | 11.13 (1H, s, NH); 7.77 (1H, d. d $^3J_{8,9}$ = 8.6, $^4J_{8,10}$ = 1.7, 8-H); 7.55...7.22 (8H, m, 5-H, 6-H, 7-H, Ph); 2.38 (3H, s, 4-$CH_3$) |
| XII | 10.76 (1H, br. s, NH); 7.45...7.31 (10H, m, 2Ph); 2.55...2.52 (4H, m, 2(5-H, 8-H)); 1.69...1.64 (4H, m, 2(6-H, 7-H)) |

*Mixture of *erythro*- and *threo*-isomers; ratio of integral signal intensities of 1:2.7; the chemical shifts and SSCC for minor and predominant isomers are reported.

*2Ratio of integral intensities in a 1:4 mixture of IVa:IVb.

*3Ratio of integral signal intensities in a 2.5:1 mixture of Va:Vb.

*4Ratio of integral signal intensities in a 1:2:1.25 mixture of VIa:VIb:VIc.

The signals of the carbon nuclei in the double bond conjugated with an amide group (155.0-150.5 and 140.9-135.8 ppm), signals of nuclei of $sp^2$-hybridized carbon atoms in position 4 and 5 (141.2-139.1, 139.6 ppm) and 5 and 6 (138.2 and 135.8 ppm) of the heterocycle are the most characteristic signals in the $^{13}C$ NMR spectra of compounds IV-VI (Table 3).

Dehydrogenation of a mixture of isomers IVa, b and VIIa-c in DMSO in the presence of KOH in the first case results in the formation of quinolin-2(1H)-one XI with a yield of 56% and in the second case, 1,4-diphenyl-5,6,7,8-tetrahydroisoquinolin-3(2H)-one (XII) with a yield of 35%.

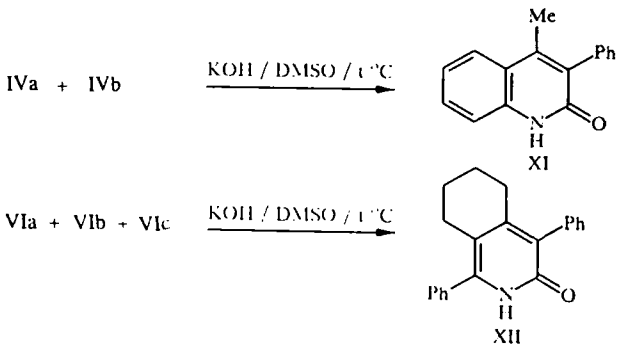

TABLE 3. Data from the $^{13}C$ NMR Spectra of the Synthesized Compounds ($\delta$, ppm, $CDCl_3$)

| Compound | CONH | C–C (C=O) | Ph | Other signals |
|---|---|---|---|---|
| I | 169,9 | (210,3) | 134,2, 128,9, 128,9, 128,5, 128,5, 126,8 | 57,4, 49,2, 43,4, 32,0, 28,2, 26,5, 24,3, 24,2 |
| II | 169,8 | (211,8) | 135,2, 129,0, 129,0, 128,5, 128,5, 126,8 | 57,2, 55,3, 44,9, 43,5, 30,8, 30,1, 29,0, 28,0, 25,4, 25,2, 21,1, 21,1 |
| III | 170,2 | (212,4) | 140,7, 134,7, 129,0, 129,0, 128,6, 128,6, 128,0, 128,0, 127,2, 127,0, 126,4, 126,4 | 55,4, 53,3, 43,7, 42,1, 32,1, 27,9, 24,0 |
| IVa | 166,8 | 152,0, 136,1 | 129,9, 127,4, 127,4, 127,4, 127,4, 126,5 | 55,0, 48,6, 44,2, 42,3, 31,8, 29,5, 27,1, 25,7, 25,3, 24,4, 23,8, 19,7, 19,5, 17,0 |
| IVb | 166,1 | 150,1, 135,7 | 129,9, 127,4, 127,4, 127,4, 127,4, 126,5 | |
| Va | 165,9 | 155,3, 136,1 | 130,6, 128,3, 128,3, 128,3, 128,3, 127,4 | 58,6, 53,7, 53,0, 49,2, 38,3, 37,2, 35,6, 34,4, 34,2, 30,3, 29,6, 29,0, 26,8, 25,9, 25,3, 25,3, 23,7, 23,0, 22,4, 22,0, 21,8, 21,6 |
| Vb | 170,5 | 138,9, 133,2 | 130,6, 128,9, 128,9, 128,9, 128,9, 127,4 | |
| VIa | 166,6 | 151,9; 135,7 | 130,2...126,7 | 62,6, 62,4, 61,7, 52,4, 51,5, 44,1, 31,3, 31,2, 28,0, 27,9, 26,7, 26,7, 26,0, 24,6, 22,5, 22,4, 22,3, 22,2 |
| VIb | 170,2 | 140,9, 138,9 | | |
| VIc | 170,2 | 141,2, 139,6 | | |

The possibility of obtaining hydrogenated derivatives of quinoline and isoquinoline from N-3-oxoalkylamides with their subsequent transformation into quinolin-2(1H)-ones and 5,6,7,8-tetrahydroisoquinolin-3(2H)-ones and the possibility of converting 5,6-dihydropyridin-2(1H)-ones into their isomeric 3,4-dihydropyridin-2(1H)-ones were thus demonstrated. In view of the broad possibilities of different methods of preparation of the starting N-3-oxoalkylamides [4, 9-17] and the simplicity of conducting the experiment, we can conclude that the proposed approach to synthesis of hydrogenated derivatives of quinoline and isoquinoline is of preparative interest.

## EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 spectrometer in solutions of $CHCl_3$, and the PMR spectra were recorded on Bruker-AC 200 P, AM-360, and Tesla BS-587 (80 MHz) instruments in $CDCl_3$. HMDS was the internal standard. The $^{13}C$ NMR spectra were made on Bruker AM-360 (90.5 MHz) and Tesla BS-587 (20 MHz) spectrometers at room temperature in the pulsed accumulation mode with subsequent Fourier transformation in complete decoupling of protons. TMS was the internal standard. The evolution of the reaction and purity of the compounds obtained were controlled by TLC on Silufol UV-254 plates with development with iodine vapors and UV light.

N-(2-Acetylcyclohexyl)phenylacetamide (I), N-[1-(2-oxocyclohexyl)cyclohexyl]phenylacetamide (II), and N-[phenyl(2-oxocyclohexyl)methyl]phenylacetamide (III) (mixture of *erythro*- and *threo*-isomers) were obtained by the method in [2, 4].

4-Methyl-4*a*,5,6,7,8,8*a*-hexahydroquinolin-2(1H)-one (IV) (mixture of *cis*- and *trans*-isomers); 4′-phenyl-1′,5′,6′,7′,8′,8′*a*-hexahydro(spirocyclohexane-1,1′-isoquinolin-3′(2′H)-one (Va) and 1′,4′,5′,6′,7′,8′-hexahydro(spirocyclohexane-1,1′-isoquinolin-3′(2′H)-one (Vb) (mixture of isomers); 1,4-diphenyl-1,5,6,7,8,8*a*-hexahydroisoquinolin-3(2H)-one (VIa), 1,4-diphenyl-1,4,5,6,7,8*a*-hexahydroisoquinolin-3(2H)-one (VIb), 1,4-diphenyl-4,4*a*,5,6,7,8*a*-hexahydroisoquinolin-3(2H)-one (VIc) (mixture of isomers); 4-methyl-3,6-diphenyl-5,6-dihydropyridin-2(1H)-one (VII) were obtained by the method in [2].

**4-Methyl-3,6-diphenyl-3,4-dihydro-2(1H)-one (VIII) and 4-Methyl-3,6-diphenyl-2-pyridone (IX).** A solution of 0.368 g (1.39 mmole) of compound VII and 0.1 g of KOH in 15 ml of DMSO was heated for 2 h. The reaction mixture was poured into 50 ml of water and the sediment was filtered off. The filtrate was extracted with chloroform (3 × 30 ml), 10 ml of hexane was added to the extract and it was washed with water, the solvent was distilled off, and the residue was combined with the sediment. The mixture of compounds VIII and IX was purified by column chromatography on silica gel (chloroform –

ethyl acetate, 95:5), yielding 0.106 g (29%) of compound VII and 0.089 (24%) of compound IX, mp = 225°C. The IR spectrum of compound IX was identical to the sample previously obtained in [2]. Mixing the samples did not depress the melting point.

**4-Methyl-3-phenylquinolin-2(1H)-one (XI)** and **1,4-diphenyl-5,6,7,8-tetrahydroisoquinolin-3(2H)-one (XII)** were prepared similar to compounds VIII and IX. Chloroform–ethyl acetate eluent, 2:1.

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