# NEW DIRECTIONS IN THE CONDENSATION REACTIONS OF CYCLOHEXANONE AND ITS MANNICH BASE

O. V. Fedotova, E. V. Kapitonova, P. V. Reshetov, and D. A. Tsimbalenko

An unusual direction was found in the condensation of cyclohexanone and its Mannich base, leading to the formation of previously unknown polycyclic spirohydrochromans. The structure of the compounds was confirmed by ^{13}C NMR and mass spectrometry.

Carbonyl-containing spirohydrochromans have become available as a result of the discovery of the ability of α,β-unsaturated ketones to enter into dimerization of the 1,4-addition type. Its characteristics and mechanism were discussed in detail in the review [1]. In [2–4] it was shown that the Mannich bases of cyclic ketones can act as synthons during their thermal decomposition, vacuum distillation [5–7], steam distillation [8], or acetolysis in acetic anhydride in the presence of sodium acetate [9, 10]. In view of the prospects concerning the scientific and applied aspects of compounds of this series we continued to develop optimum conditions of synthesis and investigate features of the transformations with regard to the existence of several reaction centers in the molecule.

The methods that we proposed for the benzannellated analog [8] were used for the production of 3,4,5,6,7,8-hexahydrospiro[chromene-2,1'-cyclohexan]-2-one (I). The substrates were N,N-dimethylaminomethylcyclohexanone (II), its hydrochloride (II·HCl), and its methiodide (II·CH$_3$I):
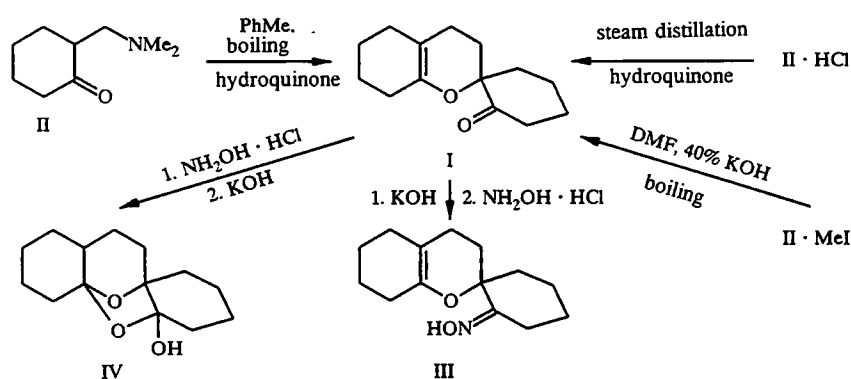

The yield of the product amounted to 57–64%, depending on the conditions [boiling the base (II) in toluene in the presence of hydroquinone, boiling the methiodide of (II) in DMFA with 40% potassium hydroxide, or steam distillation of the hydrochloride of (II)].

Compound (I) was oximated in order to confirm the presence of the C=O group in the molecule. Here it was established that the direction of the reaction was determined by the order in which the reagents (NH$_2$OH·HCl, KOH) were added. If hydroxylamine hydrochloride is added to a water–alcohol alkaline solution of the dimer of (I), the oxime (III) is formed. Addition of the reagents in the reverse order leads to the formation of 2,16-dioxatetracyclo[7.6.1.0^{3,8}.0^{1,11}]hexadecan-3-ol (IV) with a 64% yield.

If the base (II) is boiled in toluene in the absence of hydroquinone, the reaction takes place differently. During vacuum distillation of the reaction mixture I (28%) at 190-195°C (6.6 GPa) we isolated a viscous oil, identified as spiro{2-oxatetra-cyclo[7.6.1.0^{1,11}.0^{3,8}]hexadec-3(8)-ene-16,1'-cyclohexan}-2'-one (V). It can be supposed that its formation includes a stage with hydrolysis of the intermediately formed dimer of (I) under the conditions of base catalysis followed by dehydration of the hydroxy-1,6-diketone (VI) to the α,β-unsaturated ketone (VII). The latter then probably enters into Michael condensation with cyclohexanone — the product of the familiar retro-Mannich reaction under the influence of heat (110°C) [12, 13]. Subsequent cyclization of compound (VII) and dehydration lead to the spiran (V) with a 46% yield.
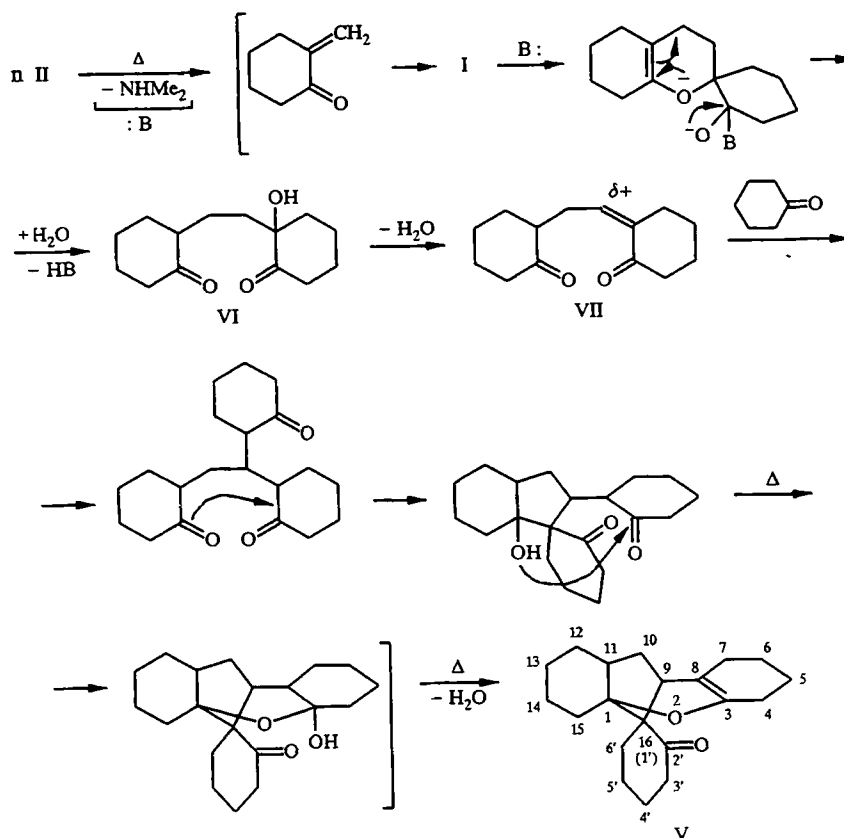
Compounds containing a spirohydrochroman fragment often accompany 1,5-diketones during their synthesis by diketone condensation or are isolated as the main products in this reaction [14, 15].

We discovered an unusual condensation of cyclohexanone with paraform in the presence of potassium methoxide, resulting in the formation of 16-hydroxy-15,22-dioxahexacyclo[12.7.1.0^{1,6}.0^{8,21}.0^{9,14}.0^{16,21}]docosane (VIII) with a yield of 50%. Transformations of such a type had not previously been observed in cyclohexanone.
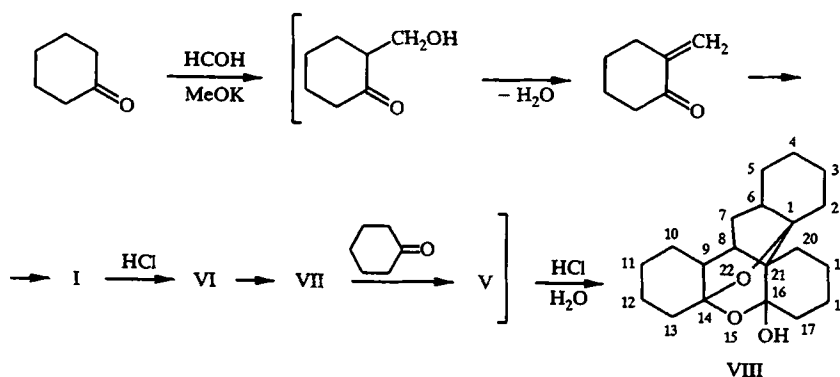
TABLE 1. ^{13}C NMR Chemical Shifts (δ, ppm) of Compounds (V, VIII) (deuterochloroform, 50 MHz)

Atom/Compound	$C_{(1)}$	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$
V	81,92	—	142,44	26,80	23,02	36,37
VIII	78,78	35,38	21,23	26,11	27,69	39,48

Atom/Compound	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	$C_{(10)}$	$C_{(11)}$
V	28,88	103,67	46,27	31,90	39,62
VIII	31,92	39,35	40,86	28,63	31,35

Atom/Compound	$C_{(12)}$	$C_{(13)}$	$C_{(14)}$	$C_{(15)}$	$C_{(16)}$
V	27,68	25,87	21,45	35,38	51,60
VIII	23,05	33,66	98,22	—	96,00

Atom/Compound	$C_{(2')}$ / $C_{(17)}$	$C_{(3')}$ / $C_{(18)}$	$C_{(4')}$ / $C_{(19)}$	$C_{(5')}$ /$C_{(20)}$	$C_{(6')}$ / $C_{(21)}$
V	203,46	30,36	27,21	20,88	36,28
VIII	31,35	25,49	21,07	28,94	37,50

TABLE 2. Normalized Mass Spectrum of Spiro{2-oxatetracyclo-[7.6.1.0^{1,11}.0^{3,8}]-hexadec-3(8)-ene-16,1'-cyclohexan}-2'-one (V)

m/z	Intensity, %	m/z	Intensity, %	m/z	Intensity, %
67	18,43	149	14,50	211	12,87
77	12,87	161	15,38	225	11,12
79	20,17	162	16,14	239	25,52
81	17,56	173	29,44	253	10,36
91	27,26	184	12,54	254	11,78
93	11,78	189	10,03	282	23,23
95	10,36	190	13,74	300	100,00
131	12,00	202	20,94	301	20,28
147	11,67	203	17,45		

It can be supposed that semiacetalization of the probable intermediate compound (V) takes place during the treatment of the reaction mixture with HCl to pH 3.

The structure of the synthesized compounds (III-V, VIII) agrees well with the results from elemental analysis and also with the data form the IR and ^{13}C NMR spectra (Table 1) and mass-spectrometric analysis (Table 2). The signals of the key atoms determining the structure of the spiran (V) and the semiacetal (VIII) were then examined. Thus, the ^{13}C NMR spectrum of compound (V) (Table 1) contains the signals of 20 carbon atoms. The presence of five quaternary carbon atoms was established by the off-resonance method. Of these the signals at 203.46, 81.92, and 51.60 ppm can be assigned to the $C_{(2')}$ (the carbon of the carbonyl group), $C_{(1)}$, and $C_{(16)}$ atoms respectively. The absorption of the two remaining quaternary atoms, observed at 142.44 and 103.67 ppm, is typical of the carbon atoms of a C=C multiple bond conjugated with an oxygen atom and, consequently, relating to the $C_{(3)}$ and $C_{(8)}$ atoms. The two doublets in the off-resonance spectrum, observed at 46.27 and 39.62 ppm, can be assigned to the tertiary carbon atoms $C_{(9)}$ and $C_{(11)}$ respectively. The remaining signals, appearing in the off-resonance spectrum in the form of triplets (methyl groups), were assigned on the basis of examination of the electronic and steric effects in the spiran (V).

The data from ^{13}C NMR spectroscopy correlate with the results of mass-spectrometric analysis for compound (V), according to which the mass of the molecular ion formed by electron impact is 301, including the ^{13}C isotope (see [16]). The sequence of the formation of the fragment ions is shown in Table 2.

The structural changes occurring during the transition from the spiran (V) to the semiacetal (VIII) are reflected in the ^{13}C NMR spectra. Thus, the signal of the carbonyl group in the region of 203.46 ppm disappears, and in place of it a signal for $C_{(16)}$ appears at 96.00 ppm, characteristic of the C atom of the semiacetal group. The presence of a functional group at the $C_{(16)}$ atom has a significant effect on the absorption of the $C_{(21)}$ and $C_{(17)}$ atoms attached to it — the signals of these atoms are shifted upfield and appear at 37.50 and 31.35 ppm respectively. The appearance of the axially oriented oxygen of the semiacetal group at the γ position to the $C_{(20)}$ atom also shifts this signal upfield (28.94 ppm). In the spiran (V), where there is no axially oriented group at the γ position to the $C_{(6')}$ atom, the chemical shift is 36.28 ppm. The formation of the oxygen bridge leads to the disappearance of the double bond and, consequently, the signals at 142.44 and 103.67 ppm, belonging to the atoms of this group. Instead, in the spectrum of compound (VIII) there is a signal at 98.22 ppm, characteristic of a carbon atom entering into the acetal functional group and assigned to the $C_{(14)}$ atom. The $C_{(9)}$ atom of the semiacetal (VIII) with sp^3 hybridization corresponds to the sp^2-hybridized $C_{(8)}$ atom of compound (V), and this gives rise to a considerable upfield shift of its signal in the C^{13} NMR spectrum — it is observed at 40.86 ppm. The structural changes that occur have hardly any steric or electronic effects on the $C_{(7)}$, $C_{(3)}$, and $C_{(1)}$ atoms compared with the analogous signals in the spiran (V), and their resonance signals in the spectra of the compounds are practically identical.

In the IR spectrum of the oxime (III), in contrast to the initial spirohydrochroman (I), the band for the C=O stretching vibrations (1720 cm^{-1}) is absent, and a band for the C=N group appears at 1637 cm^{-1}. The C−O−C (1235-1035 cm^{-1}) and C=C (1680 cm^{-1}) absorption bands do not change their position in the spectra of the compared samples. The spectra of compounds (I, IV) agree with the published data [11].

EXPERIMENTAL

The ^{13}C NMR spectra were recorded on a Varian FT-80A Fourier spectrometer at 30°C in deuterochloroform. The reactions and the purity of the products were monitored by TLC on Silufol 254 plates (4:1:1 hexane−ether−acetone). The mass spectrum was obtained on a Kratos MS-25RT instrument at 70 eV.

3,4,5,6,7,8-Hexahydrospiro[chromene-2,1'-cyclohexan]-2-one (I). A. The compound was obtained according to [11] from N,N-dimethylaminomethylcyclohexanone (II) with a 57% yield; bp 135-137°C at 8 GPa, R_f 0.76, n_D^{20} 1.5138, which corresponds to data in [11].

B. A 5.94-g sample (0.02 mole) of the methiodide (II) was heated for 8 h in 40 ml of dimethylformamide with 20 ml of a 40% solution of potassium hydroxide. The organic layer was separated, washed to a neutral reaction with water, and dried with magnesium sulfate. After vacuum distillation 1.41 g (64%) of compound (I) was obtained.

C. A 10-g sample (0.05 mole) of the hydrochloride (II) was dissolved in 300 ml of water, 0.1 g of hydroquinone was added, and the product was distilled with steam. The distillate was extracted with ether (3 × 50 ml), the extract was dried with magnesium sulfate, and 3.44 g (60%) of compound (I) similar to that described above was obtained.

3,4,5,6,7,8-Hexahydrospiro[chromene-2,1'-cyclohexan]-2-one Oxime (III). To 2.08 g (0.03 mole) of hydroxylamine hydrochloride in 10 ml of water we added a solution of 1.20 g (0.03 mole) of sodium hydroxide in 10 ml of water and 2.20 g (0.01 mole) of the spirohydroquinone (I) in 30 ml of methanol. The reaction mixture was heated for 6 h. The methanol was distilled, the residue was diluted with water, and the product was extracted with ether (3 × 50 ml). The extracts were dried with sodium sulfate, the solvent was distilled, and 0.94 g (40%) of the oxime (III) was obtained; mp 122-123°C (dioxane). Found %: C 71.32; H 8.21; N 5.41. $C_{14}H_{21}NO_2$. Calculated %: C 71.48; H 8.03; N 5.95.

2,16-Dioxatetracyclo[7.6.1.0^{3,8}.0^{1,11}]hexadecan-3-ol (IV). A 3.08-g sample (0.14 mole) of the spirohydrochroman (I) was dissolved in 50 ml of methanol and heated to 50°C. We added 2.78 g (0.04 mole) of hydroxylamine hydrochloride in 10 ml of water and then drop by drop 2.20 g (0.04 mole) of potassium hydroxide in 10 ml of water. After 3 h the methanol was distilled, and the treatment described above was repeated. We obtained 2.09 g (64%) of compound (IV).; mp 152-153°C, which agrees with published data [11].

Spiro{2-oxatetracyclo[7.6.1.0^{1,11}.0^{3,8}]hexadec-3(8)-ene-16,1'-cyclohexan}-2'-one (V). A 15.5-g sample (0.1 mole) of compound (II) was boiled in 50 ml of toluene for 7 h. By vacuum distillation we isolated 1.54 g (14%) of the spiran (I) and

3.45 g (23%) of compound (V); bp 190-195°C at 6.6 GPa; R_f 0.68; n_D^{20} 1.5564 (a thick red viscous mass). Found, %: C 80.45; H 9.61. $C_{20}H_{28}O_2$. Calculated, %: C 80.00; H 9.33.

16-Hydroxy-15,22-dioxahexacyclo[12.7.1.0^{1,6}.0^{8,21}.0^{9,14}.0^{16,21}]docosane (VIII). To 47 g (0.4 mole) of cyclo-hexanone and 5 g (0.16 mole) of paraform we added 15 ml of 2 N sodium methoxide solution. The mixture heated to $\sim 100°C$. It was stirred for 1 h and neutralized with HCl (pH ~ 3). We obtained 12.55 g (30%) of compound (VIII); mp 191-193°C (isopropyl alcohol); R_f 0.21. Found %: C 75.60; H 9.45. $C_{20}H_{30}O_3$. Calculated %: C 75.40; H 9.43.

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