ISSN 1070-4280, Russian Journal of Organic Chemistry, 2017, Vol. 53, No. 5, pp. 720–728. © Pleiades Publishing, Ltd., 2017.
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Methods of Synthesis of Alicyclic 1,5,9-Triketones. Reaction of Transaminomethylation

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Received February 15, 2017

Abstract—Alicyclic 1,5,9-triketones with various combination of 5-, 6-, 7-membereded cycles in the molecule were obtained by methods of diketone condensation, Michael reaction, and proceeding from Mannich mono- and bisbases and cycloalkanones. The latter method was accompanied with a transaminomethylation, observed for the first time at triketones preparation. The structures of cyclic forms of Michael reaction products were refined.

DOI: 10.1134/S1070428017050128

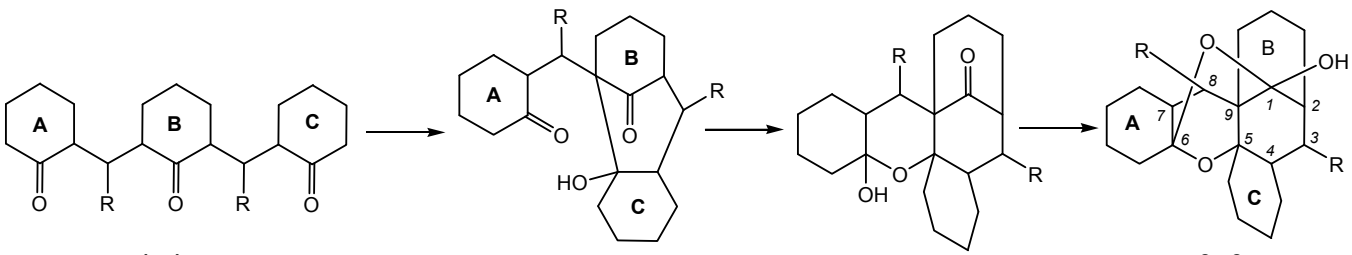
First alicyclic 1,5,9-triketones were obtained in nineteen fifties [1–3], however their reactions were investigated only recently [4–7]. Initially the attention of researchers was attracted by 1,5,9-triketone **1a**, consisting of six-membered rings A–C that under the effect of alkali easily underwent cyclization into complex scaffold structure **2a** (Scheme 1) and at melting returned in the initial state. The intramolecular cyclization is also typical of the other 1,5,9-triketones containing cycles of various size (from five- to seven-membered), but having in their structure no less than two six-membered cycles [5, 8]. In reaction with *N*-nucleophiles [4] triketone **1a** forms a derivative of quinolizidine base julolidine known for its bioactivity.

While investigating properties of alicyclic 1,5,9-triketones we were obliged at the same time to develop methods of synthesis of previously unknown compounds of this type, particularly those containing cycles of various sizes, to consider special features of their formation, check and optimize the methods of synthesis of known triketones. Methods of synthesis of alicyclic 1,5,9-triketones containing cycles of various size were unknown save those we had described in [9]. Therefore we ourselves developed methods of synthesis of alicyclic 1,5,9-triketones **1** and **3–11** with five-, six- and seven-membered rings (Scheme 2).

Alicyclic 1,5,9-triketones, as a rule, are side products in the synthesis of 1,5-diketones and are obtained in small yields. At the synthesis of 1,5,9-triketones it is necessary to create conditions that reduce the yield of 1,5-diketones and to find methods of separation of di- and triketones.

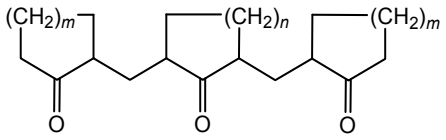
Main methods of synthesis of 1,5-diketones that may be applied to the preparation of 1,5,9-triketones are based on diketone condensation, on Michael reaction, and Robinson annulation (a version of

Scheme 1.



R = H (**a**), Ph (**b**), furan-2-yl (**c**).

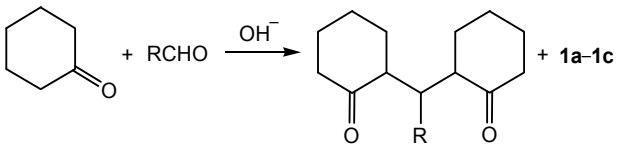
Scheme 2.



1, **3**–**11**

1, $m = 2$, $n = 2$ (6-6-6);[1] **3**, $m = 2$, $n = 2$ (7-7-7); **4**, $m = 2$, $n = 1$ (6-5-6); **5**, $m = 3$, $n = 1$ (7-5-7); **6**, $m = 1$, $n = 1$ (5-5-5); **7**, $m = 1$, $n = 2$ (5-6-5); **8**, $m = 1$, $n = 3$ (5-7-5); **9**, $m = 2$, $n = 3$ (6-7-6); **10**, $m_1 = 2$, $n = 2$, $m_2 = 3$ (6-6-7); **11**, $m = 3$, $n = 2$ (7-6-7).

Scheme 3.



12a–**12c**

R = H (**a**), Ph (**b**), furan-2-yl (**c**).

Michael reaction). By application of enamine method one of the first alicyclic 1,5,9-triketones was obtained consisting of five-membered cycles [3]. We used it only as a version in addition to Robinson method.

Diketone condensation. First alicyclic 1,5,9-triketone **1a** was obtained in a yield not exceeding 14–16% as a side product of diketone condensation of cyclohexanone with formaldehyde at the preparation of 1,5-diketone **12a** (Scheme 3) (ratio ketone–aldehyde 2 : 1, catalyst 0.2 and 4N alcohol solutions of alkali NaOH and KOH) [1, 2, 10]. In [11] for the synthesis of 1,5-diketones in anhydrous conditions paraformaldehyde, sodium methylate, and methanol were applied in a ratio ketone–aldehyde 3 : 1. The formation of 1,5,9-triketones was not mentioned.

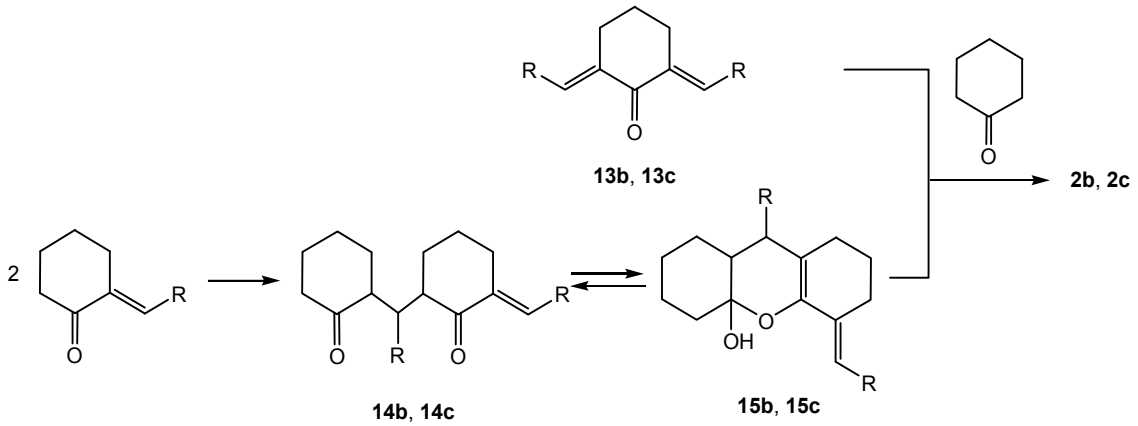
We used this method to synthesize triketones **1a** and **3** and obtained them in 25 and 29% yields. All our further attempts to increase the yield of 1,5,9-triketones by changing reaction conditions did not succeed.

Triketone **1a** was synthesized in cyclic form **2a**, and triketone **3**, in an open ketone form. It should be mentioned that triketone **3** obtained in anhydrous conditions did not form in water-alcohol solution, and diketone condensation of cycloheptanone with formaldehyde is restricted to the formation of the corresponding 1,5-diketone.

The reaction with aromatic aldehydes proceeds more difficultly. By condensation of cyclohexanone with benzaldehyde and furfural in conditions of diketone condensation in water-alcohol environment only 1,5,9-triketone **2c** was obtained in 1.5% yield [1, 10, 12]. In anhydrous medium at excess of cyclohexanone in the presence of sodium methylate the yield of compound **2c** practically did not increase.

Michael reaction. Whereas the conditions of diketone condensation allow the preparation of triketones with similar cycles, by Michael reaction it is possible to obtain 1,5,9-triketones with diverse combinations of cycles. Classic version of Michael reaction applied to the synthesis of alicyclic 1,5,9-

Scheme 4.



13b, **13c**

14b, **14c**

15b, **15c**

2b, **2c**

R = Ph (**b**), furan-2-yl (**c**).

[1] Numbers in brackets show the ring size in di- and triketones.

Characteristic signals of carbon atoms in ^{13}C NMR spectra (DEPT-135) of compounds **2a–2c**

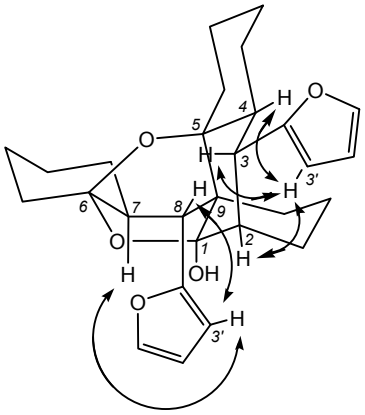
Compound no.	Quaternary carbon atoms			Tertiary carbon atoms
	C^1, C^6	C^5	C^9	C^2, C^3, C^4, C^7, C^8
2a	96.1, 98.2	79.0	37.8	39.6, 39.8, 41.1
2b	95.8, 99.2	80.8	41.6	44.8(C^4), 45.3 (C^7), 47.1 (C^3), 47.8 (C^8), 48.1 (C^2)
2c	95.4, 98.3	80.2	41.8	40.8 (C^8), 41.2 (C^3) , 44.5 (C^4), 44.7 (C^7), 44.9 (C^2)

triketones consists in cyclanones addition to diarylideneketones **13**, or to dimers of monoarylideneketones **14** that are in an equilibrium with cyclic forms **15** [13, 14] (Scheme 4).

At heating 2,6-dibenzylidene- (**13b**) and 2,6-bis-(furan-2-ylmethylidene)cyclohexan-1-one **13c** with a large excess of cyclohexanone in alkaline medium triketones **1b** and **1c** are produced in cyclic forms **2b** and **2c** in 3 and 14% yields respectively [10, 12]. At the reaction of dimer **14c** with cyclohexanone only compound **2c** was obtained in 16% yield. We repeated these syntheses taking instead of alcohol solution of NaOH a stronger base, sodium methylate, but there was no significant increase in the yield of triketones. The structure of these compounds was previously established basing on IR spectra only, now we registered the NMR spectra. The structure of compound **2a**, besides the ^{13}C NMR spectrum [9], was confirmed by X-ray diffraction analysis [15–17]. Two hydroxanthene rings in the molecule of compound **2a** are in the *boat* conformation (see the figure).

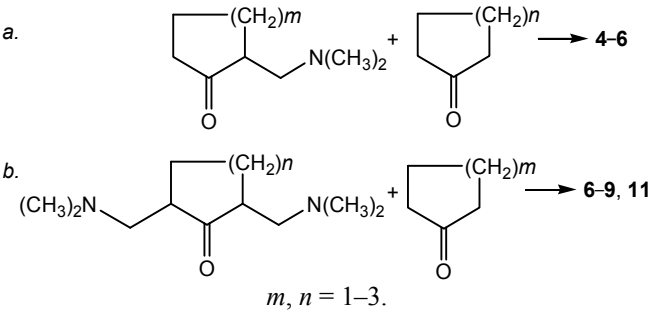
^{13}C NMR spectra of compounds **2b** and **2c** have the same characteristic signals as in the spectrum of compound **2a** (see the table), in particular, the signal of quaternary atom C^9 unbound to oxygen atoms. Such atom may appear only in the first aldol stage of cyclization (Scheme 1) involving a methine and not a methylene group, as it has been considered previously [10]. In each structure there are also two C atoms bound with two oxygen atoms (C^1 and C^6) and one (C^5) linked to a single oxygen atom. ^{13}C NMR spectra confirmed the structure similarity of **2b**, **2c**, and **2a**. The obtained data allowed a correction of the structure suggested previously [10] for cyclic forms **2b** and **2c**.

^1H NMR spectra 1D and 2D, and also ^1H-^1H NOESY experiment made it possible to establish the spatial position of phenyl and furyl substituents in compounds **2b** and **2c**. In ^1H NMR spectrum of compound **2b** the benzyl proton at C^8 appears as a doublet, δ 2.98 ppm, J 8.5 Hz that evidences its pseudo -equatorial position. Unlike that, the benzyl proton at C^3 takes the axial position, therefore it appears as a doublet of doublets at δ 3.35 ppm, J_1 4.8, J_2 12.5 Hz. In ^1H NMR spectrum of compound **2c** the proton at C^8 appears as a doublet at δ 3.03 ppm, J 8.5 Hz, and the proton at C^3 is observed as a doublet of doublets, δ 3.38 ppm, J_1 4.8, J_2 12.5 Hz. Consequently, the substituent at C^8 in the ring having a *boat* conformation is in a pseudo-axial position, and at C^3, in an equatorial position (see the figure). It is confirmed by the presence in ^1H-^1H NOESY spectrum of cross-peaks corresponding to the coupling of protons at C^7 and C^4 atoms with *ortho*-protons of the benzene ring and with the proton at $C^{3'}$ atom of the furan ring. For compound **2b** the following cross-peaks are



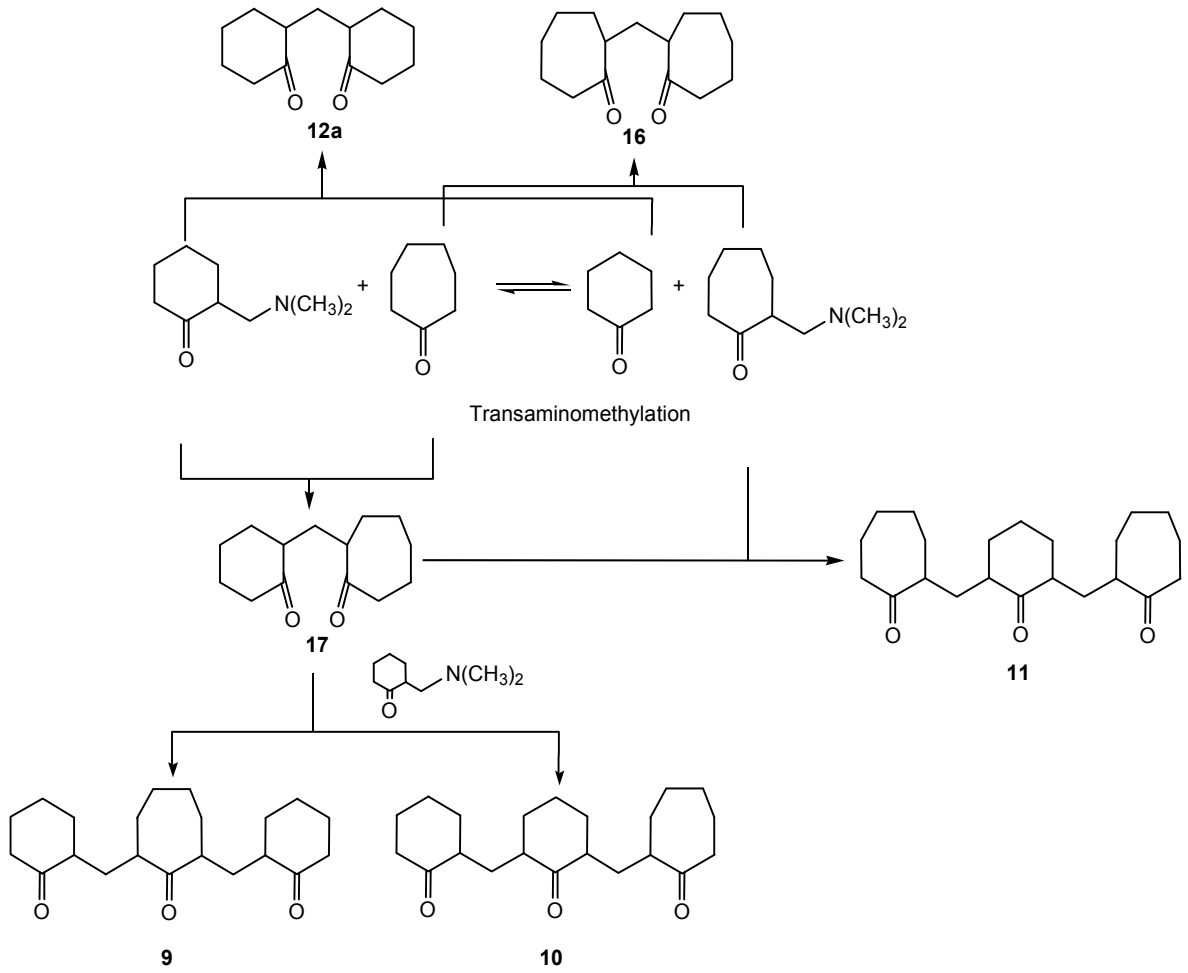
Structure of 10,18-bis(furan-2-yl)-3,22-dioxahexacyclo-[9.7.3.1^{4,12}.0^{1,2}.0^{4,9}.0^{12,17}]docosan-2-ol **2c** and spatial correlation ^1H-^1H in the NOESY experiment.

Scheme 5.



m, n = 1–3.

Scheme 6.



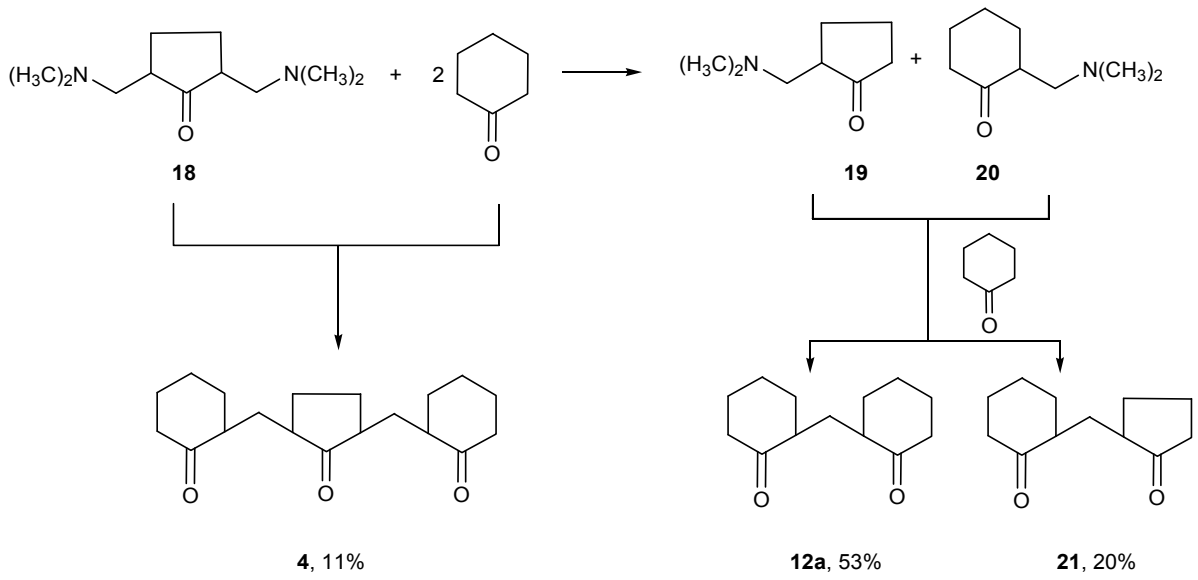
observed: C^3–Ph (*ortho*-protons)/C^4H at 7.23/2.2 ppm and C^8–Ph (*ortho*-protons)/C^7H at 7.48/2.49 ppm; for compound **2c**: C^3–Fur ($C^{3'}$H)/ C^4H at 6.05/2.21 and C^8–Fur ($C^{3'}$H)/C^7H at 6.23/2.30 ppm.

Robinson method that is a thermal option of Michael reaction is widely used in the synthesis of 1,5-diketones, and we applied it to the synthesis of 1,5,9-triketones in three versions (*a*–*c*). In the *a* version (classic method [18]) Mannich monobase obtained from ketone and cyclonone was used, 2.2 : 1 (Scheme 5, *a*).

The method is sensitive to the reagent nucleophilicity and to the reactivity of Mannich base and not always gives positive results, stopping at the stage of the formation of 1,5-diketone. Although the nucleophilicity of 5- and 6-membered cyclic ketones decreases with the increase in the cycle size, the reactivity of Mannich bases obtained from cyclohexanone is higher in this reaction than the reactivity of Mannich bases from cyclopentanone. Using cyclopentanone as nucleophile in the reaction with Mannich monobases obtained from cyclohexanone and cycloheptanone we obtained 1,5,9-triketones **4** (6-5-6) [9] and **5** (7-5-7) respectively. Yield of compound **4** is 49%, triketone **5**, 18%. We did not succeed in preparation of triketones **7** (5-6-5) or **8** (5-7-5) at interaction with Mannich monobase obtained from cyclopentanone with cyclohexanone or with cycloheptanone, only diketones form in this reaction.

The specific feature of reactions, where ketones with almost similar nucleophilicity are involved (cyclohexanone and cycloheptanone), is the appearance in the reaction mixture of all possible 1,5-diketones and 1,5,9-triketones with these cycles because simultaneously with the main reaction the reaction of transaminomethylation takes place that has been previously observed in the synthesis of arylaliphatic 1,5-diketones [19, 20].

Scheme 7.



At the attempt to synthesize triketone **9** (6-7-6) from cycloheptanone and Mannich monobase obtained from cyclohexanone (Scheme 6) we found in the reaction products 37% of 1,5-diketones **12a** (6-6), **16** (7-7), **17** (6-7), 0.3 : 1 : 1, and 17% of triketone fraction with approximately equal ratio of triketones **9** + **10** and **11** (7-6-7 or 7-7-6) (GC/MS). The same reaction products of were obtained at the attempt of synthesis of **11** (7-6-7) from cyclohexanone and Mannich monobase from cycloheptanone. In both cases the initially generated diketone **17** (6-7) reacted with the Mannich bases based on cyclohexanone or cycloheptanone. In the first synthesis from triketone fraction after treating it with alcohol solution of alkali triketone **10** was isolated in a cyclic form.

If the formation of triketones **9**, **10**, and **17** is the result of a normal reaction course, then the formation of diketones **11**, **12a**, and **16** is the result of transaminomethylation (Scheme 6). Transaminomethylation is almost absent at the application of cyclopentanone as nucleophile, and in the preparation of triketones **4** and **5** no transaminomethylation was detected.

Another approach to Robinson reaction (version *b*) is the reaction of Mannich bisbases with cyclanone in the ratio 1 : 2.2 (Scheme 5, *b*). By reaction of Mannich bisbases prepared from cyclohexanone and cycloheptanone triketones **11** (7-6-7) (47%) and **9** (6-7-6) (66 %) were obtained respectively where the fraction of products of transaminomethylation did not exceed 13%. By this method it was possible to synthesize also triketones **7** (5-6-5) (70%) and **8** (5-7-5) (47%), which failed to be obtained at the application of Mannich monobase by method *a*. Triketone **2a** is obtained in equal amount with diketone **12a** (6-6) (yield 50%).

However everything changes at application of less reactive Mannich bisbase based on cyclopentanone **18** (Scheme 7). At heating with 2 mol of cyclohexanone aiming to prepare triketone **4** (6-5-6) we obtained a mixture containing 53% of diketone **12a** (6-6), 20% of diketone **21** (5-6), and only 11% of triketone **4**. Evidently due to the low rate of the main reaction the process of transaminomethylation developes. As a result bisbase **18** turns into a mixture of monobases from cyclopentanone **19** and cyclohexanone **20**. The latter enter into the reaction with cyclohexanone and form the corresponding diketones **12a** (6-6) and **21** (5-6). The prevailing formation of particular six-membered 1,5-diketone **12a** confirms the higher reactivity of Mannich base based on cyclohexanone comparing to Mannich basis based on cyclopentanone.

The third version of triketones synthesis from Mannich bases (method *c*) consists in the reaction of Mannich bisbases with enamine of cyclanone. To obtain 1,5,9-triketone **9** (6-7-6) we brought in the reaction the Mannich bisbase based on cycloheptanone and enamine of cyclohexanone (cyclohexenylmorpholine) [22] in a ratio 1 : 2. The yield of reaction product in cyclic form was 69%, so for triketone **9** this method was the most effective comparing to others.

Hence, it is possible to obtain triketones with 5-membered cycle inside the molecule basing on Mannich bases by method *a* [**4** (6-5-6) and **5** (7-5-7)], and with 6- and 7-membered cycles inside the molecule, by method *b* [**7** (5-6-5), **8** (5-7-5), **9** (6-7-6), **11** (7-6-7)]. Triketone **6** (5-5-5) forms both by methods *a* and *b*, its yield does not exceed 45%. Method *c* is evidently the most universal for the preparation of triketones.

It is characteristic that all 1,5,9-triketones are present in the isolated reaction product as a mixture of stereoisomers with a similar decay pattern in the mass spectrum. The number of stereoisomers (GC/MS) is varying from two to seven, and usually two-three isomers are prevailing (70–80% of the mixture). The ratio of stereoisomers in the equilibrium mixture may vary due to mutual transformations [5]. We isolated individually two isomers for each of triketones **4** [5] and **6** [10] and one stereoisomer of triketone **9**.

In mass spectra obtained by electron impact the molecular ion for most triketones was not found, and in all cases an ion with the mass $[M - H_2O]^+$ was present. For all triketones, as well as for 1,5-diketones, the characteristic fission of the molecule is by the retro-Michael type, and in mass-spectra ions are present with masses $[M$ – cyclanone$]^+$, $[M$ – cyclanone – $CH_2]^+$. This type of fission is observed also at heating triketones over 170°C, as well as at distillation in a vacuum that leads to accumulation of the corresponding 1,5-diketones and compounds with the mass $[M$ – cyclanone$]^+$. Most easily the fission occurs in the triketones with 6- and 7-membered cycles. Therefore at the synthesis of, for example, triketone **11** (7-6-7) it is necessary to keep the temperature no higher than 150°C, and vacuum distillation should be used only to distill off the accompanying 1,5-diketone in a mode conserving a short presence of reaction products in the high temperature zone. As a result we obtained triketone **11** of 98% purity.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer Spectrum BX-II (Perkin Elmer). NMR spectra were registered on a spectrometer Avance-400 Bruker at working frequencies 400 (^{1}H) and 125 (^{13}C) MHz at 30°C, internal reference TMS. The assignment of signals was carried out using DEPT-135 and ^{1}H-^{1}H NOESY experiments. Spectra of compounds **2b** and **2c** were recorded in $CDCl_3$. The progress of reaction and the composition of reaction mixture was monitored with GC/MS. The chromatographic analysis was realized on gas chromatograph Agilent GC 6890 Plus with mass-selective detector 5973N at ionization with electron impact (EI, 70 eV), quartz capillary column HP-5MS (length 30 m, internal diameter 0.25 mm, layer of the stationary phase 0.25 μm thick), carrier gas helium. To record mass spectra EI of individual compounds **2b** and **2c** a system of direct input of sample HPP7 & ProbeDirect™ was applied in combination with MSD HP 5973. Melting points were determined on PTP (M) apparatus in capillaries.

By the method of diketone condensation compounds **2a**, **3**, **12a**, and **16** were prepared.

3,22-Dioxahexacyclo[9.7.3.1^{4,12}.0^{1,2}.0^{4,9}.0^{12,17}]docosan-2-ol (2a). To a mixture of 49 mL (0.48 mol) of cyclohexanone and 5 g (0.166 mol) of paraformaldehyde was added dropwise while stirring 2 mL of 2N solution of CH_3ONa, the mixture was boiled, paraformaldehyde dissolved. The rest 14 mL of 2N solution of CH_3ONa was added dropwise, maintaining weak boiling of reaction mixture (30–40 min). The mixture was heated for 1 h more at 60–70°C, cooled, neutralized with acetic acid, left for 24 h at 5°C. The precipitate was filtered off, washed with 12 mL of aqueous ethanol, 1 : 1. Yield 6.6 g (25%), white crystals, mp 193–193.5°C, individual compound according to GC-MS data. After recrystallization from diethyl ether of diethyleneglycol mp 195.5–196°C {mp 191–193°C (from benzene or chloroform) [10]}.

From the filtrate at a reduced pressure a mixture of alcohol and cyclohexanone was distilled off, the residue was extracted with ether (3 × 30 mL), the extract was washed with water, dried with $MgSO_4$, ether was distilled off. The residue (12.2 g), according to GC-MS data, was a mixture of diketone **12a** (6-6) (35%) and its cyclic form (45%), triketone **1a** (8%) and its cyclic form **2a** (12%). After distillation in a vacuum we obtained 8.2 g (23.6%) of diketone **12a**, colorless oily liquid, bp 153–156°C (3 mmHg) {bp 165–170°C (12 mmHg) [11]}.

2,7-Bis(2-oxocycloheptylmethyl)cycloheptan-1-one (3) (7-7-7). To mixture of 5 g (0.0446 mol) of cycloheptanone and 0.88 g (0.029 mol) of paraformaldehyde was added dropwise at stirring 2 mL of 2N solution of CH_3ONa. The mixture was heated at 30°C, paraformaldehyde dissolved, then the mixture was heated on a boiling water bath for 1.5 h, cooled, acidified with diluted (1 : 10) HCl, the reaction

products were extracted with ether (3 × 15 mL), the extract was washed with water till pH 7, dried with Na_2SO_4. In succession ether and cycloheptanone (at a reduced pressure) were distilled off, the residue (5.3 g) was distilled in a vacuum to obtain 1.5 g of diketone **16** (7-7) (21.9%), bp 148–152°C (3 mmHg) {bp 200–203°C (11 mmHg [11]} and 2.95 g (28%) of triketone **3**, bp 240–250°C (3 mmHg). According to GC-MS data, triketone **3** was a mixture of 7 diasteromeres, among them three isomers dominated (66%), 27.7 : 19.8 : 18.9. IR spectrum (CH_2Cl_2), ν, cm^{-1}: 1698 s (C=O cycloheptanone). Mass spectrum, *m/z* (I_{rel}, %): 360 (1.6) $[M]^+$, 342 (3.2) $[M - H_2O]^+$, 249 (19.4) $[M - C_7H_{11}O]^+$, 236 (27.4) $[M - C_7H_{11}O - CH_2]^+$, 207 (11.3), 112 (38.7) $[C_7H_{11}O]^+$, 84 (32.3), 55 (100). Found, %: C 76.61; H 9.96. $[M]^+$ 360. $C_{23}H_{36}O_3$. Calculated, %: C 76.66; H 10.00. *M* 360.

By Michael reaction compounds **2b** and **2c** were obtained.

10,18-Diphenyl-3,22-dioxahexacyclo-[9.7.3.$1^{4,12}$.$0^{1,2}$.$0^{4,9}$.$0^{12,17}$]docosan-2-ol (2b). A mixture of 30 g (0.3 mol) of cyclohexanone, 10 g (0.036 mol) of 2,6-dibenzalcyclohexan-1-one, and 30 mL of 1N alcoholic solution of NaOH was heated on a boiling water bath for 6 h. The reaction mixture was left for two days at 5°C, the separated yellow-brown amorphous precipitate was filtered off (0.550 g), washed with petroleum ether (20 mL) at 20°C, and then by portions of boiling ethanol (10 mL in all). Yield 0.525 g (3%), white amorphous powder, mp 330–333°C (decomp.) {mp 240°C (decomp.) [10]}. IR spectrum (KBr), ν, cm^{-1}: 3554 m, 3392 s (OH); 1588 w, 1502 m (Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (besides signals mentioned in the table), secondary atoms C: 21.3, 21.90, 22.1, 23.2, 25.3, 26.3, 26.5, 26.9, 31.7, 32.3, 35.8 (11 CH_2); aromatic atoms C: 125.9, 126.3, 127.4, 128.3 (=CH); 141.7, 143.3 (=C). Mass spectrum: *m/z* $[M]^+$ 470. Found, %: C 81.65; H 8.05. $C_{32}H_{38}O_3$. Calculated, %: C 81.70; H 8.08. *M* 470.

10,18-Di(furan-2-yl)-3,22-dioxahexacyclo-[9.7.3.$1^{4,12}$.$0^{1,2}$.$0^{4,9}$.$0^{12,17}$]docosan-2-ol (2c). A mixture of 30 g (0.3 mol) of cyclohexanone, 10 g (0.039 mol) of 2,6-bis[(furan-2-yl)methylidene]cyclohexan-1-one, and 30 mL of 1N alcoholic solution of NaOH was heated on a boiling water bath for 5 h, cooled, the precipitate (4.6 g) was filtered off, washed with petroleum ether (50 mL), then with ethyl acetate (15 mL) at 20°C. Yield 2.4 g (14%), white amorphous powder, mp 258–261°C (decomp.) {mp 236–237°C (decomp.) [10, 12]}. IR spectrum (KBr), ν, cm^{-1}: 3392 s (OH); 1589 m, 1503 m, 1011 s, 1066 s, 1082 s (furyl). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (besides signals mentioned in the table), secondary atoms C: 20.8, 21.90, 23.0, 23.1, 25.1, 25.8, 26.0, 26.9, 31.4, 32.0, 35.5 (11 CH_2); furan-2-yl: 106.0, 110.0, 110.1, 110.9 (=CH); 155.0, 157.7 (=C). Mass spectrum: *m/z* $[M - 18]^+$ 432. Found, %: C 74.61; H 7.51. $C_{28}H_{34}O_5$. Calculated, %: C 74.66; H 7.55. *M* 450.

Mannich monobase based on cycloalkanone. A mixture of 0.1 mol of cycloalkanone, 0.1 mol of paraformaldehyde, 0.1 mol of dimethylamine hydrochloride, 15 mL of isopropyl alcohol, and 0.3 mL of concentrated HCl was heated while stirring for 1 h. Alcohol was distilled off at a reduced pressure, the mixture was cooled and kept for 12 h at 0°C. A fully crystallized white mass of Mannich monobase hydrochloride was obtained. To the obtained salt was added at shaking by portions 20 mL of 2N solution of NaOH, Mannich base was extracted with ether (3 × 15 mL), the extract was dried with $MgSO_4$, ether was distilled off. Yield 90–95%, light-yellow oily liquid.

Mannich bisbases were obtained by same method at molar ratio cycloalkanone–paraformaldehyde–dimethylamine hydrochloride 0.05 : 0.1 : 0.1 in 25 mL of 2-propanol.

Synthesis of triketones from Mannich bases. General procedures. *a*. A mixture of Mannich monobase and cycloalkanone, 2.2 : 1, was heated for 5–7 h on an oil bath first at 130°C, and gradually the temperature was raised to 150–170°C. The mixture was cooled, acidified with diluted (1 : 5) HCl, the reaction products were extracted with ether, the extract was washed with water till pH 7, dried with $MgSO_4$, ether was distilled off. The residue was distilled in a vacuum. Yield of triketones fraction 18–50%.

b. A mixture of Mannich bisbase with cyclopentanone, cyclohexanone, or cycloheptanone was heated for 1 h on an oil bath at 110°C and, at gradually raising temperature to 165°C, for 4 h more. After cooling the mixture was worked up as in procedure *a*. After distilling off the ether the residue was distilled in a vacuum or treated with 2N alcoholic solution of NaOH.

2,5-Bis(2-oxocyclohexylmethyl)cyclopentan-1-one (4) (6-5-6) was obtained by method *a* [9]. By method *b* from Mannich bisbase based on cyclopentanone and cyclohexanone (1 : 2.2) 53% of

diketone **12a**, 20% of diketone **17** and 11% of triketone **4** were obtained.

2,5-Bis(2-oxocycloheptylmethyl)cyclopentan-1-one (5) (7-5-7). *a*. From 14 g (0.083 mol) of 2-(dimethylaminomethyl)cycloheptane-1-one and 3.36 g (0.04 mol) of cyclopentanone we obtained 12 g of semi-solid mass. After vacuum distillation was extracted 4.45 g (54%) of diketone **16** (7-7), bp 146–150°C (4 mmHg) {128°C (0.1 mmHg) [11]} and 2.4 g (18%) of triketone **5**, bp 249–255°C (4 mmHg), which according to GC/MS data contained a mixture of five main diasteromers, 3.0 : 2.1 : 1.8 : 0.9 : 0.6. IR spectrum (CH_2Cl_2), ν, cm^{-1}: 1729 (C=O cyclopentanone), 1697 (C=O cycloheptanone). Mass spectrum, *m/z* (I_{rel}, %): 332 (1.0) $[M]^+$, 314 (2.0) $[M - H_2O]^+$, 220 (27.8) $[M - C_7H_{11}O]^+$, 207 (8.2) $[M - C_7H_{11}O - CH_2]^+$, 125 (12.4) $[C_7H_{11}O - CH_2]^+$, 112 (25.8) $[C_7H_{12}O]^+$, 55 (100). Found, %: C 75.87; H 9.59. $C_{21}H_{32}O_3$. Calculated, %: C 75.90; H 9.64. *M* 332.

2,6-Bis(2-oxocyclopentylmethyl)cyclohexan-1-one (7) (5-6-5). *b*. From 6 g (0.028 mol) of 2,6-bis-(dimethylaminomethyl)cyclohexan-1-one and 5.2 g (0.062 mol) of cyclopentanone we obtained a mixture containing 11% of diketone (5-6) and 84% of triketone **7**. By distillation in a vacuum we isolated 0.43 g (8%) of diketone (5-6), bp 139–143°C (3 mmHg) and 5.74 g (70%) of triketone **7**, bp 225–230°C (3 mmHg) as a mixture of three diasteromers, 3 : 1 : 1. IR spectrum (CH_2Cl_2), ν, cm^{-1}: 1730 (C=O cyclopentanone), 1705 (C=O cyclohexanone). Mass spectrum, *m/z* (I_{rel}, %): 272 (33.0) $[M - H_2O]^+$, 207 (18.0) $[M - C_5H_7O]^+$, 198 (23.5) $[M - C_5H_7O - CH_2]^+$, 176 (25.8), 123 (43.5) $[M - 2(C_5H_7O)]^+$, 110 (100) $[C_6H_8O - CH_2]^+$, 98 (72.9) $[C_5H_7O - CH_2]^+$, 84 (55.3) $[C_5H_7O]^+$, 55 (47.1). Found, %: C 74.45; H 8.92. $C_{18}H_{26}O_3$. Calculated, %: C 74.48; H 8.96. *M* 290.

2,7-Bis(2-oxocyclopentylmethyl)cycloheptan-1-one (8) (5-7-5). *b*. From 8 g (0.035 mol) of 2,7-bis-(dimethylaminomethyl)cycloheptan-1-one and 5.88 g (0.07 mol) of cyclopentanone we obtained 7.4 g of semi-solid mass, from which as a result of a vacuum distillation were extracted 1.3 g (18%) of diketone (5-7), bp 139–143°C (3 mmHg) and 5.0 g (47%) of triketone **8**, bp 228–236°C (3 mmHg) as a mixture of four diasteromers, 3 : 1.4 : 1 : 0.6. IR spectrum (CH_2Cl_2), ν, cm^{-1}: 1730 (C=O cyclopentanone), 1696 (C=O cycloheptanone). Mass spectrum, *m/z* (I_{rel}, %): 286 (35.5) $[M - H_2O]^+$, 221 (93.3) $[M - C_5H_7O]^+$, 208 (55.5) $[M - C_5H_7O - CH_2]^+$, 137 (62.2) $[M - 2(C_5H_7O)]^+$, 112 (100) $[C_7H_{11}O]^+$, 97 (64.4) $[C_5H_7O - CH_2]^+$, 83 (95.5) $[C_5H_7O]^+$, 55 (93.3). Found, %: C 74.96; H 9.18. $C_{19}H_{28}O_3$. Calculated, %: C 75.0; H 9.21. *M* 304.

2,7-Bis(2-oxocyclohexylmethyl)cycloheptan-1-one (9) (6-7-6). *b*. From 11.0 g (0.048 mol) of 2,7-bis-(dimethylaminomethyl)cycloheptane-1-one, 11 mL (0.11 mol) of cyclohexanone we obtained 12.8 g of oily residue containing 82.5% of triketone **9** (yield 66%), 3.5% of triketone **11** (7-6-7), and 13.5% of diketones **12a** (6-6) and **17** (6-7), 1 : 3. Triketone **9** contained a mixture of 6 stereoisomers, 31 : 21 : 11 : 9 : 7 : 5. Compound **9** was isolated by two methods.

(1) The residue (12.8 g) was mixed with 18 mL of 2N alcoholic solution of NaOH, left for 1 h at room temperature and then in a refrigerator for a night. The precipitate of cyclic form of triketone **9** was filtered off, washed with ethanol. Yield 6.4 g (40%), white crystals, mp 185–187°C (ethanol) (185–187°C [21]).

(2) The residue (11.2 g) was dissolved in alcohol (20 mL) and cooled to –8°C. The precipitate formed (0.75 g) was a mixture of prevailing 3 stereoisomers of triketone **9**. After recrystallization from ethanol we obtained 0.11 g of individual stereoisomer of triketone **9**, white crystals, mp 112.3–113.0°C. IR spectrum (KBr), ν, cm^{-1}: 1705 (C=O cyclohexanone), 1696 (C=O cycloheptanone). Mass spectrum, *m/z* (I_{rel}, %): 332 (2) $[M]^+$, 314 (41) $[M_1 = M - H_2O]^+$, 235 (61) $[M - C_6H_9O]^+$, 221 (30.4) $[M - C_6H_9O - CH_2]^+$, 216 (41) $[M_1 - C_6H_9O]^+$, 204 (61) $[M_1 - C_6H_9O - CH_2]^+$, 137 (65) $[M - 2(C_6H_9O)]^+$, 124 (69) $[C_7H_{12}O - CH_2]^+$, 112 (69) $[C_6H_9O - CH_2]^+$, 98 (100) $[C_6H_9O]^+$, 79 (35), 67 (60), 55 (70). Found, %: C 75.96; H 9.58. $C_{21}H_{32}O_3$. Calculated, %: C 75.90; H 9.64. *M* 332.

c. 4-(Cyclohex-1-en-1-yl)morpholine was obtained by standard method [22]. A mixture of 2.9 g (0.0146 mol) of Mannich bisbase prepared from cycloheptanone and 5 mL (0.03 mol) cyclohexenylmorpholine was heated on an oil bath for 4 h, the temperature of reaction mixture was gradually raised from 110 to 150°C. The mixture was cooled, 5 mL of diluted (1 : 10) HCl (pH 5) was added and the reaction mixture was hydrolyzed while stirring for 40 min. Reaction products were extracted with ether (3 × 15 mL), the extract was washed with water to pH 7, dried with $MgSO_4$, ether was distilled off (traces of ether were distilled in a vacuum) to obtain 3.6 g of residue as an oily light-yellow liquid containing 96% of triketone **9** and 4% of diketone **17** (6-7). The residue was mixed with 5 mL of 2N alcoholic solution of NaOH, left

standing for 12 h at 20°C, the precipitate was filtered off, washed with ethanol (3 mL). Yield 3.3 g (69%) of cyclic form of triketone **9**, white crystals, mp 185–187°C (ethanol) (mp 185–187°C [21]).

2-(2-Oxocyclohexylmethyl)-6-(2-oxocycloheptylmethyl)cyclohexan-1-one (10) (6-6-7) (cyclic form). *a*. From 10.2 g (0.07 mol) of 2-(dimethylaminomethyl)-cyclohexane-1-one and 3.43 g (0.035 mol) of cycloheptanone we obtained 8.8 g of semi-solid mass, from which by vacuum distillation was isolated 3.2 g of diketones fraction, bp 152–168°C (4 mmHg), (36% from the mass of separated mixture) containing a mixture of diketones **12a** (6-6), **17** (6-7), and (7-7), 0.25 : 1 : 1, and 1.5 g (17% of the mass of separated mixture) of triketones fractions, bp 236–248°C (4 mmHg). The fraction of triketones, according to GC/MS data, consisted of a mixture of compounds **9** (6-7-6), **10** (6-6-7), and **11** (7-6-7) approximately in equal amounts. 1 g of triketone fraction was dissolved in 2 mL of ethanol, 5 mL of 1N alcohol solution of NaOH was added, left for one day at room temperature. The crystalline precipitate was filtered off, washed with ethanol (2 mL). Yield of compound **10** 0.12 g (12%), colorless crystals, mp 195–197°C (ethanol) (mp 195–197°C [21]). IR spectrum (KBr), ν, cm^{-1}: 3381 (OH).

2,7-Bis(cycloheptylmethyl)cyclohexan-1-one (11) (7-6-7). *b*. A mixture of 9.65 g (0.046 mol) of 2,6-bis-(dimethylaminomethyl)cyclohexan-1-one and 10.3 mL (0.10 mol) of cycloheptanone was heated for 5 h on an oil bath at temperature not exceeding 150°C. After standard workup we obtained 9.58 g of residue containing of 83% of triketone **11** and 17% of diketone **17** (6-7). Diketone **17** was quickly distilled off at 3 mmHg, the residue in the flask was triketone **11** (7.5 g, 47%) of purity 98%, mixture of 6 stereoisomers, 11 : 6 : 4 : 4 : 3 : 1. IR spectrum (KBr), ν, cm^{-1}: 1705 (C=O cyclohexanone), 1696 (C=O cycloheptanone). Mass spectrum, *m/z* (I_{rel}, %): 328 (42.6) $[M_1 = M - H_2O]^+$, 217 (14.8) $[M_1 - C_7H_{11}O]^+$, 204 (100) $[M_1 - C_7H_{11}O - CH_2]^+$, 105 (11.5) $[M - 2(C_7H_{11}O)]^+$, 91 (42), 79 (37), 67 (30), 55 (40). Found, %: C 76.26; H 9.78. $C_{22}H_{34}O_3$. Calculated, %: C 76.30; H 9.82. *M* 346.

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