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An alicyclic 1,5,9-triketone 2,6-bis[(2-oxocyclohexyl)methyl]cyclohexanone, its cyclic form and reactions with *N*-nucleophiles

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ABSTRACT

The alicyclic 1,5,9-triketone 2,6-bis[(2-oxocyclohexyl)methyl]cyclohexanone, its cyclic form, and the product of its dehydration have been studied under Leuckart reaction conditions, with ammonium acetate in acetic acid and with hydroxylamine. The composition of the melt of the cyclic form has been determined. The obtained polycyclic products of N-heterocyclization confirm the existence of intermediate forms of the cyclization of 1,5,9-triketone in the reaction mixture. The structure and stereochemistry of the reaction products were determined using 1D selective COSY, NOE difference, and 2D NMR experiments (^{1}H–^{1}H COSY, HSQC, HMBC, and NOESY).

1. Introduction

The synthesis of alicyclic 1,5,9-triketones is conducted by the same methods as used for the corresponding 1,5-diketones.[1–7] These compounds are convenient starting materials for the synthesis of heteropolycyclic structures, including analogues of natural products. Using triketone **1** as a starting material, the analogue of hexahydrojulolidine **10**, the most carefully studied system in the development of synthetic methods for some quinolizidine alkaloids, was obtained by reductive amination (Scheme 4).[8] Until now it was known that 1,5,9-triketones in basic conditions can readily undergo domino cyclization into frame structures **b**,[5–7,9–10] while the latter can be transformed back into the triketone form by melting (Scheme 1).

Previous research demonstrated[7,10] that 1,5,9-triketones, which can undergo this kind of cyclization, had at least two six-membered rings in their structures (the number corresponds to the ring size). In all cases ring A is six-membered, ring B has between five and seven carbons and ring C consists of six or seven carbon atoms. 1,5,9-Triketones with other combinations of ring sizes (5-5-5, 5-6-5, 7-7-7, 5-7-5, 7-5-7, 7-6-7) do not form similar cyclic products.[10] Apparently, the driving force of this cyclization is the high reactivity of the carbonyl group of cyclohexanone.

The first step of the cyclization (Scheme 2, m=n=2) is intramolecular aldol condensation between the rings A and B occurring by the same path as for the corresponding 1,5-diketones having different rings:[6,10] the six-membered ring A acts as the carbonyl component and the methine group of the ring B (five- to seven-membered) as the nucleophile, compound **2** is formed in this reaction. The emergence of the quaternary carbon atom (not connected with O-atoms) in structures **b** is only possible under the same direction of aldol condensation; this was confirmed by ^{13}C NMR spectroscopic data. Furthermore, the hemiacetals **3** and **4** are obtained in two subsequent stages. For the first time, the structure of compounds **b** was determined by IR and NMR spectroscopy and by isolation and characterization of the intermediate forms of the cyclization:[6,9] for 2,5-bis[(2-oxocyclohexyl)methyl]cyclopentanone (triketone 6-5-6) the intermediate cyclic form similar to the form **2** and the dehydrated form similar to the form **6** were isolated and analyzed. The configuration of **4** was also assigned by X-ray crystal analysis.[11,12] The latter allowed us to determine the mutual configuration of nonsymmetrical centers of the molecule and showed that five chiral atoms have *S* configuration and two have *R*

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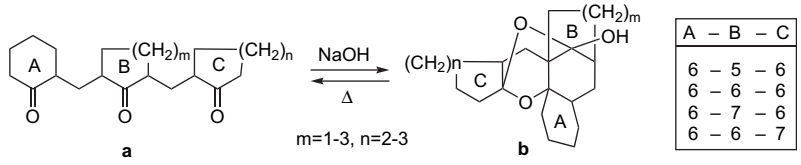
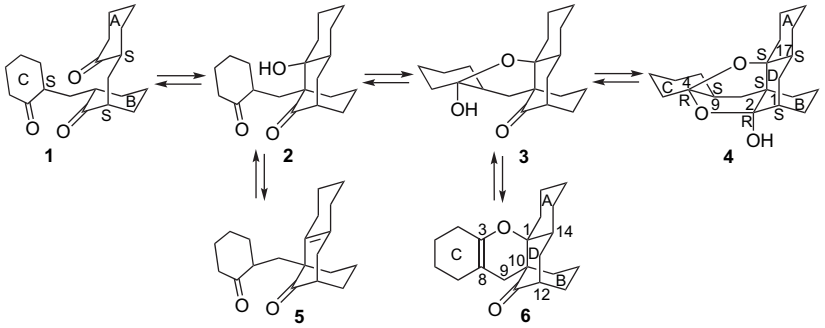


Scheme 1.



Scheme 2.

configuration (for one enantiomer).[11] The hydroxanthene rings in cyclic structures **b** are in 'boat' conformations.

We continued studying the reactions of alicyclic 1,5,9-triketones concentrating our research efforts on triketone **1**. For the first time, this compound in cyclic form **4** was obtained by Tilichenko as a by-product of diketone condensation between cyclohexanone and formaldehyde.[1] He correctly determined its molecular formula (unlike Plesek[3]) and the ability to transform into triketone **1** by melting. The structure was confirmed by the IR spectrum and the formation of its 2,4-dinitrophenylhydrazone.[5] In the same work he also first proposed a structure of its cyclic form **4**, which had to be revised later.[6]

2. Results and discussion

2.1. Composition of the melt of hemiacetal 4

The melt of **4** was analyzed by GC–MS with the purpose to determine its composition, number of diastereomers of triketone **1**, possibility of their transformation depending on the conditions (temperature and time of heating), and also expecting to discover the cyclization intermediates **2** and **3** in the melt besides the triketone form **1**.

For this reason, the decyclization of **4** was carried out at the melting temperature 194 °C and also at 210 °C, keeping the melt at the indicated temperatures for 5, 10, 30 and 60 min. The experiment demonstrated that after 5 min at 194 °C the melt consisted of a mixture of six diastereomers of triketone **1** (Table 1) with close GC–MS retention times and the same decay pattern in the mass spectra. Their ratio was I/II/III/IV/V/VI=2.7:0.9:1:4.1:0.5:0.45. Two of the diastereomers (I and IV) dominated and accounted for 67–70% of the mixture in the ratio 1:1.5, respectively. Small amounts of **4** (3–5%) still remained in the mixture. Compounds **2** and **3** were not detected. The IR spectrum of the melt showed the presence of a carbonyl group at 1705 cm^{-1} and the absence of an absorption band corresponding to an OH group. After 10 min, hemiacetal **4** disappeared completely and the total content of the prevailing diastereomers I and IV decreased to 50% with the ratio 1:2.1 while the share of the other diastereomers increased. The decrease in content of the diastereomer I was remarkably large. Its share drops from 27 to 7% during 30 min, while the share of diastereomer IV changed only from 41 to 32% and still remained prevalent in the mixture. The contents of diastereomers II, III, V and VI increased 1.7–2.6 times. After 30 min, the achieved ratio of isomers remained stable: I/II/III/IV/V/VI=0.6:1.2:1.5:2.8:1:1. Approximately the same ratio was also achieved at 210 °C after 5 min already with 5% of the initial hemiacetal **4** remaining in the mixture. Hemiacetal **4** disappeared completely after 10 min. These results indicate that the melt represents an equilibrium diastereomeric mixture of triketone **1**. The similar case of transformation of stereoisomeric forms of 1,5-diketones was described in the literature.[4]

Table 1
Change of contents of diastereomers of triketone **1** at 194 °C by GC–MS

Heating time, min	Percentage of the stereoisomers in the melt (t_R)[a]					
	I (23.55)	II (23.66)	III (23.82)	IV (24.14)	V (24.22)	VI (24.92)
5	27	9	10	41	5	4.5
10	16	14	18	34	7	10
30	7	19	18	32	10	13

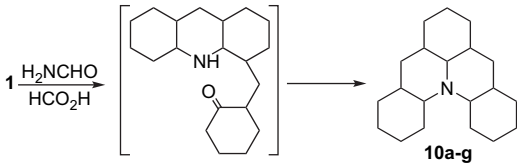
[a] By peak area ratio (average values from several chromatograms were taken).

When the melt was treated with an ethanol solution of NaOH (1 N) at room temperature, hemiacetal **4** crystallized from the reaction mixture as a single diastereomer: 52%, 10 min; 97%, 24 h (see Section4). This proves that the cyclization is stereoselective; all six diastereomers **1** transformed into the same product **4**.

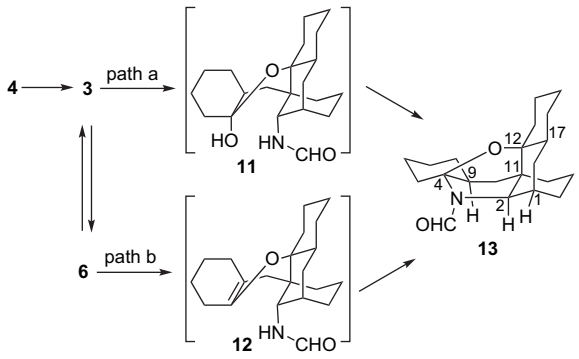
Theoretically, triketone **1** can exist as four racemic and two mesomeric forms, because it has four chiral centers. As it appears from Scheme 2, three of the four chiral carbon atoms are not involved in the cyclization of triketone **1**. Therefore, these atoms retain their configuration in structure **4**. The configuration of these centers in the structure **4** established with X-ray analysis can suggest the configuration of the corresponding C-atoms in the initial form of triketone **1**. Apparently, the intramolecular cyclization occurs on the basis of two diastereomers—a *meso* form with configuration of nonsymmetrical centers *SSSS* and a racemate *SRSS*. These diastereomers differ by the configuration of only those chiral centers, which participate in the intramolecular aldol condensation and which, taking into account the mechanism of the reaction, form the same enol intermediate. Probably, these two diastereomers prevail in the melt just after decyclization of **4**. Apparently, the remaining four diastereomers are isomerized into the aforementioned diastereomers via keto–enol tautomerism in the course of the cyclization. For that, any of them needs to change configuration of only one chiral center.

2.2. Dehydration of hemiacetal 4 in acetic acid

When refluxed in acetic acid, hemiacetal **4** completely turned into the dehydrated product **6**. This compound was prevalent in many reactions conducted with **4** in acid medium on heating. Its formation is a result of transformation of **4** into **3** with subsequent dehydration. The IR spectrum of **6** has an absorption band of carbonyl group at 1715 cm^{-1}. The ^{13}C NMR spectrum has four quaternary carbons (2 sp^3 and 2 sp^2), two tertiary, and the signal for the carbonyl group carbon. Based on the ^{13}C NMR spectroscopic data, the alternative structure **5** with the same molecular weight, which could be formed as the dehydration product of intermediate **2** has been rejected. In the ^1H NMR spectrum, the signals of protons at the tertiary carbon atoms were at low field. The multiplet signal of the C_{12}-H at δ 2.48 has $\sum J_i$=14.5 Hz, which confirms its equatorial position. The multiplet signal of the C_{14}-H at δ 2.37 has $\sum J_i$=33.4 Hz, which confirms its axial position. These data speak about preservation of stereochemistry of the rings A, B, and D in comparison with the starting material **4**. The protons of the secondary C^9 atom appear as two doublets at δ 2.13 and 1.40 with the same coupling constant J_{gem}=16.4 Hz (the signal form and coupling constant for the axial proton at δ 1.40 were estimated from HSQC experiment).



Scheme 4.



Scheme 5.

2.3. Leuckart reaction

Compounds **1**, **4**, and **6** were introduced into a Leuckart reaction (H_2NCHO, HCO_2H). It is known that the similar 1,5-diketone 2-(2-oxocyclohexylmethyl)cyclohexanone **7** and its cyclic form **7a** under Leuckart reaction conditions give the same mixture of perhydro- (PHA) and octahydroacridines (OHA) in the ratio 2:1 (Scheme 3).[13] The formation of the same products could be explained by decyclization of **7a** into diketone **7** under the reaction conditions. Leuckart reaction runs differently with dehydration product of form **7a**—ketone **8** (n=1): stereoisomers of *N*-formyl derivatives with different configuration of the bridge carbon atom are formed.[14] Similar compounds were obtained from the homologue of ketone **8** in the case of five-membered ring (n=0).[15]

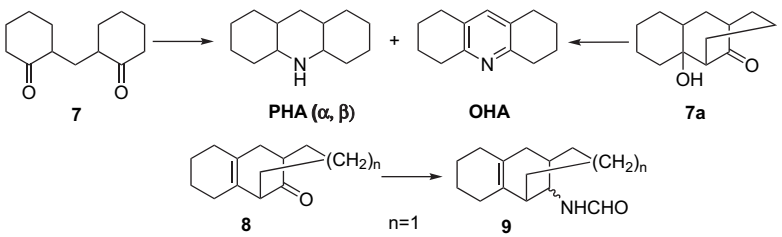
A mixture of eight diastereomers of **10** was obtained under Leuckart reaction conditions with triketone **1** (Scheme 4). Recently, we reported isolation and determination of their stereochemistry.[8]

Three of these diastereomers (**10a**,**b**,**e**) as well as compounds **13** and **15** were obtained from hemiacetal **4** under Leuckart reaction conditions. The *N*-formyl derivative **13** was a prevalent product (Scheme 5), which crystallized from the reaction mixture on cooling in 46% yield. The ratio of **10** and **15** in the residual solution was 1:1 determined by GC–MS. Formation of **13** most likely occurs from the intermediate **3** through the *N*-formyl derivative **11**. Leuckart reaction with ketone **6** gives **13** as the major product in 60% yield. Compounds **10**, **15**, and **18** are also present in the reaction mixture. Two ways of converting **6** into **13** could be suggested: (a) initially **6** undergoes hydration into hemiacetal **3** and than according to Scheme 5; (b) it is also possible that **6** initially forms the *N*-formyl derivative **12** by analogy with ketone **8**, which later transforms into **13**. It is likely that both paths take place in the reaction process.

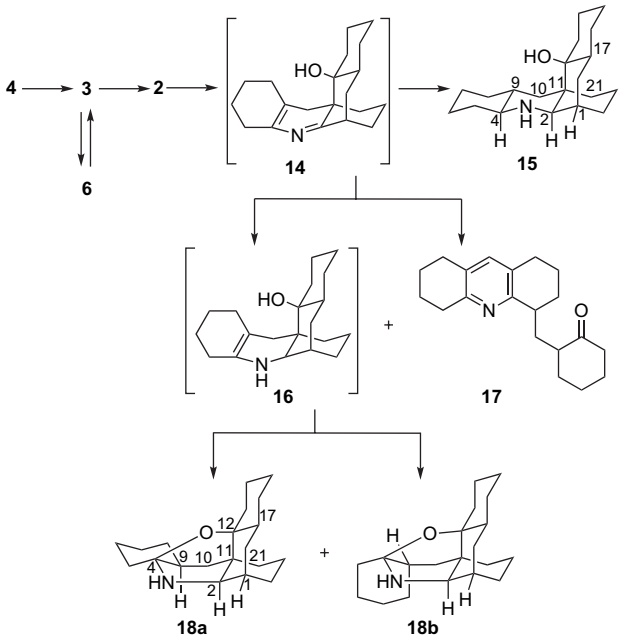
We suppose that formation of **15** and **18** from **6** occurs through the intermediate **2** (Scheme 6). It is known that the formation of PHA from 1,5-diketone **7** occurs through 1,4-dihydropyridine derivative.[16] For compound **2** containing the quaternary carbon, this stage is accompanied by formation of the 3,4-dihydropyridine intermediate **14**, which is reduced under Leuckart reaction conditions into PHA derivative **15** or **18**. We think the formation of **18** undergoes predominantly via this route, but not through hydrolysis of its *N*-formyl derivative **13**. A control experiment showed that when **13** was refluxed in 85% formic acid it was not transformed into **18**.

The IR spectrum of **13** has an absorption band at 1653 cm^{-1}, corresponding to an amide. The ^1H NMR spectrum contains the singlet signal of formyl proton at δ 8.38, the C_2-H doublet, and a multiplet signal of the equatorial proton C_1-H (Table 2). The ^{13}C NMR spectrum contains the signal of the formyl group carbon, the signals of three quaternary carbons and four tertiary carbons. For this compound, as indicated by the spectroscopic data and stereochemical models, the stereochemical character of starting material **4** is retained and six-membered rings with N- and O-heteroatoms are in 'boat' conformation.

The IR spectrum (CCl_4) of **15** shows a broad absorption band at 3231 cm^{-1} indicating the presence of a strong intramolecular hydrogen bond between OH and NH groups. When the solution was diluted 10-fold the appearance of the absorption band did not change. Such a strong intramolecular hydrogen bond can only exist



Scheme 3.



Scheme 6.

due to the spatial proximity of the OH and NH groups that correlates well with the stereochemistry of **15** suggested in Scheme 6. Besides the molecular ion peak the mass spectrum of **15** exhibits an ion peak at *m*/*z* 193 corresponding to a PHA fragment.

The ^{13}C NMR spectrum reveals the presence of two quaternary carbons and five tertiary carbons. The ^{1}H NMR spectrum of **15** shows a singlet signal of an NH group at δ 6.85 (exchangeable with CD_3OD). The C_2-H proton appears like a doublet (Table 2), the C_4-H proton is a triplet of doublets at δ 2.22 ($J_{ax,ax}$=$J_{ax,ax}$=10.3 Hz, $J_{ax,eq}$=3.4 Hz) proving its axial position. Multiplet signals of the C_9-H proton at δ 2.14 and the C_{17}-H proton at δ 1.90 have $\sum J_i$=32 Hz suggesting their axial position resulting from the trans-fusion of the rings through the C_4–C_9 and C_{12}–C_{17} bonds. This stereochemistry in the case of C_4–C_9 fusion is also confirmed by the position of the C_{10}-H_2 protons signals and their coupling picture: the equatorial proton C_{10}-H coupling with two axial C_9-H and C_{10}-H protons gives a doublet of doublets at δ 2.07 (J_{gem}=13.4 Hz, $J_{ax,eq}$=4.5 Hz), and the axial C_{10}-H proton gives a doublet of doublets at δ 0.5 (J_{gem}=13.4 Hz, $J_{ax,ax}$=11.7 Hz).

The 2D NOESY spectrum showed NOEs of the C_2-H proton with the C_4-H, C_{10}-H_{ax}, C_{21}-H_{ax}, and also with the protons of the region δ 1.71–1.86 where the C_1-H and the C_{19}-H_{ax} protons are located. The key HMBC correlations of **13** and **15** are given in Section4.

2.4. Reaction with ammonium acetate in acetic acid

Reaction with ammonium acetate in acetic acid is a traditional chemical method to confirm the presence of 1,5-diketone moieties in a molecule by converting them into the corresponding pyridine derivative. 1,5-Diketone **7** and its cyclic derivative **7a** form OHA[17] in about 70% yield under these conditions. Cupric acetate may be used as an oxidant to boost the yield above 95%.[12b,18]

Compounds **1**, **4**, and **6** were introduced into a reaction with ammonium acetate in acetic acid (reflux 4–5 h). Triketone **1** formed only the OHA derivative **17** according to GC–MS analysis. Therefore, heterocyclization occurred only at the 1,5-diketone moiety of the molecule. Hemiacetal **4** under these reaction conditions initially transformed into **6** (after 1 h of refluxing the main product is **6** by GC–MS). After refluxing for 4–4.5 h the products of N-heterocyclization **18** as a mixture of two diastereomers (the ratio 1:1, 61%) and **17** (30%) were obtained. When ketone **6** was used as a starting material, the same products **17** (40%) and **18a**,**b** (40%) were obtained.

We suppose that the process of heterocyclization of **4** and **6** proceeds via cyclic form **2** (Scheme 6) through the same intermediate **14** as under Leuckart reaction conditions. Research of the reaction pathway of the OHA formation from diketone **7** in the reaction with ammonium acetate in acetic acid has shown that 1,4-dihydropyridine derivative, 1,2,3,4,5,6,7,8,9,10-decahydroacridine, is the intermediate compound. It can undergo further transformation into OHA via two pathways[18]—either by oxidation or by disproportioning into 1,2,3,4,4a,5,6,7,8,9,9a,10-dodecahydroacridine and OHA. Apparently, the transformation of the intermediate **14** into **18** occurs as a result of the realization of the second pathway. At first **14** disproportionates into **17** and **16**, and the latter is cyclized into a mixture of diastereomers **18a**,**b**. However, this does not exclude the possibility of formation of **17** by another pathway—oxidation of **14**. Taking into account the high yield of **17**, this reaction pathway is more likely when the triketone **1** is used as a starting material.

The IR spectrum of **17** shows an absorption band of the carbonyl group at 1709 cm^{-1}. The mass spectrum besides the molecular ion peak has an ion peak at *m*/*z* 187 corresponding to OHA fragment. The structure of **17** was also confirmed by NMR spectroscopy (see Section4).

The NMR spectra of the diastereomers **18a**,**b** are similar (Table 2). The only difference between them in the ^{1}H NMR spectra is the signal position and the coupling constant of the protons adjacent to the secondary C^{10} carbon. This suggests that the distinction in the structures of **18a**,**b** is different ring fusions of the C_4–C_9 bond. As we have noted before, the *O*- and *N*-heterocycles in both structures **18a**,**b** are in 'boat' conformation. Therefore, the C_9-H and one of the C_{10}-H_2 protons are in an eclipsed position. The C_9-H hydrogen atom

Table 2
^{13}C and ^{1}H NMR data of the signals for characteristic atoms of **13**, **15** and **18a**,**b**

Position	**13**		**15**		**18a**		**18b**	
	δ ^{13}C	δ ^{1}H ()[a]	δ ^{13}C	δ ^{1}H ()[a]	δ ^{13}C	δ ^{1}H ()[a]	δ ^{13}C	δ ^{1}H ()[a]
1	28.5	2.56 (m, $\sum J_i$=22)	34.7	1.73–1.77 (m)	33.7	1.70–1.74 (m)	34.5	1.64–1.66 (m)
2	60.4	3.59 (d, 3.4)	67.4	2.59 (d, 3.4)	59.3	2.82 (d, 2.9)	60.4	2.73 (d, 2.7)
4	82.6		64.2	2.22 (td, 3.3, 10)[b]	80.3		80.7	
9	41.7	1.65–1.72 (m, $\sum J_i$=33)	40.1	2.10–2.15 (m, $\sum J_i$=32)	39.8	1.76–1.82 (m)	40.6	1.68–1.74 (m)
10	36.7	1.47 (dd, 3.6, 14)[b]	43.1	2.07 (dd, 4.5, 13.4)	37.4	1.43 (dd, 4.1, 13.5)[b]	39.0	2.0 (dd, 10.5, 13.2)
		1.36 (dd, 11.2, 14)		0.5 (dd, 11.7, 13.4)		1.35 (dd, 11.4, 13.5)[b]		0.58 (dd, 6.6, 13.2)
11	33.8		38.9		33.5		33.7	
12	77.7		76.6		76.5		76.4	
17	41.1	1.72–1.78 (m)	41.4	1.87–1.94 (m, $\sum J_i$=32)	41.2	1.66–1.69 (m)	40.7	1.68–1.74 (m)
21	32.0	1.67–1.75 (m)	35.6	1.79–1.82 (m)	31.4	1.62–1.68 (m)	31.2	1.71–1.76 (m)
		1.20 (ddd, 2.2, 5.5, 7.8)[b]		1.05 (ddd, 7.3, 12.5, 14.5)		1.05 (ddd, 7.3, 12.7, 14.7)		1.05 (ddd, 7.3, 12.5, 14.7)

[a] (Multiplicity, coupling constant or $\sum J_i$).
[b] The forms of proton signals and their coupling constants were determined from 1D selective COSY and NOE difference spectra.

is pseudoaxial in the structure **18a** and pseudoequatorial in **18b**. In the isomer **18a** the pseudoaxial C_{10}-H atom is in an eclipsed position with the pseudoaxial C_9-H atom. As a result the C_{10}-H proton in the ^{1}H NMR spectrum appears as a doublet of doublets at δ 1.35 with $J_{ax,ax}$=11.4 Hz and J_{gem}=13.5 Hz. A doublet of doublet signal of the pseudoequatorial C_{10}-H proton at δ 1.43 has the following coupling constants $J_{ax,eq}$=4.1 Hz and J_{gem}=13.5 Hz. The pseudoequatorial C_9-H proton is in an eclipsed position with the pseudoequatorial C_{10}-H proton in the isomer **18b**. As a result the C_{10}-H proton in the ^{1}H NMR spectrum appears as a doublet of doublets at δ 2.0 with $J_{eq,eq}$=10.5 Hz and J_{gem}=13.2 Hz. The pseudoaxial C_{10}-H proton gives a doublet of doublet signal at δ 0.58 with $J_{ax,eq}$=6.6 Hz and J_{gem}=13.2 Hz.

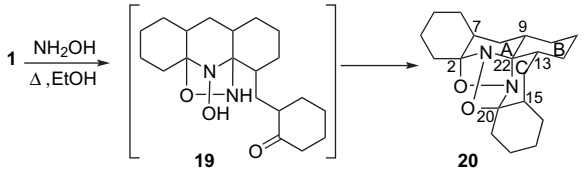
The stereochemistry of the diastereomers **18a**,**b** was confirmed also by 2D NOESY experiment: NOE was observed in the case of **18a** between the C_2-H and C_9-H protons, indicating their spatial proximity. In contrast, NOE was not observed between the same protons in **18b**. The key HMBC correlations of **18a**,**b** are given in Section4.

It is noteworthy that the values of chemical shift and coupling constants of the C_{10}-H_2 protons for **18a** are similar to the corresponding values for the analogous protons in **13** (Table 2). This fact testifies to the same pattern of rings' fusion through the C_4–C_9 bond in these compounds.

We have to point out that hemiacetal **4** forms other products in reactions with *N*-nucleophiles than triketone **1**, unlike the cyclic form of diketone **7a**, which forms the same products as diketone **7**. This occurs due to the fact that in contrast with the one-step transformation of **7a**→**7** the conversion **4**→**1** requires three steps with formation of the reactive intermediates **3** and **2**. They react with the nucleophiles in the solution before they can undergo decyclization into **1**.

2.5. Reaction with hydroxylamine

The reaction of triketone **1** with hydroxylamine hydrochloride in refluxing ethanol furnished **20**. We assume that this transformation goes through **19** (Scheme 7). A similar tetracyclic compound was obtained earlier from 1,5-diketone **7**.[19] Hemiacetal **4** does not react with hydroxylamine due to poor solubility in ethanol. Ketone **6** is transformed under these conditions into OHA **17** in 50% yield (see Section 4).



Scheme 7.

The IR spectrum of **20** reveals the absence of the absorption bands for functional groups. The ^{13}C NMR spectrum contains the signals of three quaternary carbons and the signals of four tertiary carbons. Stereochemical models demonstrated that the three rings A, B, and C in **20** are rigidly bonded with two five-membered rings and can exist only in one fusion type—trans–syn–cis.

3. Conclusion

In conclusion, we have shown that the cyclic form of 1,5,9-triketone 2,6-bis[(2-oxocyclohexyl)methyl]cyclohexanone in the melt transformed into a mixture of six diastereomers of triketone open form **1**. The composition of the diastereomers in the melt changes with the heating time duration. Under basic conditions the diastereomers **1** stereoselectivity transformed back into **4**. When the melt reacted with *N*-nucleophiles it yielded the products of heterocyclization of the open form with no traces of its isomerization into the cyclic form. On the other hand, under the same conditions the cyclic form **4** and the product of its dehydration **6** formed products suggesting their initial isomerization into intermediate cyclic forms **2**, **3**, and a small amount of the open form of triketone **1**.

4. Experimental

4.1. General

General methods have been described previously.[8] GC–MS conditions for Section4.3: $T_{injector}$=T_{column}=200 °C.

4.2. Synthesis of 3,22-dioxahexacyclo[9.7.3.1^{4,12}.0^{1,2}.0^{4,9}.0^{12,17}]-docosan-2-ol (4)

A 250 mL three-necked flask equipped with a dropping-funnel, thermometer and backflow condenser was charged with cyclohexanone (49 mL, 0.48 mol) and paraformaldehyde (5 g, 0.24 mol). A solution of 2 N CH_3ONa (0.74 g Na in 16 mL methanol) was added dropwise for 30 min. The mixture was heated instantly to 80–85 °C, turned yellow and paraformaldehyde was dissolved. Once the addition was complete, the cloudy suspension was maintained at 60–70 °C for an additional 1 h. The mixture was neutralized with acetic acid on cooling. White crystals of **4** were filtered after cooling to 0 °C for 24 h, washed with water–ethanol solution (1:1).

Yield 6.6 g (13%); mp 193–194 °C; recrystallization from diethyl ether of diethyleneglycol provided pure product, mp 195.5–196 °C; R_f 0.4 (10:1 hexane/ethyl acetate); t_R 10.67; GC–MS (EI) *m*/*z* (%): 318 (M^+, 2), 300 (M^+-H_2O, 100), 220 (57), 190 (37.5), 123 (21), 110 (52), 98 (62.5), 79 (25), 67 (30), 55 (36); IR (KBr) ν 3389 (OH), 2934, 2848, 1460, 1443, 944 cm^{-1}; ^{1}H NMR δ 2.31 (1H, s, O*H*), 2.04–1.10 (29H, m); ^{13}C NMR δ C-quaternary: 98.1 (C^2), 95.9 (C^4), 78.7 (C^{12}), 37.5 (C^{11}); C-tertiary: 40.8 (C^9), 39.5 (C^1), 39.3 (C^{17}); C-secondary: 35.3, 33.6, 31.9, 31.3, 28.9, 28.6, 28.4, 27.6, 26.1, 25.4, 23.0, 21.2, 21.0.

4.3. Thermal decyclization of hemiacetal 4 into triketone 1

Four capillaries were charged by hemiacetal **4** (3 mg) and heated in a melting point apparatus at 194 °C for 5, 10, 30 and 60 min. The same experiment was conducted at 210 °C. After cooling the resulting solid was analyzed by GC–MS (see Table 1).

In the reactions with nucleophiles triketone **1** was obtained by heating hemiacetal **4** (0.5–1 g) in a flask at 193–195 °C for 10 min.

*4.3.1. 2,6 Bis[(2-oxocyclohexyl)methyl]cyclohexanone (**1**)*

Yellow oil; t_R 23.55–24.92; GC–MS (EI) *m*/*z* (%): 300 (M^+-H_2O, 26), 220 (28), 208 (17.3), 202 (47.5), 190 (50), 123 (50), 110 (100), 98 (106), 67 (37), 55 (58); IR ($CHCl_3$) ν 3020, 2939, 2861, 1705 (C=O), 1449 cm^{-1}.

4.4. Cyclization of triketone 1 into hemiacetal (4)

Triketone **1** (0.5 g) was dissolved in ethanol (1 mL). Ethanol solution of 1 N NaOH (1.5 mL) was added. In several minutes the product crystallized from the reaction mixture. Then (after 10 min, 1 h, 2 h, 12 h and 24 h) the reaction mixture was neutralized by adding 30% HCl solution. White crystals of **4** (identified by GC–MS and mp) were filtered and washed with water–ethanol solution (1:1). Depending on time of exposure yield of **4** varied: 10 min, 52%; 1 h, 77%; 2 h, 85%; 12 h, 94%; 24 h, 97%.

4.5. Dehydration of hemiacetal 4 in acetic acid

A mixture of **4** (2 g) in acetic acid (10 mL) was refluxed for 30 min. Acetic acid was removed by distillation under reduced pressure. The residue was neutralized with a saturated aqueous NaOH solution on cooling. The obtained solid of **6** was filtered.

*4.5.1. 2-Oxapentacyclo[8.8.0.3^{10,12}.0^{3,8}.0^{1,14}]heneicos-3(8)-en-11-on (**6**)*

Yield 1.58 g (84%); white crystals; mp 116–118 °C (ethanol); R_f 0.65 (12:1 hexane/ethyl acetate); t_R 10.60; GC–MS (EI) *m*/*z* (%): 300 (M^+, 100), 288 (20), 239 (37), 173 (25), 91 (24); IR (KBr) ν 2945, 2851, 1715 (C=O), 1480, 1444, 1179, 1148, 1123, 958 cm^{-1}; for ^{1}H NMR data see the text; ^{13}C NMR δ 217.2 (C=O); C-quaternary: 142.6 (C^3), 103.8 (C^8), 82.0 (C^1), 51.7 (C^{10}); C-tertiary: 46.3 (C^{12}), 39.7 (C^{14}); C-secondary: 37.8, 36.3, 35.5, 32.0 (C^9), 27.9, 27.7, 27.3, 26.9, 25.9, 23.1, 22.9, 21.5, 20.9. Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96, H, 9.39. Found: C, 79.85; H, 9.50.

4.6. Leukart reaction with hemiacetal 4

A 50 mL three-necked flask equipped with a dropping-funnel, thermometer, and descending condenser, charged with formamide (6 mL, 0.15 mol), was heated to 160 °C. A suspension of **4** (3.5 g, 0.011 mol) in 85% formic acid (10 mL) was added for 60 min. The temperature was maintained at 160–170 °C for 2.5 h. The water formed during reaction was removed by distillation. After completion of the reaction the resulting mixture was cooled to room temperature. The obtained white solid of **13** was filtrated after 24 h and washed with petroleum ether. The solvent was removed by distillation under reduced pressure from filtrate. The residue was diluted with water. The obtained white crystals of **15** were filtered and washed with water. The filtrate was basified with a saturated aqueous Na_2CO_3 solution and extracted with CH_2Cl_2 (2×15 mL). The organic layer was washed with brine (1×20 mL), dried over $MgSO_4$ and analyzed by GC–MS as a diastereomer mixture of **10** with three prevalent isomers (**10a**,**b**,**e**, 67%) and **15**.

*4.6.1. 22-Oxa-3-azahexacyclo[9.7.3.1^{4,12}.0^{2,11}.0^{4,9}.0^{12,17}]docasan-3-carbaldegid (**13**)*

Yield 1.66 g (46%); white crystals; mp 177–178 °C (ethanol); R_f 0.54 (2:1 hexane/ethyl acetate); t_R 13.42; GC–MS (EI) *m*/*z* (%): 329 (M^+, 100), 300 (11.5), 219 (32), 204 (33), 191 (19), 174 (50), 91 (19), 55 (15); IR (KBr) ν 2932, 2850, 1653 (NCHO), 1454, 1378, 1360, 1342, 1322, 1188, 1097, 1005, 960, 776, 714, 503 cm^{-1}; for ^{1}H NMR data see Table 2; ^{13}C NMR δ 159.1 (NCHO); C-quaternary: 82.6 (C^4), 77.7 (C^{12}), 33.8 (C^{11}); C-tertiary: 60.4 (C^2), 41.7 (C^9), 41.1 (C^{17}), 28.5 (C^1); C-secondary: 36.7 (C^{10}), 33.2, 32.0 (C^{21}), 31.4, 31.2, 30.2, 29.6, 28.7, 26.1, 25.2, 22.4, 21.3, 21.0; key HMBC correlations (H to C): C_1-H/C^2, C^{11}, C^{17}, C_2-H/C^1, C^4, C^{10}, C^{11}, C^{12}, C^{21}, NCHO, C_9-H/C^4, C^{10}, C_{10}-H_2/C^2, C^4, C^9, C^{11}, C^{12}, C^{21}, C_{21}-H_{ax}/C^2, C^{10}, C^{11}, C^{12}. Anal. Calcd for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.83; H, 9.58; N, 4.13.

*4.6.2. 3-Azapentacyclo[9.7.3.0^{2,11}.0^{4,9}.0^{12,17}]heneicosan-12-ol (**15**)*

Yield 0.68 g (20.4%); white crystals; mp 199.5–200 °C (ethanol); R_f 0.49 (6:1, hexane/ethyl acetate); t_R 11.55; GC–MS (EI) *m*/*z* (%): 303 (M^+, 17.5), 193 (100), 150 (17.5); IR (KBr) ν 3254.5 (NH, OH), 2932, 2849.6, 1448.2 cm^{-1}; for ^{1}H NMR data see Table 2; ^{13}C NMR δ C-quaternary: 76.6 (C^{12}), 38.9 (C^{11}); C-tertiary: 67.4 (C^2), 64.2 (C^4), 41.4 (C^{17}), 40.1 (C^9), 34.7 (C^1); C-secondary: 43.1 (C^{10}), 35.6 (C^{21}), 33.2, 33.1, 31.9, 31.7, 31.0, 29.2, 26.6, 25.9, 25.5, 22.1, 21.7; key HMBC correlations (H to C): C_1-H/C^2, C^{11}, C_2-H/C^1, C^4, C^{10}, C^{11}, C^{12}, C_4-H/C^2, C^9, C^{10}, C_9-H/C^4, C^{10}, C_{10}-H_2/C^2, C^4, C^9, C^{11}, C^{12}, C^{21}, C_{21}-H_{ax}/C^2, C^{10}, C^{11}, C^{12}. Anal. Calcd for $C_{20}H_{33}NO$: C, 79.15; H, 10.96; N, 4.62. Found: C, 78.96; H, 10.65; N, 4.52.

4.7. Leukart reaction with ketone 6

A mixture of **6** (0.3 g, 1 mmol) and formamide (1 mL, 25 mmol) in 85% formic acid (2 mL) was heated for 1.5 h following the procedure described in Section4.6. White crystals of **13** (0.19 g, 60%) were obtained when ethanol (3 mL) was added to the reaction mixture in 24 h. The filtrate was diluted with water, basified with a saturated aqueous Na_2CO_3 solution, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and analyzed by GC–MS as a mixture of **13** (39%), **15** (14.7%), **18a**,**b** (13%), and **10** (31%, isomers **10a**,**b** prevalent).

4.8. Reaction of hemiacetal 4 with ammonium acetate in acetic acid

A mixture of **4** (1.908 g, 6 mmol) and ammonium acetate (1.908 g, 24.7 mmol) in acetic acid (12 mL) was refluxed for 4–4.5 h. The reaction was monitored by TLC. After completion of the reaction acetic acid was removed by distillation under reduced pressure. The residue was basified with a saturated aqueous Na_2CO_3 solution on cooling and extracted with CH_2Cl_2 (3×20 mL). The organic layer was washed with brine (2×20 mL) and dried over $MgSO_4$. The solvent was removed by distillation. The residue (1.61 g) was analyzed by GC–MS as a mixture of two diastereomers **18a** (29.4%) and **18b** (32%), **17** (30%), and **6** (8.5%), which were separated by column chromatography (Al_2O_3, light petroleum). Yields: **18a** (0.28 g, 17.4%), **18b** (0.38 g, 24%), **6** (0.08 g, 5.2%), **17** (0.35 g, 21.5%).

*4.8.1. 22-Oxa3-azahexacyclo[9.7.3.1^{4,12}.0^{2,11}.0^{4,9}.0^{12,17}]docosan (**18**)*

The IR ($CHCl_3$) spectra of **18a**,**b** have the same characteristic bands: ν 3338, 2923, 2850, 1446, 1268, 1030, 970 cm^{-1}; GC–MS (EI) data of **18a**,**b** are the same, *m*/*z* (%): 301 (M^+, 45), 191 (100), 258 (51); for ^{1}H NMR data of **18a**,**b** see Table 2; key HMBC correlations (H to C) of **18a**,**b**: C_1-H/C^2, C^{11}, C_2-H/C^1, C^4, C^{10}, C^{11}, C^{12}, C^{21}, C_9-H/C^4, C^{10}, C^{11}, C^{12}, C_{10}-H_2/C^2, C^4, C^9, C^{11}, C^{12}, C^{21}, C_{21}-H_{ax}/C^2, C^{10}, C^{11}, C^{12}.

*4.8.2. Isomer **18a***

White crystals; t_R 10.52; mp 92–93 °C; R_f 0.12 (2:1 hexane/ethyl acetate); ^{13}C NMR δ C-quaternary: 80.3 (C^4), 76.5 (C^{12}), 33.5 (C^{11}); C-tertiary: 59.3 (C^2), 41.2 (C^{17}), 39.8 (C^9), 33.7 (C^1); C-secondary: 37.4 (C^{10}), 36.3, 31.8, 31.4 (C^{21}), 31.0, 30.7, 29.9, 28.9, 26.4, 25.8, 22.5, 21.8, 20.9. Anal. Calcd for $C_{20}H_{31}NO$: C, 79.68; H, 10.36; N, 4.65. Found: C, 79.55; H, 10.22; N, 4.60.

*4.8.3. Isomer **18b***

Yellow oil; t_R 10.48; R_f 0.63 (6:1 hexane/ethyl acetate); ^{13}C NMR δ C-quaternary: 80.7 (C^4), 76.4 (C^{12}), 33.7 (C^{11}); C-tertiary: 60.4 (C^2), 40.7 (C^{17}), 40.6 (C^9), 34.5 (C^1); C-secondary: 39.0 (C^{10}), 36.9, 32.7, 32.0, 31.2 (C^{21}), 31.0, 30.1, 28.9, 26.2, 25.8, 23.3, 21.9, 21.2; HRMS (ESI) calcd for $C_{20}H_{31}NO$, 301.4663; found, 301.4697.

4.9. Reaction of triketone 1 with ammonium acetate in acetic acid

Following the procedure described in Section4.8, the reaction of **1** (0.636 g, 2 mmol) and ammonium acetate (0.636 g, 8 mmol) in acetic acid (5 mL) (refluxing 5 h) furnished **17** (100% by GC–MS), which was purified by column chromatography (Al_2O_3, light petroleum). Yield 0.4 g (68%).

*4.9.1. 4(2-Oxocyclohexylmethyl)1,2,3,4,5,6,7,8-octahydroacridine (**17**)*

Yellow oil; R_f 0.47 (4:1 hexane/ethyl acetate); IR (thin film) ν 2931, 2857, 1709 (C=O), 1599, 1562, 1450 cm^{-1}; t_R 12.08; GC–MS (EI) *m*/*z* (%): 297 (M^+, 3), 200 (100), 187 (81); ^{1}H NMR δ 6.98 (1H, s,

C_9-H), 2.89–1.3 (26H, m); ^{13}C NMR δ 213.8 (C=O); C-quaternary: 157.3, 153.9 (C^{4a}, C^{5a}), 129.1, 128.8 (C^{8a}, C^{9a}); C-tertiary: 137.2 (C^{9}), 48.9, 37.7 (C^{4}, C^{11}); C-secondary: 42.1, 34.8, 33.9, 32.3, 29.2, 28.5, 28.3, 28.2, 27.7, 25.0, 23.4, 19.8. HRMS (ESI) calcd for $C_{20}H_{27}NO$, 297.4345; found, 297.4372.

4.10. Reaction of ketone 6 with ammonium acetate in acetic acid

Following the procedure described in Section4.8, the reaction of **6** (0.15 g, 0.5 mmol) and ammonium acetate (0.15 g, 2 mmol) in acetic acid (3 mL) furnished a mixture of **17** (40%), **18a**,**b** (40%), and starting material **6** (10%) (by GC–MS analysis).

4.11. Reaction of triketone 1 with hydroxylamine hydrochloride

Triketone **1** (0.5 g, 1.57 mmol) was dissolved in ethanol (5 mL) and a solution of hydroxylamine hydrochloride (0.38 g, 5.5 mmol) and sodium acetate (0.9 g) in water (2 mL) was added. The mixture refluxed for 2.5 h furnished product **20**, crystallizing from the reaction mixture on cooling (0 °C) for several days. The residual solution was diluted with water and extracted with CH_2Cl_2 (2×25 mL). The organic layer was washed with brine (1×30 mL), dried over $MgSO_4$, and analyzed by TLC and GC–MS as product **17**.

*4.11.1. 1,23-Diaza-21,24-dioxaheptacyclo-[11.8.1.1^{2,23}.1^{20,22}.0^{2,7}.0^{9,22}.0^{15,20}]tetracosan (**20**)*

Yield 0.143 g (27.5%); colorless crystals; R_f 0.70 (10:1 hexane/ethyl acetate); mp 156–157 °C (ethanol); IR (KBr) ν 3007, 2994, 2925, 2858, 1449, 1424, 1153, 812 cm^{-1}; ^{1}H NMR δ 2.71 (2H, dd, J=3.4, 14.2 Hz, CH_2), 2.15 (1H, ddd, J=3.5, 6.7, 10.4 Hz, CH_2), 1.92–1.02 (27H, m); ^{13}C NMR δ C-quaternary: 104.6, 103.0 (C^2, C^{20}), 92.6 (C^{22}); C-tertiary: 39.8, 39.8, 39.1, 37.5 (C^7, C^9, C^{13}, C^{15}); C-secondary: 34.2, 33.9, 33.5, 32.1, 31.0, 30.8, 29.5, 29.0, 25.9, 24.7 (2C), 23.3, 23.1; HPLC–MS (ESI): m/z 331 $[M+H]^+$. Anal. Calcd for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.81; H, 9.07; N, 8.56.

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