

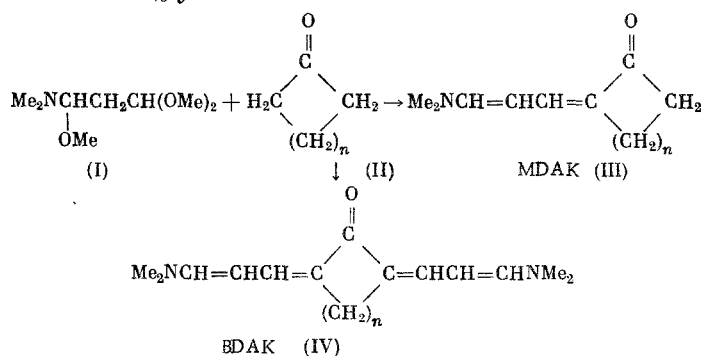
SYNTHESIS OF UNSATURATED δ -AMINO KETONES
CONTAINING A MACROCYCLIC FRAGMENT

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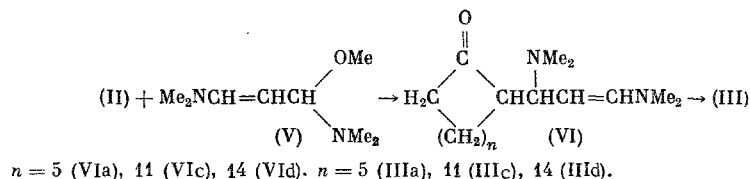
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As a continuation of studying unsaturated ω -aminocarbonyl compounds we studied in the present paper the possibility of synthesizing previously unknown dienic mono- δ -(MDAK) and bis- δ, δ' -dimethylamino ketones (BDAK) that contain macrocycles.

A simple method was described by us previously [1-3] for the synthesis of MDAK (III) and BDAK (IV) by the condensation of 1,1,3-trimethoxy-3-dimethylaminopropane (I) with cyclic ketones (II) ($n = 2, 3, 4$). When this method was applied to some macrocyclic (II) we found that only MDAK (IIIa-d), where $n = 5, 7, 11, 14$,* could be obtained by this route in 40-45% yields.



The BDAK (IV) are also not formed from macrocyclic ketones when the latter are condensed with β -dimethylaminoacrolein acetal aminal (V), whereas, when $n = 3$, (III) and (IV) were obtained in high yield from (V) and cyclohexanone. Only the MDAK can be obtained from macrocyclic ketones and (V), in which connection the reaction of (V) with (II) ($n = 11, 14$) gives diamines (VIc, d) in 70-75% yields, whose structure was confirmed by the PMR, IR, and mass spectral data. In the presence of SiO_2 and using CHCl_3 as the medium, (VIc, d) are quantitatively converted to MDAK (IIIc, d) at 20°C .



It should be mentioned that the partial cleavage of $\text{NH}(\text{CH}_3)_2$ from (VI), which leads to (III), occurs only in very dilute solutions of (VI) (hexane, CHCl_3 , or $\text{C}_2\text{H}_5\text{OH}$ when $C = 0.000015$ mole/liter), which is readily seen by the appearance of a long-wave absorption maximum in the 340-378 nm region.

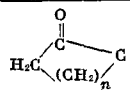
In harmony with the PMR spectral data, the reaction product from the condensation of (V) with (II) ($n = 5$) is a mixture of (VIa) and (IIIa) in a 1:2 ratio. The reaction of (V) with (II) ($n = 3, 7$) under the same conditions gave only the MDAK, while the diamines (VI) were not detected by the PMR method.

Previously [4, 5] it was postulated that the diamines (VI) are intermediates in the formation of dienic amines from (V) and compounds with an active methylene group, but we were the first to obtain experimental

*In the acyclic series the BDAK are formed only from ketones that are simultaneously devoid of substituents in the α and α' positions. Only the MDAK are formed even from diethyl ketone and dioctyl ketone.

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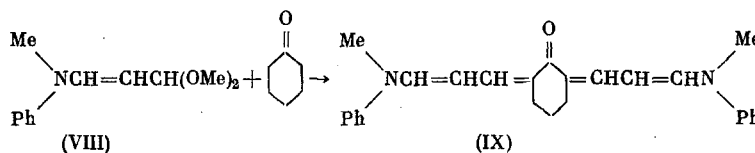
TABLE 1. PMR Spectral Data for Dienones in CDCl₃

Com- pound	δ, ppm				J, Hz		
		NMe ₂	H _β	H _γ	H _δ	J _{β,γ}	J _{γ,δ}
(IIIa) *	1,54-2,63	2,87	7,3	5,05	6,69	12,5	12,5
(IIIb)	1,25-2,47	2,82	6,81	5,06	6,54	12,5	12,5
(IIIc) *	1,28-2,47	2,88	7,21	5,16	6,66	12	12,5
(IIId)	1,2-2,62	2,82	7,05	5,07	6,55	12	12,5
(X)	1,2-2,7	3,22 †	7,24	5,56	7,19	11,5	12,5

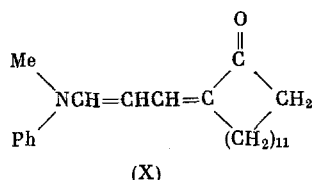
*Chemical shifts relative to TMS.

†Chemical shift of NCH₃ and protons of NC₆H₅ in 6.9-7.3 ppm region.

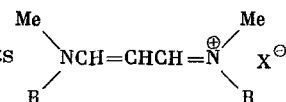
confirmation of this postulation. Together with the use of (I) and (V) to synthesize unsaturated δ-amino ketones, we checked the possibility of using some other malondialdehyde derivatives for this purpose. Thus, using the method to obtain (V) [6], we obtained from β-methylanilinoacrolein (VII) not the acetal aminal, but instead acetal (VIII), the reaction of which with cyclohexanone (2 : 1, 120°, 2 h) gives the polyenic ketone (IX) in 73% yield.



The reaction of (VIII) with cyclotetradecanone gave only dienic ketone (X) in 12% yield.



Attempts to obtain the polyenic ketone (IV) (n = 11) by condensing the trimethine salts



where R = CH₃, C₆H₅; X = I, ClO₄, with cyclotetradecanone using alkali metal alcoholates [7, 8] also proved unsuccessful.

The structure of the obtained ketones was proved by the elemental analysis data, and also by the UV, IR, PMR, and mass spectral data (see the Experimental section and Table 1). The configuration of the double bonds in the ketones was established by the PMR method on the basis of comparing the values of the SSCC between the methine protons with the values of the constants in the dimethylaminocarbonyl compounds that were studied by us previously [9]. All of the dienones have a trans configuration of the protons at the γ,δ double bond (J_{γ,δ} = 12.5 Hz) and exist predominantly as the S-trans conformers at the β,γ bond (J_{β,γ} = 11.5-12.5 Hz). In the UV spectrum of the (III) with n = 5, 7, 11, 14 the long-wave absorption maximum shows a hypsochromic shift of 10-20 nm when compared with the λ_{max} of the ketones, with n = 2, 3, 4, that were studied by us previously [1, 2], which indicates that the planarity of the conjugated system is upset somewhat as the number of units in the ring increases.

EXPERIMENTAL

The PMR spectra were taken on a Varian DA-60-1L instrument using HMDS as the internal standard, the UV spectra were taken on a Specord UV-VIS instrument, and the IR spectra were taken on a UR-10 instrument. The described experiments were run using an equimolar ratio of the cycloalkanone and either (V) or (I); a twofold excess of the latter, more drastic reaction conditions, and also the reaction of (V) or (I) with the isolated (III) dienones, failed to lead to the formation of (IV).

Condensation of Cyclooctanone with β-Dimethylaminoacrolein Acetal Aminal (V). A mixture of 0.25 g of cyclooctanone and 0.32 g of (V) was heated for 1.5 h at 80-90° and then evaporated. We obtained 0.38 g of a mixture of (VIa) and (IIIa) in a 1 : 2 ratio, which was slightly contaminated with β-dimethylaminoacrolein (XI)

(n_D^{20} 1.5380). To a solution of 0.1 g of this mixture in 2 ml of CHCl_3 was added 0.6 g of SiO_2 , and after 1 h the mixture was filtered and evaporated. We obtained 80 mg of an oily product with n_D^{20} 1.5745, which, based on the PMR spectrum, is (IIIa) contaminated with (XI). To isolate the pure (IIIa) the evaporated reaction mixture (0.28 g, n_D^{20} 1.5380) was subjected to preparative TLC on SiO_2 in the system 1 : 2 acetone-hexane, with elution by CHCl_3 . We isolated 0.15 g (49%) of (IIIa) with mp 92-93°. Found: C 75.16; H 10.23%. $\text{C}_{13}\text{H}_{21}\text{NO}$. Calculated: C 75.31; H 10.21%. Ultraviolet spectrum ($\text{C}_2\text{H}_5\text{OH}$, λ_{max} , nm): 390 (ϵ 25000). Mass spectrum (m/e): 207 (M^+). Infrared spectrum (KBr, ν , cm^{-1}): 1643 (CO), 1540, 1614 (C=C).

Condensation of Cyclodecanone with (V). A mixture of 0.21 g of cyclodecanone and 0.23 g of (V) was heated for 1.5 h at 90-95°, evaporated, dry acetone was added, and the precipitate was separated and washed well with acetone to give 0.1 g (32%) of (IIIb) with mp 122-123°. Found: C 76.40; H 10.65; N 5.78%. $\text{C}_{15}\text{H}_{25}\text{NO}$. Calculated: C 76.54; H 10.71; N 5.95%. Ultraviolet spectrum ($\text{C}_2\text{H}_5\text{OH}$, λ_{max} , nm): 377 nm (ϵ 37500). Mass spectrum (m/e): 235 (M^+). Infrared spectrum (KBr, ν , cm^{-1}): 1640 (CO), 1580, 1610 (C=C).

Condensation of Cyclotetradecanone with (V). A mixture of 0.4 g of cyclotetradecanone and 0.4 g of (V) was heated at 85-90° for 2 h and then evaporated. We obtained 0.68 g of a yellow semicrystalline product, a solution of which in dry acetone was cooled to give 0.41 g of (VIc) with mp 68-72°. PMR spectrum (CDCl_3 , δ , ppm): 1.3-2.5 m (CH_2), 2.05 s ($\text{N}(\text{CH}_3)_2$ at C_β), 2.6 s ($\text{N}(\text{CH}_3)_2$ at C_δ), 3.78 t (H_γ), 5.9 d (H_δ), $J_{\gamma,\delta} = 13.5$, $J_{\gamma,\beta} = 9$ Hz. The H_β signals are masked by the signals of the ring protons. Mass spectrum (m/e): 336 (M^+). Infrared spectrum (KBr, ν , cm^{-1}): 1700 (CO), 1605, 1635, 1653 (C=C). Ultraviolet spectrum (solvent, λ_{max} , nm, C, mole/liter): hexane, 235 (ϵ 6850), 340 (ϵ 5660), $8.48 \cdot 10^{-4}$; 235 (ϵ 4720), 340 (ϵ 11800), $1.69 \cdot 10^{-5}$; CHCl_3 , 367 (ϵ 25000), $1.52 \cdot 10^{-5}$; $\text{C}_2\text{H}_5\text{OH}$, 378 (ϵ 31400), $2 \cdot 10^{-5}$.

Cleavage of $\text{NH}(\text{CH}_3)_2$ from (VIc). a) To a solution of 0.5 g of (VIc) in 5 ml of CHCl_3 was added 1.5 g of SiO_2 , after 1 h the SiO_2 was separated, the filtrate was evaporated, and dry acetone was added to the residue. We isolated 0.4 g of (IIIc) as a yellow precipitate with mp 130-132°. Found: C 77.98; H 11.26; N 5.30%. $\text{C}_{19}\text{H}_{33}\text{NO}$. Calculated: C 78.29; H 11.41; N 4.81%. Ultraviolet spectrum (λ_{max} , nm): $\text{C}_2\text{H}_5\text{OH}$, 378 (ϵ 40200); CHCl_3 , 367 (ϵ 36400). Mass spectrum (m/e): 336 (M^+). Infrared spectrum (KBr, ν , cm^{-1}): 1635 (CO), 1570, 1600 (C=C).

b) A solution of 7 mg of (VIc) in 1 liter of CHCl_3 was evaporated in vacuo at 20° and the residue, based on the PMR spectrum in CDCl_3 , is a mixture of (IIIc) and (VIc) in a 2 : 1 ratio.

Condensation of Cycloheptadecanone with (V). A mixture of 0.35 g of cycloheptadecanone and 0.22 g of (V) was heated for 3 h at 90-95° and then evaporated. We obtained 0.4 g of (VIId) as an oil, n_D^{20} 1.5080. PMR spectrum (CDCl_3 , δ , ppm): 1.2-2.5 m (CH_2), 1.97 s ($\text{N}(\text{CH}_3)_2$ at C_β), 2.52 s ($\text{N}(\text{CH}_3)$ at C_δ), 3.69 t (H_γ), 5.81 d (H_δ), $J_{\gamma,\delta} = 13.5$, $J_{\gamma,\beta} = 9$ Hz. The H_β signals are masked by the signals of the ring protons. Ultraviolet spectrum ($\text{C}_2\text{H}_5\text{OH}$, λ_{max} , nm): 378 (ϵ 27000).

When 0.3 g of (VIId) was subjected to preparative TLC on SiO_2 in the system 1 : 2 acetone-hexane, using CHCl_3 for elution, we obtained 0.17 g of (IIIId) as a bright yellow oil, n_D^{20} 1.5680. Ultraviolet spectrum ($\text{C}_2\text{H}_5\text{OH}$, λ_{max} , nm): 378 (ϵ 36000). Infrared spectrum (ν , cm^{-1}): 1640 (CO), 1575, 1605 (C=C).

Condensation of Cyclotetradecanone with (I). A mixture of 0.2 g of cyclotetradecanone and 0.18 g of (I) was heated for 4 h at 95-100° and then evaporated in vacuo. We obtained a mixture of (IIIc) and (XI). After preparative TLC on SiO_2 (system: 3 : 2 CHCl_3 -acetone, elution with CHCl_3) we obtained 0.12 g of crystalline (IIIc).

β -Methylanilinoacrolein Acetal (VIII). As described in [5], we obtained (VIII) from (VII) in 20% yield, bp 98-103° (0.25 mm), n_D^{20} 1.5650. Found: C 69.61; H 8.27; N 6.62%. $\text{C}_{12}\text{H}_{17}\text{NO}_2$. Calculated: C 69.54; H 8.27; N 6.76%. PMR spectrum (CCl_4 , δ , ppm): 2.92 s ($\text{N}-\text{CH}_3$), 3.12 s (OCH_3), 4.36 t (H_β), 4.76 (H_α), 6.63-7.09 m (H_γ and C_6H_5), $J_{\alpha,\beta} = 5$, $J_{\beta,\gamma} = 13.5$ Hz.

Condensation of Cyclotetradecanone with (VIII). A mixture of 0.26 g of cyclotetradecanone and 0.7 g of (VIII) was heated for 1 h at 180°, evaporated, the residue was dissolved in CHCl_3 , 0.6 g of SiO_2 was added, after 1 h the SiO_2 was separated, the filtrate was evaporated, dry acetone was added to the residue, and the whole was cooled to give 50 mg of (X), mp 70-72°. Ultraviolet spectrum ($\text{C}_2\text{H}_5\text{OH}$, λ_{max} , nm): 384 (ϵ 63000), 255 (ϵ 10200).

The authors express their gratitude to S. Z. Taits and E. S. Balenkova for supplying the macrocyclic ketones.

CONCLUSIONS

A number of dienic mono- δ -dimethylamino ketones, containing a macrocyclic fragment, was synthesized by the condensation of 1,1,3-trimethoxy-3-dimethylaminopropane and β -dimethylaminoacrolein acetal aminal with macrocyclic ketones. We were unable to obtain polyenic bis- δ, δ' -dimethylamino ketones, containing a macrocyclic fragment, by this route.

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SYNTHESIS OF MACROCYCLIC COMPOUNDS

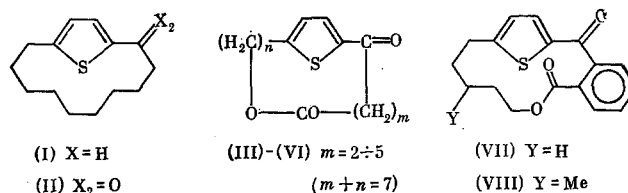
21.* PREPARATION, CONFORMATIONAL BEHAVIOR, AND REDUCTIVE

DESULFURIZATION OF 8-METHYL-2,3-BENZO-5-OXA[10]- α -CYCLOTHIEN-1,4-DIONE

F. D. Alashev, V. N. Bulgakova,
S. Z. Taitis, and Ya. L. Gol'dfarb

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The PMR spectroscopy method was used by us previously to study the conformational state of a number of macrocyclic ansa compounds (I)-(VII), which contain a thiophene ring and a 10-unit bridge.



The presence of a ring-conjugated $C=O$ group in ketone (II), as well as of an ester grouping in ketolactones (III)-(VI) at a variable distance from the $C=O$, with a constant value of the chain, has little effect on the high conformational mobility of the ansa bridge, which is capable of being located on either side of the plane of the thiophene ring [2]. The presence of a 2,3-condensed benzene ring in compound (VII) slows up the interconversions of the atropisomeric forms [3]. To study the changes in the conformational mobility, caused by modifying the structure of the ansa bridge, we synthesized ketolactone (VIII), which has a CH_3 group in the 8 position of the bridge. The insertion of a substituent in this portion of the molecule leads to the appearance of an asymmetric C atom. The reductive desulfurization products of (VII), namely didesoxynorsearalane analogs (IX), (X), and (XI), contain, in contrast to the previously described (IXa), (Xa), and (XIa), a CH_3 group in the macrocyclic skeleton, but in a different position when compared with the natural searalenone [1].

*See [1] for Communication 20.