CONCLUSIONS

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

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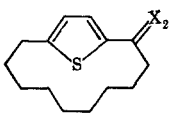
SYNTHESIS OF MACROCYCLIC COMPOUNDS

21.* PREPARATION, CONFORMATIONAL BEHAVIOR, AND REDUCTIVE DESULFURIZATION OF 8-METHYL-2,3-BENZO-5-OXA[10]-α-CYCLOTHIEN-1,4-DIONE

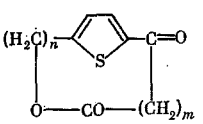
F. D. Alashev, V. N. Bulgakova, S. Z. Taits, and Ya. L. Gol'dfarb

UDC 542.91:547.73

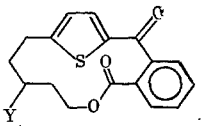
The PMR spectroscopy method was used by us previously to study the conformational state of a number of macrocyclic ansa compounds (I)-(VII), which contain a thiophene ring and a 10-unit bridge.



(I) X = H
(II) X_2 = O



(III)-(VI) m = 2÷5 (m + n = 7)



(VII) Y = H
(VIII) Y = Me

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 atropoisomeric 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 (VIII), 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.

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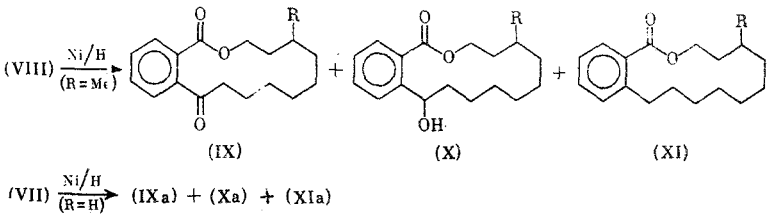
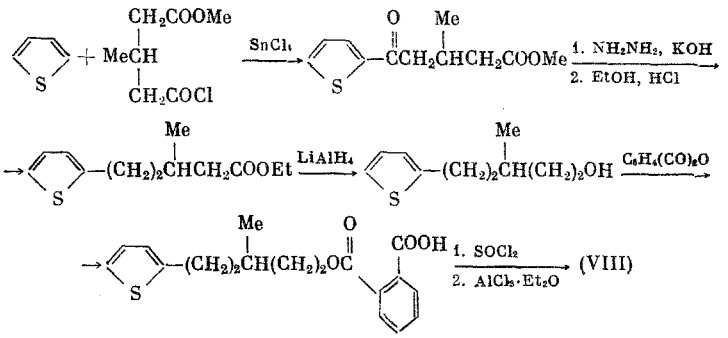


The synthesis was accomplished by the scheme



The acylation of thiophene using the monoester of methylglutaryl chloride gave the ketoester, which was reduced by the Kishner method; the thus obtained 3-methyl-5-thienylvaleric acid was converted to the ester, which by treatment with $LiAlH_4$ was converted to 3-methyl-5-thienylpentanol. Reaction of the latter with phthalic anhydride gave the monophthalate. Without isolation, the acid chloride corresponding to it was subjected to intramolecular cyclization under high dilution conditions in the presence of $AlCl_3$ etherate. Product (VIII) was isolated in 42-44% yield by chromatography on either Al_2O_3 or SiO_2. Besides (VIII), up to 20% of a noncrystallizing mixture of high-molecular-weight substances was formed, whose structure was not studied (a part of the resin is sorbed irreversibly on the support), and a small amount of other impurities.

The reductive desulfurization of (VIII) with skeletal Ni in an acetone–ethanol mixture gives, like in the case of the desulfurization of (VII) [1], a ketolactone (IX) as the main product; smaller amounts of hydroxylactone (X) and lactone (XI) were isolated (Table 1). When compared with the desulfurization of (VII) [1], the yield of (X) and (XI) is half as great. Compounds (X) and (XI) are not formed when the reaction is run in acetone [cf. a yield of 6.5% for (Xa) and 5.7% for (XIa)], but in ethanol the predominant compound is lactone (XI) [(Xa) and (XIa) were obtained in a respective yield of 21 and 27%]. The temperature possibly plays a certain role in the variation of this ratio, since due to the poor solubility of (VIII) in ethanol the reaction was run at 50°.

The steric structure of the tricyclic ketolactone (VII) in the crystalline state [4] and in solution [3] has been studied in considerable detail. Insertion of a benzene ring into the bridge gives the PMR spectrum of (VII) an appearance [3] that differs sharply from that of the spectra of [10]-ansa compounds with an unhindered shift of the ansa bridge relative to the thiophene ring [2]. In turn, the PMR spectrum of compound (VIII) has characteristic individual traits (Fig. 1). A double number of multiplets, corresponding to the methylene protons, is observed. Together with this, the region of the aromatic protons in both chemical shift and splitting of the lines duplicates the spectral picture of (VII). In harmony with the general classification [2], from the value of the chemical shift it is easy to distinguish between the signals of the 6-CH_2 groups, found adjacent to the ring oxygen (δ 4.45, 3.81 ppm), and 10-CH_2, found near the thiophene ring (3.11, 2.55 ppm). The assignment of the signals was confirmed by employing double resonance. Each signal consists of two groups of multiplets and corresponds to the pseudoaxial and pseudoequatorial protons. The H^8 and 9-CH_2 signals are depicted by a broad multiplet (1.1-1.9 ppm), and apparently one of the 7-CH_2 protons appears in the same region. The lines of the other H^7 (0.91 ppm) nearly merge with the signal of the protons of the CH_3 group

TABLE 1. Reductive Desulfurization of (VIII) under Various Conditions

Solvent	Reaction products and their yield, %		
	(IX)	(X)	(XI)
Ethanol + acetone	50,5	7,5	3,1
Acetone	96	–	–
Ethanol (50°C)	–	13	47,1

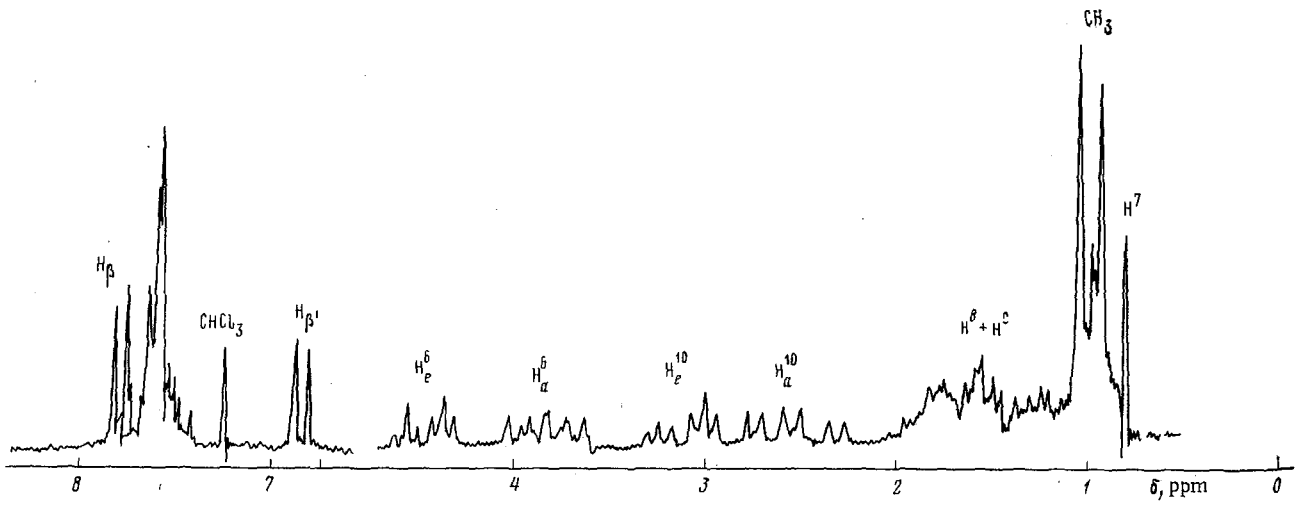


Fig. 1. PMR spectrum of compound (VIII) (25°C, $CDCl_3$).

(0.98 ppm). The shift of one of the 7-CH_2 protons upfield indicates its shielding by the diamagnetic ring current of the thiophene nucleus, in which connection to the same degree as for the corresponding group in (VII) (averaged signal 0.93 ppm), but to a less degree than in (II) (0.35 ppm) [2]. Hence it follows that the conformation of this section of the methylene bridge is the same as in compounds (VII) and (II). The structure of that portion of the molecule where the phthaloyl moiety connects to the thiophene nucleus is retained the same for compounds (VII) and (VIII). The same type of steric orientation for these fragments is supported by the identical picture of the spectra of the aromatic portion, and also by the practically coinciding dipole moment that has a high absolute value: 5.01 D for (VII) and 5.04 D for (VIII) (in benzene). As a result, insertion of a CH_3 group in the 8 position of the bridge of the discussed tricyclic ansa system does not change the conformation of the molecule, in which connection it may be assumed that the substituent occupies a position that is close to equatorial (a different position leads to the CH_3 coming closer to the S atom of the thiophene ring). However, such modification of the ansa bridge proved to be sufficient to prevent movement of the ansa bridge along the other side of the thiophene ring (the multipliticity of the spectrum of (VIII) does not change above 100°). Consequently, in solution compound (VIII) exists as a mixture of mirror isomers, which are not converted to their paired diastereomeric (atropoisomeric) forms.

The PMR spectra of (IX)-(XI) give the answer to the question of how the presence of a CH_3 group affects the conformational behavior of the macrocyclic reductive desulfurization products of (VIII). From an examination of them and a comparison with the spectra of analogs, devoid of the CH_3 group, it is clear that in (IX) and (X) the macrocyclic system is conformationally mobile, as a result of which each CH_2 group gives an averaged signal (this is especially manifest for groups that are found adjacent to C=O, O, or an aromatic nucleus). In contrast, the spectrum of lactone (XI) exhibits features that are inherent to (VIII): the signals of the H^5 and H^{14} protons are magnetically nonequivalent. This can be explained by the fact that the presence of a CH_3 group in the 12 position of the macrocyclic skeleton of (XI) imparts a stable conformation to the entire ring, whereas the steric overloading of the o-positions in the benzene ring of the functional groups in (IX) and (X) forces the other units of the macrocycle to undergo rapid dynamic transformations (on the NMR time scale), thus reducing to zero the stabilizing role of the methyl substituent.

EXPERIMENTAL

The PMR spectra were recorded on Varian DA-60-IL (60 MHz) and Tesla BS-497 (100 MHz) instruments; the concentration of the substrate was ~0.4 M, and TMS was used as the internal standard. The chemical shifts are given on the δ scale, in ppm from TMS. The values of the SSCC (J_{HH}) are given in Hz. The compounds were purified using Al_2O_3 (II activity) and SiO_2 (L and LSL-254 grade). The yield of the reaction products and their purity were determined by GLC on an LKhM-8 MD chomatograph, using a 60 cm × 3 mm stainless steel column packed with 7% SKTV deposited on silanized Chromosorb W, and a Tswett-100 chromatograph, using a 1 m × 3 mm glass column packed with 5% SE-30 deposited on silanized Chromaton N; the temperature rise was programmed in the range 170-300°, and the rate was 6-8 deg/min. The molecular weights were determined by mass spectrometry on a Varian-MAT instrument.

Methyl Ester of 3-Methyl-4-(2-thenoyl)butyric Acid. The ester was obtained as described in [5] from thiophene and the methyl ester of methylglutaryl chloride; bp 130-132° (2 mm). PMR spectrum (CCl_4): 1.02 d (CH_3, $J \approx 5$), 2.1-3.1 m (CH_2CHCH_2), 3.60 s (OCH_3), 7.06 d.d ($H_{\beta'}$, $J \approx 5$, $J \approx 4$), 7.59 d.d (H_α, $J \approx 5$, $J \approx 1$), 7.7 d.d (H_β, $J \approx 4$, $J \approx 1$).

3-Methyl-5-(2-thienyl)valeric Acid and Its Ester. A mixture of 105.5 g of the above obtained ketoester, 490 ml of diethylene glycol, and 61 ml of hydrazine hydrate was heated for 1 h, after which 83 g of KOH was added and the mixture was heated for another 2 h. The excess hydrazine and water were distilled off until the temperature in the flask reached 200°, after which the mixture was heated for another 4 h. The reaction mass was diluted with water, acidified, extracted with ether, the extract was washed with water, dried over $MgSO_4$, and the ether was evaporated. The residual acid (90.3 g) was used as such for esterification with 200 ml of ethanol, saturated with HCl. The yield of ester was 93.3 g (96.5%). PMR spectrum (CCl_4): 0.95 d (CH_3, $J = 6$), 1.17 t (CH_3, $J \approx 7$), 1.4-2.4 m (CH_2CHCH_2), 2.79 t (CH_2CO, $J \approx 7.5$), 4.03 q (OCH_2, $J \approx 7$), 6.6-7.05 m (H_{thiop}).

3-Methyl-5-(2-thienyl)pentanol. To 9.7 g of $LiAlH_4$ in 220 ml of anhydrous ether was added in a nitrogen stream, in 1 h, a solution of 90 g of ethyl 3-methyl-5-(2-thienyl)valerate and the mixture was stirred for another 2 h, after which it was cooled in ice, 300 ml of dilute (1 : 1) H_2SO_4 solution was added, and the mixture was stirred for 1 h. The ether layer was separated, washed in succession with water, $NaHCO_3$ solution, and water, and dried over $MgSO_4$. The residue (73.3 g) was distilled. We obtained 3-methyl-5-(2-thienyl)pentanol in 92% yield, bp 110-111° (0.13 mm) n_D^{20} 1.5211; d_4^{20} 1.0451. Found: C 65.25; H 8.74; S 17.07%; MR 53.70; M^+184. $C_{10}H_{16}OS$. Calculated: C 65.16; H 8.75; S 17.40%; MR 54.03; mol. wt. 184.29.

PMR spectrum (CCl_4): 0.93 d (CH_3, $J \approx 5$), 1.2-1.9 m (CH_2CHCH_2), 2.79 t ($ArCH_2$, $J \approx 7.5$), 3.5 s (OH), 3.53 t (OCH_2, $J \approx 6.5$), 6.5-7.0 m (H_{thiop}).

Mono-[3-methyl-5-(2-thienyl)pentyl] Ester of Phthalic Acid. A solution of 18.4 g of 3-methyl-5-(2-thienyl)pentanol and 15 g of phthalic anhydride in 50 ml of $CHCl_3$ was refluxed for 10 h, after which it was cooled, treated with $NaHCO_3$ solution, and the aqueous layer was separated, acidified cautiously, and extracted with ether. The extract was dried over $MgSO_4$, the solvent was evaporated, and the residue represented 30.2 g (94%) of a viscous, slightly colored liquid; neutralization equivalent (determined by titration on an automatic recording instrument (Radiometer)): 336.8; calc. mol. wt. 332.43. Found: C 65.29; H 6.18; S 9.41%. $C_{18}H_{20}O_4S$. Calculated: C 65.04; H 6.06; S 9.64%. PMR spectrum ($CDCl_3$): 0.96 d (CH_3, $J \approx 4$), 1.66 m (CH_2CH-CH_2), 2.82 t ($ArCH_2$, $J \approx 7$), 4.38 t (CH_2O, $J \approx 6$), 6.68-7.08 m (H_{thiop}), 7.4-7.9 m (H_{benz}), 10.27 s (COOH).

Intramolecular Acylation of Mono[3-methyl-5-(2-thienyl)pentyl] Ester of Phthaloyl Chloride. A $CHCl_3$ solution of the acid chloride, obtained from 5 g of the indicated monophthalate as described in [1], was added in 24 h through a high-dilution packing to a refluxing solution of 33.5 g of $AlCl_3$ etherate in 1 liter of $CHCl_3$. At the end of addition the mixture was heated for another 4 h, decomposed with a mixture of ice and dilute HCl solution, extracted with $CHCl_3$, and the extract was washed in succession with dilute HCl solution, water, $NaHCO_3$ solution, and water, dried over $MgSO_4$, and evaporated. Aliquot portions were chromatographed on either a column or plate (26 × 26 cm, thickness of sorbent layer = 2 mm) containing either Al_2O_3 or SiO_2, and using either $CHCl_3$ or a 9 : 1 $CHCl_3$–CCl_4 mixture as the eluant; the yield of ketolactone (VIII) was 42.3-44.1%; the colored resins and other impurities were not studied.

8-Methyl-2,3-benzo-5-oxa-[10]-α-cyclothien-1,4-dione (VIII), mp 159-161° (CCl_4). Found: C 68.80; H 5.75; S 10.23%; M^+ 314. $C_{18}H_{18}O_3S$. Calculated: C 68.76; H 5.77; S 10.20%; mol. wt. 314.38. PMR spectrum ($CDCl_3$): 0.9 m (7-CH_2), 0.98 d (CH_3, $J \approx 7$), 1.1-1.9 m (8-CH, 9-CH_2), 2.55 d.t (H_a^{10}), 3.11 d.t (H_e^{10}), 3.81 d.t (H_a^6), 4.45 d.t (H_e^6), 6.85 d ($H_{\beta'}$, $J \approx 4$), 7.4-7.7 m (H_{benz}), 7.80 d (H_β, $J \approx 4$).

Reductive Desulfurization of (VIII). A solution of 1.6 g of ketolactone (VIII) in a mixture of 136 ml of 95% ethanol and 52 ml of acetone was stirred with 9 g of skeletal Ni (washed with several portions of alcohol to remove the water) at ~20° until the test for sulfur was negative (2-4 h). The solution was decanted, and the precipitate was repeatedly washed with alcohol, and then with ether; the combined solutions were evaporated, and the residue was dissolved in anhydrous ether and filtered. After removal of the solvent we obtained 0.9 g of reaction product. Based on the GLC and TLC (Silufol) data, the product is heterogeneous; separation into the components was effected by preparative chromatography on Al_2O_3 (26 × 26 cm, layer thickness = 2 mm, eluant = $CHCl_3$). We isolated ketolactone (IX) in 50.5% yield, when based on (VIII), hydroxylactone (X) (7.5%), and lactone (XI) (3.1%). The ratios of the formed products when the reductive desulfurization is run in other solvents are given in Table 1 [due to the poor solubility of (VIII) in alcohol the reaction was run at elevated temperature].

12-Methyl-3,4-benzooxacyclotetradecane-2,5-dione (IX) (liquid). Found: C 74.85; H 8.12%; M^+ 288. $C_{18}H_{24}O_3$. Calculated: C 74.97; H 8.39%; mol. wt. 288.37. PMR spectrum (CCl_4): 0.87 d (CH_3, $J \approx 5$), 1.15 2.2 m (CH_2), 2.8 m ($COCH_2$), 4.3 m (OCH_2), 7.0-7.9 m (H_{benz}).

12-Methyl-5-hydroxy-3,4-benzooxacyclotetradecan-2-one (X) (viscous liquid). Found: C 74.34; H 8.99%; M^+ 290. $C_{18}H_{26}O_3$. Calculated: C 74.41; H 9.10%; mol. wt. 290.38. PMR spectrum (CCl_4): 0.86 d (CH_3, J = 7.5), 1-2 m (CH_2), 2.6 s (OH), 3.6 t (OCH_2, $J \approx 6$), 5.4 m ($OCH_3(OCH_3)$, $7.3-8_{benz}$).

12-Methyl-3,4-benzooxacyclotetradecan-2-one (XI) (liquid with a weak odor). Found: C 78.69; H 9.83%; M^+ 274. $C_{18}H_{26}O_2$. Calculated: C 78.79; H 9.87%; mol. wt. 274.44. PMR spectrum (CCl_4): 0.91 d (CH_3, $J \approx 6$), 1-2 m (CH_2), ~2.6, ~3.3 m (H_a^5, H_e^5), ~4.2, ~4.6 m (H_a^{14}, H_e^{14}), 7-7.7 m (H_{benz}).

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CONCLUSIONS

1. A tricyclic ansa ketolactone, containing a thiophene ring, and specifically 8-methyl-2,3-benzo-5-oxa-[10]-α-cyclothien-1,4-dione, was synthesized. The reductive desulfurization of this ketone gives the corresponding ketolactone, hydroxylactone, and lactone, which contain the bicyclic didesoxysearalane skeleton, in various ratios depending on the reaction conditions.

2. It was established by PMR spectroscopy that the insertion of a methyl substituent in the polymethylene bridge suppresses the conformational mobility of the ansa system.

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