SYNTHESIS OF MACROCYCLIC COMPOUNDS.

XVIII.* NEW MACROCYCLIC KETOLACTONES THAT INCLUDE A THIOPHENE RING

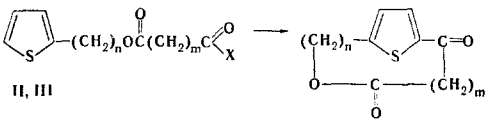
Ya. L. Gol'dfarb, S. Z. Taits,
F. D. Alashev, A. A. Dudinov,
and O. S. Chizhov

UDC 547.733'734.07

New representatives of macrocyclic ansa-ketolactones that include a thiophene ring, the differences in the yields of which during intramolecular acylation under high-dilution conditions were compared with the peculiarities of their three-dimensional structures, were synthesized. The mass spectra of the ketolactones were studied.

Macrocyclic ansa compounds have peculiar structural features due to the presence of an aromatic ring and an aliphatic bridge. Systems of this sort are of interest in both a cognitive respect and within the framework of the relationship between their structure and biological activity (for example, see the review [2] on antibiotics with an ansa structure).

We have previously reported [3] the possibility of the construction of macrocyclic systems of the I type that include a thiophene ring (in the case of ketolactone Ib) by intramolecular acylation of the chlorides (III) of mono[ω-(2-thienyl)alkyl]esters of dicarboxylic acids II:

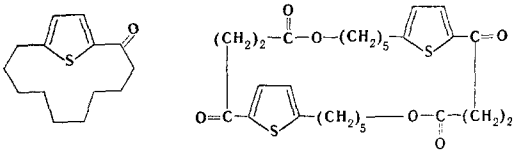


II, III — I

II X = OH; III X = Cl;

I-III a n = 5, m = 2; b n = 4, m = 3;
c n = 3, m = 4; d n = 2, m = 5; e n = 6, m = 1

It was expedient to increase the number of synthesized compounds and, in particular, to ascertain how movement of the ester group within the confines of the ten-membered ring affects the ease of formation of ketolactones, and, by comparing the results obtained with the data in [4], which pertain to the behavior of [10]-α-cyclo-1-thienone (IV), judge the effect of replacement of two methylene links by an —O—CO— grouping. The PMR spectra of the compounds [5] that we have studied reflect the differences in the geometry of the molecules as a consequence of the change in the position of the lactone group in the aliphatic bridge.



IV V

*See [1] for communication XVII.

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 40-44, January, 1975. Original article submitted July 29, 1974.

TABLE 1. Macrocyclic Ketolactones*

Compound	mp, °C	Found, %†			Yield, %
		C	H	S	
Ia	67—68	61,6	6.5	12,8	47,5
Ib	113—114	—	—	—	68‡
Ic	70—71	61,8	6,9	12,4	50,6
Id	134—135	61,6	6,3	12,9	61
V	166—170	61,7	6,3	12,9	10—15

* Peaks corresponding to the molecular ion were observed in the mass spectra of all of the ketolactones.

† Calculated for $C_{13}H_{16}O_3S$ (also for V, $C_{26}H_{32}O_6S_2$): C 61.88; H 6.39; S 12.71%.

‡ The yield (61%) of product isolated from the reaction mixture after recrystallization has been previously reported [3].

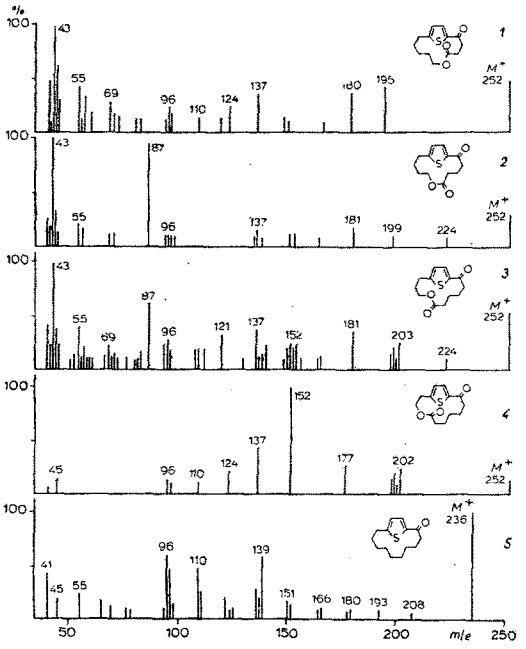


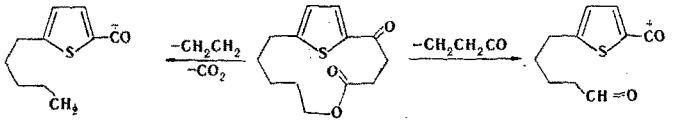
Fig. 1. Mass spectra of macrocyclic compounds: 1) 5-oxa[10]-α-cyclothiene-1,4-dione (Ia); 2) 6-oxa[10]-α-cyclothiene-1,5-dione (Ib); 3) 7-oxa[10]-α-cyclothiene-1,6-dione (Ic); 4) 8-oxa[10]-α-cyclothiene-1,7-dione (Id); 5) [10]-α-cyclo-1-thienone (IV).

In the present communication we describe the synthesis of ketolactones Ia, Ic, and Id, which are isomers of Ib [3]: all of them have bridges consisting of an identical number of links but a different number of methylene groups included between rigid fragments – the lactone group and the thenoyl residue.

The starting ester-acids (II) for the preparation of acid chlorides III were synthesized in analogy with a previously described method [3] or by means of a method that we developed [6]. In contrast to IIb [3], they are viscous syrupy liquids that do not crystallize on cooling. Disproportionation may occur on prolonged storage to give a dicarboxylic acid and the corresponding diester (in the case of II this ester was isolated and characterized). Intramolecular acylation was carried out in a homogeneous medium (see [3, 4]) with the aid of high-dilution technique. The predominant reaction products were monomeric cyclic compounds I. In addition, the formation of polymeric substances was observed in all cases. The quantitative percentage of the desired product was established by means of gas–liquid chromatography (GLC) (see [7] for the analytical method). The yields and physical constants of the compounds obtained are presented in Table 1. Under identical cyclization conditions, the yields of Ia and Ic decrease as the lactone group moves along the chain as compared with the yield of the previously obtained ketolactone Ib. This may be associated with an increase in the strain during ring formation, inasmuch as when the number of links separating the ester group and the thiophene ring is reduced, these two rigid fragments are compelled to be oriented at an angle that is unfavorable for cyclization (see [8] for illustrations of ideas of this sort in the case of cyclic diynes). It is apparent from an examination of three-dimensional models that in Ib these fragments may be situated almost parallel to one another [5]. On the other hand, it is natural to assume that a decrease in the number of methylene links between the ester and acid chloride functions should decrease the mobility of this section of the chain and lead to a more strained ring. Evidence in favor of this is the fact that the formation of a diketo dilactone (V) was noted in the cyclization of acid chloride IIIa. Thus, even under high-dilution conditions, an intermolecular interaction that competes with intramolecular acylation becomes more appreciable. However, it is seen from Table 1 that the yield of ketolactone Id is comparable to the yield of Ib. It is possible that in both cases, despite the difference in structure, the three-dimensional orientation that corresponds to the minimum transannular interaction and favors the formation of a ring can be achieved. In this connection, one's attention is directed to the alternation of the melting points in the series of compounds Ia-d. It would be interesting to trace the observed phenomena in the case of other isomeric ketolactones, but only unidenti-

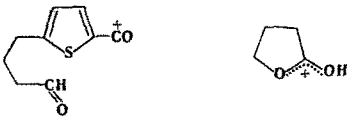
fied resinous products were formed in an attempt to cyclize the acid chloride of a malonic acid half-ester (IIIe).

In the mass spectra of ketolactones Ia-d (Fig. 1) one's attention is directed to the certain difference in the intensity of the molecular ion peak with m/e 252; this reflects in part the different stabilities of the rings with respect to electron impact. It should be noted that the presence of peaks with m/e 96, 110, 124, and 137 in all of the spectra of the investigated ketolactones apparently is not characteristic for the systems under consideration, inasmuch as the same set of fragments is observed in the mass spectrum of α-cyclothienone IV. Of the number of fragments with m/e greater than 137, the most intense for the spectrum of Ia are the peaks with m/e 195 and 180. The formation of the corresponding fragments can be represented by the following scheme:



m/e 180 Ia m/e 195

A fragment with m/e 181 (structure VI) is observed in the spectrum of Ib; the formation of VI can be explained by splitting out of a $CH_2CH_2CH_2CO$ fragment, i.e., the same bonds as in the case of Ia are cleaved, but in this case the fragment split out contains one methylene group more. The peak with m/e 87, which is absent in the spectrum of α-cyclothieone IV, is also extremely intense. Its structure apparently corresponds to formula VII. The formation of this particle could occur through the portion of the chain between C-1 and C-7; this corresponds to the general principle of cleavage of such molecules at the C-1—C-2 bond adjacent to the keto group conjugated with the heteroaromatic ring.



VI m/e 181 VII m/e 87

A fragment with m/e 87 (VII) is also observed in the mass spectrum of ketolactone Ic, although the pathways for its formation should evidently differ.

In the spectrum of Id the peak with m/e 152 is exceptionally intense. The origin of a fragment with this mass number is not completely clear; to this, one should also add that peaks with m/e 152 are also present in the spectra of Ib and Ic but they have considerably lower intensities.

EXPERIMENTAL

Gas—liquid chromatography was carried out with an LKhM-7A chromatograph at ~200°. Stainless-steel columns (length 40 cm, diameter 3 mm) with polyethylene glycol adipate (PEGA) (5%) on Chromosorb G (60-80 mesh) and PEGA (15%) on Chromosorb P (80-100 mesh) were used. α-Cyclothienone (IV) [7] was used as the internal standard for the quantitative calibration. The neutralization equivalents were determined with a Radiometer automatic titrator. The PMR spectra were recorded with a Varian DA-60-IL spectrometer with an operating frequency of 60 MHz. The mass spectra were recorded with a Varian MAT CH6 spectrometer with direct introduction into the ion source and an MKh-1303 spectrometer with a cylinder feed device.

Mono[5-(2-thienyl)pentyl] Succinate (IIa). A solution of 10.15 g of thienylpentanol [9] and 6.0 g of succinic anhydride in 25 ml of benzene was refluxed for 12 h, after which the solvent was removed in vacuo, and the residue was treated with $NaHCO_3$ solution. The mixture was extracted thoroughly with ether to separate neutral substances. The aqueous layer was acidified carefully, and the resulting oil was extracted with ether. The extract was dried over $MgSO_4$, the ether was evaporated, and the residue was extracted with several portions of boiling hexane. Workup of the hexane extract gave a slightly colored syrupy product; the overall yield of product with neutralization equivalent 273 was 11.5 g (71.5%). Found: C 57.0; H 6.5; S 11.9%. $C_{13}H_{18}O_4S$. M 270.3. Calculated: C 57.75; H 6.70; S 11.86%. Succinic acid precipitated when a sample was stored; the mixture was treated with carbon tetrachloride, the succinic acid was separated by filtration, the filtrate was evaporated, and the residue was recrystallized from hexane. Crystals of the diester with mp 35° formed when the solution was cooled. Found: C 62.4; H 7.3; S 15.1%.

$C_{22}H_{30}O_4S_2$. Calculated: C 62.53; H 7.16; S 15.17%. PMR spectrum (CCl_4): δ 2.65 (singlet, CH_2CO), 3.0 (triplet, $C_4H_3SCH_2$), 4.2 (triplet, CH_2O), 1.35-2.15 [multiplet, $(CH_2)_3$], and 6.8-7.25 (multiplet, C_4H_3S).

Intramolecular Acylation of Acid Chloride IIIa under High-Dilution Conditions. A solution of acid chloride IIIa (obtained from 5 g of acid IIa by the method in [3]) in 60 ml of anhydrous chloroform was added in the course of 22 h from a syringe doser through an adapter for high dilution [10] to a refluxing solution of 31 g of aluminum chloride etherate in 500 ml of anhydrous chloroform. At the end of the addition, the mixture was stirred for another 4 h, cooled to 10°, and treated with a mixture of 150 ml of concentrated HCl and 1 kg of ice. After the reaction mixture had decomposed, the organic layer was separated, washed successively with dilute HCl, water, $NaHCO_3$ solution, and water, and dried over $MgSO_4$. The solvent was removed by distillation, and the residue was dissolved in $CHCl_3$. An aliquot was separated with a column filled with Al_2O_3 (with elution by $CHCl_3$); the major fraction (47.5%) isolated was 5-oxa-[10]-α-cyclothiene-1,4-dione* with mp 67-68°. Subsequent elution yielded a fraction corresponding to a product with a doubled molecular weight – 5,19-dioxa[10,10]-α-cyclodithiene-1,4-15,18-tetraone (V) – with m/e 504 (the yields in different experiments ranged from 10 to 15%). Analysis of the reaction mixture by means of two-dimensional TLC showed the presence of small amounts of other substances, the nature of which was not investigated in detail. Treatment of the overall reaction product with ether and benzene gave an amorphous powder, which was a product of polymeric character. Found: Mol. wt. 1054 (ebulliographically in boiling benzene). The average degree of polymerization was ~4.

7-Oxa[10]-α-cyclothiene-1,6-dione (Ic) and 8-oxa[10]-α-cyclothiene-1,7-dione (Id), respectively, were similarly obtained from IIIc and IIId by intramolecular acylation under high-dilution conditions. The physical constants and yields are given in Table 1.

Mono-6-(2-thienyl)hexyl Malonate.† A solution of 7.5 g of malonic acid monochloride, recrystallized from butyl chloride [11], was added with stirring and cooling to a solution of 11.4 g of thienyl-hexanol [9] and 6 g of triethylamine in 64 ml of anhydrous ether. At the end of the reaction, the temperature of the mixture was raised to 28° and stirring was continued for another 30 min, after which 190 ml of ice water was added, and the organic layer was separated and washed with 0.5% HCl solution and water. It was then shaken with 7.5% $NaHCO_3$ solution, and the aqueous layer was washed with ether and acidified with HCl. The resulting oil was extracted with ether, the extract was dried with $MgSO_4$, and the solvent was removed. The residue was treated with boiling hexane, and the hexane solution was cooled to liberate 9.2 g (the yields in different experiments reached 46-56%) of the monoester as a light-yellow oil with a neutralization equivalent of 271.6. Found: C 58.4; H 6.8; S 11.5%. $C_{13}H_{18}O_4S$. M 270.3. Calculated: C 57.75; H 6.70; S 11.86%.

LITERATURE CITED

1. S. Z. Taits, É. A. Krasnyanskaya, A. L. Klyachko-Gurvich, and Ya. L. Gol'dfarb, Izv. Akad. Nauk SSSR, Ser. Khim., 1807 (1973).
2. K. L. Rinehart, Accounts of Chem. Res., 5, 57 (1972).
3. S. Z. Taits, F. D. Alashev, and Ya. L. Gol'dfarb, Izv. Akad. Nauk SSSR, Ser. Khim., 566 (1968).
4. S. Z. Taits, F. D. Alashev, and Ya. L. Gol'dfarb, Izv. Akad. Nauk SSSR, Ser. Khim., 572 (1968).
5. F. D. Alashev, A. V. Kessenikh, S. Z. Taits, and Ya. L. Gol'dfarb, Izv. Akad. Nauk SSSR, Ser. Khim., 2022 (1974).
6. S. Z. Taits, A. A. Dudinov, F. D. Alashev, and Ya. L. Gol'dfarb, Izv. Akad. Nauk SSSR, Ser. Khim., 148 (1974).
7. S. Z. Taits, É. A. Krasnyanskaya, and Ya. L. Gol'dfarb, Izv. Akad. Nauk SSSR, Ser. Khim., 754 (1968).
8. J. Dale, J. Chem. Soc., 73 (1963).
9. S. Z. Taits, F. D. Alashev, and Ya. L. Gol'dfarb, Izv. Akad. Nauk SSSR, Ser. Khim., 402 (1968).
10. Ya. L. Gol'dfarb, S. Z. Taits, and L. I. Belen'kii, Zh. Obshch. Khim., 29, 3564 (1959).
11. B. Gastambide, Bull. Soc. Chim. France, 866 (1955).

* See [10] for the nomenclature for macrocyclic compounds including a thiophene ring.
† With the participation of Z. V. Volodina.