NEW METHOD FOR THE SYNTHESIS OF MACROCYCLIC COMPOUNDS

XV.* ALKYLATION OF 2-CARBETHOXY-α-CYCLO-1-THIENONES

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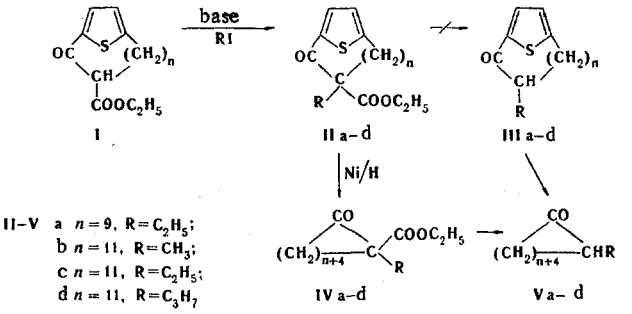
A method was developed for the preparation of macrocyclic 2-alkylcycloalkanones by alkylation of 2-carbethoxy-α-cyclothienones with subsequent desulfurization and ketone cleavage. Only C-alkylation occurs under the described conditions (potassium metal in hexamethylphosphoric triamide, sodium hydride in dioxane).

Of the studies of the synthesis of macrocyclic compounds that have the odor of musk, only a small number are concerned with methods for the synthesis of alkyl-substituted macrocyclic ketones, and these studies are primarily directed to the synthesis of 3-methylcycloalkanones, particularly d*l*-muscone [2-6].

The Ruzicka method for the preparation of alkylcycloalkanones has substantial limitations. Only 4-methylcyclotetradecanone (and not 2-methylcyclotetradecanone or 2-methylcyclopentadecanone) can be obtained in low yield by pyrolysis of yttrium or thorium salts of dicarboxylic acids [7]. Ruzicka and coworkers [7] used a more complex route for the synthesis of 2-, 3-, and 7-methylcyclopentadecanones, and it was found that the odor of 2-methylcyclopentadecanone is somewhat weaker than that of the unsubstituted ketone, while the odor of 4-methylcyclopentadecanone is not distinguishable from that of muscone [8].

2-Methylcyclopentadecanone was also obtained by acyloin condensation of the ester of 2-methyltridecane-1,13-dicarboxylic acid and subsequent dehydration of the corresponding acyloin, which was isolated from the resulting mixture of isomers, and hydrogenation of the unsaturated ketone [9]. This same ketone is formed from 2-methyltetradecanone on treatment of it with diazomethane in the presence of aluminum chloride [10]. All of these methods are quite complex and require hard-to-obtain starting compounds. The cyclization methods frequently lead to difficult-to-separate mixtures. The synthesis of 2-alkylcycloalkanones by alkylation of β-keto esters of the macrocylic series, which are synthesized from cycloalkanones by treatment with diethyl carbonate in the presence of sodium hydride, was recently described [11]. This same method was also used in the synthesis of other macrocyclic compounds [12, 13].



*See [1] for communication XIV.

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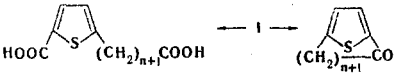
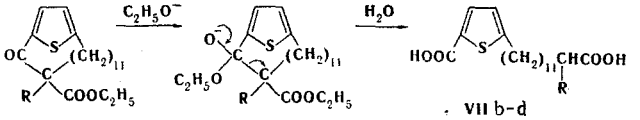
Compounds I, which contain a β-keto ester fragment, are the products of the intramolecular alkylation of 2-(ω-haloalkyl)-5-(carbethoxyacetyl)thiophenes [14-16]. It seemed of interest to investigate the possibility of introduction of substituents into these compounds using the lability of the hydrogen atoms of the β-keto ester group in order to arrive at macrocyclic 2-alkylcycloalkanones by subsequent ketone cleavage and reductive desulfurization.

It was found that when the reagents usually employed are used, alkylation of I either does not occur or proceeds with complications. Unchanged I or a mixture of I and products of acid and ketone cleavage are recovered.



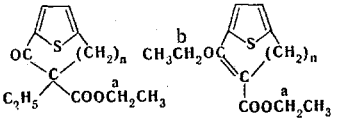
VI

In particular, starting I is practically completely recovered in the reaction of C_2H_5I in the presence of K_2CO_3 in acetone. A mixture containing [according to thin-layer chromatography (TLC)] among the neutral products the starting I, the product of its ketone cleavage (VI), and a considerable amount of alkylation product (II) was obtained both with an equimolar amount and with a twofold excess of sodium ethoxide. In addition, a product of acid character, which is apparently a dicarboxylic acid (VII, $R = C_2H_5$), was isolated in a yield up to 40% (by weight). This sort of cleavage under the influence of sodium ethoxide is characteristic for α,α-disubstituted β-ketocarboxylic acids [16, 17].



VII b-d

To suppress this process, one usually employs [16] alkoxides with a large anion volume (in particular, potassium tert-butoxides) in order to hinder nucleophilic attack of the carbonyl carbon atom. In our case, the use of potassium tert-butoxide led to a mixture of I and VI. Better results were obtained when sodium hydride in dioxane [18] or potassium metal in ether–hexamethylphosphoric triamide [19] were used. In the first case, II was obtained in 48-50% yield along with acid cleavage products (~8%), while in the second case the yields were 60-90%, and the yield of products of acid character did not exceed 1%. The alkylation product also was found to be homogeneous and, according to gas-liquid chromatography (GLC) and TLC, it did not contain O-alkylation products, although the conditions that we used for the alkylation – a polar aprotic solvent, a nonsolvating ambident anion [20-22], and the use of potassium as a gegenion [21, 23] – should have promoted O-alkylation. The use of iodides [20, 22] is a factor that promotes C-alkylation.



IIA IIb

Considering the two possible structures (IIA and IIB) that might have been formed in alkylation, it can be stated that, in the case of the development of O-alkylation product IIB, the signals of the *a* protons of the carbethoxy group and of the b protons of the ethoxy group should not coincide. In fact, only a signal from the *a* protons (quartet, 4.05 ppm, 26 Hz wide) is detected in the PMR spectrum; this is confirmed by comparison with the spectrum of starting I. In addition, it must be assumed that the signal from the b protons should be found at stronger field. If it is assumed that these signals coincide because of the effect of the adjacent groups, the peak area ratio of 4:2 (four *a* and b protons and two protons in the 3 and 4 positions of the thiophene ring) should then be retained; in fact, the integral curve gives a ratio of 2:2. It hence follows that the absence of signals at stronger field and the retention of the 2:2 ratio speak in favor of structure IIA.

The absence of O-alkylation products in our case can be explained by the peculiarities of structure I that distinguish it from acetoacetic ester. First of all, one should point out the certain lowering of the electron density on the carbonyl oxygen atom because of conjugation with the thiophene ring. In addition, the negative charge on the tertiary β-carbon atom should be increased somewhat by virtue of the inductive effect of the alkyl chain attached to it. This set of factors is also apparently the reason for the selective alkylation at the carbon atom.

TABLE 1. 2-Carbethoxy-2-alkyl-α-cyclo-1-thienones (II)

Compound	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %	
			C	H	S	C	H	S	method A	method B
IIa*	61—62	$C_{20}H_{30}O_3S$	68,3	8,5	9,0	68,5	8,6	9,2	50	61
IIb	53—55	$C_{21}H_{32}O_3S$	69,2	8,8	—	69,2	8,8	—	—	90
IIc	65—66	$C_{22}H_{34}O_3S$	69,6	9,0	8,4	69,8	9,0	8,5	48,5	65
IId	82—83,5	$C_{23}H_{36}O_3S$	70,4	9,4	8,1	70,4	9,2	8,2	—	78

*Compound IIa was subjected to reductive desulfurization, and the resulting crude IVa was subjected to ketone cleavage without purification (see Table 3).

TABLE 2. 2-Carbethoxy-2-alkylcyclo-1-alkanols (IV)

Compound	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
			C	H	C	H	
IVb	Liquid*	$C_{21}H_{38}O_3$	74,1	11,1	74,5	11,3	80
IVc	34—35,5	$C_{22}H_{40}O_3$	74,8	11,4	75,0	11,4	82
IVd	23—24	$C_{23}H_{42}O_3$	74,8	11,4	75,4	11,6	88

*n_D^{20} 1.4795, d_4^{20} 0.9777; found: MR_D 98.21; calculated: MR_D 98.64.

The alkylated two-ring compounds (II) obtained do not undergo ketone cleavage under the conditions usual for disubstituted β-keto esters. Thus refluxing with solutions of hydrochloric acid in methanol, ethanol, propyl alcohol, butyl alcohol, ethylene glycol, diethylene glycol, and triethylene glycol with variations in the heating time and acid concentration did not lead to saponification and decarboxylation of II. In addition, cleavage with alkaline agents [24], particularly $Ba(OH)_2$, did not result in the formation of ketone III – the starting II was recovered in all cases. Moreover, transesterification with monoesters of dicarboxylic acids and subsequent decarboxylation at 250-300°, which has been described for 2-carbethoxycyclohexanone and the monoester of pimelic acid [25], did not give ketone III. This resistance to cleavage led us to the idea of steric hindrance that prevents the formation of a six-membered transition state necessary for the transfer of a proton during the decarboxylation of such systems [26]. However, an examination of Stuart–Briegleb models does not confirm this assumption, since the necessary arrangement of atoms can be achieved, although not with the same ease as in alicyclic systems. The difficulty in the occurrence of the reaction under consideration apparently depends only partly on the steric shielding but primarily on the peculiarities of the structure of II, which have already been mentioned above. In fact, after desulfurization of II, as a result of which not only the rigid two-ring system but also the π electron system of the thiophene ring vanish and a 2-alkyl-2-carbethoxycycloalkanone (IV) is formed, ketone cleavage occurs completely satisfactorily on treatment with a solution of 50% sulfuric acid in acetic acid. The yields of the corresponding 2-alkylcycloalkanones (V) are 76-80%. At normal temperature, ketones V are oils and are crystallized only at low temperatures; they were therefore identified from their semicarbazones. The structure of the ketone cleavage products (V) was proved in the case of 2-ethylcyclopentadecanone by comparison of the semicarbazone obtained independently from the ketone synthesized by intramolecular acylation of 12-(5-methyl-2-thienyl)dodecanoyl chloride and subsequent desulfurization [27].

EXPERIMENTAL

The purity of the compounds obtained was monitored with an LKhM-7A chromatograph from the Mosneftekip Plant with a 400-mm-long stainless steel column 3 mm in diameter filled with polyethylene glycol adipate (5% on Chromosorb R); the column temperature was 220°, the carrier gas was helium (40 ml/min), and the substances were detected from their thermal conductivities. The PMR spectra were recorded with a Varian DA-60 spectrometer with CCl_4 as the solvent and hexamethyldisiloxane as the internal standard.

Alkylation of 2-Carbethoxy-α-cyclo-1-thienones (I). A. A 0.04-mole sample of NaH was added at 90° under dry nitrogen to a solution of 0.01 mole of 2-carbethoxy-α-cyclo-1-thienone (I, n=9) in 50 ml of anhydrous dioxane, and, after 1 h, 0.1 mole of C_2H_5I was added, and the mixture was stirred at 90° for 4-5 h. It was then cooled to 20°, acidified with glacial acetic acid, diluted with water, and extracted repeatedly with ether. The extract was washed with water, 5% sodium thiosulfate solution, water, saturated $NaHCO_3$

TABLE 3. 2-Alkylcyclo-1-alkanones (V)

Compound	Semicarbazone								Yield, %
	mp, °C	Empirical formula	Found, %			Calc., %			
			C	H	N	C	H	N	
Va	141—142,5	$C_{18}H_{35}N_3O$*	69,6	11,2	13,5	69,8	11,4	13,6	76
Vb	141—143	$C_{19}H_{37}N_3O$	70,5	11,5	13,0	70,5	11,5	13,0	87
Vc	130—136	$C_{20}H_{39}N_3O$	71,6	11,8	12,8	71,2	11,6	12,4	78

*No melting-point depression was observed for a mixture of this product with a sample of the semicarbazone of 2-ethyl-1-cyclopentadecanone, obtained by intramolecular acylation [27].

solution,* again with water, and dried with $MgSO_4$. The ether extract was evaporated, and the residue was purified by low-temperature crystallization from ether or by preparative TLC on activity II Al_2O_3 in a 2-mm-thick layer on 25 by 25 cm plates with hexane–ethyl acetate (20:1.5) as the solvent. A total of 1.2 g of product was separated on each such plate (development in UV light). Compound IIc was similarly obtained.

B. A 0.005 mole sample of I (n=9) was added to a dark-blue solution of 0.01 g-atom of potassium in a mixture of 6 ml of hexamethylphosphoric triamide and 7 ml of absolute ether, which was obtained in a stream of dry nitrogen at 20°. During the addition, the color vanished, and a yellow solution formed. This solution was stirred for 2 h, after which a solution of 0.01 mole of C_2H_5I in 3 ml of absolute ether was added to it in one portion, and the mixture was stirred at 40° for another 4 h. It was then acidified with glacial acetic acid at 0–4° and diluted with water, and the alkylation product was extracted with ether. The extract was worked up as described above. The total amount of compounds of acid character was 1%. Compounds IIb-d (R = CH_3, C_2H_5, C_3H_7, n=11) (Table 1) were similarly obtained.

Reductive Desulfurization of 2-Alkyl-2-carbethoxy-α-cyclo-1-thienones (II). A solution of 2 g (5.5 mmole) of IIb in 85 ml of alcohol and 34 ml of acetone was treated with 10 g of Raney nickel at 20° until the mixture no longer gave a positive reaction for sulfur (this required ~4-5 h). The solution was then decanted, and the precipitated nickel was washed by successive decantation with several portions of hot alcohol and ether. The bulk of the solution was combined with the wash liquid, the solvent was removed by distillation, and the residue was vacuum sublimed at 0.3-0.5 mm and a bath temperature of 100-120°. Compounds IVc, d were similarly obtained (Table 2).

Ketone Cleavage of 2-Alkyl-2-carbethoxycyclo-1-alkanols (IV). A 1-g (3 mmole) sample of IVb was refluxed for 50-60 h with a mixture of 4 ml of 50% sulfuric acid and 35 ml of acetic acid. The solution was diluted with water, and the product was extracted with ether. The extract was washed with water and sodium bicarbonate solution, dried with $MgSO_4$, and evaporated. The residue was sublimed at $4 \cdot 10^{-3}$ mm and a bath temperature of 70-80°. Ketones Va-c were similarly obtained. The yields of the ketones and the physical constants of their semicarbazones are presented in Table 3. Ketone Vd, which was obtained as an oil in 79% yield, gave a semicarbazone that was not isolated in a sufficiently pure state.

5-(12-Carboxytetradecyl)thiophene-2-carboxylic Acid (VIIc). A. A 0.47-g sample of IIc was refluxed in 15 ml of 6% aqueous alcohol solution of $Ba(OH)_2$ for 4 h, after which the solution was acidified and extracted with ether. The ether extract was washed with water, dried with $MgSO_4$, and evaporated. The residue was crystallized from benzene to give 0.27 g of VIIc with mp 104-105°. Found: C 65.0; H 8.7; S 8.6%. Equivalent wt. 184.5. $C_{20}H_{32}O_4S$. Calculated: C 65.2; H 8.8; S 8.7%. Equivalent wt. 184.2.

B. A solution of 2.3 g of I (n=11) in 8 ml of alcohol and 1.1 g of C_2H_5I in 2 ml of alcohol were added to sodium ethoxide (0.2 g of sodium in 6 ml of alcohol), and the mixture was stirred at room temperature for 16 h. The precipitate was removed by filtration and washed with ether, and the wash liquid was combined with the primary solution. The precipitate was dissolved in water, and the aqueous solution (at pH 7) was extracted with ether; this solution was also added to the primary mass. The ether solution was washed with water, sodium thiosulfate solution, sodium bicarbonate solution, and water, dried with magnesium sulfate, and evaporated to give 1 g of an oily product, which, according to TLC [activity II Al_2O_3, heptane–acetone (20:1)], contained a mixture of the starting I, the product of its ketone cleavage (VI), and a small amount of alkylation product. Acidification of the bicarbonate solution gave 0.8 g of dicarboxylic acid VIIc with mp 104-105°.

*A compound of acid character constituting ~8% of the weight of the reaction product was isolated from the wash bicarbonate solution on acidification.

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