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Abstract

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A NEW METHOD FOR THE SYNTHESIS OF MACROCYCLIC KETONES WITH A MUSKY ODOR

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Earlier ([1]), using cyclotetradecanone as an example, we showed that higher alicyclic ketones can be obtained by reductive desulfurization of the products of intramolecular acylation of acid chlorides of ω-thienylalkanoic* acids (I):

1. (I) ⟶ (II) + (III)
2. II ⟶ $\boxed{(CH_2)_{n+4}\ CO}$ (IV)

Cyclization of the acid chlorides was carried out in carbon disulfide with the use of a finely dispersed condensing agent formed upon addition of an ethereal solution of technical aluminum chloride to carbon disulfide. Subsequently it was found that carbon disulfide can successfully be replaced by chloroform ([2]).

Specially designed comparative experiments showed that the total yield and the ratio of the cyclization products depend substantially on the phase composition of the reaction mixture. If intramolecular acylation of the acid chloride of 10-thienylcapric acid is carried out in a homogeneous medium (an etherate of aluminum chloride purified by distillation was used), the yield of [10]-α-cyclothienone-1** (II, $n = 9$) decreases from 40 to 20%, and the yield of [10, 10]-α-cyclodithiendione-1,15 (III, $n = 9$) from 30 to approximately 10%, with a simultaneous increase in the amount of resin formed. Thus, the yield of cyclization products is 2–3 times lower than when the reaction is carried out in a heterogeneous medium under the conditions described earlier ([1,2]).

A study of the nature of the condensing agent led us to the idea that the cause of its heterogeneity is the admixture, in technical aluminum chloride, of products of hydrolysis of the latter by atmospheric moisture. Assuming that the heterogeneity of the condensing agent, owing to sorption on its surface and restriction of the mobility of the molecules undergoing cyclization, should favor the intramolecular course of the cyclization process, we carried out a series of experiments with the product of partial hydrolysis of aluminum chloride etherate (1 mole of water per mole of etherate), which forms a very fine suspension in chloroform.

It turned out that under these conditions the yield of α-cyclothienones-1 (II) increases by approximately 1.5 times, with a simultaneous decrease in the amount of the other cyclization product—the diketone of type III. The indicated condensing agent was used by us for carrying out cyclization of the acid chlorides of 10-thienylcapric, 11-thienylundecanoic, 12-thienyllauric, and 13-thienyltridecanoic acids. As a result, monoketones of type II with $n = 9, 10, 11, 12$ were obtained in yields of 53–63%; upon reductive desulfurization, in yields of 75–90%, they give alicyclic ketones possessing—

* Here and below, ω-(thienyl-2)-alkanoic acids are meant.
** For the nomenclature of macrocyclic compounds containing thiophene nuclei, see ([1]).

possessing a musk odor—cyclotetradecanone, cyclopentadecanone (exaltone), cyclohexadecanone, cycloheptadecanone (dihydrocivetone). The overall yield of alicyclic ketones, calculated on the ω-thienylalkanoic acids, is 40–55%, depending on the ring size.

The proposed method, both in simplicity and in yields (cf., for example, the recently described syntheses of exaltone ([3,4]) and dihydrocivetone ([3,5])), may serve as a preparative one.

Experimental Part

For the preparation of the aluminum chloride etherate, technical aluminum chloride was used. The etherate was purified by distillation in vacuo, b.p. 100–103°/0.5 mm, 108–110°/1 mm, 124–125°/3 mm, 128–129°/4 mm, about 150°/12 mm (with decomp.); m.p. about 35°, yield—up to 85% (according to literature data, the $AlCl_3$ etherate has b.p. 108°/2–3 mm ([6]), 147°/11 mm ([7]), m.p. 33–36° ([6–8])). The distilled product dissolves completely in chloroform and in carbon disulfide, forming clear solutions which do not change on boiling in the absence of moisture.

Acid chlorides of ω-thienylalkanoic acids were obtained by the action of thionyl chloride on ω-thienylalkanoic acids (for the preparation of the latter see ([9])) in abs. ether (cf. ([1])). The boiling points and yields of the acid chlorides subjected to cyclization are given in Table 1.

Table 1

Acid chlorides of ω-thienylalkanoic acids (I)

	$n = 9$	$n = 10$	$n = 11$	$n = 12$
B.p., °C/mm	157–160/1	154–155/0.2	175–180/0.7	Decomposes on attempted distillation at 0.2 mm

	$n = 9$	$n = 10$	$n = 11$	$n = 12$
Yield, %	92	91	76	

Intramolecular acylation of the acid chlorides of ω-thienylalkanoic acids is carried out in an apparatus consisting of a 3-liter flask with a thermometer, stirrer, and a special attachment for operation under conditions of high dilution, provided with a reflux condenser and a syringe doser for uniform delivery of the acid chloride solution ([1]). Into the flask is placed a solution of about 0.3 mole of aluminum chloride etherate in 300 ml of abs. ether, and into the high-dilution attachment an equimolar amount of water. When the ether is boiling, the water

Table 2

α-Cyclothienones-1 (II).

n	B.p., °C/mm	M.p., °C	Yield, %	M.p. of semicarbazone, °C
9	149-152/1.0	40-41[1]	53.6[2]	188.5-189.5[3]
10	128-132/0.05	44.5-46.5[4]	63.5	194-196[4]
11[5]	162-165/0.5	31-32	62.5[2]	214-215
12[6]	157/0.005	–	60.0	225-226.5

[1] Obtained by sublimation in vacuo followed by pressing on a porous plate; [10]-α-cyclothienone-1 was described by us previously ([1]) with m.p. 35-35.5°.

[2] When the catalyst described earlier ([1]) is used, yields of the order of 40% ([1,2]) are obtained.

[3] Found, %: N 14.29; 14.41
$C_{15}H_{23}N_3OS$. Calculated, %: N 14.32

[4] Gives no depression on melting of a mixed sample with the sample obtained previously ([10]).

[5] Found, %: C 72.64; 72.42; H 9.17; 9.28; S 12.09; 12.12
$C_{16}H_{24}OS$. Calculated, %: C 72.66; H 9.14; S 12.13

Semicarbazone: Found, %: N 13.13; 12.89
$C_{17}H_{27}N_3OS$. Calculated, %: N 13.07

[6] n_D^{20} 1.5448, d_4^{20} 1.0480; MR_D found 83.98, calculated 83.79;

Found, %: C 73.20; 73.12; H 9.16; 9.36; S 11.20; 11.31
$C_{17}H_{26}OS$. Calculated, %: C 73.31; H 9.41; S 11.52

Semicarbazone: Found, %: N 12.28; 12.23
$C_{18}H_{29}N_3OS$. Calculated, %: N 12.53

In contrast to the preceding cases, the yield of [13]-α-cyclothienone-1 is given not on the acid chloride but on 13-thienyltridecanoic acid, the acid chloride of which was used without purification.

gradually dissolves in the ether and passes with the flow of condensate into the etherate solution*. After completion of the dissolution of the water (after approximately 10 h), 1.5 liters of dry chloroform are added to the flask, the attachment and reflux condenser are replaced by a column with a total-condensation head, and the ether is distilled off until the temperature at the top of the column reaches 60–61°. In the process a fine suspension of the catalyst precipitates. Then, in place of the column, the attachment for high dilution with a reflux condenser and syringe doser is again fitted, and a solution of 0.015–0.03 mole of the acid chloride of an ω-thienylalkanoic acid is added to the flask, with the chloroform boiling, at a rate of $7 \cdot 10^{-4}$–$8 \cdot 10^{-4}$ mole per hour. After the usual work-up of the mixture formed, the corresponding α-cyclothienones-1 are isolated by crystallization, distillation, or high-vacuum sublimation. The constants and yields of the cyclization products are given in Table 2.

Reductive desulfurization of α-cyclothienones-1. A solution of 1 g of α-cyclothienone-1 in 70 ml of alcohol containing 15–20% acetone is stirred at 25–35° with a 3–5-fold amount by weight of skeletal nickel until a negative test for sulfur is obtained (about 2 h). After separation of the skeletal nickel and removal of the solvent, the corresponding polymembered alicyclic ketone is obtained.

From [10]-α-cyclothienone-1 (II, $n = 9$) cyclotetradecanone was obtained in 85% yield (see (1)); from [11]-α-cyclothienone-1 (II, $n = 10$)—exaltone, yield 75% (see (10)).

In the reductive desulfurization of [12]-α-cyclothienone-1 (II, $n = 11$), cyclohexadecanone (IV, $n = 11$) was obtained in 86% yield, m.p. 62.5–64°.

Found, %: C 80.04; 80.19; H 12.39; 12.30
$C_{16}H_{30}O$. Calculated, %: C 80.60; H 12.68

Semicarbazone, m.p. 178–180.5°.

Found, %: N 14.27; 14.49
$C_{17}H_{33}N_3O$. Calculated, %: N 14.22

Literature data for cyclohexadecanone: m.p. 63–64° [11], 65° [12]; semicarbazone, m.p. 180–181° [11], 179° [12].

By hydrazinolysis of [13]-α-cyclothienone-1 (II, $n = 12$), dihydrocivetone (IV, $n = 12$) was obtained in 90% yield, m.p. 61–63°.

Found, %: C 80.75; 80.83; H 12.56; 12.50
$C_{17}H_{32}O$. Calculated, %: C 80.88; H 12.78

Semicarbazone, m.p. 189.5-191°.

Found, %: N 13.87; 13.71
$C_{18}H_{35}N_3O$. Calculated, %: N 13.58

Literature data for dihydrocivetone: m.p. 63° [13], 64° [5]; semicarbazone, m.p. 191° [13], 191-191.5° [5].

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* When the attachment is replaced by an extractor for a heavy solvent, hydrolysis of the etherate can be carried out in chloroform.

Note: Figure translations are in progress. See original paper for figures.