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SYNTHESIS OF MACROCYCLIC COMPOUNDS CONTAINING THIOPHENE AND THIAZOLE NUCLEI

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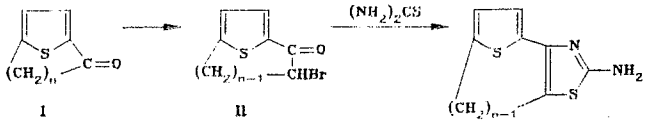
Macrocyclic ketones that contain a thiophene nucleus and have 14 or more carbon atoms in the ring can form systems with a condensed thiazole ring, in high yield.

The introduction of a macrocyclic segment into a physiologically active molecule can facilitate its directed transport through cell membranes to the appropriate receptors. Starting from this hypothesis we undertook the synthesis of pyrazolone systems condensed with a macrocycle [1]. The synthesis of macrocyclic compounds condensed with a thiazole ring has also been demonstrated [2]. The present work is devoted to a detailed description of such systems that are based on macrocyclic ketones.

The objective can be reached by various paths. If we arrange for quite simple syntheses of macrocyclic ketones of formula I that contain a thiophene ring [3], it is natural to seek a selective method for their halogenation α to the carbonyl group, and so convert them to thiazoles by the classical method [4]:



n=9, 10, 11

Macrocyclic ketones I (n = 9, 11) were obtained by intramolecular acylation of the acid chlorides of long-chain ω-thienylalkanoic acids, using the high dilution technique [3]. [11]-α-Cyclothienone-1 (I, n = 10) (for nomenclature of macrocyclic ketones containing a thiophene ring, see [3]) was obtained by ketonic cleavage of 2-carbethoxy-5-(9-iodononyl)acetylthiophene in methyl ethyl ketone in the presence of K_2CO_3 [5].

To develop the conditions for bromination of macrocyclic ketones at the α-carbon atom, 5-ethyl-2-propiothienone (IV) was synthesized as model compound (in view of the quite limited availability of ketones I). It was subjected to the action of various brominating agents:

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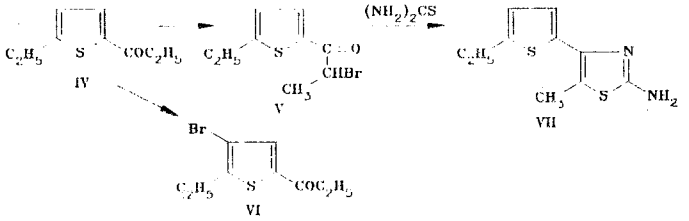
TABLE 1. Effect of Brominating Agent on Yield of Bromosubstituted Thiophenes

Brominating agent	Yield of reaction product, %	
	V	VI
$CuBr_2$	72	—
Br_2/CCl_4	88	—
N-Bromosuccinimide	—	—
Br_2/CH_3COOH	67	—
$Br_2/AlCl_3$	—	93

TABLE 2. Effect of Brominating Agents on Bromocyclothienone Yield

Brominating agent	n	Yield of α-bromosubstituted cyclothienone II, %
$CuBr_2$	9	85
$CuBr_2$	10	92
Br_2/CCl_4	9	83
Br_2/CCl_4	11	87
Br_2/CH_3COOH	9	65



The results of the bromination of IV are shown in Table 1.

According to the PMR spectral data, in the case of bromoketone V two thiophene ring protons were clearly identified. In the case of bromoketone VI only one such proton was found. The location of the bromine in the side chain was confirmed by the conversion of V to the substituted thiazole VII.

As the experimental data show, bromination without a catalyst is directed quite selectively at the carbon that is in the α-position to the carbonyl group. As might be expected [6], the addition of catalysts, viz., Lewis acids, changes the course of bromination to form the 4-bromosubstituted thiophene VI. It might be assumed that these features are fully applicable to macrocyclic ketones. Actually, with cyclothienones as examples it was shown that bromination at the α-carbon relative to carbonyl in macrocyclic ketones is quite selective and takes place in high yield (see Table 2).

Condensation of the bromosubstituted macrocyclic ketones was carried out by boiling in alcohols (methanol, ethanol). The resulting macrocyclic aminothiazoles III are quite mobile oils with an unpleasant acrid odor, which are easily purified from resinous impurities by silica gel chromatography. For analysis the solid acetyl derivatives or hydrohalide salts were used. For all the cyclothienones the yields of condensed aminothiazoles were quite high, from 76 to 88%. This is evidence that this size of macrocycle (C_{14}-C_{16}), even when it includes the "rigid" thiophene group, does not hinder the formation of a condensed system, although the "rigid" group is enlarged by the two carbon atoms conjugated with the π-system of the thiophene ring.

EXPERIMENTAL

Bromination of 5-ethyl-2-propiothienone (IV). A. A mixture of 3.36 g (20 mmole) of IV [7], 20 ml of ethyl acetate, 7.4 g (33.1 mmole) of finely ground anhydrous copper bromide, and 20 ml of chloroform was boiled for 2.5 h. The dark green copper bromide color gradually disappeared and a grayish white cuprous bromide precipitate, Cu_2Br_2, appeared. After stirring for another 10 h the precipitate was filtered off and washed with chloroform. The combined solutions were washed with water and dried. After removal of solvent, distillation yielded 0.46 g of unreacted IV and 2.9 g of 5-ethyl-(α-bromopropionyl)thiophene (V), bp 128-132°C(1.5 mm), 72% yield. Found, %: C 43.4; H 4.4; Br 32.3; S 13.0. $C_9H_{11}BrOS$. Calculated, %: C 43.7; H 4.5; Br 32.2; S 13.0. The purity of IV and V was monitored by GLC on a LKhM-8MD instrument with flame ionization detector, column 1 m × 2 mm with 2% OV-17 on Chromosorb (60-80 mesh), nitrogen carrier gas, column temperature 190°C.

B. Analogously to the procedure of [8], to a solution of 5.04 g (30 mmole) of IV in 30 ml of CCl_4 was added dropwise with stirring a solution of 5 g (31.3 mmole) of bromine in 10 ml of CCl_4 at such a rate that the solution was decolorized before the addition of the next drop. The mixture was stirred for 1 h at 20°C and poured into aqueous $NaHCO_3$ solution. The

organic portion was separated, washed with water, and dried with $MgSO_4$. After removal of solvent and distillation there was separated 6.55 g (88% yield) of bromoketone V, bp 120-122°C (0.16 mm), identical by GLC with the preparation obtained by method A.

C. As proposed in [6], to 10 g of $AlCl_3$ in 30 ml of $CHCl_3$ was added with stirring a solution of 8.4 g (49.9 mmole) of IV in 5 ml of $CHCl_3$ and 8 g (50 mmole) of bromine, and the mixture was heated for 2 h until the bromine color disappeared. After cooling the reaction mixture was poured on a mixture of ice and 15 ml of HCl, the organic layer was separated, and the aqueous solution was repeatedly extracted with chloroform. The combined organic solutions were washed with water and dried. Distillation gave 11.5 g (93% yield) of 4-bromo-5-ethyl-2-propiothienone (VI), bp 112-114°C (0.18 mm). Found, %: C 44.4; H 4.4; Br 31.9; S 12.8. $C_9H_{11}BrOS$. Calculated, %: C 43.7; H 4.5; Br 32.2; S 13.0.

2-Bromo-[10]-α-cyclothienone-1 (II, n = 9). A. To a suspension of 4.7 g (21 mmole) of finely ground copper bromide in 10 ml of ethyl acetate was added over 20 min with stirring a solution of 2.92 g (12.3 mmole) of cyclothienone I (n = 9) in 10 ml of chloroform. After 0.5 h the color of the solution changed from black to bright green, and a grayish white precipitate of Cu_2Br_2 formed. After heating for 3 h the precipitate was filtered off and washed with chloroform. After removal of chloroform the residue was dissolved in ether, and the ether solution was washed with water, sodium thiosulfate solution, and again water, and dried with $MgSO_4$. The residue after removal of the ether (3.7 g) was chromatographed on a column with silica gel L 100/60 (benzene eluent) to yield 3.23 g (85% yield) of 2-bromo-[10]-α-cyclothienone-1 (II, n = 9), which crystallized as long fan-shaped crystals, mp 58.5-59°C (from n-pentane). PMR spectrum (CCl_4): 7.73 (1H, d, J = 4 Hz, thiophene), 6.89 (1H, d, J = 4 Hz, thiophene), 4.4-4.6 (1H, q, J = 6 Hz, CHBr), 2.9 (2H, m, $\underline{CH_2}C_4H_2S$), 1.1-1.6 ppm (14H, m, $(CH_2)_7$). Found, %: C 53.9; H 6.3; Br 25.5; S 10.2; M 315. $C_{14}H_{19}BrOS$. Calculated: C 53.3; H 6.1; Br 25.4; S 10.2; M 315.

B. To a solution of 4.8 g (20.3 mmole) of cyclothienone I (n = 9) in 30 ml of CCl_4 was added with stirring at 20°C a solution of 4 g (25 mmole) of bromine in 12 ml of CCl_4 over 3.5 h; there was violent evolution of HBr and loss of bromine color. The residue after removal of CCl_4 was dissolved in ether, and the ether solution was washed with sodium carbonate solution, sodium thiosulfate solution, and water, and dried. The residue after removal of ether (6.6 g of dark oil) was chromatographed on a column with silica gel (CH_2Cl_2 eluent) and vacuum-distilled. There was obtained 5.25 g (83% yield) of 2-bromocyclothienone II (n = 9), bp 180-186°C (0.09 mm), mp 58-59°C (from n-pentane), identical by TLC with the material obtained by method (A).

2-Bromo-[11]-α-cyclothienone-1 (II, n = 10). A solution of 2.3 g (9.2 mmole) of [11]-α-cyclothienone (I, n = 10) in 10 ml of chloroform was added with stirring over 0.5 h to a suspension of 2.85 g (12.8 mmole) of copper bromide in 10 ml of ethyl acetate. After HBr evolution ceased, the mixture was heated for 4 h, and the grayish white cuprous bromide precipitate was filtered off and washed with chloroform. The combined chloroform solutions were washed with water and sodium carbonate solution and dried. The residue after removal of chloroform was separated from the resin by chromatography on silica gel (CCl_4 eluent) and vacuum distilled to yield 2.8 g (92% yield) of 2-bromo-[11]-α-cyclothienone (II, n = 10), bp 174-175°C (0.09 mm). Found, %: C 54.7; H 6.6; Br 24.7; S 9.9%. $C_{15}H_{21}BrOS$. Calculated, %: C 54.7; H 6.4; Br 24.3; S 9.7.

2-Bromo-[12]-α-cyclothienone-1 (II, n = 11). To a solution of 4.6 g (17.7 mmole) of [12]-α-cyclothienone (I, n = 11) in 20 ml of CCl_4 was added over 2 h a solution of 5.1 g (32 mmole) of bromine in 22 ml of CCl_4. The mixture was stirred for 1 h and treated with water, and the organic layer was washed with water, sodium carbonate solution, and sodium thiosulfate solution. The residue after removal of CCl_4 was chromatographed on a column of silica gel (benzene eluent). There was obtained 6.4 g of crystalline bromination product, which after recrystallization from hexane yielded 5.3 g (87% yield) of 2-bromo-[12]-α-cyclothienone (II, n = 11), mp 79-79.5°C. Found, %: Br 23.9; S 10.0; M 342. $C_{16}H_{23}BrOS$. Calculated, %: Br 23.3; S 9.4; M 343.

2-Amino-[10]-α-cyclothieno[1,2-d]thiazole (III, n = 9). A solution of 10.65 g (340 mmole) of 2-bromo-[10]-α-cyclothienone (II, n = 9) in 40 ml of methanol was added to a solution of 2.7 g (350 mmole) of thiourea in 20 ml of methanol and the mixture was boiled for 6 h. When the resulting solution of aminothiazolium bromide III (n = 9) was cooled a small amount of it (0.41 g) precipitated as crystals, mp 126-127°C (from heptane). Found, %: C 48.2; H 5.6; Br 21.0; N 7.0; S 17.3. $C_{15}H_{21}BrN_2S_2$. Calculated, T: C 48.2; H 5.6; Br 21.0;

N 7.5; S 17.2. The residue after removal of methanol was treated with 25 ml of 40% NaOH solution and extracted with ether. After removal of ether and chromatography on silica gel (benzene eluent), free base III (n = 9) was separated as a bright yellow oil with an acrid odor, 8.7 g (88% yield). IR spectrum (tablets with KBr): 1630 (NH_2 of N=C–NH_2 group), 2850, 2830 cm^{-1} [$(CH_2)_8$]. UV spectrum (in $CHCl_3$), λ_{max} (log ε): 225 (8.6), 294 nm (4.8). PMR spectrum ($CDCl_3$): 7.0 (1H, d, J = 4 Hz, thiophene), 6.7 (1H, d, J = 4 Hz, thiophene), 5.1 (2H, m, NH_2), 2.9-2.7 (4H, m, CH_2 adjacent to heterocycle), 1.6-1.0 ppm [12H, m, $(CH_2)_6$]. Found, %: C 61.2; H 6.8; N 9.0; S 21.5%; M 292. $C_{15}H_{20}N_2S_2$. Calculated, %: C 61.6; H 6.9; N 9.6; S 21.9; M 292. From 0.9 g of thiazole III (n = 9) boiling with acetic anhydride yielded the N-acetyl derivative, yield 0.6 g, mp 206-207°C (from 1:1 heptane–toluene). Found: C 61.0; H 6.6; N 8.4; S 19.0. $C_{17}H_{22}N_2S_2O$. Calculated, %: C 61.0; H 6.6; N 8.4; S 18.2.

2-Amino-[11]-α-cyclothieno[1,2-d]thiazole (III, n = 10). To a solution of 1 g (12 mmole) of thiourea in 10 ml of methanol was added a solution of 1.93 g (6 mmole) of 2-bromocyclothienone II (n = 10) in 20 ml of methanol and the mixture was boiled for 5 h. After removal of precipitated thiazolium bromide III (n = 10) (0.12 g, mp 112-113°C) the solvent was evaporated, and the residue was treated with 10 ml of 40% NaOH and extracted with ether. There was obtained 1.7 g of clear oil, which after chromatography on silica gel (benzene eluent) yielded free base III (n = 10), 1.37 g yield, 76%. IR spectrum (in $CHCl_3$): 1630 (N=C–NH_2), 2850, 2930 cm^{-1} [$(CH_2)_9$]. From 0.4 g of aminothiazole III (n = 10) after treatment with alcoholic HCl and evaporation there was obtained aminothiazole hydrochloride III (n = 10), 0.44 g yield (100%), mp 185°C (from heptane–toluene). Found, %: C 55.5; H 6.0; Cl 10.5; N 8.2; S 10.0. $C_{16}H_{23}ClN_2S_2$. Calculated, %: C 56.0; H 6.7; Cl 10.4; N 8.2; S 10.4.

2-Amino[12]-α-cyclothieno[1,2-d]thiazole (III, n = 11). A solution of 3.46 g (10 mmole) of 2-bromo-[12]-α-cyclothienone II (n = 11) in 15 ml of ethanol was added to a solution of 0.9 g (10 mmole) of thiourea in 8 ml of ethanol and the mixture was heated for 6 h at 70°C. The residue after removal of solvent was treated with 8 ml of conc. HBr and evaporated to dryness. There was obtained 5.2 g of aminothiazole hydrobromide III (n = 11). Yield 97%, mp 122-124°C from ethyl acetate). Found, %: C 49.8; H 6.0; Br 19.2; N 6.8; S 16.8. $C_{17}H_{25}BrN_2S_2$. Calculated, %: C 50.7; H 6.3; Br 19.9; N 7.0; S 16.0. Free base III (n = 11) separated as oil after treatment of the main amount of III hydrobromide (n = 11) with 40% NaOH and extraction with ether, 2.54 g (83% yield).

2-Amino-5-methyl-4-(2-ethylthienyl-5)thiazole (VII). A mixture of 6.55 g (38 mmole) of bromoketone V, 2 g (26 mmole) of thiourea, and 5.3 ml of water was boiled for 2 h; the two-phase system became homogeneous after 20 min. The solution was cooled. The precipitate was filtered off, recrystallized from water and dried to yield 5.79 g (64% yield) of 2-amino-5-methyl-4(2-ethylthienyl-5)thiazole hydrobromide, mp 203.5-205.5°C. Found, %: C 39.7; H 4.4; Br 25.7; N 9.2; S 21.0. $C_{10}H_{13}BrN_2S_2$. Calculated, %: C 39.4; H 4.3; Br 25.8; N 9.2; S 21.0.

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