SYNTHESIS OF MACROCYCLIC COMPOUNDS THAT ARE CONDENSED WITH A PYRAZOLE RING

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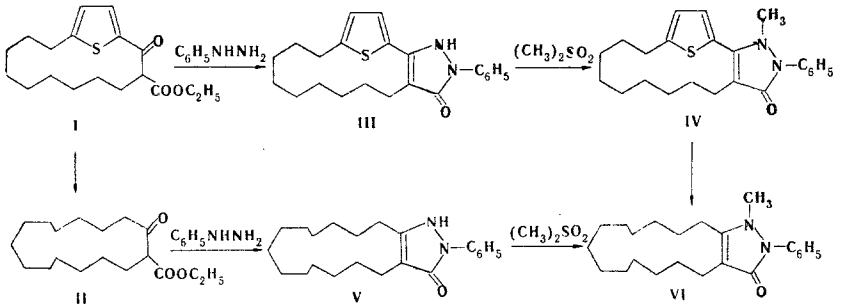
UDC 547.734'779'898.07

2-Carbethoxy-[11]-α-cyclothien-1-one, 2-carbethoxycyclopentadecanone, and 2,15-dicarbethoxy-[9,9]-α-cyclodithiene-1,14-dione were converted to 2-phenyl-1-methyl-[11]-α-cyclothieno[1,2-d]pyrazol-3-one, 2-phenyl-1-methyl-4,5-tridecamethylenepyrazol-3-one, and 2,16-diphenyl-1,15-dimethyl-[9,9]-α,α'-cyclodithienobis[(1,2-d,14,15-d')pyrazole]-3,17-dione, respectively, by condensation with phenylhydrazine and subsequent methylation.

A large number of physiologically active macrocyclic compounds, particularly macrolide antibiotics [1], jatrophone, which is active against certain malignant cells [2], and nonsteroid estrogens of the zearalenone type [3], have been described in recent years. There is some basis for the assumption that a macrocyclic fragment is necessary in some cases for the development of a biological effect, since this grouping may either correspond to the structure of the biological receptor or may affect the permeability through biological membranes. In this connection, the interest in the preparation of synthetic macrocyclic compounds that are condensed with various heterocyclic groupings that have known physiological activity is understandable. A comparative study of the properties of the compounds obtained with the properties of compounds that have physiological activity but do not have a macrocyclic link could serve as a starting point in their study.

With this end in mind, we selected a method for the synthesis of macrocyclic systems that are condensed with a pyrazole ring on the basis of our previously obtained macrocyclic β-keto esters [4]. The presence of a macrocyclic ring that is condensed in the 3 and 4 positions of the pyrazole ring is important in the respect that, as is well known [5], an increase in the length of the carbon chains in the indicated positions of the pyrazole ring, just as the presence of a tetramethylene chain that connects these positions [6], promotes a certain increase in the activity and a decrease in the toxicity of antipyrene derivatives.

Pyrazolones of this type were obtained by the reaction of macrocyclic β-keto esters with phenylhydrazine and subsequent methylation. 2-Carbethoxy-[11]-α-cyclothien-1-one (I) (our proposed nomenclature for macrocyclic compounds that include a thiophene ring [7] is used here and subsequently for brevity) was obtained by cyclization of 2-(9-iodononyl)-5-carbethoxyacetylthiophene in the presence of K_2CO_3 in methyl ethyl ketone with the use of high-dilution technique, as described in [4, 8]. 2-Carbethoxycyclopenta-decan-1-



one (II) was prepared from macrocyclic β-keto ester I by reductive desulfuration by means of Raney nickel.

The condensation of macrocyclic β-keto esters with phenylhydrazine was realized by heating solutions in toluene at 120°C in an inert gas atmosphere. Alkylation of the pyrazolones obtained with dimethyl sulfate gave the products in almost quantitative yields. As a result of the study, we found synthetic conditions under

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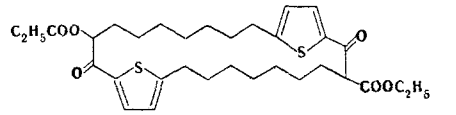
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 920-923, July, 1980. Original article submitted December 26, 1979.

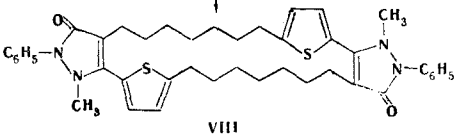
0009-3122/80/1607-0711$07.50

which pyrazolone IV was formed in 63% yield, while pyrazolone VI was formed in 85% yield. Pyrazolone VI was also obtained in 88% yield by reductive desulfuration of pyrazolone IV; this is simultaneously a confirmation of the structure of IV. It is noteworthy that not only does the ring not undergo hydrogenolysis, but the double bond of the pyrazolone ring also is not involved in the reductive desulfuration.

In the course of our study we were also able to obtain a macrocyclic system with 26 carbon atoms in a ring that includes two thiophene rings and is condensed with two pyrazolone rings. Thus, bispyrazolone VIII was obtained by condensation of 2,15-dicarbethoxy-[9,9]-α-cyclodithiene-1,14-dione (VII) with 2 moles of phenylhydrazine and subsequent methylation:



VII



VIII

EXPERIMENTAL

2-Carbethoxycyclopentadecan-1-one (II). Raney nickel (30 g) was added to a solution of 5.73 g (16.6 mmole) of 2-carbethoxy-[11]-α-cyclothien-1-one (I) in 400 ml of ethanol and 150 ml of acetone, and the mixture was stirred at 20°C for 3 h. The catalyst was then removed by filtration and washed with acetone, and the solvents were removed by distillation. The residue was distilled in vacuo to give 4.9 g (93%) of keto ester II with bp 120-122°C (0.02 mm). Found: C 72.9; H 10.9%. $C_{18}H_{32}O_3$. Calculated: C 72.9; H 10.9%. UV spectrum (in chloroform), λ_{max}: 245 nm (log ε 3.02). According to the data in [9], this compound has bp 168-169°C (1 mm).

2,15-dicarbethoxy-[9,9]-α-cyclodithiene-1,14-dione (VII) was obtained by cyclization of 2-(7-iodoheptyl)-5-carbethoxyacetylthiophene in the presence of K_2CO_3 in accordance with the method in [10].

2-Phenyl-1-methyl-[11]-α-cyclothieno[1,2-d]pyrazol-3-one (IV). A 0.94-g (8.7 mmole) sample of phenylhydrazine was added with stirring in a steam of argon to a solution of 2.72 g (8.4 mmole) of keto ester I in 3.5 ml of toluene, and the mixture was heated at 100°C for 2 h with removal of the resulting water by distillation. The temperature was then raised to 120°C, and the mixture was heated with a reflux condenser for another 5 h until the liberation of alcohol vapors ceased. The toluene was removed by distillation, as a result of which a transparent glassy mass was obtained. A 1.3-g (9-mmole) sample of dimethyl sulfate was added with stirring to 3 g of the resulting III dissolved in 5 ml of toluene, and the mixture was heated at 130°C for 4 h. It was then cooled to 60°C, and 3 ml of water, 3 ml of benzene, and 10 ml of 40% aqueous NaOH solution were added. After 4 h, the light-yellow solution was separated from the bright-crimson alkaline solution, washed with a saturated solution of K_2CO_3, and dried over K_2CO_3. The solvents were removed by distillation to give 1.85 g of IV. Extraction of the alkaline solution with benzene yielded another 0.05 g of pyrazolone IV for an overall yield of 63% based on starting β-keto ester I. The crystallized substance has mp 104-104.5°C (from heptane). Found: C 72.5; H 7.5; N 7.4; S 8.4%; M^+ 376. $C_{23}H_{28}N_2OS$. Calculated: C 72.6; H 7.4; N 7.4; S 8.4%; M 381. UV spectrum (in chloroform): λ 270 and 350 nm (log ε 3.85 and 3.79). IR spectrum (KBr pellets): 1675 (C=O); 2850, 2920 cm^{-1} (CH_2 of the polymethine chain). PMR spectrum (in C_5D_5N), δ: 6.9-7.7 (m, 7H, aromatic), 2.8 (s, 3H, CH_3N), 2.48 (m, 2H, $CH_2C=C$), and 1.3-1.6 ppm[$(CH_2)_9$, unresolved multiplet at strong field].

Crystalline 2-carbethoxy-[11]-α-cyclothienone phenylhydrazone [1.26 g (100%)], with mp 152.5-153°C (from heptane), was isolated when 1.13 g of β-keto ester I in 4 ml of toluene was heated with 0.39 g of phenylhydrazine at 110°C for 1 h after the solvent was removed by distillation. Found: C 69.2; H 7.2; N 6.8; S 8.1%. $C_{24}H_{32}N_2O_2S$. Calculated: C 69.8; H 7.8; N 6.8; S 7.8%.

2-Phenyl-1-methyl-4,5-tridecamethylenepyrazol-3-one (VI). A) A 0.87-g (8-mmole) sample of phenylhydrizine was added with stirring to a solution of 1.69 g (5.7 mmole) of 2-carbethoxycyclopentadecanone (II) in 4 ml of toluene, and the reaction mixture was heated at 90°C for 2 h with removal of the water by distillation. It was heated at 130°C for another 3 h until the liberation of alcohol vapors ceased. It was then cooled

and dissolved in ether, and the solution was filtered. The ether was evaporated, and the residue was recrystallized from heptane to give 1.53 g (79%) of crystalline 2-phenyl-4,5-tridecamethylenepyrazolone (V) with mp 126.5-128°C. Found: C 77.4; H 9.6; N 8.1%; M^+ 340. $C_{22}H_{32}N_2O$. Calculated: C 77.6; H 9.5; N 8.3%; M 340.5.

A 1.4-g sample of dimethyl sulfate was added with stirring at 20°C to a solution of 1.89 g of hydrazone V in 6 ml of toluene, and the mixture was heated at 120°C for 1.5 h. It was then diluted with 4 ml of toluene, and the mixture was allowed to stand overnight. The free pyrazolone base VI was isolated after stirring for 1.5 h with 15 ml of 40% aqueous NaOH and extraction with hot benzene and removal of the solvents by distillation. The glassy red residue (2.8 g) was dissolved in methylene chloride and chromatographed with a column filled with silica gel to give 1.75 g (91%) of pyrazolone VI with mp 76-76.5°C (from heptane). Found: C 78.1; H 9.9; N 8.1%; M 354. $C_{23}H_{34}N_2O$. Calculated: C 77.9; H 9.7; N 7.9%; M 354. UV spectrum (in chloroform): λ_{max} 245 and 280 nm (log ε 3.84 and 3.70). IR spectrum (KBr pellets): 1675 (C=O); 2855, 2925 cm^{-1} [$(CH_2)n$]. PMR spectrum (in C_5D_5N), δ: 7.0-7.5 (m, 5H, aromatic), 2.81 (s, 3H, CH_3N), and 1.3-1.6 ppm [m, 26H, $(CH_2)_{13}$].

B) A solution of 0.85 g (2.8 mmole) of 2-carbethoxycyclopentanone (II) and 0.31 g (3 mmole) of phenyl hydrazine in 2.5 ml of m-xylene was heated at 110°C for 1 h and at 140°C for another 3 h, after which it was cooled and treated with 3 ml of xylene and 1.3 g of dimethyl sulfate. The mixture was then heated at 140°C for 4 h, after which it was cooled to 60°C and treated with 10 ml of benzene and 10 ml of 40% aqueous NaOH. The mixture was then stirred for 2 h, after which the solvents were removed by distillation, and 1.13 g of the residue was crystallized from heptane to give 0.85 g (85%) of 2-phenyl-1-methyl-4,5-tridecamethylenepyrazol-3-one (VI- with mp 76°C.

2,16-Diphenyl-1,15-dimethyl-[9,9]-α,α'-cyclodithienobis[(1,2-d,14,15-d')pyrazole]-3,17-dione (VIII). A 1.76-g (16-mmole) sample of phenylhydrazine was added with stirring at 90°C to a solution of 3.82 g (6.4 mmole) of bis(β-keto ester) VII in 5 ml of toluene, and the mixture was heated at 100°C for 1 h and at 120°C for 5 h. It was then cooled and treated with 8 ml of toluene and 1.72 g (13.6 mmole) of dimethyl sulfate, and the mixture was stirred at 120°C for 4 h. The dark-yellow spongy mass that formed after cooling to 20°C and stirring for 1.5 h with 20 ml of 40% aqueous NaOH solution was extracted with hot benzene, and the solvents were removed by distillation to give a powder that melted at 90°C. Purification by chromatography on silica gel (elution with heptane–ethyl acetate) gave 3.3 g (72%) of bispyrazolone VIII with mp 90-92°C. Found: C 71.3; H 7.1; N 7.4; S 8.9%; M^+ 700. $C_{42}H_{48}N_4O_2S_2$. Calculated: C 71.5; H 6.9; N 8.0; S 9.1%; M 704. IR spectrum (KBr pellets): 1680 (C=O), 1730 (amide I), and 2935 cm^{-1} [$(CH_2)n$].

Reductive Desulfuration of 2-Phenyl-1-methyl-[11]-α-cyclothieno]1,2-d]pyrazol-3-one. A 1.02-g sample of pyrazolone IV was dissolved in a mixture of 55 ml of ethanol and 20 ml of acetone, 7 g of freshly prepared Raney nickel was added, and the mixture was refluxed for 1 h. The catalyst was removed by filtration, and the solvents were removed from the filtrate by evaporation to give 0.84 g (88%) of completely crystallized 2-phenyl-1-methyl-4,5-tridecamethylenepyrazolone (VI) with mp 76.5°C. No melting-point depression was observed for a mixture of this product with a genuine sample of pyrazolone VI.

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