UNSATURATED LACTONES

XXXV.* SYNTHESIS AND PROPERTIES OF 5-BUTENOLIDYLPYRAZOLE-3-CARBOXYLIC ACIDS

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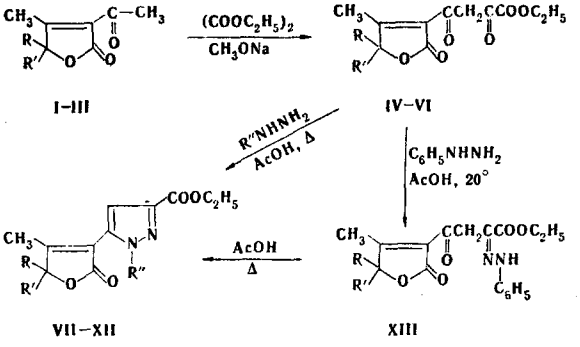
New, biologically active pyrazole derivatives containing an unsaturated γ-lactone ring were obtained by condensation of 2-(1-ethoxycarbonyl-1,3-diketopropyl)-2-buten-4-olides with phenylhydrazine and hydrazine hydrate. A number of transformations of the resulting pyrazole-3-carboxylic acid esters were realized.

It is known that pyrazole and its derivatives have a broad spectrum of biological activity. In addition, compounds containing lactone rings are widely distributed in nature and many of them, including their synthetic analogs find application in the manufacture of medicinal preparations, herbicides, insecticides, etc. Pyrazoles that contain an unsaturated γ-lactone ring as a substituent are unknown. In order to synthesize compounds of this type we obtained 2-(1-ethoxycarbonyl-1,3-diketopropyl)-3,4,4-trialkyl-2-buten-4-olides (IV-VI) by condensation of 2-acetyl-2-buten-4-olides (I-III) with diethyl oxalate. The IR spectra of the products contain absorption bands at 1750-1760, 1720-1726, 1690-1698, and 1620-1625 cm^{-1}, which are characteristic for lactone, ester, and ketone carbonyl groups and the C=C bond.

Esters of the corresponding 5-(3,4,4-trialkyl-2-buten-4-olid-2-yl)pyrazole-3-carboxylic acids (VII-XII) are easily formed from diketo esters IV-VI by heating with phenylhydrazine and hydrazine hydrate in the presence of glacial acetic acid. The absorption bands at 1758-1760, 1714-1720, and 1614-1620 cm^{-1} in the IR spectra of pyrazoles VII-XII should be assigned to the vibrations of lactone and ester carbonyl groups and the C=N bond. The absorption bands at 3110-3112 cm^{-1} correspond to the stretching vibrations of the CH groups of the phenyl ring in VII-IX. The absorption of the NH group in pyrazoles X-XII is characterized by two bands at 1666-1680 and 3255-3268 cm^{-1}.



I, IV, VII, X, XIII R=R′=CH_3; II, V, VIII, XI R=CH_3, R′=C_2H_5; III, VI, IX, XII RR′=$(CH_2)_5$; VII–IX R″=C_6H_5; X–XII R″=H

Monophenylhydrazone XIII was isolated when the reaction was carried out under milder conditions (at room temperature with traces of acetic acid). In this case it may be assumed that the condensation proceeds at the keto group that is under the influence of the electron-acceptor ester grouping. The resulting hydrazone also undergoes cyclization to the corresponding pyrazole VII when it is refluxed in acetic acid. Absorption

*See [1] for communication XXXIV.

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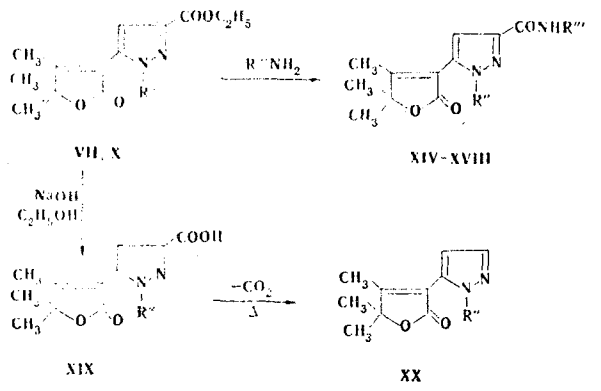
TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
IV	96—98	58,4	6,4	—	$C_{13}H_{16}O_6$	58,2	6,0	—	84
V	88—90	59,3	6,3	—	$C_{14}H_{18}O_6$	59,6	6,4	—	80
VI	104—106	62,5	6,7	—	$C_{16}H_{20}O_6$	62,3	6,5	—	97
VII	140—142	67,1	5,8	8,0	$C_{19}H_{20}N_2O_4$	67,1	5,9	8,2	77
VIII	128—130	67,5	6,1	7,8	$C_{20}H_{22}N_2O_4$	67,8	6,2	7,9	62
IX	165—166	69,6	6,1	7,4	$C_{22}H_{24}N_2O_4$	69,5	6,3	7,4	68
X	156—158	58,6	6,6	11,0	$C_{13}H_{17}N_2O_4$	58,9	6,4	11,6	78
XI	135—136	60,5	6,8	10,2	$C_{14}H_{19}N_2O_4$	60,4	6,5	10,1	70
XII	170—172	63,3	6,4	9,3	$C_{16}H_{21}N_2O_4$	63,2	6,6	9,2	74
XIV	130—131	66,0	5,6	13,4	$C_{17}H_{17}N_3O_3$	65,6	5,5	13,5	66
XV	138—140	68,7	7,0	11,3	$C_{21}H_{25}N_3O_3$	68,7	6,8	11,4	80
XVI	148—150	72,0	6,4	10,3	$C_{24}H_{25}N_3O_3$	71,8	6,2	10,5	73
XVII	151—152	56,0	5,5	17,7	$C_{11}H_{13}N_3O_3$	56,1	5,5	17,9	41
XVIII	160—162	66,9	6,0	12,8	$C_{18}H_{19}N_3O_3$	66,5	5,9	12,9	65

bands at 1750 (lactone C=O), 1722 (ester C=O), 1618 (C=N), 1680 and 3270 (NH), and 3110 cm^{-1} (C_6H_5) are observed in the IR spectrum of hydrazone XIII. The PMR spectra contain signals of protons of a butenolide (2.15 and 1.40 ppm) and an ester (1.30 ppm), methylene groups of a side chain (3.80 ppm) and an ester (4.27 ppm), and of an NH group (10.58 ppm).

The 5-butenolidylpyrazole-3-carboxylic acid esters react with ammonia and amines to give the corresponding amides XIV-XVIII in 41-80% yields. The alkaline hydrolysis of ester VII leads to acid XIX, which undergoes decarboxylation to 1-phenyl-5-(3,4,4-trimethyl-2-buten-4-olid-2-yl)pyrazole (XX) when it is heated in the presence of bronze.



XIV, XVII $R'''=H$; XV $R'''=C_4H_9$; XVI, XVIII $R'''=C_6H_5CH_2$; XIV-XVI, XIX, XX $R''=C_6H_5$; XVII, XVIII $R''=H$

The synthesized pyrazoles are biologically active compounds. Thus ethyl 1-phenyl-5-(3,4,4-trimethyl-2-buten-4-olid-2-yl)pyrazole-3-carboxylate (VII) affects the respiratory system of the mitochondria of the brain and liver and is a potential inhibiting agent.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with an IKS-14 spectrometer. The PMR spectrum of a solution in chloroform was recorded with a Hitachi – Perkin – Elmer R-20B spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard.

2-(1-Ethoxycarbonyl-1,3-diketopropyl)-3,4,4-trialkyl-2-buten-4-olides (IV-VI). A 4-g (0.074 mole) sample of dry sodium methoxide was added in small portions with vigorous stirring to a solution of 0.036 mole of 2-acetyl-3,4,4-trialkyl-2-buten-4-olide (I-III) in 13.8 ml (0.1 mole) of diethyl oxalate, and the mixture was heated at 70-80°C for 11-12 h. It was then treated with cold 3% acetic acid, and the resulting precipitate was removed by filtration, washed with water, acidified with acetic acid, and recrystallized from petroleum ether (Table 1).

Ethyl 1-Phenyl-5-(3,4,4-trialkyl-2-buten-4-olid-2-yl)pyrazole-3-carboxylates (VII-IX). A solution of 12 mmole of diketo ester IV-VI and 1.3 g (12 mmole) of phenylhydrazine in 40 ml of glacial acetic acid was refluxed

with stirring for 5-6 h, after which the mixture was cooled and poured into 300 ml of water. The resulting precipitate was removed by filtration and purified by recrystallization from petroleum ether (Table 1).

Ethyl 5-(3,4,4-Trialkyl-2-buten-4-olid-2-yl)pyrazole-3-carboxylates (X-XII). A mixture of 6 g (0.12 mole) of hydrazine hydrate, 0.012 mole of diketo ester IV-VI, 12 ml of glacial acetic acid, and 30 ml of absolute isopropyl alcohol was refluxed with stirring for 3-4 h, after which the alcohol was removed by distillation, and the residue was treated with 200 ml of water. The crystals were removed by filtration and recrystallized from aqueous alcohol (Table 1).

2-(1-Ethoxycarbonyl-1,3-diketopropyl)-3,4,4-trimethyl-2-buten-4-olide Phenylhydrazone (XIII). An ether solution of 1 g (4 mmole) of diketo ester IV, 0.65 g (6 mmole) of phenylhydrazine, and one drop of glacial acetic acid was allowed to stand at room temperature for 8-10 days, and the precipitated crystals were separated and recrystallized from 30% aqueous alcohol to give 0.9 g (63%) of a product with mp 153-154°C. Found: C 63.9; H 6.1; N 7.7%. $C_{19}H_{22}N_2O_5$. Calculated: C 63.7; H 6.1; N 7.8%.

Cyclization of Phenylhydrazone XIII. A solution of 0.9 g (2.5 mmole) of XIII in 15 ml of glacial acetic acid was refluxed for 6 h, after which it was cooled and treated with 100 ml of water. The precipitated crystals were removed by filtration to give 0.75 g (88%) of pyrazole VII with mp 141-142°C (from petroleum ether). No melting-point depression was observed for a mixture of this product with a sample of VII obtained by the method presented above.

5-Butenolidylpyrazole-3-carboxylic Acid Amides (XIV-XVIII). A solution of 2.9 mmole of ester VII or X in 5 ml of 25% ammonium hydroxide was allowed to stand at room temperature for 2-3 days, and the precipitated crystals were separated and recrystallized from aqueous alcohol.

The reaction with butylamine was also carried out at room temperature, and the reaction with benzylamine was carried out at 50-60°C. IR spectra: 1755-1758 (lactone C=O), 1653-1655 (amide C=O), 1660-1675 and 3268-3270 (NH), and 3109-3113 cm^{-1} (C_6H_5). The yields and constants of amides XIV-XVIII are presented in Table 1.

1-Phenyl-5-(3,4,4-trimethyl-2-buten-4-olid-2-yl)pyrazole-3-carboxylic Acid (XIX). A mixture of 1 g (2.9 mmole) of ester VII, 20 ml of 2 N NaOH, and 20 ml of ethanol was refluxed with stirring for 4 h, after which it was cooled, diluted with 100 ml of water, and neutralized with 2 N hydrochloric acid. The precipitate was separated to give 0.8 g (89%) of acid XIX with mp 196-198°C (from ether). IR spectrum: 1760 (lactone C=O), 1700 (acid C=O), 1621 (C=N), 3110 (C_6H_5), and 3346 cm^{-1} (OH). Found: C 65.5; H 5.5; N 8.9%. $C_{17}H_{16}N_2O_4$. Calculated C 65.4; H 5.1; N 9.0%.

1-Phenyl-5-(3,4,4-trimethyl-2-buten-4-olid-2-yl)pyrazole (XX). A mixture of 0.8 g (2.6 mmole) of acid XIX and a small amount of bronze was heated at 200-210°C until CO_2 evolution ceased (6-7 h). The melt was then cooled and crystallized from benzene–hexane to give 0.5 g (71%) of pyrazole XX with mp 119-120°C. IR spectrum: 1758 (C=O), 1618 (C=N), and 3118 cm^{-1} (C_6H_5). Found: C 71.9; H 6.1; N 10.1%. $C_{16}H_{16}N_2O_2$. Calculated: C 71.6; H 6.0; N 10.5%.

LITERATURE CITED

1. A. A. Avetisyan, A. N. Dzhandzhapanyan, S. Kh. Karagëz, and M. T. Dangyan, Arm. Khim. Zh., 30, 90 (1977).