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CHEMISTRY OF HETEROANALOGS OF ISOFLAVONES

IV.* SYNTHESIS OF PYRAZOLE ANALOGS OF ISOFLAVONES

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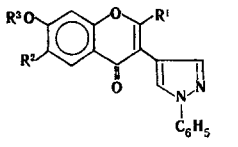
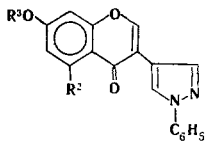
Pyrazole analogs of isoflavones were synthesized from substituted α-(4-pyrazolyl)-2,4-dihydroxyacetophenones.

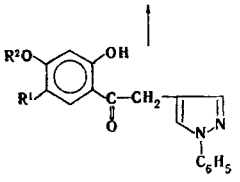
In a continuation of our study of substituted chromones [2] we have synthesized 3-pyrazolylchromones (VIII-XIV) containing a substituent in the 6 position and analogs (XV-XVII) of natural isoflavones.



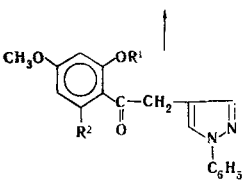
VIII–XIV, XVIII, XIX



XV–XVII, XX, XXI



I–IV



V–VII

For this, we carried out the condensation of 1-phenyl-4-pyrazolylacetonitrile with 4-hexylresorcinol in boron trifluoride etherate in the presence of hydrogen chloride [2]. The formation of two isomeric acetophenones (I) and 2,6-dihydroxy-3-hexyl-α-(1-phenyl-4-pyrazolyl)acetophenone is possible in this reaction, and this is confirmed by the results of thin-layer chromatography (TLC). After we recrystallized the condensation product from alcohol, we isolated the intermediately formed isomer I, the PMR spectrum [3] of which attests to an unsymmetrical orientation of the substituents in the benzene ring: the signals at 12.55 and 10.80 ppm are related to the protons of hydroxyl groups (2-OH and 4-OH), the singlets at 6.55 and 7.96 ppm are related to the aromatic protons of the phenol portion of the acetophenone (3-H and 5-H), and the signals at 8.58 and 7.88 ppm are related to the protons of the pyrazole ring (3-H and 5-H). The indicated assignment of the signals of the protons of the hydroxyl groups is in agreement with the spectra obtained for 4-methoxyacetophenone (III) and 7-hydroxychromone (XII), obtained from I. In the first case, the signal of the 4-OH vanishes, and one peak at 12.75 ppm (2-OH) is present in the region of the signals of hydroxyl groups. In the second case, one peak at 10.86 ppm (7-OH) is observed in the indicated region. The structure of II, obtained as a result of the condensation of 1-phenyl-4-pyrazolylacetonitrile with 4-chlororesorcinol, was similarly proved. The signal of the 4-OH group in the PMR spectrum of II is broadened to such an extent that it cannot be noticed, probably because of the low rate of proton exchange with the solvent. The IR spectrum of acetophenone II, in which the absorption band of the stretching vibrations of the 4-OH group is found at 3100 cm^{-1}, also serves as a confirmation of its structure.

*See [1] for communication III.

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TABLE 1. α-(1-Phenyl-4-pyrazolyl)acetophenones (I-VII)*

Compound	R¹	R²	mp, °C	Empirical formula	N, % found	N, % calc.	λ_{max}, nm (lg ε)	Yield, %
I	C_6H_{13}	H	140	$C_{23}H_{26}N_2O_3$	7,5	7,4	276(4,35); 330(4,01)	79
II	Cl	H	184	$C_{17}H_{13}ClN_2O_3$	10,7†	10,8†	265(4,42); 340(4,26)	14
III	C_6H_{13}	CH_3	98	$C_{24}H_{28}N_2O_3$	7,3	7,1	270(4,40); 330(3,79)	77
IV	Cl	CH_3	190	$C_{18}H_{15}ClN_2O_3$	10,5†	10,3†	270(4,52); 324(4,08)	80
V	H	H	134	$C_{18}H_{16}N_2O_3$	9,1	9,1	275(4,48); 315(4,07)	77
VI	H	CH_3	95	$C_{19}H_{18}N_2O_3$	8,6	8,7	265(4,32)	61
VII	CH_3	H	105	$C_{19}H_{18}N_2O_3$	8,7	8,7	270(4,33); 302(3,88)	59

*Recrystallized from alcohol or aqueous alcohol.
† Cl, %.

TABLE 2. 3-(1-Phenyl-4-pyrazolyl)chromones (VIII-XXI)*

Compound	R¹	R²	R³	mp, °C	Empirical formula	N, % found	N, % calc.	λ_{max}, nm (lg ε)	Yield, %
VIII	$COOC_2H_5$	C_6H_{13}	H	143	$C_{27}H_{28}N_2O_5$	6,2	6,1	275(4,36); 330(3,99)	82
IX	$COOC_2H_5$	Cl	H	227	$C_{21}H_{15}ClN_2O_5$	8,6†	8,6	275(4,73); 350(4,15)	98
X	CF_3	C_6H_{13}	H	212	$C_{25}H_{23}F_3N_2O_3$	6,0	6.1	260(4,48); 320(4.15)	97
XI	CF_3	Cl	H	226	$C_{19}H_{10}ClF_3N_2O_3$	8,8†	8,7	270(4,39); 330(3,76); 363(3,85)	98
XII	H	C_6H_{13}	H	182	$C_{24}H_{24}N_2O_3$	7,3	7.2	270(4,47)	81
XIII	H	C_6H_{13}	CH_3	117	$C_{25}H_{26}N_2O_3$	7,2	7,0	270(4,12)	75
XIV	H	C_6H_{13}	$COCH_3$	135	$C_{26}H_{26}N_2O_4$	6 8	6,8	270(4,31)	90
XV	—	H	CH_3	175	$C_{19}H_{14}N_2O_3$	8,8	8,8	270(4,12)	70
XVI	—	H	H	231	$C_{18}H_{12}N_2O_3$	9,3	9,2	270(4,61)	97
XVII	—	CH_3	H	222	$C_{19}H_{14}N_2O_3$	9,1	8,8	273(4,44)	90
XVIII	CF_3	C_6H_{13}	CH_3	153	$C_{26}H_{25}F_3N_2O_3$	5,9	6,0	260(4.20); 315(3,88)	80
XIX	CF_3	C_6H_{13}	C_2H_5	119	$C_{27}H_{27}F_3N_2O_3$	5,7	5,8	260(4,20); 315(3,90)	71
XX	—	H	$COCH_3$	180	$C_{20}H_{14}N_2O_4$	8,2	8.1	270(4.42)	79
XXI	—	CH_3	$COCH_3$	149	$C_{21}H_{16}N_2O_4$	7.7	7,8	270(4,31)	81
XXII²	CH_3	H	H					268(4,24)	
XXIII²	CH_3	H	$COCH_3$					255(4.35)	
XXIV²	CF_3	H	H					255(4,38); 310(4,02)	
XXV²	$COOC_2H_5$	H	H					265(4,26); 310(3,92)	

*Recrystallized from alcohol.
† Cl, %.

The reaction of pyrazolylacetophenones I and II and 2,4-dihydroxy- and 2,4-dihydroxy-6-methyl-α-(1-phenyl-4-pyrazolyl)acetophenones [2] with 1 mole of dimethyl sulfate in acetone solution yielded their 4-methoxy derivatives (III-VI). 2,4-Dimethoxyacetophenone (VII) is formed by the action of 2 moles of dimethyl sulfate on α-(1-phenyl-4-pyrazolyl)-2,4-dihydroxyacetophenone. Compound VII was also obtained from acetophenone V and 1 mole of dimethyl sulfate (Table 1).

Ketones I and II were converted by the methods in [4, 5] to chromones VIII-XI with ethoxycarbonyl and trifluoromethyl groups in the 2 position. In order to obtain pyrazolylchromones (XII-XVII) that are unsubstituted in the 2 position we treated the appropriate pyrazolylacetophenones with methyl formate in the presence of sodium tert-butoxide [6] or heated them with ethyl orthoformate in pyridine solution [7]. In the case of XII, it is more convenient to acylate the crude products and remove the acyl group after purification of acetyl derivative XIV.

The action of methyl iodide or ethyl iodide on 2-trifluoromethyl-3-pyrazolylchromone X in acetone gives the corresponding 7-alkoxy derivatives XVIII and XIX. The possibility of acylation of the phenolic hydroxyl group under mild conditions was shown in the case of 7-hydroxy- and 5-methyl-7-hydroxychromones XVI and XVII. Brief heating of 7-acetoxy compounds XX and XXI with dilute alkali gives starting 7-hydroxychromones XVI and XVII (Table 2).

The structures of the synthesized chromones were confirmed by the results of analysis and the UV spectra. As seen from Table 2, the principal absorption maximum in the UV spectra of 3-pyrazolylchromones is found at 260-275 nm. The UV spectra of most of the 3-pyrazolylchromones that have a substituent in the 2 position contain another absorption maximum at 310-350 nm.

Of the compounds tested for biological activity, chromone XVI displayed considerable antiblastic activity in in vitro experiments in a Staphylococcus aureus UF_3 culture [8].

EXPERIMENTAL

The UV spectra of $5 \cdot 10^{-5}$ mole solutions of the substances in ethanol were measured with an SF-4A spectrophotometer. The PMR spectra of 0.25 mole solutions in dimethyl sulfoxide (DMSO) were recorded with a ZKR-60 spectrometer with an operating frequency of 60 MHz at 25° with tetramethylsilane as the internal standard. The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrometer. The purity of the individual compounds and the course of the reactions were monitored by TLC on Merck silica gel G. A mixture of chloroform and methanol or benzene and ethanol (9:1) was used as the eluent.

α-(1-Phenyl-4-pyrazolyl)-2,4-dihydroxy-5-hexylacetophenone (I). A stream of hydrogen chloride was bubbled with stirring in the course of 1 h at 20° and 9 h at 50° into a solution of 3.66 g (20 mmole) of 1-phenyl-4-pyrazolylacetonitrile [2] and 3.88 g (20 mmole) of 4-hexylresorcinol in 25 ml of boron trifluoride etherate, after which the mixture was allowed to stand overnight at room temperature. It was then poured into 200 ml of water, and the aqueous mixture was refluxed for 1.5 h. It was then cooled, and the yellow precipitate was removed by filtration. IR spectrum, cm^{-1}: 3165 (ν_{OH}), 1640 ($\nu_{C=O}$), and 1470 (δ_{CH_2}).

α-(1-Phenyl-4-pyrazolyl)-2,4-dihydroxy-5-chloroacetophenone (II). This compound was similarly obtained from 3.66 g (20 mmole) of 1-phenyl-4-pyrazolylacetonitrile, 2.25 g (20 mmole) of 4-chlororesorcinol in 20 ml of boron trifluoride etherate. PMR spectrum, ppm: 12.13 (2-OH), 6.73 and 8.18 (benzene ring 3-H and 6-H), 8.56 and 7.86 (pyrazole ring 3-H and 5-H), and 4.48 (CH_2). IR spectrum, cm^{-1}: 3100 (ν_{OH}) and 1650 (ν_{CO}).

α-(1-Phenyl-4-pyrazolyl)-2-hydroxy-4-methoxyacetophenones (III-VI). A 10-mmole sample of neutral dimethyl sulfate and 30 mmole of freshly calcined potassium carbonate were added to a hot solution of 10 mmole of α-(1-phenyl-4-pyrazolyl)-2,4-dihydroxyacetophenone in absolute acetone, and the mixture was refluxed for 4-6 h, after which the inorganic precipitate was removed by filtration, the filtrate was acidified with three to four drops of glacial acetic acid, and the solvent was evaporated.

α-(1-Phenyl-4-pyrazolyl)-2,4-dimethoxyacetophenone (VII). A solution of 0.16 g (0.5 mmole) of VI and 0.06 g (0.5 mmole) of dimethyl sulfate in 20 ml of acetone was refluxed for 2 h in the presence of 0.21 g (1.5 mmole) of potassium carbonate. The mixture was then worked up as in the preceding experiment.

2-Ethoxycarbonyl-3-(1-phenyl-4-pyrazolyl)-7-hydroxychromones (VIII, IX). A 2-mmole sample of ethoxalyl chloride was added dropwise to a cooled (to 2-3°) solution of 1 mmole of the acetophenone (I, II) in the minimum amount of absolute pyridine, after which the mixture was allowed to stand at room temperature for 24-30 h. It was then added to 80-100 ml of ice water, and the resulting oil crystallized on standing. The solid product was washed with water until it was odorless.

2-Trifluoromethyl-3-(1-phenyl-4-pyrazolyl)-7-hydroxychromones (X, XI). A 2-mmole sample of trifluoroacetic anhydride was added dropwise to a cooled (to 2-3°) solution of 1 mmole of acetophenone (I, II) in the minimum amount of absolute pyridine, and the mixture was cooled while shaking for 5-10 min, after which it was allowed to stand at room temperature for 24 h. It was then added to 70-90 ml of water, and the solidified product was removed by filtration.

3-(1-Phenyl-4-pyrazolyl)-7-hydroxychromones (XII, XVI, and XVII) and 3-(1-Phenyl-4-pyrazolyl)-7-methoxychromones (XIII, XV). A solution of 1 mmole of the acetophenone (I, III, V) or 2,4-dihydroxy- or 2,4-dihydroxy-6-methyl-α-(1-phenyl-4-pyrazolyl)acetophenone [2], 6 mmole of ethyl orthoformate in 1 ml of absolute pyridine containing two drops of piperidine was heated at 120-130° for 1-4 h [the end of the reaction was determined from a negative test of a sample of the reaction mixture with an alcohol solution of ferric chloride or by means of thin-layer chromatography (TLC) in benzene–ethanol (9 : 1 or 19 : 1)]. The precipitate that formed when the mixture was cooled was removed by filtration and washed successively on the filter with a small amount of pyridine, alcohol, and ether. If the product did not precipitate at the end of the reaction, the reaction mixture was added to 25 ml of water, and the resulting solid product was removed by filtration.

3-(1-Phenyl-4-pyrazolyl)-7-methoxychromone (XV). A 1.44-g (15 mmole) sample of sodium tert-butoxide was added with stirring in an inert gas atmosphere to a cooled (to 0-3°) solution of 0.46 g (1.5 mmole) of ace-

tophenone V in 30 ml of methyl formate. After 10-15 min, the mixture was heated to 20-25°, and stirring was continued for 4 h, after which the solvent was evaporated. A mixture of 1 ml of glacial acetic acid, 1.5 ml of concentrated hydrochloric acid, and 1-2 ml of water was added to the dry residue until the pH of the mixture was 0.5-1. The oil that formed initially solidified completely. A solution or suspension of the product in 12 ml of alcohol was refluxed for 40 min with 0.2 ml of concentrated hydrochloric acid, and the solid material was removed by filtration from the cold solution and washed free of acid to give 0.4 g (84%) of product.

2-Trifluoromethyl-3-(1-phenyl-4-pyrazolyl)-5-hexyl-7-alkoxychromones (XVIII, XIX). An acetone solution of 1 mmole of chromone X and 4-5 mmole of dimethyl sulfate or ethyl iodide was stirred at 50-60° with 3 mmole of freshly calcined potassium carbonate for 4-5 h (the end of the reaction was determined by means of TLC), after which the hot solution was filtered. The solvent was evaporated, and the residue was washed with a small amount of alcohol.

3-(1-Phenyl-4-pyrazolyl)-7-acetoxychromones (XX, XXI). A 5-mmole sample of acetic anhydride was added to a warm solution of 1 mmole of the chromone (XVI, XVII) in the minimum volume of pyridine, and the mixture was allowed to stand at room temperature for 24 h, after which the product was removed by filtration and washed on the filter with ether.

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SYNTHESIS OF Δ^2-IMIDAZOLINES IN ETHYLENE GYLCOL

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The use of ethylene glycol as the solvent in the condensation of carboxylic acid and their derivatives with ethylenediamine or its salts makes it possible to obtain various Δ^2-imidazolines in good yields. The ionization constants and the characteristic frequencies of the IR spectra of the synthesized compounds are presented.

Δ^2-Imidazolines have valuable pharmacological properties and are used as starting materials for the preparation of medicinals [1, 2]. However, the physicochemical properties of Δ^2-imidazolines have not been adequately studied. The aim of the present research consisted in the development of a convenient method for the synthesis of these compounds and the determination of their ionization constants and the characteristic frequencies of their IR spectra.

A promising method for the synthesis of Δ^2-imidazolines based on the condensation of carboxylic acids with ethylenediamine (EDA) or its salts has certain disadvantages – the necessity of heating to high temperatures or under pressure and the low yields of final products [3-5]. We have established that these difficulties can be eliminated if the reaction is carried out in ethylene gylcol.

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