CYCLIZATION OF o-ACYLPHENYLACETIC ACIDS TO 1-ARYL-3-HYDROXYISOQUINOLINES*

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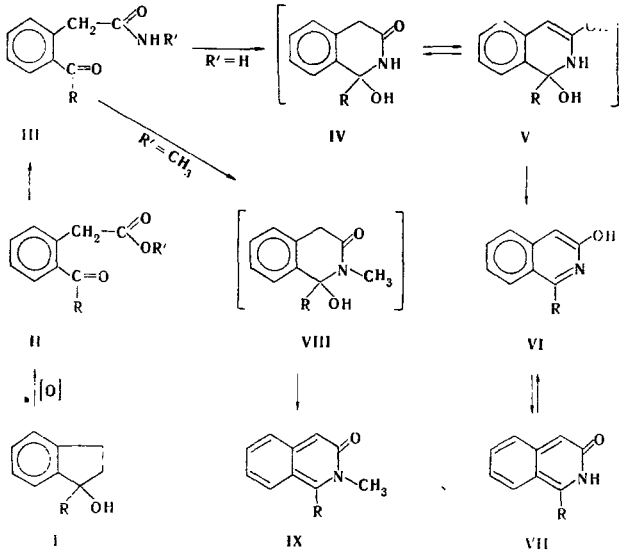
Methyl o-acylphenylacetates react with urea to give 1-aryl-3-hydroxyisoquinolines. 1-Phenyl-2-methyl-3-isoquinolone was obtained by the action of methylamine on methyl o-benzoylphenylacetate. The lactim-lactam tautomerism of 1-aryl-3-hydroxyisoquinolines is discussed on the basis of their UV and IR spectra. The biological activity of some 1-aryl-3-hydroxyisoquinolines with respect to 16 strains of bacteria was studied.

1-Alkyl- and 1-aryl-3-hydroxyisoquinolines are of interest in connection with the problem of lactim-lactam tautomerism [1-4] and the possibility of their use as biologically active substances [4-6].

The aim of the present research was the synthesis of new 1-arylisoquinoline derivatives by reactions of esters of o-acylphenylacetic acids with urea, ammonia, and methylamine and an investigation of the tautomeric transformations and biological activity of some 1-aryl-3-hydroxyisoquinolines.

1-Aryl-1-indanols (Ia-g), which were oxidized to o-acylphenylacetic acids IIa-g (R' = H), were used as the starting compounds. The corresponding 1-aryl-3-hydroxyisoquinolines (VIa-g, method A), which were identical to the compounds synthesized by the method described in [1] by the action of ammonia on esters II (method B, Table 1), were obtained by heating the methyl esters of these acids (IIa-g, R' = CH_3) with urea.



I—IX a R = C_6H_5; b R = *m*-$CH_3C_6H_4$; c R = *p*-$CH_3C_6H_4$; e R = *p*-$C_2H_5C_6H_4$; д R = *p*-$(CH_3)_2CHC_6H_4$; g R = *p*-$CH_3OC_6H_4$

Methyl o-benzoylphenylacetate (IIa, R' = CH_3) was treated with an alcohol solution of methylamine to obtain 1-phenyl-2-methyl-3-isoquinolone (IXa), which was used as a model compound. This reaction gave a mixture

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TABLE 1. 1-Aryl-3-hydroxyisoquinolines (VI)

Compound	mp, °C	Empirical formula	Found				Calculated				IR spectrum, ν, cm⁻¹	Yield, %	
			C, %	H, %	N, %	M*	C, %	H, %	N, %	M		A	B
VIa[2]	211—212	$C_{15}H_{11}NO$	81,2	5,1	6,2	211	81,4	5,0	6,3	221	1640 1605	84	70
VIb	166—167	$C_{16}H_{13}NO$	81,4	5,6	6,1	225	81,6	5,5	5,9	235	1675 1610	70	65
VIc	209—210	$C_{16}H_{13}NO$	81,5	5,5	5,8	250	81,6	5,5	5,9	235	1645 1620	70	50
VId	161—162	$C_{17}H_{15}NO$	81,6	6,2	6,0	241	81,9	6,0	5,6	249	1625 1605	80	60
VIe	168—169	$C_{18}H_{17}NO$	82,2	6,4	5,2	268	82,1	6,5	5,3	263	1630 1605	80	65
VIf	167—168	$C_{16}H_{13}NO_2$	76,4	5,4	5,5	245	76,4	5,2	5,5	251	1660 1610	70	57
VIg[6]	213—214	$C_{16}H_{13}NO_2$	76,3	5,0	5,6	255	76,4	5,2	5,5	251	1635 1610	80	50

*By the Rast method.

TABLE 2. UV Spectra and Ratios of the Lactim and Lactam Forms of 1-Arylhydroxyisoquinolines VI

Compound	Diethyl ether		Ethanol			Chloroform			Carbon tetrachloride		
	λ_{max}, nm	ε	λ_{max}, nm	ε	VI : VII	λ_{max}, nm	ε	VI : VII	λ_{max}, nm	ε	VI : VII
VIa	352	9700	350 433	5700 2280	5 : 2 —	355 440	5380 2170	2 : 1 —	353 438	7050 1410	5 : 1 —
VIb	352	7200	350 433	6720 4480	2 : 1 —	355 437	3800 2400	3 : 2 —	353 440	6600 1310	5 : 1 —
VIc	353	8800	350 433	5820 2910	2 : 1 —	355 440	7300 5030	3 : 2 —	353 440	7080 1020	7 : 1 —
VId	353	8600	357 422	7380 4000	2 : 1 —	355 440	5200 3300	3 : 2 —	353 440	7000 1040	7 : 1 —
VIe	353	8100	350 433	5320 3390	3 : 2 —	355 440	8200 6550	2 : 1 —	353 439	6500 1310	5 : 1 —
VIf	353	7900	350 420	5300 2350	2 : 1 —	355 438	1800 1150	3 : 2 —	353 440	5300 940	6 : 1 —
VIg	353	8200	350 433	5660 2830	2 : 1 —	355 440	5500 3300	3 : 2 —	353 440	4320 864	5 : 1 —

of methylamide IIIa ($R' = CH_3$) and IXa. The primary method for the preparation of the latter was heating amide IIIa ($R' = CH_3$) with acetic anhydride.

In all likelihood, the reaction of esters II ($R' = CH_3$) with urea, ammonia, or methylamine proceeds in two steps. The amide of the corresponding acid [2] (III) is formed in the first step, and a hydroxy lactam (IV⇌V), which is dehydrated to the corresponding 1-phenyl-3-hydroxyisoquinoline, is formed in the second step.

Esters IIc, e, g ($R' = CH_3$) [6] and aryl ketones have similar electronic spectra in ethanol solution. The IR spectra (of mineral oil suspensions and KBr pellets) at 1600-1800 cm^{-1} contain two intense bands at 1710 and 1660 cm^{-1}. The first should be assigned to an isolated ester group and the second to an arylcarbonyl group. On the basis of these data it can be concluded that IIc, e, g ($R' = CH_3$) exists in the open form both in solution and in the solid state. In order to investigate the lactim-lactam tautomerism of 1-arylisoquinolines VI we examined their electronic spectra (for example, see [2]). At 340-440 nm the spectra of ether solutions of these compounds contain only one band at 353 nm (Table 2). 1-Chloro-3-hydroxyisoquinoline, which is in the lactim form in all solvents [1, 2], also absorbs in the same region. 3-Hydroxyisoquinoline (λ_{max} 342 nm) [1, 2] also has a similar UV spectrum. One band at ~355 nm, which corresponds to the lactim form of VI, is observed in the spectra of ethanol, chloroform, and carbon tetrachloride solutions of the investigated 1-arylisoquinolines; another band is observed at ~440 nm, and this corresponds to the lactam form of VII, since isoquinolone IXa (λ_{max} 438 nm) also absorbs in this interval in the same solvents. The quantitative ratios of the tautomers in the solutions were calculated by comparison of the extinctions of the lactim and lactam forms. It follows from the data presented that the VI⇌VII tautomeric equilibrium is shifted to favor the lactim form in the investigated solvents (Table 2). We also established that the positions and intensities of both bands in the spectra of an alcohol solution of VIa are independent of the temperature (20°, 40°, and 60°). The starting compound remains unchanged when an ether solution of VIa is treated with diazomethane.

TABLE 3. Bacteriostatic Activity and Bactericidal Properties of 1-Aryl-3-hydroxyisoquinolines*

No.	Strain	1-Arylisoquinolines					
		VI a		VI c		VI g	
		pH 8,0		pH 8,3		pH 8,1	
		BB	BS	BB	BS	BB	BS
1	Staphylococcus aureus	5	5	5		5	
2	Staphylococcus pyogenes	5	0,05	5	0.5	5	
3	Staphylococcus epidermitis	5	0,5	5	5	5	
4	Staphylococcus mannitolo negative	5	5	5	0,5	5	
5	Streptococcus fecalis	0,5	0,05	5	0,0005	5	0,05
6	Streptococcus pyogenes	5	0,0005	5	0,0005	5	0,0005
7	Streptococcus fecalis	5	0,5	5	0,0005	5	0,0005
8	Streptococcus pyogenes	5	0,5	5		5	
9	Bacillus substiiiitis	5	0,5	5	0,5	5	
10	Escherichia coli 0:56	5		5	5	5	
11	Escherichia coli nonpathogenic	5		5		5	
12	Proteus vulgaris	5	0,5	5		5	
13	Proteus vulgaris	5	5	5	0,5	5	
14	Klebsiella sheathes	5		5		5	
15	Klebsiella sheathes	5		5		5	
16	Candida aibicans	5		5		5	

*The Department of Microbiology of the Polish Medical Academy has access to the bacteriological characteristics of the investigated strains. When two strains of one group were used, the microorganisms were distinguished by different resistances to the action of standard antibiotics. The pH values were determined in broths containing 0.1 mg of the compounds in 1 ml of nutritive medium. The following abbreviations are used: BB is the concentration of compounds that act bactericidally in milligrams per milliliter of nutritive medium, and BS indicates the concentration of compounds that are characterized by bacteriostatic activity in milligrams per milliliter of nutritive medium.

The bactericidal properties and bacteriostatic activity of some 1-arylisoquinolines (Table 3) were also studied.* The examined compounds act most effectively on Gram-positive bacteria (Nos. 1-9). Colon bacilli (Nos. 10-15) and yeasts (No. 16) are relatively insensitive to the action of the investigated arylhydroxyisoquinolines.

EXPERIMENTAL

The IR spectra of mineral oil suspensions and KBr pellets of the compounds were recorded with a UR-10 spectrometer. The UV spectra were recorded with a Specord UV-vis spectrophotometer. The samples for the UV studies were initially dissolved in 1 ml of chloroform, after which 99 ml of the appropriate solvent was added. Chromatography was carried out with a column filled with activity II (Brockmann classification) Al_2O_3.

o-Acylphenylacetic Acids (II, R' = H). A solution of 0.1 mole of the appropriate aryl bromide in 100 ml of absolute ether was added dropwise to 2.4 g (0.1 g-atom) of magnesium and 20 ml of absolute ether, after which a solution of 13.2 g (0.1 mole) of 1-indanone [7] in 100 ml of absolute ether was added dropwise. At the end of the reaction, ~200 ml of a saturated aqueous solution of ammonium chloride was added, and the ether layer was separated and dried with Na_2SO_4. The solvent was removed by distillation to give crude 1-aryl-1-indanol as a light-yellow oil. Water (550 ml), 50 ml of concentrated sulfuric acid, 0.8 g of sodium benzenesulfonate, and 20 g of sodium dichromate were added, after which the crude 1-aryl-1-indanol was added dropwise in the course of 25 min with vigorous stirring, during which the temperature of the mixture was maintained at 50-55°. The solution was stirred for another 30 min at the same temperature, after which it was cooled and treated with 200 ml of ice water. The precipitated acid was removed by filtration, dissolved in 100 ml of 10% NaOH, and extracted twice with 50 ml of ether. The aqueous layer was acidified with hydrochloric acid, and the liberated oxidation product was crystallized successively from water containing activated charcoal and from benzene. No melting-point depressions were observed for mixtures of the products with previously synthesized o-acylphenylacetic acids, and their IR spectra were also identical [8].

*The studies were carried out in the Department of Microbiology of the Polish Medical Academy in Szczecin.

The yields of acids II (R'=H) based on the 1-indanone, and their melting points were as follows: IIa, 30%, mp 132-133°; IIb, 25%, mp 133-134°; IIc, 25%, mp 140-141°; IId, 25%, mp 105-106°; IIe, 26%, mp 109-110°; IIf, 24%, mp 151-152°; IIg, 30%, mp 156-157°.

Methyl o-Acylphenylacetates (II, R'=CH_3). An anhydrous ether solution of diazomethane was added to a solution of 1.25 g (0.005 mole) of acid II (R'=H) in a mixture of absolute ether and methanol (1 : 1) until a persistent yellow color appeared, after which the mixture was allowed to stand for 2 h. The solvent was removed by distillation, and the reaction product was crystallized from alcohol. Ester II (R'=CH_3), with mp 39-40°, was obtained in 92% yield as a colorless crystalline substance that was soluble in acetone and ether. IR spectra: 1739, 1655 cm^{-1} (in mineral oil); 1732, 1645 cm^{-1} (in KBr). UV spectrum: λ_{max} 260 nm; ε 14,500. Found: C 72.0; H 5.6%. $C_{17}H_{16}O_3$. Calculated: C 71.8; H 5.7%.

Compounds IIa, b, d, f (R'=CH_3) were obtained as oils, the purity of which was sufficient for the subsequent syntheses.

1-Aryl-3-hydroxyisoquinolines (VI). A) A mixture of 0.005 mole of ester II (R'=CH_3) and 0.025 mole of urea was heated in a thick-walled sealed test tube at 190-200° for 3 h, after which the cyclization product was refluxed for 10 min in 50 ml of water. The supernatant liquid was decanted, and the residue was dissolved in chloroform. The organic layer was dried with Na_2SO_4, the solvent was removed by vacuum distillation, and the residue was crystallized from alcohol.

B) A solution of 0.005 mole of ester II (R'=CH_3) in 50 ml of an anhydrous solution of ammonia in methanol was allowed to stand at room temperature without access to daylight for 7 days, after which the solvent was removed by vacuum distillation, and the residue was crystallized from alcohol. No melting-point depression was observed for mixtures of the products with compounds synthesized by method A, and their UV and IR spectra were also identical.

Compounds VIa-g were obtained as yellow or yellow-orange crystalline substances that were soluble in chloroform (to give yellow solutions) and ether (the solutions in aqueous NaOH were also colorless); they reacted in the same way as phenols with ferric chloride and underwent partial decomposition on prolonged storage, particularly in sunlight. The isoquinolines were soluble in 70-95% sulfuric acid and formed colorless solutions.

o-Benzoylphenylacetic Acid Methylamide (IIIa, R'=CH_3). A 1-ml sample of a 35% alcohol solution of methylamine was added to a solution of 2.2 g (0.005 mole) of ester IIa (R'=CH_3) in 50 ml of alcohol, and the solution was allowed to stand in the dark at room temperature for 3 days. The solvent was then removed by vacuum distillation, and the residual dark-orange oil was chromatographed with a column [elution with benzene–ether (9 : 1)]. The eluate was evaporated, and the residue was again chromatographed; workup of the intermediate fraction yielded 1.5 g (60%) of IIIa as a viscous light-yellow oil. IR spectrum: 1655 and 1528 cm^{-1}. Found: C 75.5; H 5.7; N 5.4%. $C_{16}H_{15}NO_2$. Calculated: C 75.8; H 5.9; N 5.5%. The picrate had mp 189-190° (dec.). The orange eluate (chloroform) was evaporated, and the residue was rechromatographed; workup of the intermediate fraction gave 110 mg (5%) of 1-phenyl-2-methyl-3-isoquinolone (IXa) as a dark-orange oil [the yield was based on acid IIa (R'=H)]. IR spectrum: 1650, 1610 cm^{-1}. UV spectrum: λ_{max} 438 nm, ε 5200. Found: C 81.3; H 5.3; N 5.7%. $C_{16}H_{13}NO$. Calculated: C 81.6; H 5.5; N 5.9%. The picrate had mp 182-183°.

1-Phenyl-2-methylisoquinolone (IXa). A mixture of 2.53 g (0.01 mole) of amide IIIa (R'=CH_3) and 20 ml of acetic anhydride was heated on a water bath for 3 h, after which it was poured into ice water, and the aqueous mixture was neutralized with ammonia and extracted with chloroform. The organic layer was dried with Na_2SO_4, the solvent was removed by evaporation, and the residue was chromatographed with a column as indicated above to give 1.4 g (60%) of IXa. The picrate had mp 182-183°. The synthesized compound and the previously obtained 1-phenyl-2-methylisoquinolone had identical UV and IR spectra. No melting-point depression was observed for a mixture of the picrate of IXa with the picrate previously obtained. The properties of isoquinolone IXa changed after a few days, probably because of oxidation [5].

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CHEMISTRY OF HETEROANALOGS OF ISOFLAVONES

IV.* SYNTHESIS OF PYRAZOLE ANALOGS OF ISOFLAVONES

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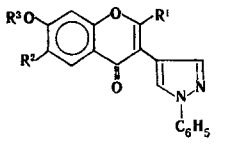
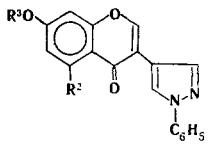
Pyrazole analogs of isoflavones were synthesized from substituted α-(4-pyrazolyl)-2,4-dihydroxyacetophenones.

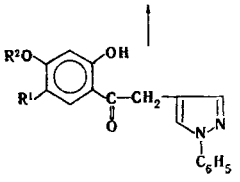
In a continuation of our study of substituted chromones [2] we have synthesized 3-pyrazolylchromones (VIII-XIV) containing a substituent in the 6 position and analogs (XV-XVII) of natural isoflavones.



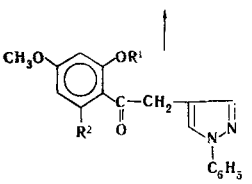
VIII–XIV, XVIII, XIX



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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