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CHEMISTRY OF HETEROANALOGS OF ISOFLAVONES

III.* SYNTHESIS OF BENZIMIDAZOLE AND BENZOTHIAZOLE ANALOGS OF ISOFLAVONES

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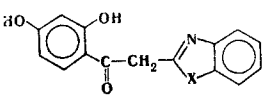
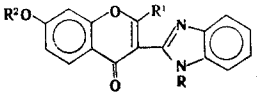
UDC 547.814.5'789.6

Condensation of cyanomethyl derivatives of benzimidazole and benzothiazole with resorcinol gave the corresponding 2,4-dihydroxy-α-hetarylacetophenones. The latter were converted to 3-hetarylchromones with methyl, trifluoromethyl, and ethoxycarbonyl groups in the 2 position or to chromones without substituents in this position.

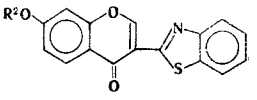
Continuing our study of chromones containing nitrogen heterorings in the 3 position [2, 3], we have synthesized benzimidazole and benzothiazole analogs of isoflavones (IV-XII). The starting α-hetaryl-2,4-dihydroxyacetophenones (I-III) were obtained by condensation of the appropriate 2-hetarylacetonitriles with resorcinol by the method in [2]. Boron trifluoride etherate, which also served as the solvent, was used as the catalyst.



I-III



IV-IX, XI



X, XII

I X=NH; II X=NCH_3; III X=S; IV R=R^2=H, R^1=CF_3; V R=CH_3, R^1=CF_3, R^2=H; VI R=R^2=H, R^1=$COOC_2H_5$; VII R=CH_3, R^1=$COOC_2H_5$, R^2=H; VIII R=R^1=CH_3, R^2=$COCH_3$; IX R=CH_3, R^1=R^2=H; X R^2=H; XI R=CH_3, R^1=H, R^2=$COCH_3$; XII R^2=$COCH_3$

Chromones IV-VII containing trifluoromethyl and ethoxycarbonyl groups in the 2 position were obtained by reaction of α-benzimidazolylacetophenones I and II with trifluoroacetic anhydride by our modification of the method in [4] or by reaction of ethoxyallyl chloride [5] in pyridine in the cold. The pyrone ring in the indicated reactions is formed considerably more readily than in the case of α-hetarylacetophenones with thiazole [2] and pyrazole [3] residues; this is apparently explained by the increased reactivity of the methylene group of ketones I and II. The activating effect of the benzimidazole rings shows up particularly clearly in reactions leading to 2-methylchromone derivatives. Thus, for example, the reaction of acetic anhydride with acetophenone II proceeds smoothly in pyridine at room temperature to give 2-methyl-7-acetoxychromone VIII, while prolonged heating at 120-150° in triethylamine (which is a stronger base than pyridine) is necessary for realization of the analogous cyclization of the above mentioned α-hetarylacetophenones [2, 3] and α-phenylbenzyl ketones [6]. Under these conditions acetophenone II gives a difficult-to-purify resinous product. Chromones IX and X, which

*See [1] for communication II.

T. G. Shevchenko Kiev State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1593-1595, December, 1975. Original article submitted December 23, 1974.

TABLE 1. α-Hetarylacetophenones (I-III)

Compound	mp, °C	Empirical formula	Found, %	Calc., %	IR spectrum, cm^{-1}			R_f	Yield, %
					ν_{OH}	$\nu_{C=O}$	δ_{CH_2}		
I	252	$C_{15}H_{12}N_2O_3$	N 10,2	N 10,5	3420 m	1635 s	1460 m	0,31	55
II	243	$C_{16}H_{14}N_2O_3$	N 10,2	N 9,9	3440 m	1635 s	1450 m	0,41	76
III	214,5	$C_{15}H_{11}NO_3S$	S 11,0	S 11,3	3080 m	1640 s	1450 m	0,52	50

TABLE 2. 3-Hetarylchromones (IV-XII)

Compound	mp, °C	Empirical formula	N, %		IR spectrum, ν, cm^{-1}			R_f	Yield, %
			found	calc.	OH	C=O chromone	C=C chromone		
IV	244	$C_{17}H_9F_3N_2O_3$	8,3	8,1	3430 w	1638 s	1590 s		99
V	248	$C_{18}H_{11}F_3N_2O_3$	8,0	7,8	3440 w	1638 s	1580 s	0,39	98
VI	252	$C_{19}H_{14}N_2O_5$	8,2	8,0	3380 w	1637 s	1600 s	0.32	62
VII	216*	$C_{20}H_{16}N_2O_5$	7,7	7,7	3430 w	1638 s	1605 s	0,33	61
VIII	295	$C_{20}H_{16}N_2O_4$	8,2	8,0					60
IX	300	$C_{17}H_{12}N_2O_3$	9,8	9,6	3090 w	1635 s	1585 m	0,41	82
X	>315	$C_{16}H_9NO_3S$	4,6	4,7	3100 m	1627 s	1586 s	0,47	81
			10,9†	10,9†					
XI	221	$C_{19}H_{14}N_2O_3$	8,6	8,4				0,63	87
XII	225	$C_{18}H_{11}NO_4S$	9,2†	9,5†				0,91	78

*With decomposition.

†This value is the percent sulfur.

do not contain substituents in the 2 position of the chromone system, were synthesized by heating acetophenones II and III with ethyl orthoformate in pyridine in the presence of piperidine [7]. 3-Hetaryl-7-hydroxychromones are readily acylated. Thus 7-acetoxychromones XI and XII are formed as a result of the reaction of IX and X with acetic anhydride in pyridine.

The IR spectra of the chromones and acetophenones are characterized by the presence of intense absorption bands corresponding to the stretching vibrations of the carbonyl and hydroxyl groups and the aromatic ring (Tables 1 and 2).

Studies of the biological activity of the compounds that we obtained under the conditions in [8] showed that 3-(2-benzimidazolyl)-7-hydroxychromones have moderate antiblastic activity (the diameter of the zone of suppression of the growth of Staphylococcus aureus UF_3 is 15-20 mm) that is weaker by a factor of two to three than the corresponding activity observed for benzofuran analogs of isoflavones [8].

EXPERIMENTAL

The IR spectra of potassium bromide pellets of the compounds were recorded with a UR-10 spectrometer. Thin-layer chromatography (TLC) was carried out on Merck G silica gel. A chloroform–methanol mixture (9 : 1) was used as the eluent.

α-(2-Benzimidazolyl)-2,4-dihydroxyacetophenone (I). Hydrogen chloride was bubbled with stirring for 2 h at 2-3° and for 8 h at 40° into a mixture of 3.14 g (20 mmole) of 2-benzimidazolylacetonitrile [9] and 2.2 g (20 mmole) of resorcinol in 25 ml of boron trifluoride etherate, after which the mixture was allowed to stand at room temperature overnight. It was then poured into 120 ml of water, after which the mixture was refluxed for 2 h and made alkaline to pH 3-4 with ammonia. The crude product was reprecipitated from alkaline solution and recrystallized from aqueous alcohol.

α-(1-Methyl-2-benzimidazolyl)-2,4-dihydroxyacetophenone (II). This compound was similarly obtained from 3.42 g (20 mmole) of 1-methyl-2-benzimidazolylacetonitrile [10], 2.2 g (20 mmole) of resorcinol, and 25 ml of boron trifluoride etherate.

α-(2-Benzothiazolyl)-2,4-dihydroxylacetophenone (III). This compound was similarly obtained from 2.25 g (13 mmole) of 2-benzothiazolylacetonitrile [11] and 1.71 g (15.5 mmole) of resorcinol in 16 ml of boron trifluoride etherate. Hydrogen chloride was bubbled through the reaction mixture at 60° for 10-12 h.

2-Trifluormethyl-3-hetaryl-7-hydroxychromones (IV, V). A 2-mmole sample of trifluoroacetic anhydride was added dropwise to a cooled (to 2-3°) solution of 1 mmole of α-hetaryl-2,4-dihydroxyacetophenone (I, II) in the minimum volume of absolute pyridine, after which the mixture was cooled and shaken for 5-10 min. It was then allowed to stand at room temperature overnight, after which it was poured into 70-90 ml of water. The

resulting solid precipitate was removed by filtration and recrystallized from aqueous alcohol to give the product as colorless needles.

2-Ethoxycarbonyl-3-hetaryl-7-hydroxychromones (VI, VII). A 2-mmole sample of ethoxallyl chloride was added dropwise at 2-3° to a solution of 1 mmole of ketones I and II in the minimum volume of absolute pyridine, after which the mixture was allowed to stand at room temperature for 30-40 h. It was then poured into 80-100 ml of water, and the liberated oil crystallized on standing. The product was washed with water until it was odorless, after which it was recrystallized from aqueous alcohol.

2-Methyl-3-(1-methyl-2-benzimidazolyl)-7-acetoxychromone (VIII). A 0.51-g (5 mmole) sample of acetic anhydride was added to a solution of 0.28 g (1 mmole) of ketone II in 2 ml of absolute pyridine, after which the mixture was allowed to stand at room temperature overnight. It was then poured into 50 ml of water, and the resulting precipitate was removed by filtration to give 0.2 g of colorless crystals (from acetonitrile).

3-Hetaryl-7-hydroxychromones (IX, X). A mixture of 1 mmole of ketone II or III in 1 ml of absolute pyridine, 6 mmole of ethyl orthoformate and two drops of piperidine was heated at 120-130° for 1-4 h (the end of the reaction was determined from a negative test a sample of the reaction mixture with alcoholic ferric chloride solution or by means of TLC in a benzene–ethanol system 90:10 or 95:5). The precipitate that formed on cooling was removed by filtration and washed successively on the filter with a small amount of pyridine, alcohol, and ether. Compound IX was crystallized from alcohol, whereas X was crystallized from dioxane or dimethyl sulfoxide.

3-Hetaryl-7-acetoxychromones (XI, XII). A 5-mmole sample of acetic anhydride was added to a warm solution of 1 mmole of hydroxychromone IX or X in the minimum volume of pyridine, and the mixture was allowed to stand at room temperature for 24 h. The product was removed by filtration, washed on the filter with ether, and recrystallized from benzene.

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