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CHEMISTRY OF THE HETEROANALOGS OF ISOFLAVONES. 20.* BENZIMIDAZOLE ANALOGS OF ISOFLAVONES

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3-(2-Benzimidazolyl)chromones with electron-donating and electron-withdrawing substituents and also chromones unsubstituted at position 2 were obtained by the reaction of alkyl-α-(2-benzimidazolyl)-2,4-dihydroxy-5-acetophenones with carboxylic acid anhydrides and chlorides. Reactions with cleavage and with retention of the pyrone ring were carried out.

While continuing investigations into the chemistry and pharmacology of chromones with nitrogen-containing heterocycles, we synthesized the benzimidazole analogs of isoflavones (see the scheme), which were first reported in [2-6], and studied some of their properties.

The starting compounds for the synthesis of the new 3-(2-benzimidazolyl)chromones were α-(1-methyl-2-benzimidazolyl)-2,4-dihydroxy-5-methylacetophenone (Ia), α-(1-methyl-2-benzimidazolyl)-2,4-dihydroxy-5-ethylacetophenone (Ib), α-(1-methyl-2-benzimidazolyl)-2,4-dihydroxy-5-propylacetophenone (Ic), α-(1-methyl-2-benzimidazolyl-2,4-dihydroxy-5-hexylacetophenone (Id), α-(2-benzimidazolyl-2,4-dihydroxy-5-ethylacetophenone (Ie), and α-(2-benzimidazolyl-2,4-dihydroxy-5-hexylacetophenone (If), obtained by the condensation of 2-benzimidazolylacetophenone and 1-methyl-2-benzimidazolylacetophenone with 4-alkylresorcinols under modified conditions of the Hoesch reaction.

The ketones (Ia-c) are colorless and (Id-f) are slightly yellowish high-melting crystalline substances, giving colored chelate complexes with an alcohol solution of ferric chloride. The dark-yellow color of these complexes indicates the presence of keto–enol tautomerism for compounds (Ia-f) in solution. The very low solubility of these ketones in organic solvents did not make it possible to investigate the ratio between the ketone and enolic forms in nonpolar or slightly polar solvents. In deuterated dimethyl sulfoxide these ketones are enolized by 80-85% (Tables 1 and 2), as shown by the double number of protons of the hydroxyl groups and by the integral intensity of the nonexchanging aromatic protons of the phenol part.

The reaction of the ketones (Ia-c, e, f) with triethyl orthoformate in pyridine in the presence of catalytic amounts of piperidine with heat gave the chromones (IIa-c, e, f), while the reaction of the ketone (Id) with acetic formic anhydride in triethylamine gave the chromone (IId).

The reaction of the ketones (Ib) and (Id) with trifluoroacetic acid and of the ketone (Ic) with ethoxalyl chloride in pyridine in the cold gave the corresponding chromones (IIIa, b, IV) containing a trifluoromethyl and ethoxycarbonyl group respectively at position 2 of the chromone ring. Similarly, the ketone (Ib) was converted by treatment with acetic anhydride in pyridine at room temperature into the corresponding 2-methyl-3-(1-methyl-2-benzimidazolyl)-6-ethyl-7-acetoxychromone (Va). Hydrolysis of the latter in an alkaline medium led to the formation of the corresponding 7-hydroxychromone (Vb). Under analogous conditions the reaction of the ketone (Ib) with benzoyl chloride followed by hydrolysis gave 7-hydroxy-3-(1-methyl-2-benzimidazolyl)-6-ethylflavone (Vc). When gently heated with succinic anhydride in pyridine the same ketone was converted into 7-hydroxy-2-(β-carboxyethyl)-3-(1-methyl-2-benzimidazolyl)-6-ethylchromone (Vd).

*For Communication 19, see [1].

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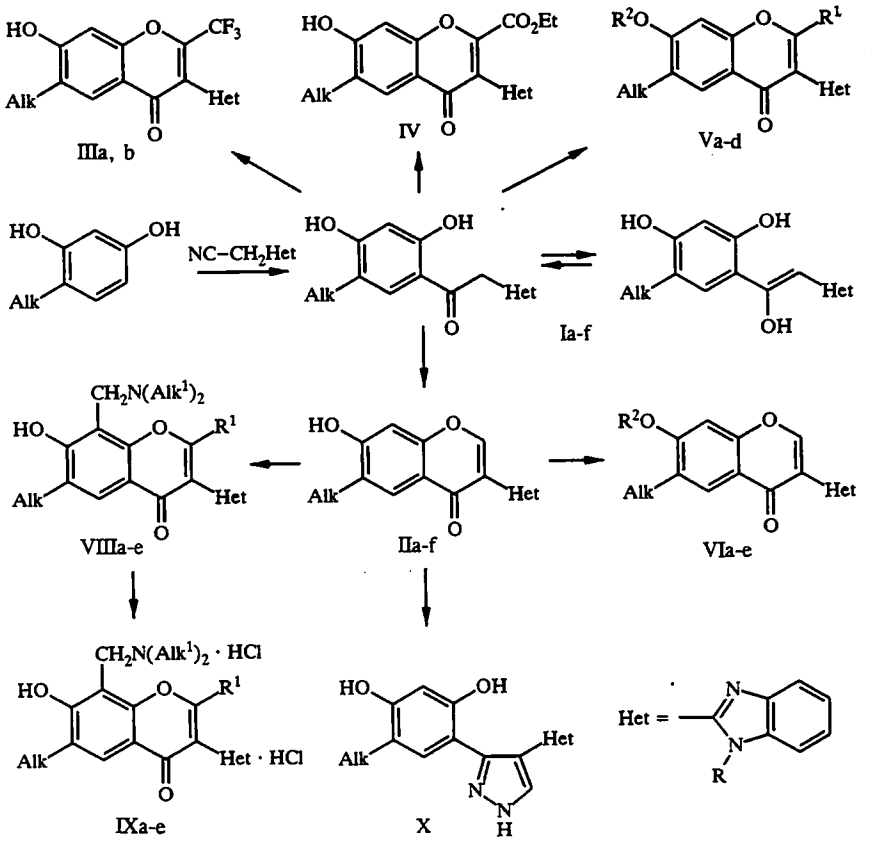

Ia-d, IIa-d, IIIa, b, IV—VII, VIIIa,b,d,e, IXa,b,d,e, X R = CH_3; Ie,f, IIe,f R = H; Va, Vb, VIIId, IXd R^1 = CH_3; Vc R^1 = C_6H_5; Vd R^1 = $(CH_2)_2COOH$; VIIIa-c,e, IXa-c,e R^1 = H; Vb, Vd R^2 = H; Va, VIa R^2 = CH_3CO; VIb R^2 = CH_3SO_2; VIc R^2 = p-$CH_3OC_6H_4CO$; VId R^2 = C_6H_5CO; VIe R^2 = 2-furoyl; Ia, IIa, X Alk = CH_3; Ib,e, IIb,e, IIIa, Va—VII, VIIIa,c,d, IXa,c,d Alk = C_2H_5; Ic, IIc, IIIb, IV, VIIIb,f, IXb,e Alk = C_3H_7; Id,f, IId,f IIIb Alk = C_6H_{13}; VIIIa-d Alk^1 = CH_3; VIIIe, IXe Alk^1 = C_2H_5

The ease with which the ketones (Ia-d) are converted into the corresponding chromones demonstrates the enhanced activity of the α-methylene unit, which in turn is due to the electron-withdrawing characteristics of the benzimidazole ring. During an attempt at the crystallization of 2-trifluoromethylchromone (IIIb) from solvents containing water it was found that it dissociated to the initial ketone (Ib). It was possible to purify this chromone by crystallization from absolute isopropyl alcohol.

In the PMR spectra of the chromones (IIa-d to Va-d), unlike the corresponding initial ketones (Ia-f), there are no signals for the protons of the methylene ring and the 2-OH group. In addition, the complete transformation of the ketones (Ia-f) into the corresponding chromones is demonstrated by the presence of signals for the 2-H protons and for the methyl, ethoxycarbonyl, phenyl, and β-carboxyethyl groups in the PMR spectra, a signal for the trifluoromethyl group in the ^{19}F NMR spectra of compounds (IIIa, b), and a negative reaction with an alcoho' solution of ferric chloride (Tables 3 and 4).

Evidence for fact that 7-hydroxy-2-(β-carboxyethyl)-3-(1-methyl-2-benzimidazolyl)-6-ethylchromone (Vd) is produced as a result of the cyclization of the ketone (Ib) with succinic anhydride is provided by the solubility of this compound in a 4% solution of sodium hydroxide in the cold and also in a saturated solution of sodium bicarbonate with heat. It is also soluble in concentrated hydrochloric acid. In the PMR spectrum of this chromone, measured in deuterated dimethyl sulfoxide, peaks were found at 12.56 and 11.02 ppm, corresponding to the protons of the carboxyl and hydroxyl groups respectively. In addition, in the region corresponding to the absorption of the aliphatic protons peaks were found at 2.85 and 2.67 ppm, corresponding to the absorption of the protons of the methyl groups of the substituents at positions 2 and 5 of the chromone ring. Analysis of the integral curve shows that two protons absorb at 2.85 ppm and four at 2.67 ppm. This made it possible to assign compound (Vd) the structure of 7-hydroxychromone and not the succinate at the 7-OH group.

TABLE 1. Characteristics of 5-Alkyl-α-(2-benzimidazolyl)-2,4-dihydroxyacetophenones (Ia-f)*

Compound	N found, %	Molecular formula	N calculated, %	mp, °C	Yield, %
Ia	9,40	$C_{17}H_{16}N_2O_3$	9,45	>360	63
Ib	9,19	$C_{18}H_{18}N_2O_3$	9,03	297...298	61
Ic	8,70	$C_{19}H_{20}N_2O_3$	8,64	263...264	64
Id	7,83	$C_{22}H_{26}N_2O_3$	7,64	231...232	61
Ie	9,80	$C_{17}H_{16}N_2O_3$	9,45	305...307	80
If	7,83	$C_{21}H_{24}N_2O_3$	7,95	217...218	61

*Compounds (Ia-f) were purified by reprecipitation from an alkaline solution followed by crystallization of the ketones (Ia-c, e) from DMFA and (Id, f) from acetonitrile.

TABLE 2. PMR Spectra of 5-Alkyl-α-(2-benzimidazolyl)-2,4-dihydroxyacetophenones (Ia-f) in DMSO-d_6, δ, ppm (chemical shifts of the protons for the tautomeric enolic forms are given in parentheses*)

Compound	2-OH	3-H	4-OH	5-Alk	6-H	α-CH_2 (—C(OH)=CH—)	Protons of benzimidazole fragment		
							1-R	4-, 7-H	5-, 6-H
Ia	12,10 (12,50)	6,32 (6,18)	10,47 (9,73)	2,10	7,83 (7,58)	4,72 (15,0, 5,81)	3,74 (3,69)	7,50	7,25
Ib	12,06 (12,59)	6,30 (6,19)	10,43 (9,72)	1,15, 2,50	7,80 (7,60)	4,74 (15,0, 5,81)	3,74 (3,69)	7,58	7,23
Ic	12,15 (12,56)	6,33 (6,20)	10,50 (9,63)	0,93, 1,61, 2,51	7,80 (7,53)	4,70 (14,9, 5,78)	3,75	7,47	7,16
Id	11,94 (12,59)	6,37 (6,19)	10,62 (9,61)	0,87, 1,30, 2,50	7,77 (7,56)	4,74 (15,0, 5,74)	3,74 (3,67)	7,45	7,23
Ie	— (12,20)	6,34 (6,18)	— (9,71)	1,12, 2,48	7,80 (7,30)	4,57 (15,0, 5,81)	—	7,42	7,15
If	— (12,16)	6,36 (6,22)	— (9,72)	0,86, 1,28, 2,48	7,76 (7,30)	4,59 (15,1, 5,72)	—	7,42	7,18

*Degree of enolization is 83% for the ketone (Ia), 85% for the ketones (Ib, d-f), and 80% for the ketone (Ic).

The benzimidazole analogs of the isoflavones that we synthesized are easily acylated at the phenolic hydroxyl. Thus, the action of acetic anhydride, methanesulfonyl chloride, *p*-anisoyl chloride, or benzoyl chloride on the chromone (IIb) in pyridine solution at room temperature leads to the formation of the corresponding 7-acetoxy-, mesyloxy-, *p*-anisoyloxy-, and benzoyloxychromones (VIa-d). The action of 2-furoyl chloride on the chromone (IIb) in solution in dimethylformamide in the presence of triethylamine gave 7-furoyloxychromone (VIe).

However, it was not possible to obtain the desired 7-acetoxychromone during an attempt at the acetylation of 2-trifluoromethylchromone (IIIa) with acetic anhydride in pyridine. In view of the lability of the chromone (IIIa) we conducted its acylation in glacial acetic acid. 7-Acetoxychromone (VIII) was obtained after distillation of the solvent and excess acetic anhydride.

The 7-o-acyloxychromones are transformed by the action of a 1 N solution of sodium hydroxide into the initial 7-hydroxychromone (IIb).

TABLE 3. Characteristics of 3-(2-Benzimidazolyl)chromones (II-VIII)

Compound	N found, %	Molecular formula	N calculated, %	mp, °C	Yield, %
IIa	9,18	$C_{18}H_{14}N_2O_3$	9,15	>345	83
IIb	8,91	$C_{19}H_{16}N_2O_3$	8,74	>360	93
IIc	8,33	$C_{20}H_{18}N_2O_3$	8,38	>360	82
IId	7,58	$C_{23}H_{24}N_2O_3$	7,44	282...284	97
IIe	9,15	$C_{18}H_{14}N_2O_3$	9,15	>360	32
IIf	7,89	$C_{22}H_{22}N_2O_3$	7,73	298...300	15
IIIa	7,46	$C_{20}H_{15}F_3N_2O_3$	7,21	325...326	83
IIIb	6,50	$C_{24}H_{23}F_3N_2O_3$	6,30	208...210	67
IV	6,70	$C_{23}H_{22}N_2O_5$	6,89	266...267	80
Va	7,67	$C_{22}H_{20}N_2O_4$	7,44	173...175	70
Vb	8,61	$C_{20}H_{18}N_2O_3$	8,38	>360	83
Vc	6,85	$C_{25}H_{20}N_2O_3$	7,07	240...241	20
Vd	7,19	$C_{22}H_{20}N_2O_5$	7,14	295...297	80
VIa	8,05	$C_{21}H_{18}N_2O_4$	7,73	205...207	76
VIb	6,48	$C_{22}H_{17}F_3N_2O_4$	6,51		95
VIc	7,13	$C_{20}H_{18}N_2O_5S$	7,03	206...207	70
VId	6,45	$C_{27}H_{22}N_2O_5$	6,16	238...239	91
VIe	6,85	$C_{26}H_{20}N_2O_4$	6,60	191...192	75
VII	6,51	$C_{22}H_{17}F_3N_2O_4$	6,76	182...184	92
VIIIa	11,50	$C_{22}H_{23}N_3O_3$	11,13	171...172	80
VIIIb	10,77	$C_{23}H_{25}N_3O_3$	10,73	161...162	83
VIIIc	11,77	$C_{21}H_{21}N_3O_3$	11,56	179...180	93
VIIId	10,77	$C_{23}H_{25}N_3O_3$	10,73	139...141	78
VIIIe	10,16	$C_{25}H_{29}N_3O_3$	10,02	137...139	76

When heated with bis(dimethylamino)methane in absolute dioxane, the chromones (IIb, d, e) and (Vb) give the respective Mannich bases (VIIIa-d). The chromone (IIc) reacts with bis(diethylamino)methane under similar conditions with the formation of compound (VIIIe).

The PMR spectra of the obtained compounds do not contain the 8-H proton of the chromone ring, and in contrast to the initial compounds there are peaks for the methyl or ethyl and methylene groups. In the PMR spectrum of compound (VIIIc) there was only one (dimethylamino)methyl group, which to judge from the disappearance of the peak of the 8-H proton enters at position 8 of the chromone ring even in the presence of the acidic 1-NH proton of benzimidazole with a significant excess of the alkylating agent. In the case of the pyrazole analogs of the isoflavones [7] under analogous conditions a compound with two dimethylaminomethyl groups, i.e., at positions 1 of the pyrazole and 8 of the pyrone rings, were obtained.

When gaseous hydrogen chloride was passed into benzene or chloroform solutions of compounds (VIIIa-e), the hydrochlorides of the corresponding Mannich bases (IXa-e) were obtained. They are hygroscopic crystalline compounds.

Under the influence of hydrazine hydrate the chromone (IIa) undergoes recyclization into the pyrazole (X), the structure of which was confirmed by chemical reactions and spectral data. The pyrazole dissolves in an aqueous solution of alkali and gives a positive reaction with an alcohol solution of ferric chloride, indicating the presence of a free hydroxyl group situated close to the nitrogen atom of the pyrazole ring. In the PMR spectrum of the pyrazole (X) there were broad singlets at 13.18 and 10.80 ppm and a narrow singlet at 9.44 ppm, corresponding to the absorption of the NH protons of pyrazole and the 4-OH and 2-OH protons of the phenol fragment respectively.

EXPERIMENTAL

The ^1H and ^{19}F NMR spectra were measured on Bruker WP 100SY and Varian VXR-300 instruments at 100 and 300 MHz respectively. The reactions and the purity of the obtained compounds were monitored by TLC on Silufol UV-254 plates. Mixtures of chloroform and methanol (9:1, 95:5) were used as eluant, and ethyl acetate was used as Mannich base.

The characteristics of the compounds are given in Tables 1 and 2 for ketones (I), in Tables 3 and 4 for the chromones (II-VIII), and in Table 5 for the hydrochlorides (IX).

TABLE 4. PMR Spectra of 3-(2-Benzimidazolyl)chromones (II-VIII), δ, ppm*

Compound	2-R	5-H	6-R	7-R	8-R	Benzimidazole protons		
						1-R	4-, 7-H	5-, 6-H
IIa	8,59	7,89	2,26	10,79	6,99	3,69	7,63	7,27
IIb	8,62	7,87	1,19, 2,74	11,00	7,00	3,69	7,58	7,23
IIc	8,62	7,87	0,92, 1,60, 2,64	11,00	7,00	3,69	7,63	7,29
IId	8,59	7,85	0,85, 1,31, 1,58, 2,65	10,97	6,99	3,69	7,62	7,26
IIe	9,19	7,92	1,21, 2,67	12,52	6,96	12,52	7,65	7,17
IIf	9,17	7,89	0,84, 1,29, 1,58, 2,63	10,97	6,97	12,57	7,64	7,15
IIIa	— (8,88) †	7,86	1,21, 2,70	11,38	7,06	3,70	7,68	7,32
IIIb	— (8,90) †	7,83	0,86, 1,30, 1,57, 2,66	11,31	7,04	3,69	7,66	7,39
IV	0,68, 4,01	7,81	0,91, 1,63, 2,65	11,22	7,03	3,66	7,64	7,27
Va	2,40	8,12	1,27, 2,66	2,40	7,29	3,70	7,80	7,35
Vb	2,31	7,79	1,19, 2,65	10,99	6,95	3,62	7,63	7,28
Vc	7,83	7,57	1,20, 2,68	11,07	7,05	3,64	7,76	7,25
Vd	12,56, 2,85, 2,67	7,80	1,19, 2,67	11,02	6,96	3,63	7,64	7,26
VIa	8,44	8,21	1,29, 2,68	2,40	7,35	3,78	7,80	7,40
VIb	8,82	8,16	1,26, 2,84	3,66	7,87	3,72	7,64	7,30
VIc	8,45	7,49	1,30, 2,75	3,91, 8,23; 7,02	7,28	3,80	7,79	7,30...7,45
VId	8,46	7,50	1,31, 2,70	7,3...8,3	7,28	3,81	7,63	7,35
VIe	8,76	8,15	1,23, 2,73	6,84	7,84	3,73	7,65	7,29
VII	—	8,07	1,19, 2,68	2,41	7,83	3,72	7,68	7,33
VIIIa	8,59	7,81	1,20, 2,66	10,63	2,45, 4,11	3,69	7,63	7,27
VIIIb	8,34	7,99	0,99, 1,69, 2,69	10,8	2,43, 4,01	3,79	7,77	7,35
VIIIc	9,17	8,03	1,30, 2,74	11,97	2,44, 4,02	8,92	7,62	7,26
VIIId	2,33	7,73	1,18, 2,63	11,20	2,43, 4,10	3,62	7,63	7,25
VIIIe	8,33	7,97	1,.00, 1,71, 2,68	10,97	1,18, 2,71, 4,12	3,79	7,76	7,35

*The spectra of compounds (IIa-f, IIIa, b, IV, IVb-d, VIIIa, c, d) were measured in DMSO-d_6, and those of compounds (Va, VIa-e, VII, VIIIb, e) were measured in deuterochloroform.

†The chemical shifts for the 2-CF_3 groups with reference to deuterotrifluoroacetic acid (the ^{19}F NMR spectra).

TABLE 5. Characteristics of the Hydrochlorides (IXa-e)

Compound	Found, %		Molecular formula	Calculated, %		mp, °C	Yield, %
	N	Cl		N	Cl		
IXa	9,50	15,95	$C_{22}H_{25}Cl_2N_3O_3$	9,33	15,74	223...225	96
IXb	9,12	15,20	$C_{23}H_{27}Cl_2N_3O_3$	9,05	15,27	208...210	98
IXc	9,61	16,61	$C_{21}H_{23}Cl_2N_3O_3$	9,63	16,25	245...247	95
IXd	9,30	15,98	$C_{23}H_{27}Cl_2N_3O_3$	9,05	15,27	130...132	95
IXe	8,63	14,57	$C_{25}H_{31}Cl_2N_3O_3$	8,57	14,46	162...164	98

2,4-Dihydroxy-α-(1-methyl-2-benzimidazolyl)-5-ethylacetophenone (Ib). A strong stream of dry hydrogen chloride was passed into a mixture of 8.45 g (50 mmole) of 2-benzimidazolyl-1-methylacetonitrile and 7.04 g (51 mmole) of 4-ethylresorcinol in 50 ml of boron trifluoride etherate with stirring and heating at 60°C for 10-12 h. When the absorption of hydrogen chloride had stopped, a moderate stream of hydrogen chloride was passed while the stirring and heating were continued. The reaction mixture was left overnight, poured with stirring into 500 ml of water that had been heated to 80°C. The mixture was then boiled for 1.5-2 h and filtered. The precipitate was transferred to 500 ml of water, treated with ammonia to pH 7, and filtered. The residue was then reprecipitated from an alkaline solution and recrystallized from dimethylformamide.

The ketones (Ia, c-f) were obtained similarly.

7-Hydroxy-3-(1-methyl-2-benzimidazolyl)-6-ethylchromone (IIb). A mixture of 3.1 g (10 mmole) of the ketone (Ib), 10 ml (60 mmole) of triethyl orthoformate, and 10 ml of dry pyridine was heated at 120-130°C for 8-10 h until the reaction mixture stopped giving a positive reaction with an alcohol solution of ferric chloride. The solution was cooled to room temperature and left overnight. The crystals were filtered off, washed with isopropyl alcohol, and crystallized from dimethylformamide. The mother solution was poured onto ice, and after the reaction mixture had hardened the crystals were filtered off. The overall yield was 2.97 g.

The chromones (IIa, c, d, f) were obtained similarly.

6-Hexyl-7-hydroxy-3-(1-methyl-2-benzimidazolyl)chromone (IIe). To a mixture of 2 g (5.5 mmole) of the ketone (Ie) and 1.32 ml of acetic formic anhydride while cooling with ice and salt we added two drops and then 2.6 ml of triethylamine so that the temperature of the reaction mixture did not rise above 0°C. The reaction mixture was stirred and cooled for 1 h, and 0.8 ml of acetic formic anhydride and 1.1 ml of triethylamine were then added in succession. The mixture was kept for a further 1 h at 0°C and 15 min at 80-100°C, and cooled. The crystals were filtered off, washed with alcohol, and recrystallized from dimethylformamide. The yield was 2.0 g.

7-Hydroxy-2-trifluoromethyl-3-(1-methyl-2-benzimidazolyl)-6-ethylchromone (IIIa). To a suspension of 4.8 g (15.5 mmole) of the ketone (Ib) in 20 ml of dry pyridine, while cooling with ice, we added dropwise 8.8 ml (62 mmole) of trifluoroacetic anhydride. The mixture was stirred and cooled for 10 min and left overnight. It was then poured onto ice, and the crystals were filtered off and recrystallized from absolute isopropyl alcohol. The yield was 5 g (83%).

Compound (IIIb) was obtained similarly.

7-Hydroxy-2-ethoxycarbonyl-3-(1-methyl-2-benzimidazolyl)-6-propylchromone (IV). To a mixture of 3.2 g (10 mmole) of the ketone (I) in the smallest amount of dry pyridine with stirring we added dropwise 2.23 ml (20 mmole) of ethoxalyl chloride. The reaction mixture was then left for 48 h and poured onto ice. The crystals were filtered off and recrystallized from alcohol. The yield was 3.2 g (80%).

7-Acetoxy-2-methyl-3-(1-methyl-2-benzimidazolyl)-6-ethylchromone (Va). While stirring and gently heating we dissolved 3.1 g (10 mmole) of the ketone (Ib) in 10 ml of pyridine and 5 ml (53 mmole) of acetic anhydride. The reaction mixture was left for 24 h, poured onto ice, and kept for not less than 24 h to crystallize. The precipitate was filtered off, washed with water, and recrystallized from petroleum ether. The yield was 2.6 g (70%).

7-Hydroxy-3-(1-methyl-2-benzimidazolyl)-6-ethylflavone (Va). To a suspension of 1.55 g (5 mmole) of the ketone (Ib) in 10 ml of pyridine we added dropwise 3 ml (25 mmole) of benzoyl chloride. The mixture was left overnight. The solution was then poured onto ice and left for 24 h to hydrolyze the excess of the benzoyl chloride. The oily residue was washed with water, dissolved in 50 ml of chloroform, and washed (2 × 10 ml) with 2% sodium hydroxide solution, 50 ml of water, 20 ml of 1 N hydrochloric acid, and 50 ml of water. The chloroform solution was dried over sodium sulfate and evaporated to dryness. The remaining oil was dissolved in 50 ml of alcohol, 1 ml of concentrated hydrochloric acid was added, and the mixture was boiled for 4 h to hydrolyze the 7-O-benzoyloxyflavone. The solution was cooled, diluted with 30 ml of water,

neutralized with a 2% solution of sodium hydroxide to pH 7, and left to crystallize. The precipitate was filtered off and recrystallized from aqueous isopropyl alcohol. The yield was 0.4 g (20% on the initial ketone).

7-Hydroxy-2-(β-carboxyethyl)-3-(1-methyl-2-benzimidazolyl)-6-ethylchromone (Vb). A suspension of 1.55 g (5 mmole) of the ketone (Ib), 3 g (30 mmole) of succinic anhydride, and 10 ml of dry pyridine was heated at 40 °C and left for 72 h. The reaction mixture was poured onto ice and acidified to pH 2-3 with concentrated hydrochloric acid. After the ice had melted, the solution was treated with 5% sodium hydroxide solution to pH 6-7. The crystals were filtered off, washed with cold water, and reprecipitated from alkaline solution with dilute hydrochloric acid. The precipitate was filtered off and recrystallized from a mixture of DMFA and water. The yield was 1.58 g (80%).

7-Hydroxy-2-methyl-3-(1-methyl-2-benzimidazolyl)-6-ethylchromone (Vd). We dissolved 1.9 g (5 mmole) of the chromone (IV) in 30 ml of alcohol. The solution was heated to boiling, 5 ml of 1 N sodium hydroxide solution was added, and the mixture was boiled for 3-4 min. The product was neutralized to pH 7 with hydrochloric acid, diluted with 200 ml of water, and left to crystallize. The precipitate was filtered off and crystallized from aqueous alcohol. The yield was 1.37 g (83%).

7-Acetoxy-3-(1-methyl-2-benzimidazolyl)-6-ethylchromone (VIa). A mixture of 1.6 g (5 mmole) of the chromone (IIb), 2 ml (21 mmole) of acetic anhydride, and 10 ml of pyridine was boiled for 0.5-1 h. The solution was cooled, and the crystals that separated were filtered off, washed with cold isopropyl alcohol, and crystallized from isopropyl alcohol. The yield was 1.38 g (76%).

7-Acyloxy-3-(1-methyl-2-benzimidazolyl)-6-ethylchromones (VIc-e). We mixed 5 mmole of the chromone (IIb), 10 mmole of the respective acid chloride, and 10 ml of pyridine and left the mixture for 2-3 h. The solution was poured onto ice, and the precipitate that separated was filtered off and crystallized from isopropyl alcohol.

7-Acetoxy-3-(1-methyl-2-benzimidazolyl)-2-trifluoromethyl-6-ethylchromone (VII). To a mixture of 1 g of the chromone (IIIa) in 20 ml of acetic acid we added 1 ml of acetic anhydride, and we heated the mixture until completely dissolved. After cooling, the solvent and the excess of the anhydride were evaporated to dryness on a rotary evaporator, and the residue was rubbed with petroleum ether. The crystals that separated were filtered off, washed with petroleum ether, and recrystallized from a mixture of petroleum ether and toluene.

3-(2-Benzimidazolyl)-7-hydroxy-8-dialkylaminomethyl-6-ethylchromones (VIIIa-e). A suspension of 5 mmole of the chromone and 10 mmole of bis(dialkylamino)methane in 10 ml of absolute dioxane was boiled for 2-3 h until completely dissolved. The excess of the reagent and the solvent were evaporated to dryness under vacuum, the oily product was rubbed with petroleum ether, and the precipitate was filtered off and crystallized from hexane, petroleum ether, or a mixture of petroleum ether and toluene.

3-(2-Benzimidazolyl)-7-hydroxy-8-dialkylaminomethyl-6-ethylchromone Hydrochlorides (IXa-e). The respective Mannich base was dissolved in dry chloroform, petroleum ether, or benzene, and a stream of dry hydrogen chloride was passed into it until the formation of a precipitate had stopped. The precipitate was filtered off and crystallized from a suitable solvent (Table 5).

3-(2,4-Dihydroxy-5-methylphenyl)-4-(1-methyl-2-benzimidazolyl)pyrazole (X). To a suspension of 1 g (3.2 mmole) of the chromone (IIa) in 20 ml of isopropyl alcohol while heating we added 1.5 ml (40 mmole) of 85% hydrazine hydrate. The mixture was boiled and poured into water. The precipitate was filtered off, dried, and crystallized from aqueous alcohol. The yield was 1 g (almost quantitative), and the product formed colorless crystals; mp 221-223°C. Found %: N 17.49. $C_{18}H_{16}N_4O_2$. Calculated %: N 17.75. PMR spectrum (DMSO-d_6, δ, ppm): pyrazole protons, 13.18 s 1-NH, 8.03 s 5-H; protons of phenol part, 9.44 s 2-OH, 6.41 s 3-H, 10.80 s 4-OH, 1.93 s 5-CH_3, 6.89 s 6-H; benzimidazole protons, 3.58 s 1-CH_3, 7.56 m 4-, 7-H, 7.25 m 5-, 6-H.

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