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SYNTHETIC AND MODIFIED ISOFLAVONOIDS. XX. SYNTHESIS OF WATER-SOLUBLE SALTS OF DERIVATIVES OF 1,3-BENZODIOXOLE, 1,4-BENZODIOXANE, AND 1,5-BENZODIOXEPANE ANALOGS OF ISOFLAVONES

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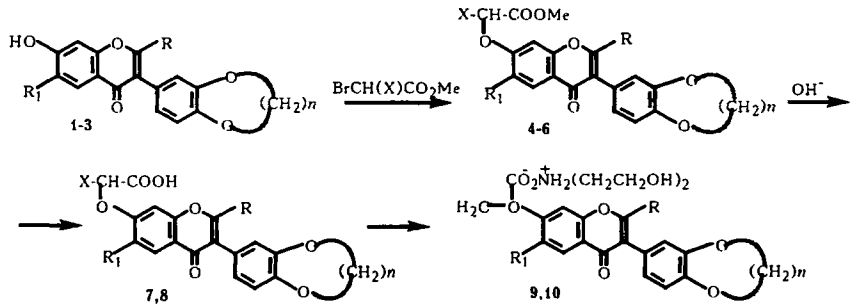
Water-soluble diethanolamine and morpholine salts of derivatives of 1,3-benzodioxole, 1,4-benzodioxane, and 1,5-benzodioxepane analogs of isoflavones have been synthesized.

Isoflavones containing hydroxy, alkoxy, glycosyloxy, or alkyl substituents in various positions of the chromone ring are widely distributed in the vegetable kingdom. Initially these compounds were synthesized predominantly with the aim of proving the structures of products isolated from natural raw material. At the present time, the synthesis of isoflavones is acquiring practical interest, in addition to that of purely scientific knowledge. It has been found that compounds of this series possess a broad spectrum of biological action. The biological action of isoflavones is being studied intensively and patented.

In the chemical literature, there are numerous patents and reports devoted to 7-alkoxycarbonylmethoxy- and 7-carboxymethoxyisoflavones possessing various biological activities [2, 3]. In view of this, it appeared of interest to synthesize 7-alkoxycarbonylmethoxy derivatives of isoflavone analogs – 3-hetarylchromones – that we had obtained previously [4-8].



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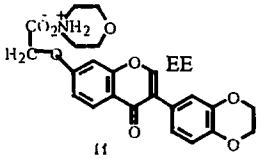
1,4,7,9: n=1; 2,5,8,10: n=2; 3,4: n=3



11

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TABLE 1. Characteristics of Compounds (**4-11**)

Compound	Yield, %	mp, °C	Empirical formula	Compound	Yield, %	mp, °C	Empirical formula
4b	94	177–178	$C_{21}H_{18}O_7$	7b	97	213–214	$C_{20}H_{16}O_7$
4c	86	137–138	$C_{22}H_{20}O_7$	7c	90	206–207	$C_{21}H_{18}O_7$
4e	98	122–123	$C_{22}H_{20}O_7$	7e	97	202–203	$C_{21}H_{18}O_7$
4f	78	116–117	$C_{23}H_{22}O_7$	7f	91	112–113	$C_{22}H_{20}O_7$
4h	80	153–154	$C_{22}H_{17}F_3O_7$	8a	95	242–243	$C_{19}H_{14}O_7$
4i	77	137–138	$C_{23}H_{19}F_3O_7$	8b	92	213–214	$C_{21}H_{18}O_6$
4p	73	123–124	$C_{24}H_{21}F_3O_7$	8c	89	222–223	$C_{22}H_{20}O_7$
5a	100	187–188	$C_{20}H_{16}O_7$	8d	90	217–218	$C_{20}H_{16}O_7$
5b	84	156–157	$C_{22}H_{20}O_7$	8e	98	238–239	$C_{22}H_{20}O_7$
5c	96	121–122	$C_{23}H_{22}O_7$	8f	97	203–204	$C_{23}H_{22}O_7$
5d	95	174–175	$C_{21}H_{18}O_7$	8i	86	128–130	$C_{23}H_{19}F_3O_7$
5e	75	151–152	$C_{23}H_{22}O_7$	8j	82	220–221	$C_{21}H_{18}O_7$
5f	86	142–143	$C_{24}H_{24}O_7$	8q	82	232–233	$C_{22}H_{20}O_5$
5g	91	159–160	$C_{21}H_{15}F_3O_7$	9b	86	142–143	$C_{24}H_{27}NO_9$
5h	79	177–178	$C_{23}H_{19}F_3O_7$	9c	84	159–160	$C_{25}H_{29}NO_9$
5i	94	147	$C_{24}H_{21}F_3O_7$	9e	94	153–154	$C_{25}H_{29}NO_9$
5j	99	172–173	$C_{22}H_{20}O_7$	9f	77	135–137	$C_{26}H_{31}NO_9$
5k	84	168–169	$C_{24}H_{24}O_7$	10a	77	167–168	$C_{23}H_{25}NO_9$
5*l*	89	174–175	$C_{21}H_{18}O_7$	10b	90	141–142	$C_{25}H_{29}NO_9$
5m	90	144–145	$C_{23}H_{22}O_7$	10c	75	143–145	$C_{26}H_{31}NO_9$
5n	95	125–126	$C_{23}H_{22}O_7$	10d	97	148–149	$C_{24}H_{27}NO_9$
5o	82	124–125	$C_{24}H_{24}O_7$	10e	89	146–148	$C_{26}H_{31}NO_9$
5p	87	121–122	$C_{25}H_{23}FO_7$	10f	83	152–154	$C_{27}H_{33}NO_9$
5q	71	110–111	$C_{23}H_{22}O_5$	10i	50	158–160	$C_{27}H_{30}NF_3O_9$
6d	77	144–145	$C_{22}H_{20}O_7$	**11**	46	175–177	$C_{25}H_{27}NO_8$
6r	50	100–101	$C_{26}H_{28}O_7$				

The 7-methoxycarbonylmethoxy and 7-(1-methoxycarbonylethoxy) derivatives of the 1,3-benzodioxole, 1,4-benzodioxane, and 1,5-benzodioxepane analogs of isoflavones – the 3-hetarylchromones (**4-6**) – are formed readily and with high yields by boiling the corresponding 7-hydroxyisoflavone analogs (**1-3**) [4-8] with methyl bromoacetate and methyl β-bromopropionate in acetone in the presence of potash.

To obtain water-soluble compounds from the 7-alkoxycarbonylmethoxy derivatives of isoflavone analogs (**4, 5**), they were subjected to alkaline hydrolysis to give the free acids (**7, 8**), from which the water-soluble diethanolamine and morpholine salts (**9-11**) were obtained. The isoflavone analogs (**4-8**) are colorless crystalline substances readily soluble in the usual organic solvents, while their diethanolamine and morpholine salts are soluble in water.

The structures and compositions of the compounds were confirmed by analytical and spectral results.

The results of analyses, constants, yields, and details of PMR spectra of compounds (**4-11**) are given in Tables 1-3.

The PMR spectra of compounds (**4-8**) lacked signals of the protons of phenolic hydroxyls, while each of them had the signal of a methoxy group at 3.8-3.9 ppm and, in the case of compounds (**7, 8**), that of the proton of a carboxy group in the 13.0-16.2 ppm region.

Thus, alkylation at the phenolic hydroxyls permits the formation of new, original compounds with specific fragments that, in a number of cases, are water-soluble, which is particularly important for pharmacological trials.

EXPERIMENTAL

The course of the reactions and the purity of the substances obtained were monitored by TLC on Silufol UV-254 plates. The eluent used was benzene–ethanol (9:1). PMR spectra were measured on a Bruker WP-100SY instrument in DMSO-d_6 or $CDCl_3$ with TMS as internal standard. The elementary analyses of all the compounds corresponded to the calculated values.

3-Hetaryl-7-methoxycarbonylmethoxychromones (4b, c, e, f, h, i, p; 5a-k; 6d, r) and the 3-Hetaryl-7-(1-methoxycarbonylethoxy)chromones (4p; 5*l*-q). To a hot solution of 15 mmole of the appropriate 7-hydroxyisoflavone analog in 200 ml of dry acetone were added 1.63 ml (17.9 mmole) of methyl monobromoacetate (or 17.9 mole of methyl β-bromopropionate) and 6.23 g (45 mmole) of freshly calcined potash, and the mixture was boiled for 2-4.5 h. Then the inorganic deposit was filtered off, and the solvent was distilled off under water-pump vacuum. The residue was crystallized from ethanol (see Table 1), except for compounds (**4e**) and (**5a**), which were crystallized from aqueous ethanol.

TABLE 2. PMR Spectra of the 7-Alkoxycarbonylmethoxyisoflavone Analogs (**4-6**) (in $CDCl_3$)

Compound	PMR spectrum, δ, ppm (J, Hz)						
	Protons of the chromone ring					Protons of the hetero residue	$O(CH_2)_nO$
	R-2	H-5	R-6	$MeOOCH_2CO$-7 or MeOOC(Me)HCO-7	H-8		
1	2	3	4	5	6	7	8
4b	7.85s	8.05s	2.74q, 1.29t	4.72; 3.78	6.64	6.96 (m, H-4, H-6, H-7)	5.92s
4c	7.90s	8.07s	2.80t, 1.75m, 1.0t	4.79; 3.87	6.70s	7.03 (m, H-4, H-6, H-7)	6.01s
4e	2.26	8.06s	2.77q, 1.25t,	4.73; 3.81	6.75s	6.74 (m, H-4, H-6, H-7)	5.97s
4f	2.25	8.03s	2.75t, 1.7m	4.75; 3.81	6.64s	6.7 (m, H-4, H-6, H-7)	5.92s
4h	–	8.01s	2.79q, 1.29t	4.74; 3.83	6.72s	6.72 (m, H-4, H-6, H-7)	5.96s
4i	–	7.97s	2.75t, 1.71m, 0.96t	4.77; 3.82	6.72s	6.72 (m, H-4, H-6, H-7)	5.98s
4p	–	7.96s	2.73t, 1.71m, 0.96t	4.89q; 1.71d; 3.80s	6.72s	6.69 (b, 1H, H-4); 6.69 (d.d, 1H, H-6); 6.87 (d, 1H, H-7)	6.01s
5a	7.86s	8.23d (8.5)	6.96 dd. (8.5; 2.5)	4.74; 3.84	6.96d (2.5)	6.84 (m, H-5, H-7, H-8)	4.28s
5b	7.86s	8.09s	2.84q, 1.31t	4.79; 3.85	6.70s	7.04 (m, H-5, H-7, H-8)	4.30s
5c	7.96s	8.14s	2.82t, 1.79m 1.03t	4.82; 3.89	6.75s	7.10 (m, H-5, H-7, H-8)	4.33s
5d	2.33s	8.17d (8.5)	7.00 dd (8.5; 2.5)	4.79; 3.86	6.83d (2.5)	6.83 (m, H-5, H-7, H-8)	4.31s
5e	2.30s	7.99s	2.81q, 1.29t	4.80; 3.85	6.68s	6.83 (m, H-5, H-7, H-8)	4.29s
5f	2.31s	8.04s	2.80t, 1.73m 0.99t	4.82; 3.87	6.73s	6.86 (m, H-5, H-7, H-8)	4.31s
5g	–	8.17d (8.5)	7.08 dd. (8.5; 2.5)	4.80; 3.86	6.90d	6.84 (m, H-5, H-7, H-8)	4.30s
5h	–	8.06s	2.86q, 1.31t	4.84; 3.88	6.78s	6.84 (m, H-5, H-7, H-8)	4.31s
5i	–	8.0s	2.77t, 1.73m 0.98t	4.81; 3.85	6.74s	6.78 (m, H-5, H-7, H-8)	4.30s
5j	2.50q; 1.18t	7.95d (8.5)	7.11 dd.. (8.5; 2.5)	5.0; 3.73	7.18d (2.5)	6.74 (d, 1H, J=2Hz, H-5) 6.68 (d.d, 1H, J=8; 2.0Hz, H-7) 6.90 (d, 1H, J=8Hz, H-8)	4.28s
5k	2.69q; 1.18t	7.78s	2.69q. 1.18t	5.05; 3.74	7.14s	6.72 (d, 1H, J=2Hz, H-5) 6.67 (d.d. 1H, J=8; 2.0Hz, H-7) 6.90 (d, 1H, J=8Hz, H-8)	4.28s

TABLE 2 (continued)

Compound	PMR spectrum, δ, ppm (J, Hz)						
	Protons of the chromone ring					Protons of the hetero residue	$O(CH_2)_nO$
	R-2	H-5	R-6	$MeOOCH_2CO$-7 or MeOOC(Me)HCO-7	H-8		
1	2	3	4	5	6	7	8
5l	7.89s	8.21d (8.5)	7.0 ,dd.. (8.5; 2.5)	4.87q; 1.68d, 3.79s	6.78d (2.5)	6.94 (d, 1H, J=2Hz, H-5) 7.06 (d.d, 1H, J=8; 2.0Hz, H-7) 6.90 (d, 1H, J=8Hz, H-8)	4.28s
5m	2.29s	8.12d (8.5)	6.94.dd (8.5; 2.5)	4.85q; 1.67d, 4.24q; 1.27t	7.0,d(2.5)	6.79(d, 1H, J=2Hz, H-5) 6.72 (d.d, 1H, J=8; 2.0Hz, H-7) 6.85(d, 1H, J=8Hz, H-8)	4.29s
5n	7.87	8.05s	2.76q, 1.27 t	4.86q; 1.69d, 3.77s	6.63s	7.08(d, 1H, J=2Hz, H-5) 7.04 (d.d, 1H, J=8; 2.0Hz, H-7) 6.90(d, 1H, J=8Hz, H-8)	4.26s
5o	7.87s	8.04s	2.72t, 1.69m, 0.97 t	4.85q; 1.69d, 3.77s	6.62s	7.09(d, 1H, J=2Hz, H-5) 7.04 (d.d, 1H, J=8; 2.0Hz, H-7) 6.91(d, 1H, J=8Hz, H-8)	4.29s
5p	–	7.96s	2.74t, 1.64m, 0.96 t	4.90q; 1.72d, 3.80 s	6.70s	6.76(d, 1H, J=2Hz, H-5) 6.72 (d.d. 1H, J=8; 2.0Hz, H-7) 6.92(d, 1H, J=8Hz, H-8)	4.29s
5q	2.51q, 1.18 t	7.93d (8.5)	7.06,dd.. (8.5; 2.5)	5.28q; 1.56d, 3.71s	7.09,d(2.5)	6.74(d, 1H, J=2Hz, H-5) 6.88 (d.d, 1H, J=8; 2.0Hz, H-7) 6.90(d, 1H, J=8Hz, H-8)	4.28s
6d	2.29s	8.13d (8.5)	6.90,d.d. (8.5; 2.5)	4.74; 3.84	7.04,d (2.5)	6.89(d, 1H, J=2Hz, H-6) 6.82 (d.d, 1H, J=8; 2Hz, H-8) 7.04(d, 1H, J=8Hz, H-9)	4.25 t 2.20q
6r	2.55t, 1.66m, 0.85 t	7.78s	2.71q, 1.19t	5.04; 3.74	7.1s	6.83 (d, 1H, J=2Hz, H-6) 6.78 (d.d, 1H, J=8; 2Hz, H-8) 7.02(d, 1H, J=8Hz, H-9)	4.17 t 2.14 q

TABLE 3. PMR Spectra of the 7-Carboxymethoxyisoflavone Analogs in DMSO-d_6

Compound	PMR spectrum, δ, ppm (J, Hz)						
	Protons of the hetero residue					Protons of the chromone ring	$O(CH_2)_nO$
	R-2	H-5	R-6	$HOOCH_2CO$-7 or HOOC(Me)HCO-7	H-8		
7b	8.26s	7.83s	2.73q, 1.22t	4.88s	7.10s	6.96 (m, H-4, H-6, H-7)	5.99s
7c	8.36s	7.88s	2.74t, 1.70m, 0.93t	4.94s, 16.23s	7.09s	7.09 (m, H-4, H-6, H-7)	6.07s
7e	2.27s	7.83s	2.74q, 1.23t	4.94s	7.83s	6.85 (d, 1H, J=2Hz, H-4) 6.74 (d.d, 1H, J=8; 2Hz, H-6) 6.88(d, 1H, J=8Hz, H-7)	6.10s
7f	2.26s	7.74s	2.69t, 1.65m, 0.91t	4.90s	7.01s	6.80 (d, 1H, J=2Hz, H-4) 6.69 (d.d, 1H, J=8; 2Hz, H-6) 6.95 (d, 1H, J=8Hz, H-7)	6.04s
8a	8.36s	8.04d (8.3)	7.04d.d (8.3; 2.2)	4.91s	7.11d (2.2)	7.01 (m, H-5, H-7, H-8)	4.27s
8b	8.35s	7.89s	2.77q, 1.24t	4.96s	7.15s	7.04 (m, H-5, H-7, H-8)	4.31s
8c	8.37s	7.90s	2.75t, 1.69m, 0.97t	4.96s	7.19s	7.05 (m, H-5, H-7, H-8)	4.31s
8d	2.31s	7.95d	7.05d.d. (8.5; 2.5)	4.93s	7.11,d(2.5)	6.84 (m, H-5, H-7, H-8)	4.32s
8e	2.31s	7.85s	2.77q, 1.25t	4.96s	7.09s	6.85 (m, H-5, H-7, H-8)	4.34s
8f	2.26s	7.72s	2.68t, 1.64m 0.91t	4.90; 13.0	7.00s	6.79 (m, H-5, H-7, H-8)	4.27s
8i	–	7.89s	2.78t, 1.69m, 0.95t	5.05s	7.32s	6.89 (m, H-5, H-7, H-8)	4.37s
8j	2.51q; 1.18t	7.94d (8.5)	7.06d.d (8.5; 2.5)	4.89s	7.11d (2.5)	6.74 (d, 1H, J=2Hz, H-5) 6.68 (d.d, 1H, J=8; 2Hz, H-7) 6.90 (d, 1H, J=8Hz, H-8)	4.28s
8q	2.52q; 1.18t	7.93,d (8.5)	7.03d.d. (8.5; 2.5)	5.11; 1.57	7.03d (2.5)	6.73 (d, 1H, J=2Hz, H-5) 6.68 (d.d, 1H, J=8; 2Hz, H-7) 6.90 (d, 1H, J=8Hz, H-8)	4.28s

3-Hetaryl-7-carboxymethylchromones (7b, c, e, f; 8a-f, i, j) and 2-Ethyl-3-(1,4-benzodioxan-6-yl)-7-(1-carboxymethylethoxy)chromone (8q). To a boiling suspension of 0.01 mole of the appropriate 7-(methoxycarbonylmethoxy)isoflavone analog (**4, 5**) or 2-ethyl-3-(1,4-benzodioxan-6-yl)-7-(1-carboxymethylethoxy)chromone (**5q**) in 50 ml of alcohol was added 8.0 ml of a 5% solution of caustic soda, and the mixture was boiled for 15-60 min. The end of the reaction was determined by TLC. The reaction mixture was neutralized with dilute hydrochloric acid (1:1). It was then diluted with water, and the precipitate that deposited was filtered off and crystallized from alcohol (see Table 1).

Diethanolamine Salts of the 3-Hetaryl-7-carboxymethoxychromones (9b, c, e, f; 10a-f, i). With stirring, 0.47 g of diethanolamine was added to a paste of 45 mmole of a 7-carboxymethoxyisoflavone analog in 1.9 ml of water heated to 70-75°C, and heating at this temperature was continued until the paste had been completely converted into a solution. Then 8.1 ml of isopropyl alcohol was added, the mixture was left in the refrigerator, and the precipitate that deposited was filtered off and washed with cold isopropyl alcohol. It was recrystallized from alcohol (see Table 1).

Morpholine Salt of 2-Ethyl-3-(1,4-benzodioxan-6-yl)-7-carboxymethoxychromone (11). This was obtained in an analogous way to compounds (**9** and **10**) from the 2-ethyl-7-carboxymethoxyisoflavone analog (**8k**) and morpholine (see Table 1).

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