ALKYLATION OF 7-HYDROXY-3-FURYLCHROMONE AND 7-HYDROXYISOFLAVONE WITH HALOGEN DERIVATIVES OF THE HETEROCYCLIC SERIES

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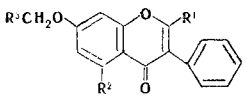
UDC 547.814.5'722'732'789:542.953

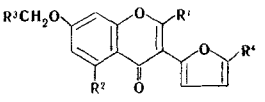
Products of the alkylation of compounds of the isoflavone type – 7-hydroxyisoflavone, 2-methyl-7-hydroxyisoflavone, 2-ethoxycarbonyl-7-hydroxyisoflavone, 2-methyl-5,7-dihydroxyisoflavone, 2-methyl-3-furyl-7-hydroxychromone, and 2-ethoxycarbonyl-3-furyl-7-hydroxychromone – were obtained by reaction with chloromethyl derivatives of heterocycles.

Increased interest in 7-carbomethoxyisoflavone derivatives has developed, inasmuch as they are analogs of the medicinal preparation Recordil [1]. Attempts [2-5] have been made to synthesize various analogs of this preparation in order to increase the pharmacological activity.

The present paper is devoted to the synthesis of heterocyclic derivatives of 7-hydroxyisoflavone, 2-methyl-7-hydroxyisoflavone, 2-methyl-5,7-dihydroxyisoflavone, and 3-furyl-7-hydroxychromone containing heterocycles – furan, thiophene, thiazole, and benzothiazole – in the 7 position. Compounds with structures A and B (Tables 1 and 2) were obtained by alkylation of these compounds with chloromethyl derivatives of the heterocycles.

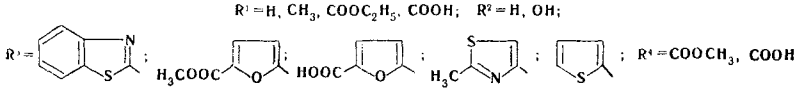


A



B

R^1 = H, CH_3, $COOC_2H_5$, COOH; R^2 = H, OH;



R^4 = $COOCH_3$, COOH

By comparing the data in Tables 1 and 2 it may be noted that a longer time is required for completion of the reactions leading to isoflavone derivatives than for the analogous compounds in the 3-furylchromone series. In most cases the alkylations with chloromethyl derivatives of thiazole and benzothiazole proceed with much greater difficulty than the alkylations with similar derivatives of furan and thiophene. The introduction of an ethoxycarbonyl group into the 2 position of the compounds undergoing alkylation accelerates the reaction considerably.

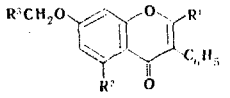
Two compounds are formed as a result of some of the alkylation reactions: one of them is a compound with an ester group (XVI), while the other is a compound with a carboxyl group (XVII).

EXPERIMENTAL

The purity of the compounds and the course of the reactions were monitored by thin-layer chromatography on Merck silica gel G with elution by dichloroethane–methanol (95 : 5).

T. G. Shevchenko Kiev State University. L. Kossuth Debrecen University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1321-1323, October, 1972. Original article submitted July 28, 1971.

TABLE 1



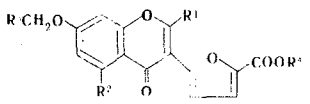
Compound	R¹	R²	R³	Reaction time, h	mp, °C	Empirical formula	Found, %			Calc., %			λ_{max}, nm	Yield, %
							C	H	S	C	H	S		
I	CH_3	H	2-Benzothiazolyl	29	158	$C_{24}H_{17}NO_3S$†	—	—	8,4	—	—	8,0		85
II	CH_3	H	2-Methyl-4-thiazolyl	26	130	$C_{21}H_{17}NO_3S$‡	—	—	8,7	—	—	8,8	240	67
III	CH_3	H	2-Thienyl*	6	137	$C_{21}H_{16}O_3S$	—	—	8,7	—	—	9,2		63
IV	H	H	2-Benzothiazolyl	26	228	$C_{23}H_{15}NO_3S$	—	—	8,3	—	—	8,3	225	61
V	$COOC_2H_5$	H	2-Benzothiazolyl	24	161	$C_{26}H_{19}NO_5S$	—	—	6,6	—	—	7,0	233	57
VI	COOH	H	2-Benzothiazolyl		242	$C_{24}H_{15}NO_5S$	—	—	7,7	—	—	7,5	240	75
VII	$COOC_2H_5$	H	2-Methyl-4-thiazolyl	27	135	$C_{26}H_{19}NO_5S$	—	—	7,8	—	—	7,6	240	62
VIII	CH_3	OH	2-Benzothiazolyl	20	191	$C_{24}H_{17}NO_4S$	—	—	7,7	—	—	7,7		82
IX	CH_3	H	5-Methoxycarbonyl-2-furyl	27	153	$C_{23}H_{18}O_6$	70,5	4,7	—	70,7	4,7	—		88
X	CH_3	H	5-Carboxy-2-furyl		180	$C_{22}H_{16}O_6$	70,3	4,4	—	70,2	4,3	—	250	Quantitative
XI	H	H	5-Methoxycarbonyl-2-furyl	22	161,5	$C_{22}H_{16}O_6$	70,2	4,3	—	70,2	4,3	—	255	76
XII	$COOC_2H_5$	H	5-Methoxycarbonyl-2-furyl	29	133	$C_{25}H_{20}O_8$	66,8	4,5	—	66,9	4,5	—	255	80
XIII	CH_3	OH	5-Methoxycarbonyl-2-furyl	17	152	$C_{23}H_{18}O_7$	68,0	4,4	—	68,0	4,5	—		61
XIV	CH_3	OH	5-Carboxy-2-furyl		220	$C_{22}H_{16}O_7$	68,0	4,4	—	67,3	4,1	—		95

*2-Chloromethylthiophene was obtained by the method in [6].

† Found: N 3.4%. Calculated: N 3.5%.

‡ Found: N 3.7%. Calculated: N 3.8%.

TABLE 2



Compound	R¹	R²	R³	R⁴	Reaction time, h	mp, °C	Empirical formula	S, % found	S, % calc.	λ_{max}, nm	Yield, %
XV	CH_3	H	2-Benzothiazolyl	CH_3	18	178	$C_{24}H_{17}NO_6S$	7,3	7,2		53
XVI	CH_3	H	2-Methyl-4-thiazolyl	CH_3	12	145	$C_{21}H_{17}NO_6S$	7,6	7,9	287	12
XVII	CH_3	H	2-Methyl-4-thiazolyl	H		229,5	$C_{20}H_{15}NO_6S$	7,7	8,1	290	29
XVIII	$COOC_2H_5$	H	2-Benzothiazolyl	CH_3	9	209	$C_{26}H_{19}NO_8S$	6,5	6,3	218	89
XIX	$COOC_2H_5$	H	2-Methyl-4-thiazolyl	CH_3	12	151	$C_{23}H_{19}NO_8S$	7,1	6,8	287	86
XX	CH_3	H	2-Thienyl	CH_3	5	162	$C_{21}H_{16}O_6S$	7,9	8,1		68
XXI	CH_3	OH	2-Thienyl	CH_3	17	140	$C_{21}H_{16}O_7S$	7,3	7,8		31
XXII	CH_3	H	5-Methoxycarbonyl-2-furyl	CH_3	10	182	$C_{23}H_{12}O_9$*	—	—		65
XXIII	$COOC_2H_5$	H	5-Methoxycarbonyl-2-furyl	CH_3	7	162,5	$C_{25}H_{20}O_{11}$†	—	—		77

* Found: C 63.1; H 4.2%. Calculated: C 63.0; H 4.1%.
† Found: C 61.0; H 4.2%. Calculated: C 60.5; H 4.1%.

2-Methyl-7-(2-benzothiazolylmethoxy)isoflavone (I). A mixture of 1.25 g (5 mmole) of 2-methyl-7-hydroxyisoflavone, 1.83 g (10 mmole) of 2-chloromethylbenzothiazole [7], and 1.36 g (10 mmole) of freshly calcined potassium carbonate in 90 ml of absolute acetone was stirred and refluxed for 29 h. The hot reaction mixture was filtered and washed with acetone. The solvent was evaporated, and the residue was washed with ether to give 2.66 g of crude product. Crystallization from alcohol gave 1.7 g of shiny colorless plates.

Compounds II-V, VII-IX, and XI-XIII were similarly obtained. Compound IV was crystallized from toluene, while the rest were crystallized from alcohol.

2-Carboxy-7-(2-benzothiazolylmethoxy)isoflavone (VI). A 1-g (2.2 mmole) sample of V was dissolved in the minimum amount of acetone by heating, and 1.76 ml of 5% sodium hydroxide solution was added. The solution was boiled for a few seconds, diluted to twice its original volume with water, and refluxed for 3-5 min. It was then acidified to pH 3 to give 0.7 g of product.

2-Methyl-7-[(5-carboxy-2-furyl)methoxy]isoflavone (X). A total of 9.2 ml of 5% sodium hydroxide solution was added dropwise to a hot alcohol solution of 2 g (5.1 mmole) of IX. After a few minutes the yellow solution was diluted with 25 ml of water and acidified to pH 3 with dilute hydrochloric acid to give 1.93 g of product.

2-Methyl-5-hydroxy-7-[(5-carboxy-2-furyl)methoxy]isoflavone (XIV). A 0.6-g (1.48 mmole) sample of XIII in 15 ml of methanol was refluxed for 10 min with 1.5 ml of 2 N sodium hydroxide, and the mixture was acidified to pH 3 with dilute hydrochloric acid to give 0.55 g of plates (from alcohol).

2-Methyl-3-[2-furyl-5-methoxycarbonyl]-7-[(5-methoxycarbonyl-2-furyl)methoxy]chromone (XXII). A mixture of 1.1 g (3.3 mmole) of 2-methyl-3-[2-furyl-5-methoxycarbonyl]-7-hydroxychromone, 2.3 g (1.3 mmole) of 2-chloromethyl-5-methoxycarbonylfuran [8], and 1.4 g (10 mmole) of freshly calcined potassium carbonate in 250 ml of absolute acetone was stirred and refluxed for 10 h. The hot solution was filtered, and the acetone was removed by distillation. The residue on the filter was washed with ether to give 0.74 g of plates (from alcohol).

Compounds XV, XVIII-XXI, and XXIII were similarly obtained and were crystallized from alcohol.

2-Methyl-3-[2-(5-methoxycarbonyl)furyl]-7-[(2-methyl-4-thiazolyl)methoxy]chromone (XVI) and 2-Methyl-3-(2-furyl-5-carboxy)-7-[(2-methyl-4-thiazolyl)methoxy]chromone (XVII). A mixture of 0.5 g (1.6 mmole) of 2-methyl-3-(2-furyl-5-methoxycarbonyl)-7-hydroxychromone, 0.9 g (6.4 mmole) of 2-methyl-4-chloromethylthiazole [9], and 0.8 g (6 mmole) of calcined potassium carbonate in 110 ml of absolute ace-

tone was refluxed and stirred for 8 h, and the hot solution was filtered. The acetone was removed by distillation, and the residue was washed with ether to give 0.08 g of XVI.

The acetone-insoluble residue was diluted with water, and the precipitated potassium salt of XVII was removed by filtration. It was suspended in alcohol, and dilute hydrochloric acid was added with heating to dissolve it. The resulting solution was diluted with water, and the precipitate was removed by filtration to give 0.27 g of product.

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