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MANNICH REACTION IN THE SERIES OF 7-HYDROXY–3-PHENOXYCHROMONES AND THEIR DERIVATIVES

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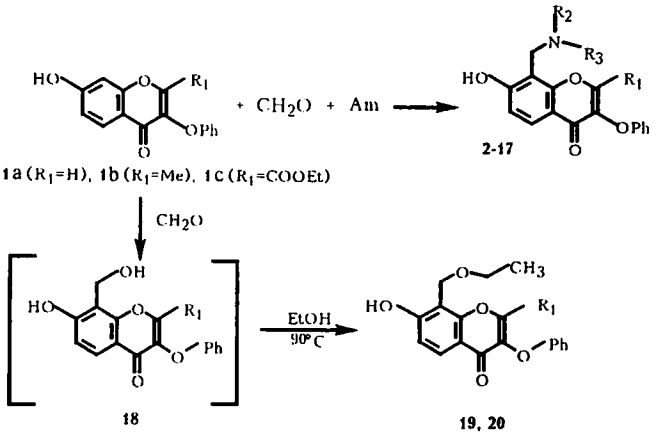
The Mannich condensation of amino acids with 3-phenoxychromones and polyhydroxy-α-phenoxyacetophenones has given a series of 8-carboxyalkylaminomethylchromones and 3-carboxymethylaminomethyl-2,4-dihydroxy-α-phenoxyacetophenones. Some features of the course of the Mannich reaction as a function of the structures of the chromones and acetophenones have been studied.

One of the most promising routes to the synthesis of new biologically active compounds is the chemical modification of natural bioregulators. Among bioregulators a special place is occupied by substances obtained from amino acids and flavonoids. The high biological activity of these compounds is due to the presence of several pharmacophoric centers. The Mannich reaction is one of the methods of chemical modification leading to the introduction into the molecule of the function of a base which on conversion into an ammonium salt makes the molecule insoluble [sic] in aqueous solutions. N-Substituted aminomethyl derivatives of flavonoids have proved to be extremely active stimulators of the activity of the central nervous system and of the respiratory tracts [1-4] and substances capable of increasing the weight of animals [5, 6]. These compounds also exhibit high anticonvulsive, antiallergic, and analgesic activities [7-9]. Several biologically active compounds have been obtained by the aminomethylation of phenols with primary and secondary amino acids [10]. It was therefore of interest, in our view, to carry out the Mannich reaction with 3-phenoxychromones using amino acids and their derivatives as the amino components.



Aminomethylation was conducted by condensing a chromone (**1a-c**) with formalin and an amino acid (Am) in boiling 50% ethanol. The aminomethyl grouping entered position 8 of the chromone system.

As the amino components we used glycine (R_2 = H, R_3 = CH_2COOH); alanine (R_2 = H, R_3 = $CH(COOH)CH_3$); valine (R_2 = H, R_3 = $CH(COOH)CH(CH_3)_2$); leucine (R_3 = $CH(COOH)CH_2CH(CH_3)_2$, R_2 = H); isoleucine (R_2 = H,

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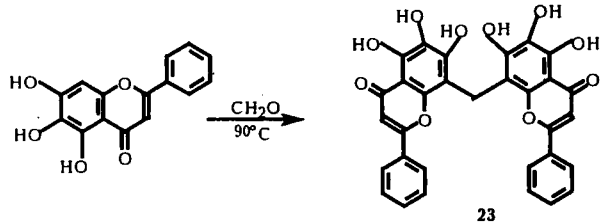
TABLE 1. Properties of the 8-Carboxyalkylaminomethylchromones (2)-(17)

Compound	Empirical formula	Yield, %	mp, °C	Details of the PMR spectra, δ, ppm; solvent – DMSO-d_6					
				protons of the chromone ring			phenoxyl protons, m	CH_2, m	protons of the amino acid fragments
				R-2, s	H-5, d	H-6, d			
2	$C_{19}H_{17}NO_6$	42	258	H 8.20	8.48	7.11	7.11 (H-3,4,5) 7.45 (H-2,6)	4.94	CH_3 CH 1.93; 4.50
3	$C_{21}H_{21}NO_6$	46	264	H 8.62	7.84	6.98	7.05 (H-3,4,5) 7.30 (H-2,6)	4.11	$(CH_3)_2$ CH CH 0.92; 1.97; 3.31
4	$C_{22}H_{23}NO_6$	49	261	H 8.61	7.85	6.97	7.05 (H-3,4,5) 7.30 (H-2,6)	4.15	$(CH_3)_2$ CH CH_2 CH 0.88; 1.76; 1.51; 3.31
5	$C_{22}H_{23}NO_6$	52	273	H 8.62	7.95	6.95	7.02 (H-3,4,5) 7.30 (H-2,6)	4.10	CH_3 CH_2 CH (CH_3) CH 0.83; 1.56; 1.72; 0.91; 3.18
6	$C_{21}H_{19}NO_6$	78	264	H 8.60	7.89	7.00	7.05 (H-3,4,5) 7.30 (H-2,6)	4.23	-CH_2 CH_2 CH_2 CH- 3.09; 1.80; 1.80; 3.53
7	$C_{22}H_{23}NO_6$	42	268	H 8.47	7.72	7.00	6.97 (H-3,4,5) 7.30 (H-2,6)	4.16	N-CH_2 CH_2 CH_2 CH_2-CO 2.71; 1.50; 1.50; 1.50; 2.19
8	$C_{25}H_{21}NO_6$	61	284	H 8.56	7.82	7.00	7.00 (H-3,4,5) 7.30 (H-2,6)	4.06	Ph CH_2 CH 7.30; 2.89; 3.54
9	$C_{24}H_{25}NO_6$	41	249	H 8.63	7.88	7.00	7.00 (H-3,4,5) 7.30 (H-2,6)	4.18	t- BuOOC CH_2CH 1.37; 2.52; 3.59
10	$C_{27}H_{32}N_2O_6$	39	218	H 8.60	7.87	7.00	7.00 (H-3,4,5) 7.30 (H-2,6)	4.15	BocNH CH_2 CH_2 CH_2 CH_2 CH 1.36; 2.90; 1.40; 1.40; 1.60; 3.29
11	$C_{19}H_{17}NO_6$	42	286	CH_3 2.35	7.82	6.95	6.95 (H-3,4,5) 7.27 (H-2,6)	4.20	CH_2 3.33
12	$C_{22}H_{23}NO_6$	49	271	CH_3 2.36	7.81	6.96	7.00 (H-3,4,5) 7.30 (H-2,6)	4.11	$(CH_3)_2$ CH CH 0.94; 2.01; 3.12
13	$C_{23}H_{25}NO_6$	46	269	CH_3 2.35	7.80	6.97	7.00 (H-3,4,5) 7.30 (H-2,6)	4.10	CH_3 CH_2 CH (CH_3) CH 0.83; 1.59; 1.70; 0.90; 3.17
14	$C_{22}H_{21}NO_6$	74	256	CH_3 2.38	7.85	6.97	7.00 (H-3,4,5) 7.30 (H-2,6)	4.29	-CH_2 CH_2 CH_2 CH- 3.19; 1.83; 1.83; 3.59
15	$C_{23}H_{25}NO_6$	42	259	CH_3 2.37	7.69	6.69	6.95 (H-3,4,5) 7.30 (H-2,6)	4.19	N-CH_2 CH_2 CH_2 CH_2-CO 2.73; 1.45; 1.45; 1.45; 2.19
16	$C_{26}H_{23}NO_6$	56	258	CH_3 2.35	7.75	6.94	6.95 (H-3,4,5) 7.25 (H-2,6)	4.03	Ph CH_2 CH 7.25; 2.95; 3.51
17	$C_{24}H_{23}NO_8$	69	251	COOEt 4.27;1.14	7.87	7.00	7.00 (H-3,4,5) 7.25 (H-2,6)	4.23	-CH_2 CH_2 CH_2 CH- 3.14; 1.82; 1.82; 3.57
21	$C_{21}H_{18}FNO_7$	32	262	H 8.56	OH	6.28	7.10 (H-2,3,5,6)	4.26	-CH_2 CH_2 CH_2 CH- 3.13; 1.89; 1.89; 3.57

TABLE 2. Properties of Compounds (**19**), (**20**), (**22**), (**23**)

Compound	Empirical formula	Yield, %	mp, °C	PMR spectrum, δ, ppm; solvent – DMSO-d_6						
				protons of the chromone ring					CH_2	OEt
				R-2	R-3	H-5	H-6	OH-7	s	
19	$C_{18}H_{16}O_5$	25	218	H 8.68	OPh: 7.03 (H-3,4,5) 7.29 (H-2,6)	7.91	6.96	11.00	4.65	3.53; 1.13
20	$C_{21}H_{20}O_7$	23	226	COOEt 4.28; 1.14	OPh: 7.01 (H-3,4,5) 7.25 (H-2,6)	7.87	6.98	11.16	4.66	3.56; 1.14
22	$C_{31}H_{18}F_2O_{10}$	69	230	H 8.63	O-4FPh: 7.10 (H-2,3,5,6)	OH 12.18	6.28	10.95	4.38	-
23	$C_{31}H_{20}O_{10}$	85	205	Ph: 7.83 (H-2,6) 7.49 (H-3,4,5)	H 6.87	OH 12.84	OH 9.92	9.13	4.40	-



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R_3 = CH(COOH)CH(CH_3)CH_2CH_3); proline (R_2R_3 = CH(COOH)$CH_2CH_2CH_2$); ε-aminocaproic acid (R_2 = H, R_3 = $CH_2CH_2CH_2CH_2CH_2COOH$); phenylalanine (R_3 = CH(COOH)CH_2Ph, R_2 = H); β-*tert*-butyl aspartate (R_2 = H, R_3 = CH(COOH)$CH_2COOC(CH_3)_3$); and ε-*tert*-butoxycarbonylaminolysine (R_2 = H, R_3 = CH(COOH)$CH_2CH_2CH_2CH_2NHCOOC(CH_3)_3$).

The 8-carboxyalkylaminomethylchromone derivatives (**2**)-(**17**) were high-melting (mp > 250°C, with decomposition) colorless crystalline substances sparingly soluble in water. The physicochemical constants of compounds (**2**)-(**17**) are given in Table 1.

The structure of the 8-carboxyalkylaminomethylchromone derivatives obtained was shown by the results of quantitative elementary analysis and PMR spectroscopy. The PMR spectra of compounds (**2**)-(**17**), measured in DMSO-d_6, showed the following differences from the spectra of the initial chromones: the signal of the H-8 proton of the chromone system had disappeared, being replaced by the signal of the protons of a methylene group in the 4.0-4.3 ppm region and the signals of an amino acid residue; and the protons of the phenolic hydroxyl of the chromone fragment, the carboxyl, and the amino group of the amino acid residue appeared in the form of a broadened peak at 11-12 ppm.

The highest yield in the Mannich reaction was obtained with the secondary amino acid proline, while primary amino acids gave relatively low yields (40-60%), owing to the presence in the reaction mixture of 8-hydroxymethylchromone (**18**), which takes part in a number of competing reactions, and also to the low activity of amino acids as the amino components. Thus, in the case of the 7-hydroxy-3-phenoxychromones (**1a**) and (**1c**) the compounds (**19**) and (**20**) were isolated from the reaction mixture as by-products with yields of 25 and 23%. In our opinion, the formation of these compounds is the result of the condensation of 8-hydroxymethylchromone with ethanol under the conditions of the synthesis.

When 3-(4-fluorophenoxy)-5,7-dihydroxychromone was used, the yield of product, 8-[(1-carboxy-1-methyl)methyl]aminomethyl-5,7-dihydroxy-3-(4-fluorophenoxy)chromone [sic] (**21**), fell considerably (Table 1). This is explained by the fact that, in addition to the formation of 8-ethoxymethylchromone, a side-reaction of the formation of the bis(5,7-dihydroxychromon-8-yl)methane (**22**) took place because of the high sensitivity of position 8 of the chromone system to electrophilic substitution reactions.

In an analogous reaction, both in the presence and in the absence of an amino acid, 5,6,7-trihydroxyflavanone (baicalein) formed bis(5,6,7-trihydroxyflavon-8-yl)methane (**23**) — i.e., the C-alkylation reaction became the main one.

The physicochemical constants of compounds (**19**), (**20**), (**22**), and (**23**) are given in Table 2.

The Mannich reaction with α-phenoxyhydroxyacetophenones (**24**), in the molecule of which there are two reaction centers capable of participating in this reaction — the methylene group and the phenol nucleus — was carried out under the same conditions. It is known that in this case the direction of the reaction depends on the acidity of the reaction medium. At low pH values the methylene group of a hydroxyacetophenone undergoes attack, while in neutral and alkaline media the new grouping enters the phenolic part of the molecule [11].

The experiments gave good yields of the 3-carboxyalkylaminomethyl derivatives of α-phenoxy-2,4-dihydroxyacetophenones (**25**)-(**31**). Alanine, phenylalanine, and proline were used in this reaction. In our opinion, the high yields (75-85%) on the use of ketones are due to their greater reactivity. With ketones the reaction takes 1-2 h, while with chromones longer heating (6-8 h) is necessary, and this is accompanied by side-reactions.

The structure of the amino acid derivatives of α-phenoxy-2,4-dihydroxyacetophenones was shown on the basis of quantitative elementary analysis and PMR spectroscopy. In the PMR spectra of compounds (**25**)-(**31**) measured in DMSO-d_6 the following differences from the spectra of the initial ketones were observed: the signal of the H-3 proton of the resorcinol fragment had disappeared and in its place there were the signal of the protons of a methylene group in the 3.88-4.14 region and the signals of the protons of the amino acid residue; the protons of the phenolic hydroxyls, the carboxyl, and the amino groups were represented in the form of a broadened peak in the 11-12 ppm region.

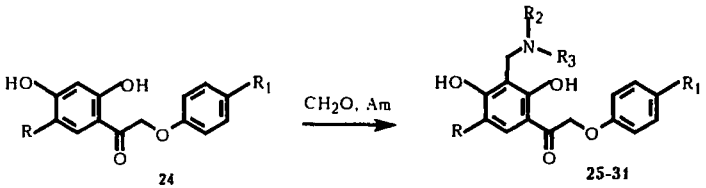
As also in the case with polyhydroxychromones, the Mannich reaction of α-phenoxy-2,4,6-trihydroxyacetophenones with amino acids led to the exclusive formation of bis(α-phenoxy-2,4,6-trihydroxyacetophenon-3-yl)methane (**32**). The physicochemical constants of compounds (**25**)-(**32**) are given in Table 3.

EXPERIMENTAL

The course of the reactions was followed and the purity of the compounds obtained was checked by TLC on Silufol UV-254 plates (Czechoslovakia) using chloroform–methanol (4:1) as eluent. PMR spectra were measured on a Bruker WP-100 SY instrument (Germany) in trifluoroacetic acid and DMSO-d_6 relative to TMS (internal standard).

TABLE 3. Properties of the 3-Carboxyalklyaminomethyl-α-phenoxy-2,4-dihydroxyacetophenones

Compound	Empirical formula	Yield, %	mp, °C	Details of the PMR spectra, δ, ppm; solvent – DMSO-d_6					
				protons of the phenol part					protons of the amino acid fragment
				H-5	H-6	CH_2	phenoxyl protons, m	CH_2 m	
25	$C_{16}H_{19}NO_6$	72	265	6.52	7.85	5.43	7.00 (H-3,4,5) 7.30 (H-2,6)	4.04	CH_3CH 1.34; 3.38
26	$C_{20}H_{21}NO_6$	85	254	6.50	7.87	5.47	6.95 (H--3,4,5) 7.30 (H-2,6)	4.08	$-CH_2$ CH_2 CH_2 CH- 3.20;1.80; 1.80; 3.59
27	$C_{24}H_{23}NO_6$	81	286	6.41	7.76	5.36	6.90 (H-3,4,5) 7.30(H-2,6)	3.88	Ph CH_2CH 7.30; 2.97; 3.50
28	$C_{20}H_{20}BrNO_6$	79	251	6.59	7.74	5.50	6.93 (H-3,5) 7.43 (H-2,6)	4.14	$-CH_2$ CH_2 CH_2 CH- 3.28; 1.80; 1.80; 3.68
29	$C_{20}H_{20}FNO_6$	80	258	6.51	7.79	5.55	7.10 (H-2,3,5,6)	4.05	$-CH_2$ CH_2 CH_2 CH- 3.22; 1.90; 1.90; 3.65
30	$C_{22}H_{27}NO_6$	78	254	Et 2.53; 1.17	7.69	5.50	6.96 (H-3,4,5) 7.28 (H-2,6)	4.00	$-CH_2$ CH_2 CH_2 CH- 3.18; 1.86; 1.86; 3.53
31	$C_{26}H_{27}NO_6$	83	283	Et 2.53; 1.14	7.59	5.42	6.91 (H-3,4,5) 7.30 (H-2,6)	3.91	Ph CH_2CH 7.30; 2.98; 3.50
32	$C_{29}H_{24}O_{10}$	26	239	5.86	OH 12.10	5.31	7.30 (H-2,3,4,5,6)	4.35	



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R=H, Et; R_1=H, F, Br

25-31

The initial hydroxy-α-phenoxyacetophenones and 3-phenoxychromones were obtained by methods described previously [12].

General Procedure for Obtaining the 8-Carboxyalkylaminomethylchromones (2)-(17) and 3-Carboxyalkylaminomethyl-2,4-dihydroxy-α-phenoxyacetophenones (25)-(31). A solution of 4 mmole of an amino acid in 20 ml of water was treated with 4 mmole (0.36 ml) of 35% formalin, the resulting mixture was kept for 1 h, and then a solution of 4 mmole of the appropriate 3-phenoxychromone or α-phenoxyhydroxyacetophenone in 20 ml of ethanol was added to it. The reaction mixture was kept at 90°C for 6-8 h (in the case of ketones, for 1-2 h). The precipitate that deposited was filtered off from 50% ethanol [sic]. The yields and constants of the derivatives are given in Tables 1 and 3.

To isolate compounds (**19**) and (**20**), the mother solution of the reaction mixture was evaporated in vacuum and the residue was crystallized from propan-2-ol.

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