Chemistry of Natural Compounds, Vol. 36, No. 5, 2000

MODIFIED COUMARINS. II. MANNICH REACTION OF SUBSTITUTED 4-PHENYLCOUMARINS

M. M. Garazd,[1] Ya. L. Garazd,[2] S. V. Shilin,[2] and V. P. Khilya[2]

UDC 547.9:582.89

Aminomethylation of 5-hydroxy- and 7-hydroxy-4-phenylcoumarins by substituted 1,1-diaminomethanes is studied. Mannich condensation of amino acids and their esters with 7-hydroxy-4-phenylcoumarin gives a series of 8-aminoacylmethylcoumarins and 4-phenyl-9,10-dihydro-2H,8H-chromeno[8,7-e][1,3]oxazin-2-ones.

Key words: 5-hydroxy- and 7-hydroxy-4-phenylcoumarins, 8-dialkylaminomethyl-4-phenylcoumarins, 6-dialkylaminomethyl-4-phenylcoumarins, 8-aminoacylmethyl-7-hydroxy-4-phenylcoumarins, synthesis.

Chemical modification of natural bioregulators is one of the most promising methods of synthesizing new biologically active compounds. The bioregulators exhibit high biological activity owing to the presence of several pharmacophoric centers. Neoflavones, which are based on the 4-phenylcoumarin core, are widely distributed in the plant kingdom and possess various pharmacological properties. The Mannich reaction is one method for chemical modification that introduces a basic function into a molecule. Converting it to the ammonium salt makes the molecule soluble in aqueous solutions. Most aminomethyl derivatives of coumarins act as central-nervous-system stimulants and barbiturate antagonists [1-4].

We synthesized Mannich bases from 5-hydroxy- and 7-hydroxy-4-phenylcoumarins. The required 4-phenylcoumarins **1**-**6** were prepared by Pechmann condensation of polyphenols and ethylbenzoylacetate in the presence of trifluoroacetic acid (TFA). It should be noted that using resorcinol, 2-methylresorcinol, 4-chloro-, and 4-alkylresorcinols in this reaction produces the corresponding 7-hydroxy-4-phenylcoumarins. Using orcinol produces the 5-hydroxy derivative of 4-phenylcoumarin [5].

The classical conditions of the Mannich reaction for hydroxy compounds based on benzopyran provide for the reaction of substrate, amine, and formaldehyde in alcohol with prolonged heating [6]. In our opinion, the use of substituted 1,1-diaminomethanes is more convenient for introducing an aminomethyl into a benzopyran system because the rate of such a reaction is high and side products are not formed.

According to the literature, the position *ortho* to the hydroxyl is most preferred for attack in a Mannich reaction for all phenolic derivatives. This is explained by the reaction mechanism, according to which a H-bond is formed first between the Mannich reagent and the substrate. This is followed by attack at the *ortho* position [6].

The C-aminomethylation reaction was performed by boiling 4-phenylcoumarins with substituted 1,1-diaminomethanes in absolute dioxane. The aminomethyl group occupies the 8-position of the coumarin system in the reaction of **1**-**4**. For **5** and **6**, it occupies the 6-position according to PMR spectroscopy results.

According to the experimental results, 7-hydroxy-4-phenylcoumarin (**1**) is the most active substrate in the aminomethylation reaction. The reaction occurs in 30-60 min. If 6-substituted 7-hydroxy-4-phenylcoumarins **2**-**4** are used, longer heating (2-4 h) is required. In our opinion, the fact that even longer heating (10-20 h) is required to carry out the Mannich reaction with 8-methyl-7-hydroxy-4-phenylcoumarin (**5**) proves that the 6-position is unreactive toward aminomethylation. The reactivity of the 6-position increases sharply if a OH is introduced in the 5-position. The reaction takes 1-3 h for 7-methyl-5-hydroxy-4-phenylcoumarin (**6**).

1) Institute of Bioorganic and Petroleum Chemistry, National Academy of Sciences, Ukraine, 02094, Kiev, ul. Murmanskaya, 1; 2) Taras Shevchenko Kiev National University, 01033, Kiev, ul. Vladimirskaya, 64. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 383-388, September-October, 2000. Original article submitted November 6, 2000.

0009-3130/00/3605-0485$25.00

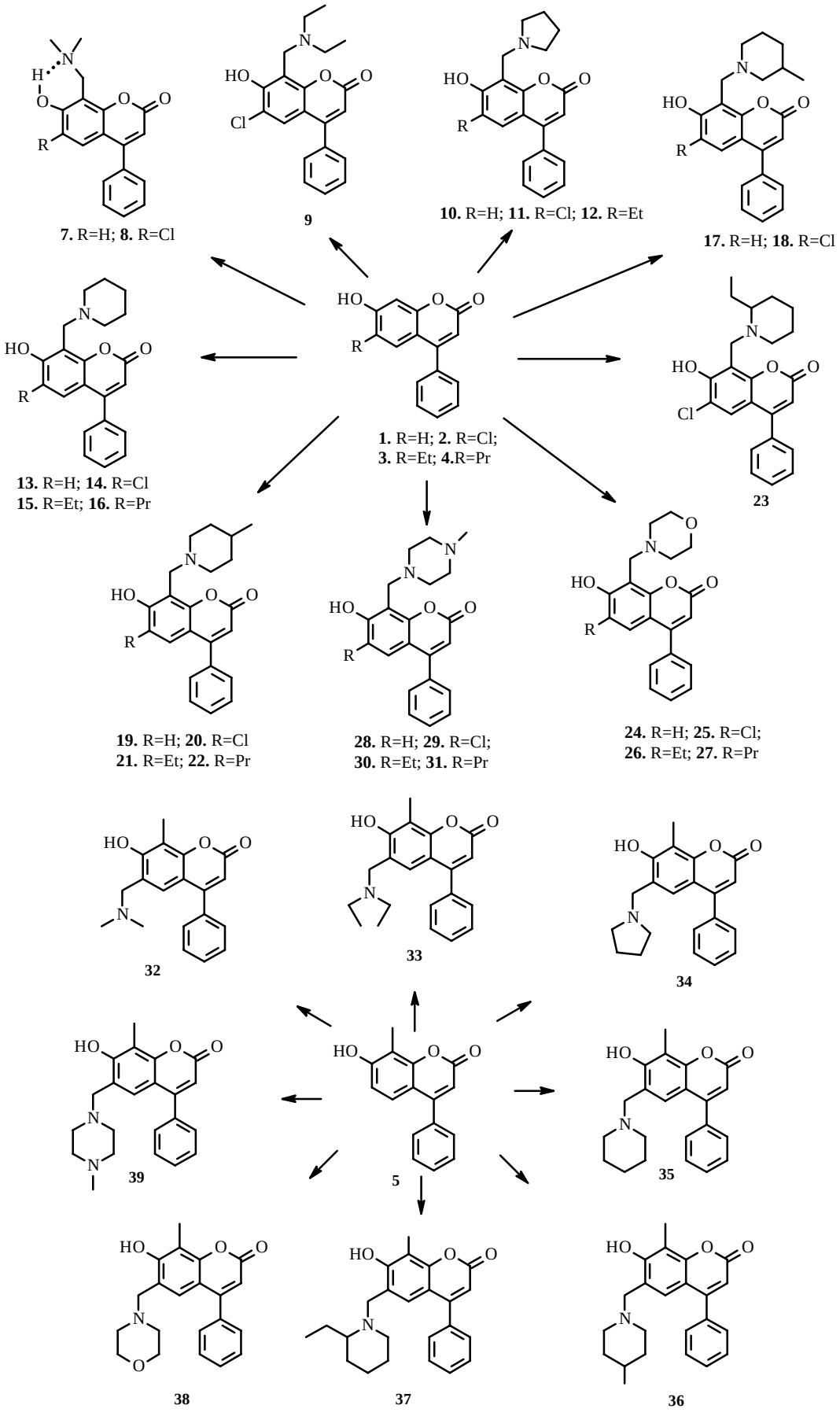

7. R=H; 8. R=Cl
9
10. R=H; 11. R=Cl; 12. R=Et
17. R=H; 18. R=Cl
13. R=H; 14. R=Cl
15. R=Et; 16. R=Pr
1. R=H; 2. R=Cl;
3. R=Et; 4.R=Pr
23
19. R=H; 20. R=Cl
21. R=Et; 22. R=Pr
28. R=H; 29. R=Cl;
30. R=Et; 31. R=Pr
24. R=H; 25. R=Cl;
26. R=Et; 27. R=Pr
32
33
34
39
5
35
38
37
36

TABLE 1. Properties of 8-Dialkylaminomethyl-4-phenylcoumarins **7-31**

Compound	Empirical formula	Yield, %	mp, °C	PMR spectrum, δ, ppm, SSCC (J, Hz), $CDCl_3$ solvent						
				coumarin ring protons						dialkylamino protons
				3-H, s	4-Ph, m	5-H, d, J = 8.0	6-H, d, J = 8.0	7-OH, s	8-CH_2, s	
7	$C_{18}H_{17}NO_3$	81	174	6.15	7.52	7.29	6.69	11.05	4.08	2.52 (6H, s, CH_3)
8	$C_{18}H_{16}ClNO_3$	88	229	6.14	7.50	7.39 (s)	-(Cl)	11.08	4.15	2.52 (6H, CH_3)
9	$C_{20}H_{20}ClNO_3$	72	177	6.11	7.50	7.37 (s)	-(Cl)	11.00	4.26	2.86 (4H, q, CH_2), 1.25 (6H, t, CH_3)
10	$C_{20}H_{19}NO_3$	74	156	6.07	7.48	7.24	6.67	10.99	4.25	2.78 (4H, m, CH_2), 1.91 (4H, m, CH_2)
11	$C_{20}H_{18}NO_3$	79	198	6.11	7.50	7.38 (s)	-(Cl)	9.00	4.33	2.93 (4H, m, CH_2), 2.00 (4H, m, CH_2)
12	$C_{22}H_{23}NO_3$	71	172	6.12	7.50	7.12 (s)	2.57 (q, 2H); 1.14 (t, 3H) (Et)	11.44	4.25	2.77 (4H, m, CH_2), 1.91 (4H, m, CH_2)
13	$C_{21}H_{21}NO_3$	82	178	6.12	7.47	7.23	6.66	9.57	4.08	2.63 (4H, m, CH_2), 1.64 (6H, m, CH_2)
14	$C_{21}H_{20}ClNO_3$	89	196	6.15	7.50	7.39 (s)	-(Cl)	11.43	4.19	2.80 (4H, m, CH_2), 1.78 (6H, m, CH_2)
15	$C_{23}H_{25}NO_3$	79	176	6.11	7.49	7.11 (s)	2.60 (q, 2H); 1.13 (t, 3H) (Et)	11.08	4.09	2.60 (4H, m, CH_2), 1.68 (6H, m, CH_2)
16	$C_{24}H_{27}NO_3$	64	118	6.12	7.50	7.09 (s)	2.54 (t, 2H); 1.53 (m, 3H); 0.92 (t, 3H) (Pr)	10.64	4.09	2.60 (4H, m, CH_2), 1.66 (6H, m, CH_2)
17	$C_{22}H_{23}NO_3$	69	131	6.15	7.51	7.28	6.68	10.10	4.04	3.09 (2H, m), 2.27 (2H, m), 1.1-1.8 (5H, m), 0.89 (3H, d)
18	$C_{22}H_{22}ClNO_3$	72	163	6.12	7.49	7.38 (s)	-(Cl)	10.30	4.19	3.06 (2H, m), 2.33 (2H, m), 1.1-1.8 (5H, m), 0.93 (3H, d)
19	$C_{22}H_{23}NO_3$	74	196	6.13	7.48	7.24	6.65	10.17	4.09	3.05 (2H, m), 2.27 (2H, m), 1.1-1.8 (5H, m), 0.95 (3H, d)
20	$C_{22}H_{22}ClNO_3$	76	204	6.12	7.50	7.37 (s)	-(Cl)	11.57	4.17	3.14 (2H, m), 2.42 (2H, m), 1.1-1.8 (5H, m), 0.98 (3H, d)
21	$C_{24}H_{27}NO_3$	68	128	6.12	7.50	7.10 (s)	2.57 (q, 2H); 1.13 (t, 3H) (Et)	9.30	4.10	3.05 (2H, m), 2.30 (2H, m), 1.1-1.8 (5H, m), 0.98 (3H, d)
22	$C_{25}H_{29}NO_3$	65	118	6.12	7.50	7.08 (s)	2.54 (t, 2H); 1.53 (m, 3H); 0.92 (t, 3H) (Pr)	9.83	4.09	3.02 (2H, m), 2.28 (2H, m), 1.1-1.8 (5H, m), 0.94 (3H, d)
23	$C_{23}H_{24}ClNO_3$	62	181	6.07	7.49	7.39 (s)	-(Cl)	12.00	4.14; 4.50*	3.20 (2H, m), 2.52 (1H, m), 1.4-2.0 (8H, m), 1.00 (3H, t)
24	$C_{20}H_{19}NO_4$	75	226	6.16	7.48	7.29	6.68	9.01	4.12	3.80 (4H, m, CH_2), 2.69 (4H, m, CH_2),
25	$C_{20}H_{18}ClNO_4$	79	217	6.20	7.50	7.39 (s)	-(Cl)	8.90	4.14	3.82 (4H, m, CH_2), 2.75 (4H, m, CH_2),
26	$C_{22}H_{23}NO_4$	71	156	6.14	7.50	7.14 (s)	2.58 (q, 2H); 1.13 (t, 3H) (Et)	7.90	4.13	3.80 (4H, m, CH_2), 2.69 (4H, m, CH_2),
27	$C_{23}H_{25}NO_4$	62	112	6.13	7.50	7.10 (s)	2.52 (t, 2H); 1.54 (m, 3H); 0.90 (t, 3H) (Pr)	9.20	4.09	3.80 (4H, m, CH_2), 2.68 (4H, m, CH_2),
28	$C_{21}H_{22}N_2O_3$	79	208	6.14	7.48	7.27	6.67	8.06	4.12	2.74 (4H, m), 2.59 (4H, m), 2.33 (3H, s)
29	$C_{21}H_{21}ClN_2O_3$	86	211	6.18	7.50	7.39 (s)	-(Cl)	7.90	4.16	2.78 (4H, m), 2.59 (4H, m), 2.34 (3H, s)
30	$C_{23}H_{26}N_2O_3$	73	129	6.13	7.50	7.13 (s)	2.59 (q, 2H); 1.13 (t, 3H) (Et)	8.40	4.13	2.70 (4H, m), 2.59 (4H, m), 2.33 (3H, s)
31	$C_{23}H_{26}N_2O_3$	75	113	6.13	7.50	7.10 (s)	2.53 (t, 2H); 1.55 (m, 3H); 0.92 (t, 3H) (Pr)	8.20	4.13	2.72 (4H, m), 2.53 (4H, m), 2.33 (3H, s)

*Protons of the methylene group are diastereotopic and resonate as two doublets with SSCC 15 Hz.

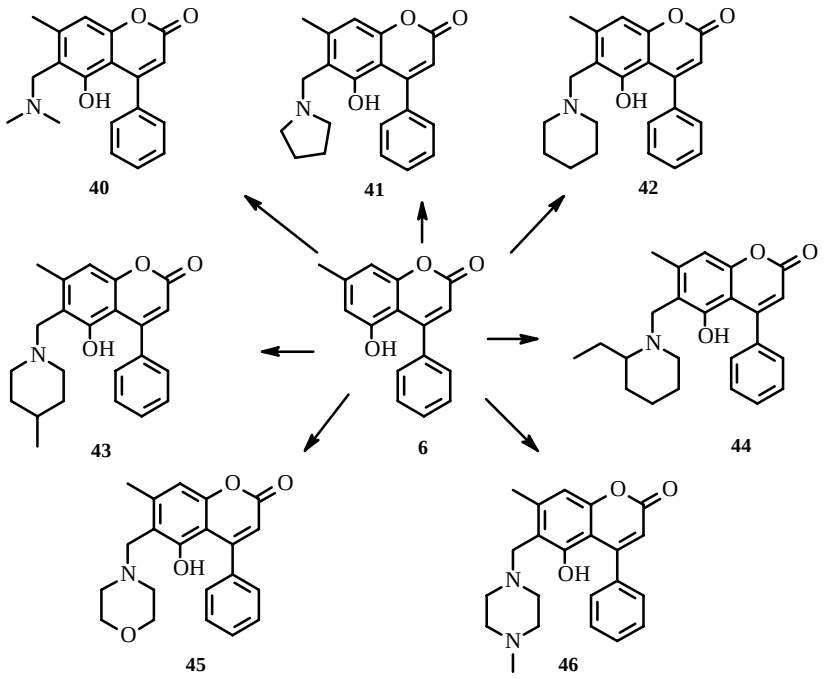
TABLE 2. Properties of 6-Dialkylaminomethyl-4-phenylcoumarins **32-46**

Compound	Empirical formula	Yield %	mp, °C	PMR spectrum, δ, ppm, SSCC (J, Hz), $CDCl_3$ solvent						
				coumarin ring protons						dialkylamino protons
				H-3, s	4-Ph, m	5-R, s	6-CH_2, s	7-R, s	8-R, s	
32	$C_{21}H_{21}NO_3$	83	156	6.13	7.48	6.90(H)	3.79	10.00(OH)	2.34(CH_3)	2.62 (4H, m, CH_2), 1.85 (4H, m, CH_2)
33	$C_{21}H_{23}NO_3$	64	122	6.14	7.48	6.90(H)	3.75	9.50(OH)	2.35(CH_3)	2.62 (4H, q, CH_2), 1.11 (6H, t, CH_3)
34	$C_{21}H_{21}NO_3$	69	143	6.13	7.48	6.90(H)	3.79	10.00(OH)	2.34(CH_3)	2.62 (4H, m, CH_2), 1.85 (4H, m, CH_2)
35	$C_{22}H_{23}NO_3$	72	154	6.13	7.48	6.89(H)	3.63	10.00(OH)	2.34(CH_3)	2.50 (4H, m, CH_2), 1.58 (6H, m, CH_2)
36	$C_{23}H_{25}NO_3$	70	135	6.13	7.48	6.90(H)	3.64	8.93(OH)	2.34(CH_3)	2.94 (2H, m), 2.10 (2H, m) , 1.1-1.8(5H, m), 0.95 (3H, d)
37	$C_{24}H_{27}NO_3$	61	148	6.12	7.47	6.88(H)	3.58; 4.12*	10.00(OH)	2.33(CH_3)	2.73 (2H, m), 2.28 (1H, m) , 1.1-1.8(8H, m), 0.85 (3H, t)
38	$C_{21}H_{21}NO_4$	75	173	6.15	7.48	6.93(H)	3.68	10.00(OH)	2.34(CH_3)	3.76 (4H, m, CH_2), 2.56 (4H, m, CH_2)
39	$C_{22}H_{24}N_2O_3$	86	158	6.15	7.48	6.93(H)	3.68	8.40(OH)	2.35(CH_3)	2.70 (4H, m), 2.59 (4H, m), 2.32 (3H, s)
40	$C_{19}H_{19}NO_3$	81	176	6.06	7.38	10.00(OH)	3.65	2.31(CH_3)	6.69(H)	2.35 (6H, CH_3)
41	$C_{21}H_{21}NO_3$	69	178	6.05	7.39	8.43(OH)	3.79	2.30(CH_3)	6.68(H)	2.59 (4H, m, CH_2), 1.78 (4H, m, CH_2)
42	$C_{22}H_{23}NO_3$	77	189	6.06	7.39	8.38(OH)	3.64	2.29(CH_3)	6.68(H)	2.47 (4H, m, CH_2), 1.53 (6H, m, CH_2)
43	$C_{23}H_{25}NO_3$	70	162	6.06	7.39	9.19(OH)	3.65	2.29(CH_3)	6.68(H)	2.88 (2H, m), 2.07 (2H, m), 1.1-1.8(5H, m), 0.91 (3H, d)
44	$C_{24}H_{27}NO_3$	61	151	6.06	7.37	8.80(OH)	3.55; 4.01*	2.28(CH_3)	6.66(H)	2.78 (2H, m), 2.30 (1H, m) , 1.1-1.8(8H, m), 0.86 (3H, t)
45	$C_{21}H_{21}NO_4$	84	207	6.07	7.39	8.90(OH)	3.68	2.31(CH_3)	6.72(H)	3.62 (4H, m, CH_2), 2.51 (4H, m, CH_2)
46	$C_{22}H_{24}N_2O_3$	88	192	6.06	7.38	9.20(OH)	3.67	2.27(CH_3)	6.69(H)	2.63 (4H, m), 2.45 (4H, m), 2.30 (3H, s)

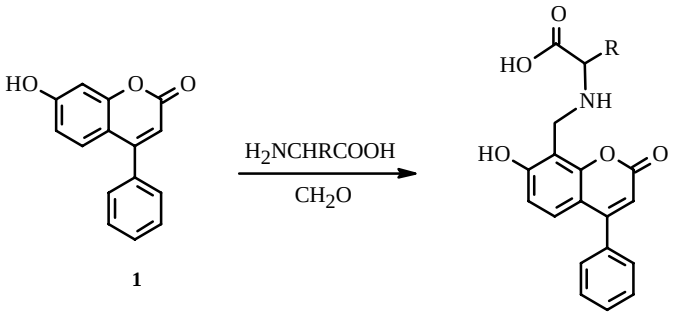
*Protons of the methylene group are diastereotopic and resonate as two doublets with SSCC 15 Hz.

Aminals of dimethylamine, diethylamine, pyrrolidine, piperidine, 2-ethylpiperidine, 3-methylpiperidine, 4-methylpiperidine, morpholine, and 1-methylpiperazine underwent the Mannich reaction. The most reactive of the 1,1-diaminomethanes was bis(dimethylamino)methane. Use of the other aminals requires longer heating.

The structures of the resulting Mannich bases were confirmed by quantitative elemental analysis and PMR spectroscopy. The PMR spectra of **7-31** lack signals at 6.7-6.8 ppm for H-8 of the coumarin system. The spectrum is simplified as a result. Protons in the 5- and 6-positions resonate as doublets with SSCC 8 Hz at 7.2 and 6.8 ppm, respectively (for compounds **7**, **10**, **13**, **17**, **19**, **24**, **28**). For compounds **8**, **9**, **11**, **12**, **14-16**, **18**, **20-23**, **25-27**, and **29-31**, which contain a substituent in the 6-position, H-5 resonates at 7.1-7.4 ppm as a 1H singlet. The spectra of compounds **32-46** lack a signal for H-6 of the benzopyran ring. Proton H-8 appears as a singlet at 6.6-6.7 ppm (for compounds **32-39**). For compounds **40-46**, H-5 is observed at 6.9 ppm. The spectra of compounds **7-46** also contain signals for a methylene at 4.1-4.2 ppm and signals characteristic for aminoalkyl substituents. It is interesting that the methylene protons in Mannich bases **23**, **37**, and **44** are diasterotopic and, therefore, appear as two doublets with SSCC 15 Hz. The hydroxyl protons of 7-OH and 5-OH resonate at weak field (9-11 ppm) because they are involved in an intramolecular H-bond with the N of the dialkylaminomethyl group. The properties of Mannich bases **7-46** are listed in Tables 1 and 2.



We also studied the Mannich reaction of 7-hydroxy-4-phenylcoumarin with amino acids and their derivatives. It was found that prolonged heating of a mixture of 7-hydroxy-4-phenylcoumarin, the corresponding amino acid, and an equivalent amount of formalin produces 7-hydroxy-8-(N-aminoacyl)methyl-4-phenylcoumarins (**47**-**53**). This reaction produced derivatives of alanine (**47**), 2-aminobutanoic acid (**48**), norvaline (**49**), leucine (**50**), isoleucine (**51**), norleucine (**52**), and phenylalanine (**53**).



1. $R_1=R_2=R_3=R_4=H$

2. $R_1=R_2=R_4=H$; $R_3=OH$

3. $R_1=H$; $R_2=R_3=OH$; $R_4=C_6H_5CO$

4. $R_1=R_4=H$; $R_2=R_3=OH$

5. $R_1=R_2=R_3=OH$; $R_4=H$

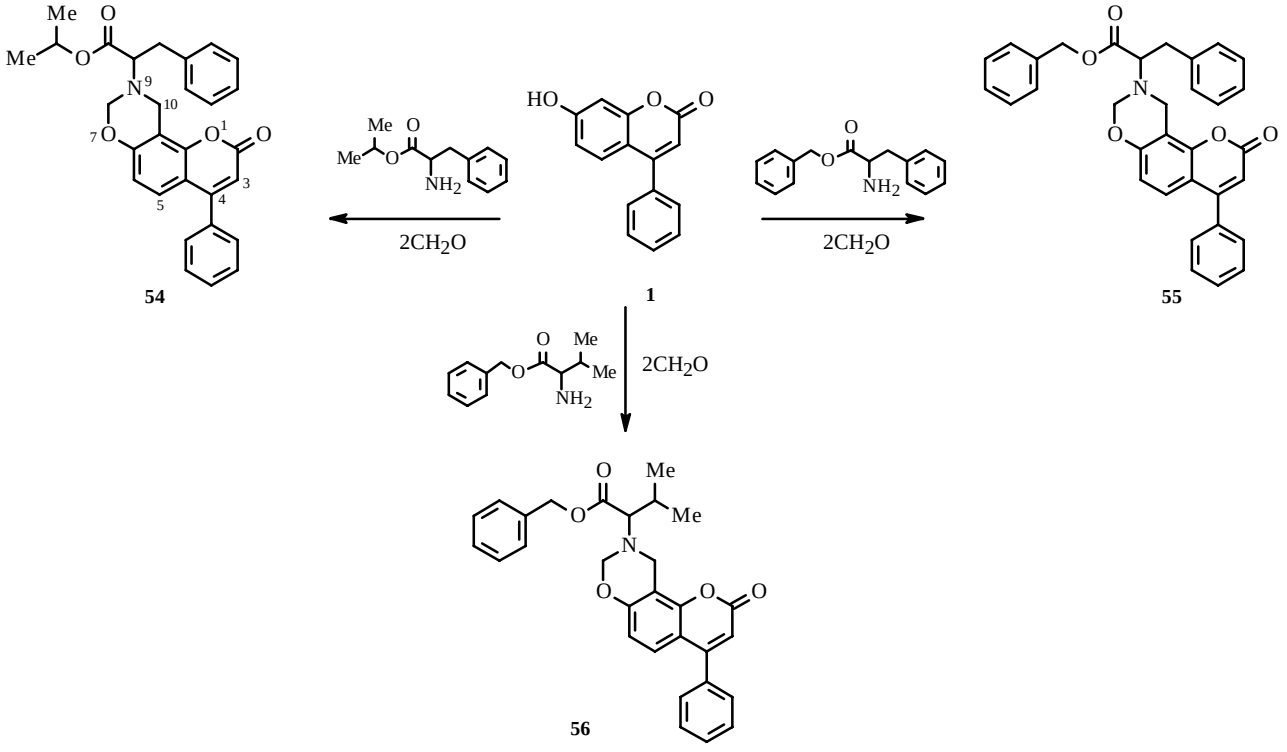
The structures of the resulting 8-aminoacylmethyl derivatives of 4-phenylcoumarin were confirmed by quantitative elemental analysis and PMR spectroscopy. The PMR spectra of compounds **47**-**53**, which were recorded in TFA, are simplified in the aromatic region of the coumarin system because coupling with H-8 is avoided. The aromatic protons H-5 and H-6 resonate as doublets with SSCC 9 Hz at 7.8 and 7.2 ppm, respectively. The PMR spectra of the resulting Mannich bases also exhibit signals for the amino acid. A 2H signal for the methylene appears at 5.0 ppm. The physicochemical properties of compounds **47**-**53** are listed in Table 3.

TABLE 3. Properties of 8-Aminoacylmethyl-7-hydroxy-4-phenylcoumarins **47-53**

Compound	Empirical formula	Yield, %	mp, °C	PMR spectrum, δ, ppm, TFA solvent						
				coumarin ring protons				CH_2, m	amino-acid fragment	
				H-3, s	Ph-4, m	H-5, d	H-6, d		CH, m	R
47	$C_{19}H_{17}NO_5$	49	305	6.61	7.50-7.60	778	7.20	4.91	4.42	$-CH_3$ 1.51
48	$C_{20}H_{19}NO_5$	61	287	6.61	7.52-7.62	7.82	7.19	4.98	4.45	$-CH_2$, $-CH_3$ 2.37; 1.26
49	$C_{21}H_{21}NO_5$	55	292	6.62	7.50-7.60	7.79	7.18	4.90	4.38	$-CH_2$ $-CH_2$ $-CH_3$ 2.29; 1.57; 1.25
50	$C_{22}H_{23}NO_5$	51	284	6.60	7.50-7.60	7.80	7.15	4.93	4.41	$-CH_2$ $-CH$ $-(CH_3)_2$ 2.31; 1.69; 1.21
51	$C_{22}H_{23}NO_5$	56	276	6.61	7.50-7.60	7.78	7.19	4.95	4.40	$-CH(CH_3)$ CH_2 $-CH_3$ 2.45; 1.25; 1.51; 1.19
52	$C_{22}H_{23}NO_5$	65	295	6.61	7.50-7.60	7.83	7.18	4.94	4.41	$-CH_2$ $-CH_2$ $-CH_2$ $-CH_3$ 2.36; 1.68; 1.39; 1.26
53	$C_{25}H_{21}NO_5$	72	288	6.60	7.50-7.60	7.75	7.18	4.87	4.47	$-CH_2$ -Ph 3.27; 7.20-7.30

It is known that several products are formed if primary amines are used in the Mannich reaction [6]. In particular, aminomethylation of 7-hydroxy-4-methylcoumarin by primary amines showed that different products are formed depending on the formaldehyde equivalent. If one equivalent is used, 7-hydroxy-8-aminomethyl-4-methylcoumarins is formed. For two equivalents, dihydrobenzoxazines are produced [7]. Dihydrobenzoxazines are known to be intermediates in the synthesis of bis-(2-hydroxybenzyl)amines and secondary Mannich bases [6]. It is also known that dihydrobenzoxazines based on coumarins are antifungal and antitumor agents [8].

Condensation of 7-hydroxy-4-phenylcoumarin, a double equivalent of formalin solution (35%) and valine benzyl ester, phenylalanine isopropyl ester, or phenylalanine benzyl ester in dioxane at 100°C produces dihydrooxazino[7,8-e]coumarins (**54-56**).



54 **1** **55** **56**

The structures of the resulting 4-phenyl-9,10-dihydro-2H,8H-chromeno[8,7-e][1,3]oxazin-2-ones were confirmed by quantitative elemental analysis and PMR spectroscopy. Thus, the PMR spectra of compounds **54-56** exhibit the following differences from the spectrum of the starting coumarin. Instead of signals for OH-7 and H-8 of the coumarin, the corresponding signals for the amino acid and methylenes of the dihydrooxazine ring appear at 4.3-4.5 and 4.7-5.0 ppm. It is interesting that the methylene protons are diastereotopic, appearing as two doublets with the corresponding constants.

EXPERIMENTAL

The course of the reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates. The eluents were mixtures of $CHCl_3$ and CH_3OH (9:1 and 95:5). PMR spectra were recorded on a Varian VXR-300 instrument in TFA and $CDCl_3$ (TMS internal standard).

Starting coumarins **1-6** were prepared according to the literature [5].

General Synthesis of Mannich Bases 7-46. A solution or suspension of coumarin **1-6** (4 mmol) in absolute dioxane (25-30 ml) was treated with the appropriate 1,1-diaminomethane (4.5 mmol). The reaction was heated (100°C) for 0.5-20 h (completion of the reaction was determined by TLC). The solvent was removed under vaccum when the reaction was completed. The solid or oil was crystallized from hexane—diethylether (1:1). Yields and properties of synthesized Mannich bases **7-46** are listed in Tables 1 and 2.

General Synthesis of 8-Aminoacylmethyl-7-hydroxy-4-phenylcoumarins 47-53. A warm solution of 7-hydroxy-4-phenylcoumarin (1.19 g, 5 mmol) in ethanol (30 ml) was treated with the appropriate amino acid (5 mmol) in water (20 ml) and formalin (35%, 0.45 ml, 5 mmol). The reaction mixture was heated (80-90°C) for 6-8 h. The resulting precipitate was filtered off and crystallized from ethanol (50%). Yields and properties of compounds **47-53** are listed in Table 3.

General Synthesis of Dihydrooxazino[7,8-e]coumarins 54-56. A suspension of the hydrochloride of the appropriate amino-acid alkyl ester (4 mmol) in absolute dioxane (20 ml) was cooled (0°C), stirred vigorously, and treated with freshly distilled triethylamine (0.56 ml, 5 mmol). The mixture was stirred for 30 min. The resulting precipitate (triethylammonium chloride) was filtered off. The filtrate was treated with formalin (35%, 0.72 ml, 8 mmol). The resulting mixture was held at room temperature, stirred for 4 h, treated with 7-hydroxy-4-phenylcoumarin (0.95 g, 4 mmol), and heated at 90-100°C for 1-2 h (completion of the reaction was determined by TLC). Dioxane was evaporated under vacuum. The oil was crystallized by treatment with diethylether—hexane (1:1).

2-(2-Oxo-4-phenyl-9,10-dihydro-2H,8H-chromeno[8,7-e][1,3]oxazin-9-yl)-3-phenylpropanoic acid isopropyl ester (54): Yield 69%, mp 111°C, $C_{29}H_{27}NO_5$. PMR spectrum (300 MHz, $CDCl_3$): 0.89, 1.06 (two doublets, J = 6.3 Hz, 6H, isopropyl methyls), 3.12 (d, J = 7.8 Hz, 2H, phenylalanine CH_2), 3.81 (t, 1H, phenylalanine CH), 4.41, 4.49 (two doublets, J = 17.4 Hz, 2H, CH_2-10), 4.76 (m, 1H, isopropyl CH), 5.00, 5.06 (two doublets, J = 12.9 Hz, 2H, CH_2-8), 6.21 (s, 1H, H-3), 6.68 (d, J = 9 Hz, 1H, H-6), 7.20 (m, 5H, phenylalanine phenyl), 7.26 (d, J = 9 Hz, 1H, H-5), 7.45 (m, 5H, Ph-4).

2-(2-Oxo-4-phenyl-9,10-dihydro-2H,8H-chromeno[8,7-e][1,3]oxazin-9-yl)-3-phenylpropanoic acid benzyl ester (55): Yield 76%, mp 104°C, $C_{33}H_{27}NO_5$. PMR spectrum (300 MHz, $CDCl_3$): 3.17 (m, 2H, phenylalanine CH_2), 3.91 (t, 1H, phenylalanine CH), 4.43, 4.51 (two doublets, J = 17.4 Hz, 2H, CH_2-10), 4.77, 4.83 (two doublets, J = 13 Hz, 2H, CH_2-8), 5.03 (s, 2H, benzyl CH_2), 6.18 (s, 1H, H-3), 6.66 (d, J = 8.4 Hz, 1H, H-6), 7.00-7.20 (m, 10H, benzyl and phenylalanine phenyls), 7.26 (d, J = 8.4 Hz, 1H, H-5), 7.45 (m, 5H, Ph-4).

3-Methyl-2-(2-oxo-4-phenyl-9,10-dihydro-2H,8H-chromeno[8,7-e][1,3]oxazin-9-yl)butanoic acid benzyl ester (56): Yield 73%, mp 133°C, $C_{29}H_{27}NO_5$. PMR spectrum (300 MHz, $CDCl_3$): 0.93, 1.06 (two doublets, J = 6.6 Hz, 6H, valine methyls), 2.27 (m, 1H, valine CH), 3.17 (d, J = 10.5 Hz, 1H, valine α-CH), 4.32, 4.49 (two doublets, J = 17.4 Hz, 2H, CH_2-10), 4.71, 4.87 (two doublets, J = 12.6 Hz, 2H, CH_2-8), 5.01 (s, 2H, benzyl CH_2), 6.15 (s, 1H, H-3), 6.64 (d, J = 9 Hz, 1H, H-6), 7.20 (m, 5H, benzyl phenyl), 7.25 (d, J = 9 Hz, 1H, H-5), 7.45 (m, 5H, Ph-4).

REFERENCES

1. LIPHA, D. Molho and E. Boschetti, Fr. Pat. No. 1,310,535, Nov. 30, 1962, Appl., July 28, 1961; *Chem. Abstr.*, **58**, 12517f (1963).

2. LIPHA, D. Molho, E. Boschetti, and L. Fortaine, Fr. Addn. 82,454 (Cl. A 67*k*, C07*d*), Feb. 21, 1964, Appl., May 21, 1962, 11 pp., Addn. to Fr. Pat. No. 1,310,535; *Chem. Abstr.*, **61**, 1837 (1964).
3. LIPHA, D. Molho, E. Boschetti, and L. Fontaine, Fr. M 2472 (Cl. A 67*k* C07*d*), May 19, 1964, Appl., Jun. 8, 1962; *Chem. Abstr.*, **61**, 11975b (1964).
4. E. Boschetti, D. Molho, J. Aknin, L. Fontaine, and M. Grand, *Chim. Ther.*, **7**, 403 (1966).
5. L. L. Woods and J. Sapp, *J. Org. Chem.*, **27**, No. 10, 3703 (1962).
6. M. Tramontini, *Synthesis*, **12**, 703 (1973).
7. R. B. Desai, *J. Org. Chem.*, **26**, 5251 (1961).
8. M. E. Kuehne (to CIBA Corp.), U.S. Pat. No. 3,142,676 (Cl. 260-244), Jul. 28, 1964, Appl., Jun. 14, 1961, 8 pp.; *Chem. Abstr.*, **61**, 8319e (1964).