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# AMINOMETHYLATION OF 3-ARYL-7-HYDROXYCOUMARINS

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*The reaction of the analogs of natural 3-arylbenzopyran-2-ones with electrophilic reagents of aminal structure was studied. Substituted 8-aminomethyl-3-aryl-7-hydroxycoumarins were synthesized. The optimum conditions were determined for the production of 9-alkyl- and 9-(het)arylmethyl derivatives of 3-aryl-9,10-dihydro-2H,8H-chromeno[8,7-e][1,3]oxazin-2-one in the series of analogs of natural 3-arylbenzopyran-2-ones.*

**Keywords**: 9,10-dihydro-2H,8H-chromeno[8,7-*e*][1,3]oxazin-2-one, coumarin, C- and O-aminomethylation, electrophilic substitution.

Coumarins, which are widely represented among compounds of vegetable origin, have a wide spectrum of pharmacological activity. More than 30 types of biological activity have been found in coumarins [1]. An advantage of products from vegetable raw material is the low toxicity and the possibility of prolonged use without risk of the appearance of side effects. In this connection the urgency of seeking new methods of introducing pharmacophoric groups into the molecules of natural compounds and their analogs is constantly increasing.

The introduction of a basic amino group, which is a structural feature of alkaloids, is one prospective method of modifying the compounds. While continuing research into the reactivity of the analogs of natural 3-arylbenzopyrones we studied electrophilic substitution in the series of 3-aryl-7-hydroxycoumarins for the case of the aminomethylation reaction, by means of which it is possible to obtain derivatives of aliphatic tertiary amines and their water-soluble salts.

The initial substituted 3-aryl-7-hydroxycoumarins **1a-d** were obtained under the conditions of the Perkin reaction by the condensation of substituted phenylacetic acids with 2,4-dihydroxybenzaldehyde or 2,4-dihydroxyacetophenone in acetic anhydride in the presence of potassium acetate as base [2-7] followed by deacylation of the acetoxy derivatives.

As known, the aminomethylation of 7-hydroxybenzopyran-2-ones takes place at position 8 of the coumarin ring [8-14] or at position 6 if position 8 is occupied [14, 15]. The presence of an electron-withdrawing heterocyclic substituent at position 3 of the benzopyran ring significantly reduces the reactivity of such compounds to the action of electrophilic reagents [9-11], whereas electron-donating groups can favor reaction in other directions [8, 16-18]. In this connection it was interesting to study features of the aminomethylation of the analogs of natural coumarins containing electron-donating alkoxy groups in the 3-aryl substituent.

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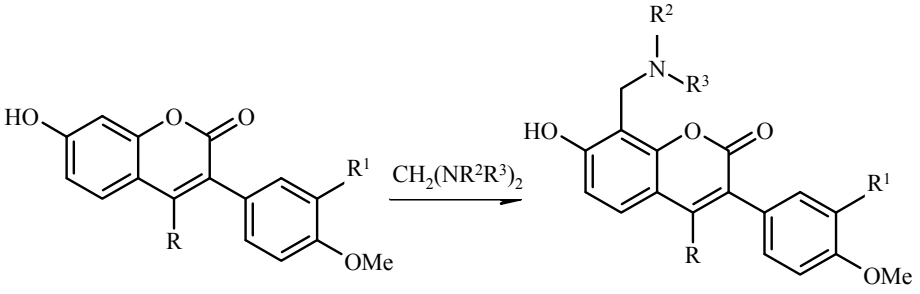
TABLE 1. The Characteristics of Amino Derivatives **2a-i** and **3a-i**

| Compound | Empirical formula | Found, % / Calculated, % | | | mp, °C | Yield, % |
|---|---|---|---|---|---|---|
| | | C | H | N | | |
| **2a** | $C_{19}H_{19}NO_5$ | 69.93 / 70.14 | 5.82 / 5.89 | 4.25 / 4.30 | 154-155 | 70 |
| **2b** | $C_{20}H_{21}NO_5$ | 67.90 / 67.59 | 6.03 / 5.96 | 3.98 / 3.94 | 142-143 | 75 |
| **2c** | $C_{21}H_{23}NO_4$ | 71.02 / 71.37 | 6.68 / 6.56 | 4.12 / 3.96 | 92-93 | 76 |
| **2d** | $C_{22}H_{25}NO_5$ | 69.12 / 68.91 | 6.46 / 6.57 | 3.76 / 3.65 | 139-140 | 70 |
| **2e** | $C_{22}H_{23}NO_6$ | 66.68 / 66.49 | 6.02 / 5.83 | 3.27 / 3.52 | 189-190 | 70 |
| **2f** | $C_{22}H_{23}NO_5$ | 69.12 / 69.28 | 5.84 / 6.08 | 3.28 / 3.67 | 193-195 | 78 |
| **2g** | $C_{23}H_{26}N_2O_4$ | 70.25 / 70.03 | 6.87 / 6.64 | 6.82 / 7.10 | 136-138 | 80 |
| **2h** | $C_{24}H_{28}N_2O_5$ | 68.12 / 67.91 | 6.81 / 6.65 | 6.54 / 6.60 | 163-165 | 85 |
| **2i** | $C_{25}H_{30}N_2O_6$ | 65.91 / 66.06 | 6.49 / 6.65 | 6.27 / 6.16 | 100-101 | 82 |
| **3a** | $C_{27}H_{25}NO_4$ | 76.92 / 75.86 | 6.00 / 5.89 | 3.12 / 3.28 | 129-130 | 75 |
| **3b** | $C_{27}H_{25}NO_6$ | 70.43 / 70.58 | 5.56 / 5.48 | 3.32 / 3.05 | 157-158 | 84 |
| **3c** | $C_{24}H_{20}N_2O_4$ | 72.22 / 71.99 | 5.12 / 5.03 | 6.84 / 7.00 | 161-162 | 78 |
| **3d** | $C_{22}H_{21}NO_6S$ | 62.03 / 61.81 | 4.98 / 4.95 | 3.18 / 3.28 | 233-234 | 68 |
| **3e** | $C_{27}H_{25}NO_6$ | 70.42 / 70.58 | 5.55 / 5.48 | 2.95 / 3.05 | 151-152 | 78 |
| **3f** | $C_{25}H_{22}NO_6$ | 69.48 / 69.76 | 5.31 / 5.15 | 6.62 / 6.51 | 166-167 | 80 |
| **3g** | $C_{23}H_{23}NO_5$ | 69.98 / 70.22 | 5.97 / 5.89 | 3.40 / 3.56 | 228-230 | 65 |
| **3h** | $C_{25}H_{23}NO_6$ | 68.93 / 69.27 | 5.45 / 5.35 | 3.34 / 3.23 | 159-160 | 70 |
| **3i** | $C_{26}H_{30}N_2O_6$ | 67.15 / 66.94 | 6.39 / 6.48 | 5.82 / 6.00 | 133-134 | 67 |

In consideration of the results of previous investigations of the aminomethylation of coumarin derivatives [8-11] the synthesis of the Mannich bases was realized by the action of the aminals of secondary amines on the 3-aryl-7-hydroxycoumarins **1a-d**.




**1a–d** **2a–i**

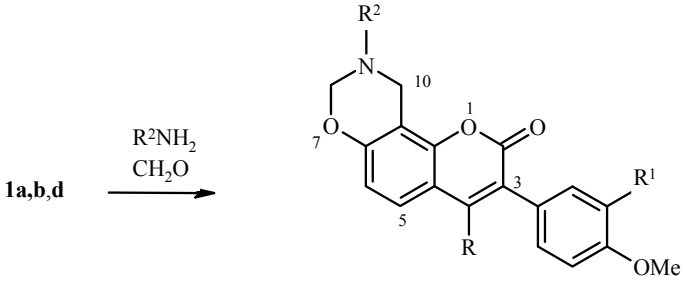
**1a** R = $R^1$ = H, **b** R = H, $R^1$ = OMe; **c** R = Me, $R^1$ = H, **d** R = Me, $R^1$ = OMe; **2a**,**c**,**g** R = $R^1$ = H;
**b**,**d**,**e**,**h** R = H, $R^1$ = OMe, **f** R = Me, $R^1$ = H, **i** R = Me, $R^1$ = OMe; **a**,**b** $R^2$ = $R^3$ = Me;
**c**,**d** $R^2$ = $R^3$ = Et; **e**,**f** $NR^2R^3$ = morpholin-4-yl, **g**,**h** $NR^2R^3$ = 4-ethylpiperazin-4-yl;
**i** $NR^2R^3$ = 4-(3-(2-hydroxyethyl)piperazin-4-yl

As we expected the 3-aryl substituent with the electron-donating methoxy groups significantly increases the reactivity of the coumarin ring to electrophilic attack. Whereas in the case of 3-hetarylcoumarins the introduction of the aminomethyl group requires heating of the reaction mixture for 8-10 h, the reaction of 3-aryl-7-hydroxycoumarins **1a-d** with aminals takes 1-2 h, and the yields of the Mannich bases **2a-i** here amount to 70-85%.

In the $^1$H NMR spectra of the synthesized compounds **2a-i**, unlike the $^1$H NMR spectra of the initial 7-hydroxycoumarins **1a-d**, singlets appear in the region of 4.04-4.15 ppm, corresponding to the signals of the protons of the methylene unit, and there are also signals for the protons of the amine fragment. It should be noted that on account of rapid exchange in most cases it was not possible to determine the exact position of the signals for the protons of the phenolic hydroxyl groups of the aminomethyl derivatives of the coumarin series.

It is known that under the conditions of the Mannich reaction with the substrate, amine, and formaldehyde in the appropriate ratios various products can be formed, including derivatives of 3,4-dihydro-1,3-benzoxazines [8]. If equivalent amounts of the primary amine and 7-hydroxycoumarin are used with a twofold excess of potassium hydroxide as catalyst dihydropyranobenzoxazines are formed as a result of electrophilic substitution [19-22]. The annelation of the oxazine ring to a coumarin ring by the reaction of previously synthesized N,N-bis(hydroxymethyl)amines with hydroxycoumarins in the presence of N,N-dimethylaminopyridine (DMAP) [23] and also by the cyclization of aminomethyl derivatives of 7-hydroxybenzopyran-2-ones by the action of formalin has been described [19].

In view of the results of the previous investigations we studied the reaction of 3-aryl-7-hydroxycoumarins **1a-d** with primary aliphatic amines and formalin. As it turned out the reaction takes place with satisfactory yields when the reaction mixture is heated in 2-propanol in the presence of a catalytic amount of DMAP without the previous production of the N,N-bis(hydroxymethyl)amines. As a result of the simultaneous C- and O-aminomethylation of the benzopyran-2-one ring we synthesized derivatives of 9,10-dihydro-2H,8H-chromeno[8,7-*e*][1,3]oxazin-2-one **3a-i**, containing benzyl, alkyl, or heterylalkyl substituents at position 9.




**3a–i**

**3a–d** R = $R^1$ = H, **a** $R^2$ = $(CH_2)_3Ph$, **b** $R^2$ = $CH_2C_6H_3(OMe)_2$-3,4, **c** $R^2$ = 4-picolyl,
**d** $R^2$ = sulfolan-3-yl; **e**,**f** R = H, $R^1$ = OMe, **e** $R^2$ = $CH_2C_6H_4OMe$-4,
**f** $R^2$ = 3-picolyl; **g–i** R = Me, $R^1$ = OMe, **g** $R^2$ = cyclopropyl,
**h** $R^2$ = 2-furanylmethyl, **i** $R^2$ = 2-(morpholin-4-yl)ethyl

The structure of the synthesized derivatives **3a-i** was confirmed by the data from NMR spectroscopy. Thus, in the $^1$H NMR spectra the signal for the H-8 proton of the coumarin ring disappears, and signals for the methylene groups 10-$CH_2$ and 8-$CH_2$ in the regions of 4.21-4.28 and 4.93-5.07 ppm and, accordingly, signals for the protons of the amine residue appear. This assignment of the signals was made on the basis of correlation of the chemical shifts of the protons of the 8-aminomethyl group in the derivatives **2a-i** and the 10-$CH_2$ group in compounds **3a-i**.

TABLE 2. The $^1$H NMR Spectra of 8-Aminomethyl-3-aryl-4H-chromen-2-ones **2a-i** ($CDCl_3$, δ, pp, *J*, Hz)

| Compound | Chemical shifts **2a–i** ($CDCl_3$), δ, ppm (*J*, Hz) | | | | | |
|---|---|---|---|---|---|---|
| | Protons of chromone fragment | | | | 3-Ar | Protons of amine residue |
| | R-4 (s) | H-5 (1H, d, $^3J$ = 8.7) | H-6 (1H, d, $^3J$ = 8.7) | 8-$CH_2$ (2H, s) | | |
| **2a** | 7.68 (1H) | 7.31 | 6.78 | 4.05 | 3.84 (3H, s); 6.97 (2H, d, $^3J$ = 9.0); 7.63 (2H, d, $^3J$ = 9.0) | 2.42 (6H, s) |
| **2b** | 7.70 (1H) | 7.33 | 6.78 | 4.05 | 3.92, 3.94 (6H, 2s); 6.93 (1H, d, $^3J$ = 8.3); 7.24 (1H, dd, $^4J$ = 2.1, $^3J$ = 8.3); 7.27 (1H, d, $^4J$ = 2.1) | 2.41 (6H, s) |
| **2c** | 7.68 (1H) | 7.30 | 6.74 | 4.15 | 3.85 (3H, s); 6.96 (2H, d, $^3J$ = 9.0); 7.64 (2H, d, $^3J$ = 9.0) | 1.17 (6H, t, $^3J$ = 7.6); 2.72 (4H, q, $^3J$ = 7.6) |
| **2d** | 7.71 (1H) | 7.31 | 6.75 | 4.15 | 3.92, 3.94 (6H, 2s); 6.93 (1H, d, $^3J$ = 8.3); 7.24 (1H, dd, $^4J$ = 2.1, $^3J$ = 8.3); 7.27 (1H, d, $^4J$ = 2.1) | 1.17 (6H, t, $^3J$ = 7.6); 2.72 (4H, q, $^3J$ = 7.6) |
| **2e** | 7.70 (1H) | 7.35 | 6.80 | 4.11 | 3.92, 3.94 (6H, 2s); 6.93 (1H, d, $^3J$ = 8.3); 7.24 (1H, dd, $^4J$ = 2.1, $^3J$ = 8.3); 7.27 (1H, d, $^4J$ = 2.1) | 2.70 (4H, m); 3.80 (4H, m) |
| **2f** | 2.27 (3H) | 7.49 | 6.80 | 4.11 | 3.85 (3H, s); 6.98 (2H, d, $^3J$ = 9.0); 7.22 (2H, d, $^3J$ = 9.0) | 2.68 (4H, m); 3.79 (4H, m) |
| **2g** | 7.68 (1H) | 7.31 | 6.76 | 4.11 | 3.85 (3H, s); 6.97 (2H, d, $^3J$ = 9, H-3',5'); 7.63 (2H, d, $^3J$ = 9, H-2',6') | 1.10 (3H, t, $^3J$ = 7.6); 2.46 (2H, q, $^3J$ = 7.6); 2.00-3.20 (8H, m) |
| **2h** | 7.70 (1H) | 7.33 | 6.77 | 4.11 | 3.92, 3.94 (6H, 2s); 6.93 (1H, d, $^3J$ = 8.3); 7.24 (1H, dd, $^4J$ = 2.1, $^3J$ = 8.3); 7.27 (1H, d, $^4J$ = 2.1) | 1.10 (3H, t, $^3J$ = 7.6); 2.46 (2H, q, $^3J$ = 7.6); 2.00-3.20 (8H, m) |
| **2i** | 2.28 (3H) | 7.49 | 6.79 | 4.13 | 3.88, 3.93 (6H, 2s); 6.81 (1H, d, $^4J$ = 2.1); 6.83 (1H, dd, $^4J$ = 2.1, $^3J$ = 8.3); 6.95 (1H, d, $^3J$ = 8.3) | 2.30-3.10 (8H, m); 2.60 (2H, t, $^3J$ = 5.0); 3.65 (2H, t, $^3J$ = 5.0) |

TABLE 3. The $^1$H NMR Spectra of 9,10-Dihydro-2H,8H-chromeno[8,7-*e*][1,3]oxazin-2-ones **3a-i**

| Compound | Chemical shifts ($CDCl_3$), δ, ppm (*J*, Hz) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Protons of heterocyclic fragment | | | | | 3-Ar | N(9) substituent |
| | R-4 (s) | H-5 (1H, d, $^3J$ = 8.7) | H-6 (1H, d, $^3J$ = 8.7) | 8-$CH_2$ (2H) | 10-$CH_2$ (2H) | | |
| **3a** | 7.68 (1H) | 7.34 | 6.74 | 4.94 (s) | 4.22 (s) | 3.85 (3H, s, 4'-$OCH_3$); 6.97 (2H, d, $^3J$ = 9.0); 7.64 (2H, d, $^3J$ = 9.0) | 1.91 (2H, m); 2.69 (2H, m); 2.76 (2H, m); 7.14-7.32 (5H, m) |
| **3b** | 7.69 (1H) | 7.31 | 6.79 | 4.93 (s) | 4.23 (s) | 3.84 (3H, s); 6.96 (2H, d, $^3J$ = 9.0); 7.63 (2H, d, $^3J$ = 9.0) | 3.85 (2H, s); 3.89, 3.90 (6H, 2s); 6.84-6.96 (3H, m) |
| **3c** | 7.69 (1H) | 7.33 | 6.80 | 4.95 (s) | 4.21 (s) | 3.84 (3H, s); 6.96 (2H, m); 7.63 (2H, m) | 3.95 (2H, s); 7.33 (2H, m); 8.60 (2H, m) |
| **3d** | 8.13 (1H) | 7.54 | 6.83 | 5.03, 5.11 (2d, $^2J$ = 10.6) | 4.19, 4.28 (2d, $^2J$ = 13.5) | 3.80 (3H, s); 7.02 (2H, d, $^3J$ = 9.0); 7.66 (2H, d, $^3J$ = 9.0) | 2.13, 2.38 (2H, 2m); 3.10, 3.34 (4H, 2m); 3.72 (1H, m) |
| **3e** | 7.71 (1H) | 7.32 | 6.80 | 4.93 (s) | 4.22 (s) | 3.92, 3.94 (6H, 2s, 3'- and 4'-$OCH_3$); 6.93 (1H, d, $^3J$ = 8.3); 7.24 (1H, d. d, $^4J$ = 2.1, $^3J$ = 8.3); 7.27 (1H, d, $^4J$ = 2.1) | 3.82 (3H, s); 3.86 (2H, s); 6.88 (2H, d, $^3J$ = 8.5); 7.28 (2H, d, $^3J$ = 8.5) |
| **3f** | 7.72 (1H) | 7.34 | 6.82 | 4.94 (s) | 4.22 (s) | 3.92, 3.94 (6H, 2s, 3'- and 4'-$OCH_3$); 6.93 (1H, d, $^3J$ = 8.3); 7.23 (1H, m); 7.25 (1H, m) | 3.95 (2H, s); 7.31 (1H, m); 7.76 (1H, m); 8.58 (2H, m) |
| **3g** | 2.30 (3H) | 7.47 | 6.83 | 4.97 (s) | 4.31 (s) | 3.89, 3.93 (6H, 2s); 6.81, 6.58 (2H, m); 6.95 (1H, d, $^3J$ = 8.3) | 0.60 (4H, m); 2.35 (1H, m) |
| **3h** | 2.29 (3H) | 7.47 | 6.85 | 4.96 (s) | 4.26 (s) | 3.88, 3.92 (6H, 2s, 3'- and 4'-$OCH_3$); 6.81 (1H, m); 6.83 (1H, m); 6.95 (1H, d, $^3J$ = 8.3) | 3.92 (2H, s); 6.28, 6.35, 7.42 (3H, 3m) |
| **3i** | 2.29 (3H) | 7.45 | 6.81 | 4.98 (s) | 4.27 (s) | 3.89, 3.93 (6H, 2s, 3'- and 4'-$OCH_3$); 6.81 (1H, d, $^4J$ = 2.1); 6.83 (1H, d. d, $^4J$ = 2.1, $^3J$ = 8.3); 6.95 (1H, d, $^3J$ = 8.3) | 2.60, 2.91 (4H, 2m); 2.48 (4H, m); 3.71 (4H, m) |

Thus, we have studied electrophilic substitution in the series of 3-aryl-7-hydroxybenzopyran-2-ones by the action of reagents with aminal structure. It was shown that the methoxylated 3-arylcoumarins are more active than the 3-hetaryl-7-hydroxycoumarins to the action of aminals. The presence of the electron-donating substituent at position 3 of the benzopyrone ring favors simultaneous C- and O-aminomethylation with the formation of the 1,3-oxazine ring.

## EXPERIMENTAL

The $^1$H NMR spectra were measured on a Varian VXR-300 instrument (300 MHz) in $CDCl_3$ with TMS as internal standard. The reactions and the purity of the products were monitored by TLC on Sorbfil UV-254 (Russia) and Merck (Germany) plates. The eluents were 9:1 and 95:1 mixtures of toluene and ethanol.

**Synthesis of Compounds 2a-i (General Method)**. The aminal (2.1-2.2 mmol) was added to a hot solution of the respective 3-aryl-7-hydroxycoumarin **1a-d** (2 mmol) in absolute dioxane (10 ml). The reaction mixture was boiled for 1-2 h (the end of the reaction was determined by TLC) and cooled. The dioxane, the amine that was released, and the unreacted aminal were evaporated under vacuum. The residue was crystallized from hexane.

**Synthesis of the Derivatives 3a-i (General Method)**. The primary amine (2.2 mmol), formalin (1.2 ml), and DMAP (5 ml) were added to a hot solution of of the respective 3-aryl-7-hydroxycoumarin **1a**,**b**,**d** (2 mmol) in 2-propanol (20 ml). The reaction mixture was boiled for 2-8 h (the end of the reaction was determined by TLC) and cooled, and the solution was evaporated under vacuum. The residue was crystallized from a mixture of 2-propanol and hexane.

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