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SYNTHESIS OF 6-ALKYL-2-DIALKYLAMINOMETHYL-7-HYDROXY-3-(4-METHYLTHIAZOL-2-YL)-4*H*-CHROMEN-4-ONES

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Amination of 6-alkyl-2-chloromethyl-7-hydroxy-3-(4-methylthiazol-2-yl)-4H-chromen-4-ones by secondary cyclic amines gives the corresponding 2-dialkylaminomethyl derivatives.

Keywords: 2-dialkylaminomethyl-3-thiazolylchromones, 2-chloromethyl-3-thiazolylchromones.

The modification of flavonoid molecules by the introduction of aminomethyl groups is one of the promising routes in the chemistry of this class of compounds. Mannich bases are readily formed by the direct aminomethylation of chromones or *via* amination of a corresponding halomethyl group. They are generally soluble in water after conversion to the quaternary ammonium salts, have high biological activity, and can serve as starting materials in the preparation of other classes of heterocyclic compounds [1].

By direct aminomethylation (using aminals) of a series of 3-hetarylchromones, we have obtained *N*-substituted aminomethyl derivatives at the positions 6 and 8 of the chromone system for isoxazole [2], pyrazole [3], thiazole [4], benzothiazole [5], benzimidazole [6], or triazole [7] analogs. Several of these show hypoglycemic, analeptic, antimicrobial, or anti-inflammatory activity.

2-Aminomethyl-3-hetaryl chromones were unknown to this time.

Analysis of literature data has shown that *N*-substituted 2-aminoalkylchromones prepared *via* amination of 2-halomethylchromones are antiblastic and immunosuppressive agents [8], active CNS stimulants [9]. They are α-adrenoceptor blockers [10], selective σ-ligands, and can be used in the treatment of psychoses [11, 12].

Derivatives of isoflavone thiazole analogs also are promising medicinal substances with a set of useful properties (analeptic, hypoglycemic, hypolipidemic, cytoprotective, anti-inflammatory, and diuretic activity) [4, 13-18].

The aim of this study was the synthesis of 2-dialkylaminomethyl-7-hydroxy-3-(4-methylthiazol-2-yl)-chromones by the amination of the corresponding 2-chloromethyl derivatives with secondary cyclic amines.

In this work, 5-alkyl-2,4-dihydroxy-α-(4-methylthiazol-2-yl)acetophenones **1a**,**b** [19] were treated at room temperature or with heating with an excess of chloroacetic acid anhydride or chloroacetyl chloride in dioxane or acetonitrile in the presence of an organic base (pyridine or triethylamine). In selecting optimal conditions for the preparation of the 6-alkyl-7-chloroacetoxy-2-chloromethyl-3-(4-methylthiazol-2-yl)chromones **2a**,**b** we were guided by such criteria as product purity, yield, and simplicity of performing the synthesis. The choice of solvent

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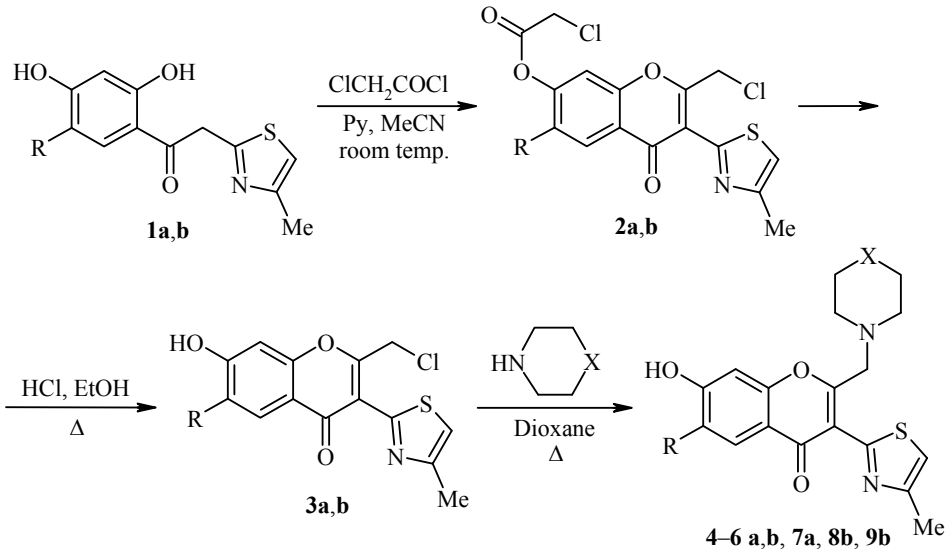
proved to be important. When the reaction of compounds **1a**,**b** with chloroacetyl chloride occurred in acetonitrile unlike in dioxane, the chromones **2a**,**b** precipitated along with pyridine hydrochloride (which could be readily removed by treating the precipitate with water). The compounds **2a**,**b** thus obtained were chromatographically pure. When compounds **1a**,**b** were acylated using chloroacetic acid anhydride in acetonitrile, or the reaction was performed in dioxane, the chromones **2a**,**b** did not precipitate from the reaction mixture. Preparation of these compounds in a pure state needed more prolonged isolation process (evaporation of solvent and treatment with water) and recrystallization. Variation of the base and heating the reaction mixture on a water bath for 2 h did not give an increased yield of compounds **2a**,**b**. Hence the best results for the synthesis of chromones **2a**,**b** were obtained when carrying out the reaction in acetonitrile at room temperature with an acetophenone–chloroacetyl chloride–pyridine ratio of 1:3:3.



The ^{1}H NMR spectra of compounds **2a**,**b** were characterized by two singlets for the methylene protons of the 7-chloroacetoxy group at 4.64-4.68 ppm and the 2-CH_2Cl group at 5.55-5.56 ppm. The IR spectra of these compounds showed C=O stretching absorption bands for the chromone ring at 1639 cm^{-1} and for the acyloxy group at 1778 (compound **2a**) or 1749 cm^{-1} (compound **2b**).

It should be noted that the 7-chloroacetoxy group in compounds **2a**,**b** is quite labile. Washing the precipitated chromones **2a**,**b** with water results in partial hydrolysis (indicated by ^{1}H NMR data for these compounds). The 2-chloromethyl-7-hydroxychromones **3a**,**b** were prepared by refluxing compounds **2a**,**b** in ethanol in the presence of hydrochloric acid. The ^{1}H NMR spectra of compounds **3a**,**b** show the absence of the methylene group singlet at 4.64-4.68 ppm and the appearance of a singlet for the 7-OH proton at 10.72-10.90 ppm.

The reaction of the 2-chloromethylchromones **3a**,**b** with a twofold excess of secondary cyclic amines (morpholine, piperidine and its 4-benzyl derivative, and *N*-alkyl(aryl)piperazines) in dioxane gives the 2-dialkylaminomethyl-7-hydroxy-3-(4-methylthiazol-2-yl)chromones **4-9** in high yields. Compounds **4-9** are colorless crystalline substances, insoluble in water and a 5% hydrochloric acid solution, but soluble in a 5% alkali solution and polar solvents. The structure and composition of compounds **4-9** were proved using spectroscopic methods and elemental analysis (Table 1). In their IR spectra, the C=O stretching vibrations for

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds **2b**, **3b**, **4a**,**b**, **5a**,**b**, **6a**,**b**, **7a**, **8b**, **9b**

Compound	Empirical formula	Found, % / Calculated, %				Mp, °C	Yield, %	R_f
		C	H	N	S			
2b	$C_{19}H_{17}Cl_2NO_4S$	53.67 / 53.53	4.32 / 4.02	3.27 / 3.29	7.52 / 7.52	141-142	55	0.94
3b	$C_{17}H_{16}ClNO_3S$	58.03 / 58.37	4.90 / 4.61	4.27 / 4.00	9.00 / 9.17	209-210	79	0.87
4a	$C_{20}H_{22}N_2O_4S$	61.90 / 62.16	5.45 / 5.74	7.02 / 7.25	8.08 / 8.30	140-141	81	0.68
4b	$C_{21}H_{24}N_2O_4S$	62.76 / 62.98	6.16 / 6.04	7.22 / 6.99	8.02 / 8.01	149-150	65	0.63
5a	$C_{21}H_{24}N_2O_3S$	65.37 / 65.60	6.53 / 6.29	7.51 / 7.29	8.21 / 8.34	174-175	84	0.46
5b	$C_{22}H_{26}N_2O_3S$	66.46 / 66.31	6.85 / 6.58	6.82 / 7.03	7.96 / 8.05	162-163	63	0.44
6a	$C_{28}H_{30}N_2O_3S$	70.66 / 70.86	6.33 / 6.37	6.09 / 5.90	6.78 / 6.76	219-220	79	0.76
6b	$C_{29}H_{32}N_2O_3S$	71.42 / 71.28	6.89 / 6.60	5.71 / 5.73	6.48 / 6.56	207-208	82	0.78
7a	$C_{21}H_{25}N_3O_3S$	62.79 / 63.13	6.60 / 6.31	10.52 / 10.52	8.05 / 8.03	132-133	84	0.32
8b	$C_{29}H_{31}N_3O_5S$	65.53 / 65.27	5.97 / 5.86	8.10 / 7.87	6.30 / 6.01	191-192	58	0.71
9b	$C_{27}H_{28}FN_3O_3S$	65.48 / 65.70	5.96 / 5.72	8.69 / 8.51	6.38 / 6.50	179-180	64	0.75

the chromone carbonyl are observed at 1639-1636 cm^{-1}. A characteristic feature of the ^1H NMR spectra of these compounds is a marked upfield shift by 1.4 ppm of the position 2 aminomethyl group, and also the presence of proton signals for the groups or fragments at the tertiary nitrogen atom. Signals for the chromone ring, thiazole substituent, and 7-OH group protons (10.56-10.72 ppm) are observed in the same regions as in the starting 2-chloromethyl derivatives **3a,b** (Table 2).

The ^1H NMR spectra of compounds **6a,b** proved less easy to interpret. For a reliable signal assignment in the spectrum of compound **6b** its COSY-90 spectrum was recorded. The correlations discovered and the corresponding chemical shift values are given in Figure 1.

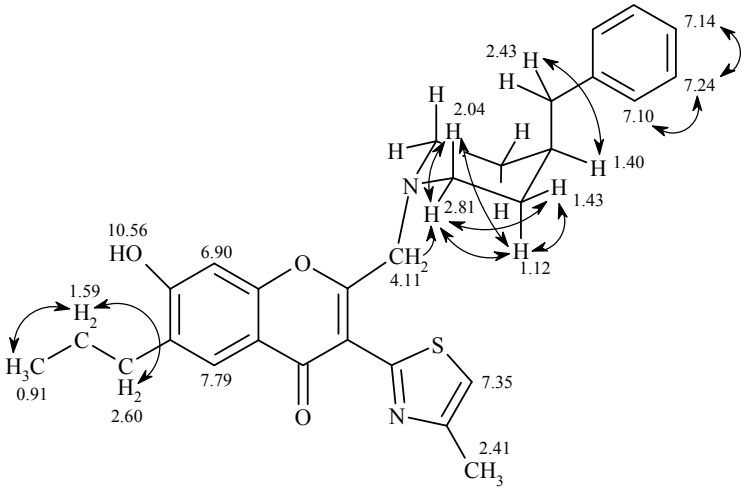


Fig. 1. Correlations observed in the COSY spectrum (↔) of compound **6b**. The NOE correlation (→) is also shown for the piperidine fragment protons with additional irradiation at the frequency of the 2-methylene group signal.

TABLE 2. Spectroscopic Characteristics of Compounds **2b**, **3b**, **4a**,**b**, **5a**,**b**, **6a**,**b**, **7a**, **8b**, **9b**

Com-pound	IR spectrum, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)
2b	1639*, 1749*[2]	0.98 (3H, t, *J* = 7.2, $C\underline{H}_3CH_2CH_2$); 1.65 (2H, sextet, *J* = 7.2, $CH_3C\underline{H}_2CH_2$); 2.52 (3H, s, 4'-CH_3); 2.66 (2H, t, *J* = 7.2, $CH_3CH_2C\underline{H}_2$); 4.64 (2H, s, $COCH_2Cl$); 5.55 (2H, s, 2-CH_2Cl); 7.29 (1H, s, H-5'); 7.62 (1H, s, H-8); 8.09 (1H, s, H-5)
3b	1611*[3]	0.97 (3H, t, *J* = 7.2, $C\underline{H}_3CH_2CH_2$); 1.65 (2H, sextet, *J* = 7.2, $CH_3C\underline{H}_2CH_2$); 2.53 (3H, s, 4'-CH_3); 2.62 (2H, t, *J* = 7.2, $CH_3CH_2C\underline{H}_2$); 5.49 (2H, s, 2-CH_2Cl); 6.89 (1H, s, H-8); 7.19 (1H, s, H-5'); 7.80 (1H, s, H-5); 10.72 (1H, s, 7-OH)
4a	1639*	1.23 (3H, t, *J* = 7.2, $C\underline{H}_3CH_2$); 2.46 (3H, s, 4'-CH_3); 2.55 (4H, br. s, CH_2NCH_2); 2.66 (2H, q, *J* = 7.2, $CH_3C\underline{H}_2$); 3.54 (4H, br. s, CH_2OCH_2); 4.22 (2H, s, 2-CH_2N); 6.87 (1H, s, H-8); 7.19 (1H, s, H-5'); 7.80 (1H, s, H-5); 10.70 (1H, s, 7-OH)
4b	1636*	0.97 (3H, t, *J* = 7.2, $C\underline{H}_3CH_2CH_2$); 1.65 (2H, sextet, *J* = 7.2, $CH_3C\underline{H}_2CH_2$); 2.46 (3H, s, 4'-CH_3); 2.54 (4H, br. s, CH_2NCH_2); 2.63 (2H, t, *J* = 7.2, $CH_3CH_2C\underline{H}_2$); 3.54 (4H, br. s, CH_2OCH_2); 4.22 (2H, s, 2-CH_2N); 6.86 (1H, s, H-8); 7.15 (1H, s, H-5'); 7.78 (1H, s, H-5); 10.64 (1H, s, 7-OH)
5a	1639*	1.23 (3H, t, *J* = 7.2, $C\underline{H}_3CH_2$); 1.36 (2H, br. s, $N(CH_2CH_2)_2C\underline{H}_2$); 1.47 (4H, br. s, $N(CH_2C\underline{H}_2)_2CH_2$); 2.46 (3H, s, 4'-$CH_3$); 2.49-2.53 (4H, m, CH_2NCH_2); 2.67 (2H, q, *J* = 7.2, $CH_3C\underline{H}_2$); 4.13 (2H, s, 2-CH_2N); 6.86 (1H, s, H-8); 7.19 (1H, s, H-5'); 7.80 (1H, s, H-5); 10.66 (1H, s, 7-OH)
5b	1636*	0.97 (3H, t, *J* = 7.2, $C\underline{H}_3CH_2CH_2$); 1.37 (2H, br. s, $N(CH_2CH_2)_2C\underline{H}_2$); 1.49 (4H, br. s, $N(CH_2C\underline{H}_2)_2CH_2$); 1.65 (2H, sextet, *J* = 7.2, $CH_3C\underline{H}_2CH_2$); 2.47 (3H, s, 4'-CH_3); 2.54 (4H, br. s, CH_2NCH_2); 2.63 (2H, t, *J* = 7.2, $CH_3CH_2C\underline{H}_2$); 4.14 (2H, s, 2-CH_2N); 6.86 (1H, s, H-8); 7.13 (1H, s, H-5'); 7.77 (1H, s, H-5); 10.56 (1H, s, 7-OH)
6a	1637*	1.17-1.24 (5H, m, $C\underline{H}_3CH_2$, $C\underline{H}_ACH(CH_2Ph)C\underline{H}_A$); 1.40-1.46 (1H, m, $C\underline{H}CH_2Ph$); 1.50 (2H, d, *J* = 12.4, $C\underline{H}_BCH(CH_2Ph)C\underline{H}_B$); 2.09 (2H, t, *J* = 10.8, $C\underline{H}_ANC\underline{H}_A$); 2.45-2.53 (5H, m, 4'-$CH_3$, $C\underline{H}_2Ph$); 2.65 (2H, q, *J* = 7.2, $CH_3C\underline{H}_2$); 2.84 (2H, d, *J* = 10.4, $C\underline{H}_BNC\underline{H}_B$); 4.16 (2H, s, 2-$CH_2N$); 6.84 (1H, s, H-8); 7.05 (2H, d, *J* = 7.6, H-2,6 Ph); 7.10 (1H, t, *J* = 7.6, H-4 Ph); 7.14 (1H, s, H-5'); 7.19 (2H, d, *J* = 7.6, H-3,5 Ph); 7.79 (1H, s, H-5); 10.63 (1H, s, 7-OH)
6b	1639*	0.91 (3H, t, *J* = 7.2, $C\underline{H}_3CH_2CH_2$); 1.12 (2H, m, $C\underline{H}_ACH(CH_2Ph)C\underline{H}_A$); 1.40 (1H, m, $C\underline{H}CH_2Ph$); 1.43 (2H, d, *J* = 12.0, $C\underline{H}_BCH(CH_2Ph)C\underline{H}_B$); 1.59 (2H, sextet, *J* = 7.2, $CH_3C\underline{H}_2CH_2$); 2.04 (2H, t, *J* = 10.4, $C\underline{H}_ANC\underline{H}_A$); 2.41-2.43 (5H, m, 4'-$CH_3$, $C\underline{H}_2Ph$); 2.60 (2H, t, *J* = 7.2, $CH_3CH_2C\underline{H}_2$); 2.81 (2H, d, *J* = 10.4, $C\underline{H}_BNC\underline{H}_B$); 4.11 (2H, s, 2-$CH_2N$); 6.90 (1H, s, H-8); 7.10 (2H, d, *J* = 7.2, H-2,6 Ph); 7.14 (1H, t, *J* = 7.2, H-4 Ph); 7.24 (2H, d, *J* = 7.2, H-3,5 Ph); 7.35 (1H, s, H-5'); 7.79 (1H, s, H-5); 10.56 (1H, s, 7-OH)
7a	1639*	1.23 (3H, t, *J* = 7.2, $C\underline{H}_3CH_2$); 2.14 (3H, s, NCH_3); 2.30 (4H, br. s, $C\underline{H}_2N(CH_3)C\underline{H}_2$); 2.46 (3H, s, 4'-$CH_3$); 2.49-2.53 (4H, m, CH_2NCH_2); 2.66 (2H, t, *J* = 7.2, $CH_3C\underline{H}_2$); 4.19 (2H, s, 2-CH_2N); 6.86 (1H, s, H-8); 7.19 (1H, s, H-5'); 7.79 (1H, s, H-5); 10.72 (1H, s, 7-OH)
8b	1639*	0.98 (3H, t, *J* = 7.2, $C\underline{H}_3CH_2CH_2$); 1.65 (2H, sextet, *J* = 7.2, $CH_3C\underline{H}_2CH_2$); 2.32 (4H, br. s, $C\underline{H}_2N(CH_2Ar)C\underline{H}_2$); 2.46 (3H, s, 4'-$CH_3$); 2.56 (4H, br. s, CH_2NCH_2); 2.62 (2H, t, *J* = 7.2, $CH_3CH_2C\underline{H}_2$); 3.31 (2H, s, $NC\underline{H}_2Ar$); 4.21 (2H, s, 2-CH_2N); 5.92 (2H, s, OCH_2O); 6.65-6.67 (2H, m, H-5,6 Ar); 6.75 (1H, s, H-2 Ar); 6.85 (1H, s, H-8); 7.13 (1H, s, H-5'); 7.78 (1H, s, H-5); 10.57 (1H, s, 7-OH)
9b	1636*	0.98 (3H, t, *J* = 7.2, $C\underline{H}_3CH_2CH_2$); 1.67 (2H, sextet, *J* = 7.2, $CH_3C\underline{H}_2CH_2$); 2.48 (3H, s, 4'-CH_3); 2.54 (4H, br. s, CH_2NCH_2); 2.63 (2H, t, *J* = 7.2, $CH_3CH_2C\underline{H}_2$); 2.74 (4H, br. s, $CH_2N(Ar)CH_2$); 4.31 (2H, s, 2-CH_2N); 6.81-6.93 (5H, m, H-8, H Ar); 7.16 (1H, s, H-5'); 7.79 (1H, s, H-5); 10.61 (1H, s, 7-OH)

* C(4)=O.

*[2] 7-$ClCH_2\underline{CO}O$.

*[3] Overlapping C=O and C=C Ar stretching bands.

Hence potential biologically active 2-dialkylamino derivatives of 2-chloromethyl-7-hydroxy-3-(4-methyl-thiazol-2-yl)chromones have been synthesized.

EXPERIMENTAL

IR spectra were recorded on a Perkin Elmer BX instrument in KBr pellets. ^{1}H NMR spectra were recorded on a Varian Mercury 400 spectrometer (400 MHz) using DMSO-d_6 with TMS as internal standard. COSY-90 and homonuclear NOE experiments were carried out by the Varian Company standard methods. Elemental analysis was performed on a Perkin Elmer CHN analyzer. Melting points were determined on a mini Boetius hot stage apparatus with a VEB Analytic PHMK 0.5 visual system. The course of the reaction and purity of the compounds obtained were determined by TLC using Silufol UV-254 plates with $CHCl_3$–MeOH (95:5) as eluent.

Compounds **2a** and **3a** were obtained by a literature method and their physicochemical and spectroscopic parameters agreed with those given in the study [20].

2-Chloromethyl-3-(4-methyl-1,3-thiazol-2-yl)-4-oxo-6-*n*-propyl-4*H*-chromen-7-yl Chloroacetate (2b). Pyridine (1.19 g, 15 mmol) and chloroacetyl chloride (1.69 g, 15 mmol) were added to a solution of compound **1b** (1.46 g, 5 mmol) in MeCN (15 ml) and held for 1 day at room temperature. The precipitate formed was filtered off, washed with MeCN and ice water, and recrystallized from MeCN.

2-Chloromethyl-7-hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-6-*n*-propyl-4*H*-chromen-4-one (3b). 37% HCl (1 ml) was added to a solution of compound **2b** (1.24 g, 3 mmol) in EtOH (50 ml), refluxed for 1.5-2.0 h, held for 1 day at room temperature, and the precipitate formed was filtered off and recrystallized from EtOH.

6-Alkyl-2-dialkylaminomethyl-7-hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-4*H*-chromen-4-ones 4-9 (General Method). The secondary amine (2 mmol) was added to a solution of compound **3a**,**b** (1 mmol) in dioxane (7 ml), refluxed for 0.5-3.0 h, and held for 1 day at room temperature. Compounds **5b**, **6a**,**b**, **8b** formed precipitates which were filtered off, washed with dioxane and water, and recrystallized from dioxane. In the other cases, the solvent was evaporated and compounds **4a**, **5a**, **7a** were recrystallized from ethyl acetate, while compounds **4b**, **9b** were recrystallized from dioxane.

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