Synthesis of 3-(Substituted Methyl)-2-phenyl-4*H*-1-benzothiopyran-4-ones

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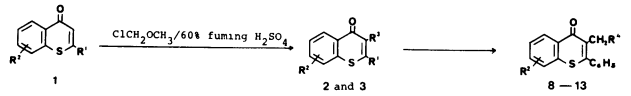
Synopsis. Reaction of 2-phenyl-4*H*-1-benzothiopyran-4-ones and related compounds with chloromethyl methyl ether and fuming sulfuric acid gave mainly 3-chloromethyl compound, whereas chloromethylation of methoxy-substituted thioflavones took place at another position or gave tris(chloromethyl) compound. 3-(Chloromethyl)thioflavone could be easily converted into various 3-(substituted methyl)-thioflavones which showed significant antimicrobial activity against *Trichophytons*.

We have attempted to prepare some 2-phenyl-4*H*-1-benzothiopyran-4-one (thioflavone) (**1**) which would be biologically and pharmacologically effective compounds.[1,2] We now examine the introduction of specific substituent groups (chloromethyl and acetoxymethyl) into the 3-position of **1**, because the introduction of these groups into the corresponding position of 1,4-naphthoquinones[3] and 4*H*-1-benzothiopyran-4-one 1,1-dioxides[4] is required for bioactivation. However, it is well known that no chloromethylation directly occurs at the 3-position of 4*H*-1-benzothiopyran-4-ones (thiochromones).[4] 3-(Chloromethyl)thioflavone **2a** may be a key compound, one which can be efficiently converted into other pharmacologically active compounds. Few reports are available on the preparation of the title compounds. In this paper, we report the direct chloromethylation of various thioflavones and related compounds.

A common chloromethylation of thiochromone 1,1-dioxides with formaldehyde and hydrogen chloride is well known; however, the thiochromone[4] and **1a** are not chloromethylated by the same method. Chloromethylation of **1a**[6] was accomplished by use of chloromethyl methyl ether and 60% fuming sulfuric acid, which were previously applied in the chloromethylation of benzyl chloride.[5] The chloromethyl derivative was determined to be 3-(chloromethyl)thioflavone **2a** on the basis of ^{1}H-NMR spectrum, in which



1 2 and 3 8—13

	R^1, R^2		R^1, R^2, R^3		R^2, R^4
1a	C_6H_5, H	**2a**	C_6H_5, H, CH_2Cl	**8**	H, NHC_6H_5
1b	CH_3, H	**2b**	CH_3, H, CH_2Cl	**9**	H, $N(CH_2CH_2)_2O$
1c	C_6H_5, 6-CH_3	**2c**	C_6H_5, 6-CH_3, CH_2Cl	**10**	H, $N(CH_2CH_2OH)_2$
1d	C_6H_5, 6-CH_3O	**2d**	C_6H_5, 6-CH_3O-5-CH_2Cl, H	**11**	H, OR
1e	4′-$CH_3OC_6H_4$, H	**2e**	3′5′-$(CH_2Cl)_2$-4′-$CH_3OC_6H_2$, H, CH_2Cl	**12**	H, $OCOCH_2CH_3$
1f	C_6H_5, 8-CO_2CH_3	**2f**	C_6H_5, 8-CO_2CH_3, CH_2Cl	**13**	6-CH_3, OCH_2CH_3
1g	4′-$NO_2C_6H_4$, H	**2g**	4′-$NO_2C_6H_4$, H, CH_2Cl		
1h	C_6H_5, 8-CH_3	**2h**	C_6H_5, 8-CH_3, CH_2Cl		
1i	4′-$CH_3C_6H_4$, H	**2i**	4′-CH_3-3′-$CH_2ClC_6H_3$, H, CH_2Cl		
		2j	4′-CH_3-3′-$CH_2OHC_6H_3$, H, CH_2Cl		
		3a	C_6H_5, H, CH_2OH		
		3b	CH_3, H, CH_2OH		
		3f	C_6H_5, 8-CO_2CH_3, CH_2OH		

Scheme 1.

a signal for a chloromethyl group appeared at δ 4.52 and a signal for a vinyl proton (δ 7.20) in the 3-position of **2a** disappeared. When the chloromethylation was carried out at 75°C, compound **3a** was isolated as the main product. 2-(Methyl)thiochromone **1b** and other thioflavones **1c—1i** were chloromethylated under the same conditions. In the case of 6-(methoxy)thioflavone **1d**, which possesses a powerful electron-donating group, chloromethylation did not take place at the 3-position, but at the 5-position. The ^{1}H-NMR signal for a chloromethyl group of product **2d** was shifted downfield to δ 5.58. On the other hand, a weak electron-donating methyl group at the same position led to 3-chloromethylated product **2c**. Methyl group and methoxycarbonyl group at the 8-position also led to 3-chloromethylated products **2h** and **2f**, respectively. Compound **3f** was isolated as a by-product. Chloromethylation of the thioflavone was also influenced by a substituent group in a phenyl group at the 2-position. Methoxyl and methyl substituent in the phenyl group led to tris(chloromethyl) compound **2e**, bis(chloromethyl) compound **2i**, and **2j**, respectively. The structure of compound **2j** was determined to be 3-(chloromethyl)-3′-(hydroxymethyl) derivative by means of its ^{1}H-NMR signal, which was shifted upfield to δ 2.44 for a OH proton of hydroxymethyl group, while the signal of the same group at the 3-position of compounds **3a**, **3b**, and **3f** appeared at δ 3.27—3.63. An electron-withdrawing nitro group at the 4′-position led to 3-chloromethyl compound **2g**. These results show that reaction of the thioflavone with chloromethyl methyl ether and fuming sulfuric acid generally gives only a 3-chloromethyated compound. The same chloromethylation of **1b**, flavone, and 2-methylchromone gave 3-chloromethyl derivatives **2b**, **4**, and **5** in 19—76% yields, respectively. New 3-(substituted methyl)thioflavones were easily prepared by reaction of **2a** with nucleophilic reagents, as shown in Scheme 1. For examples, reaction of **2a** with an excess of aniline, morpholine, bis(2-hydroxyethyl)amine, and sodium alkoxides[7] gave compounds **8—13**, respectively. The chlorine atom of a chloromethyl group of flavone derivative **4** was also converted into ethoxyl and acetoxyl group (compounds **6** and **7**) in good yields. The described method should be advantageous for direct transformation of thioflavones or flavone into their 3-(substituted methyl) derivatives.

An introduction of a chloromethyl group in the 3-position of **1a** resulted in significant antimicrobial activity against *Trichophytons* (MIC 0.195 μg/ml). 3-(Substituted methyl)thio-flavones **3a**, **9**, and **13** (MIC 0.00488—6.25 μg/ml), as well as 3-(alkoxymethyl)thioflavone **11**,[7] also exhibited activity against *Trichophytons*. On the other hand, the MIC of 3-(substituted methyl) flavones (MIC 1.56—25.0 μg/ml) became higher (*ca.* 10—200-fold) than that of the corresponding thioflavones.

TABLE 1. PHYSICAL DATA OF 3-(CHLOROMETHYL)THIOFLAVONES (**2**) AND 3-(HYDROXYMETHYL)THIOFLAVONES (**3**)

Compd	Yield[a] /%	Mp θ_m/°C	^{1}H-NMR (δ, in $CDCl_3$)	ν_{CO} /cm^{-1}	Mass, *m/z* (rel intensity)	Formula	Found (Calcd)(%) C	H	N
2a	76	130—132	4.52 (s,2H,CH_2) 7.46—7.61 (m,8H) 8.60 (m,1H,H-5)	1610	288 (M^++2,6) 286 (M^+,13) 251 (62) 250 (100)	$C_{16}H_{11}OSCl$	66.87 (67.01)	3.56 (3.87)	
2b	19	127—129	2.61 (s,3H,CH_3) 4.81 (s,2H,CH_2) 7.57—7.73 (m,3H) 8.64 (m,1H,H-5)	1610	226 (M^++2 20) 224 (M^+,50) 189 (97) 188 (51) 161 (100)	$C_{11}H_9OSCl$	58 77 (58.80)	3.83 (4.04)	
2c	59	154—157	2 50 (s,3H,CH_3) 4.43 (s,2H,CH_2) 7.43—7.58 (m,7H) 8.40 (s,1H,H-5)	1613	302 (M^++2,7) 300 (M^+,17) 265 (91) 264 (100)	$C_{17}H_{13}OSCl$	68 21 (67.88)	3.96 (4.36)	
2d	11	165—166	3 93 (s,3H,OCH_3) 5 58 (s,2H,CH_2) 7.22—7.66 (m,8H)	1605	318 (M^++2,16) 316 (M^+,37) 281 (36) 265 (76), 252 (100)	$C_{17}H_{13}O_2SCl$	64 13 (64.45)	3.98 (4.14)	
2e	8.0[b]	188—190	4.03 (s,3H,OCH_3) 4.51 (s,2H,CH_2) 4.72 (s,4H,CH_2) 7 65—7 71 (m,5H) 8 65 (m,1H,H-5)	1620	416 (M^++4,8) 414 (M^++2,21) 412 (M^+,20) 376 (80), 341 (73) 327 (97), 293 (100)	$C_{19}H_{15}O_2SCl_3$	54.99 (55.16)	3 42 (3.65)	
2f	77	146—148	4 02 (s,3H,OCH_3) 4.54 (s,2H,CH_2) 7.55—7.78 (m,6H) 8.54 (d,1H,J=8 Hz,H-5) 9.03 (d,1H,J=8 Hz,H-7)	1715 1608	346 (M^++2,5) 344 (M^+,12) 309 (71) 308 (100)	$C_{18}H_{13}O_3SCl$	62 54 (62.70)	3 73 (3.80)	
2g	50	220—222	4.46 (s,2H,CH_2) 7.20—7 88 (m,5H) 8.30—8.62 (m,3H)	1610	333 (M^++2,7) 331 (M^+,21) 296 (53) 295 (57), 250 (100)	$C_{16}H_{10}NO_3SCl$	57.68 (57.92)	2 68 (3 04)	3.87 (4.22)
2h	29	153—154	2.49 (s,3H,CH_3) 4.52 (s,2H,CH_2) 7 44—7 62 (m,7H) 8.52 (m,1H,H-5)	1615	302 (M^++2,17) 300 (M^+,43) 265 (75) 264 (100)	$C_{17}H_{13}OSCl$	67.58 (67 88)	4.16 (4 36)	
2i	14	164—167	2.48 (s,3H,CH_3) 4.50 (s,2H,CH_2) 4 66 (s,2H,CH_2) 7.35—7.71 (m,6H) 8 60 (m,1H,H-5)	1630	350 (M^++2,14) 348 (M^+,20) 313 (40) 312 (61), 311 (72) 276 (100)	$C_{18}H_{14}OSCl_2$	61 73 (61.90)	3.81 (4.04)	
2j	39	182—183	2 44 (s,1H,OH) 2 51 (s,3H,CH_3) 4 54 (s,2H,CH_2) 4.67 (s,2H,CH_2) 7.35—7.65 (m,6H) 8.59 (m,1H,H-5)	1605	332 (M^++2,10) 330 (M^+,23) 312 (42) 295 (17), 277 (71) 263 (94), 262 (100)	$C_{18}H_{15}O_2SCl$	65 73 (65.35)	4.56 (4.57)	
3a	38	175—177	3.60 (t,J=7 Hz,1H, OH) 4.47 (d,J=7 Hz,2H, CH_2) 7.30—7 58 (m,8H) 8.38 (m,1H,H-5)	1605	268 (M^+,26) 250 (100) 221 (39)	$C_{16}H_{12}O_2S$	71 94 (71 62)	4.22 (4.51)	
3b	9.0	147—149	2.52 (s,3H,CH_3) 3.63 (b,1H,OH) 4.75 (s,2H,CH_2) 7.58 (m,3H) 8.53 (m,1H,H-5)	1605	206 (M^+,100) 191 (54) 188 (78)	$C_{11}H_{10}O_2S$	63 94 (64 05)	4.62 (4.89)	
3f	6.3	149—150	3 27 (b,1H,OH) 3.95 (s,3H,CO_2 CH_3) 4.53 (s,2H,CH_2) 7.42—7.67 (m,6H) 8.40 (m,1H,H-5) 8.80 (dd,J=8 and 1.5 Hz,1H,H-7)	1710 1608	326 (M^+,21) 309 (23) 308 (100) 307 (33)	$C_{18}H_{14}O_4S$	65.88 (66.24)	4 22 (4.32)	

a) Yield based on the converted substrate (**1a—1i**). b) Isolated yield.

TABLE 2. PHYSICAL DATA OF 3-(SUBSTITUTED METHYL)THIOFLAVONES

Compd	Yield[a] /%	Mp θ_m/°C	^{1}H-NMR (δ, in $CDCl_3$)	ν_{CO} /cm^{-1}	Mass, *m/z* (rel intensity)	Formula	Found (Calcd)(%) C	H	N
8	46	116—118	4.18 (s,2H,CH_2) 6 21—7 05 (m,5H) 7.35—7.50 (m,8H) 8 43 (m,1H,H-5)	1610	343 (M^+,14) 252 (100)	$C_{22}H_{17}NOS$	76.58 (76 94)	4 57 (4.99)	3 99 (4.08)
9	65	164—166	2.25—2 41 (m,4H) 3.46—3.64 (m,6H) 7 35—7 57 (m,8H) 8.55 (m,1H,H-5)	1610	337 (M^+,15) 251 (100)	$C_{20}H_{19}NO_2S$	70.91 (71 19)	5 36 (5 68)	4 05 (4 15)
10	36	98—101	2 45 (t,J=6 Hz,4H, N-CH_2-), 3 25 (b, 2H,OH), 3 53 (t,J= 6 Hz,4H,-CH_2-O), 3.73 (s,2H,-CH_2 -N), 7.49—7.70 (m,8H), 8.65 (m, 1H,H-5)	1608	337 (17) 324 (20) 310 (23) 251 (100)	$C_{20}H_{21}NO_3S$	67 60 (67 58)	5 95 (5 96)	3 95 (3 94)
12	77	120—122	1 12 (t,J=7 Hz,3H, CH_2-CH_3) 2 27 (q,J=7 Hz,2H, CH_2-CH_3) 4 93 (s,2H,CH_2O) 7.37—7 53 (m,8H) 8 49 (m,1H,H-5)	1730 1615	—	$C_{18}H_{16}O_3S$	70 10 (70 35)	4.64 (4 97)	
13	66	99—101	1 15 (t,J=6 Hz,3H, CH_2-CH_3), 2 49 (s, 3H, CH_3-6), 3.52 (q,J=6 Hz,2H, CH_2-CH_3), 4 37 (s,2H,CH_2-O), 7.47—7.75 (m,7H) 8 47 (s,1H,H-5)	1618	—	$C_{19}H_{18}O_2S$	73.55 (73 52)	5 79 (5 85)	

a) Isolated yield

Experimental

All the melting points are uncorrected. ^{1}H-NMR spectra were taken on a JEOL JNM-MH-100 spectrometer with tetramethylsilane as an internal standard. IR spectra were recorded on a Shimazu IR-420 spectrometer using KBr pellets. Elemental analyses were recorded on a Yanaco CHN recorder MT-2. Mass spectra were recorded on a Hitachi RMU-6E mass spectrometer operating at 80 eV.

*2-Phenyl-4H-1-benzothiopyran-4-ones and 2-Methyl-4H-1-benzothiopyran-4-one (**1a—1i**).* Thioflavones and 2-methylthiochromone were generally prepared by Bossert's method.[6] The physical data of new derivative **1i** are as follows. **1i**; mp 120—121°C; 1608 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=2.42 (s, 3H, CH_3), 7.20—7.36 (m,3H), 7.48—7.70 (m, 5H), and 8.57 (m, 1H, H-5); MS *m/z* (rel intensity) 252 (M^+, 100), 224 (96), and 223 (26). Anal. ($C_{16}H_{12}OS$) C, H.

General Procedure for Chloromethylation. Fuming sulfuric acid (60%; 14 ml) was added dropwise to a solution of approriate thioflavone **1** (35 mmol) in chloromethyl methyl ether (56 ml) with stirring. The reaction mixture was stirred at 60°C for 24 h, and then poured into cold water. The oily precipitate soon solidified, and the resulting solid was collected and washed with water. The crude product was chromatographed on silica gel, using benzene as an eluent, to give **2**. Recrystallization from benzene/hexane (10:1) gave a pure chloromethyl derivative **2**. The yields, mp's and spectral data of **2a—2j** and **3a**, **b**, **f** are summarized in Table 1.

Compounds **4** and **5** were similarly prepared from flavone[8] and 2-methylchromone,[9] respectively. Compound **4**: yield 47%; mp 155—156°C (lit,[10] 156°C). Compound **5**: yield 76%; mp 103—104°C (lit,[10] 103—108°C).

*3-(Substituted Methyl)-2-phenyl-4H-1-benzothiopyran-4-ones and 3-(Substituted Methyl)-2-phenyl-4H-1-benzopyran-4-ones (**6—13**).* A mixture of compound **2a** and appropriate amine, sodium alkoxide or sodium propionate was heated at reflux for 2—5 h in dioxane, alcohol or propionic acid. The mixture was worked up as described above to give pure compounds **8—13**. The physical data of these compounds are listed in Table 2.

Compounds **6** and **7** were similarly prepared. 3-(Ethoxymethyl)flavone **6**: yield 75%; mp 102—114°C; 1640 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=1.31 (t, J=7 Hz, 3H, -$CH_2\underline{CH_3}$), 3.73 (q, J=7 Hz, 2H, -$\underline{CH_2}CH_3$), 4.48 (s, 2H, -CH_2O), 7.52—7.84 (m, 6H), 7.99—8.13 (m, 2H), and 8.45 (d, J=7.5 Hz, 1H, H-5). Anal. ($C_{18}H_{16}O_3$) C, H. 3-(Acetoxymethyl)flavone **7**: yield 80%; mp 118—119°C (lit,[11] 115—118°C).

Determination of in Vitro Antimicrobial Activity. The minimal inhibitory concentrations (MIC) were determined by a standard two-fold serial dilution method using agar media for *Trichophyton rubrum, Trichophyton mentagrophytes,* and *Candida albicans.*

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