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Reactions of 4*H*-1-Benzothiopyran-4-ones and Related Compounds with Dimethyl Sulfate[†]

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4*H*-1-Benzothiopyran-4-ones (thiochromones) and isomeric 2*H*-1-benzothiopyran-2-ones (thiocoumarins) have been allowed to react with dimethyl sulfate (DMS) to study the differences in reactivity on methylation. Methylation of 2-methyl(thiochromones) with DMS afforded the blue colored dimerization products, 4-(4-methoxy-1-benzothiopyran-2-ylidenemethyl)-2-methyl-1-benzothiopyrylium perchlorates, while that of 7-methoxy-4-methyl(thiocoumarin) gave the *O*-methylated yellow salt, 2,7-dimethoxy-4-methyl-1-benzothiopyrylium perchlorate. Methylations of oxa analogues (coumarins) and aza analogues (2-quinolones) of thiocoumarins with DMS have also been examined. It has been found that the ease of formation of methylation products is affected by the hetero atom and carbonyl group.

In a previous paper,[1)] the spectral characterization of 4*H*-1-benzothiopyran-4-ones (thiochromones) was proposed to distinguish them from 2*H*-1-benzothiopyran-2-ones (thiocoumarins). However, it was very difficult to distinguish only on the basis of spectral data. The methylation of these compounds with dimethyl sulfate (DMS) is an attempt to distinguish them. Tolmachev *et al.*[2)] reported the methylation of 2-methyl(thiochromone), however, the systematic study of the methylation of thiochromones, thiocoumarins and the oxa analogues (coumarins) and the aza analogues (2-quinolones) with DMS have not been reported. In this paper, the differences in methylation of these heterocyclic compounds with DMS will be reported.

Experimental

All the melting points are uncorrected. Infrared spectra were recorded on a Hitachi ESI-S2 spectrophotometer using KBr pellets. ^{1}H-NMR spectra were taken on a Hitachi R-24A spectrometer with tetramethylsilane as an internal standard. Elemental analyses were recorded on a Yanaco CHN recorder MT-2. DTA-TG analysis was taken on a Rigaku DTA-TG instrument at 10 °C/min under nitrogen.

*4-(4-Methoxy-1-benzothiopyran-2-ylidenemethyl)-2-methyl-1-benzothiopyrylium Perchlorate Derivatives (**2a**—**2c**).* 2-Methyl(thiochromone)[1)] **1a** (3.5 g) was added to dimethyl sulfate (2 ml). The mixture was stirred at 70 °C for 5 h and after cooling, H_2O (2 ml) was added to the reaction mixture, followed by the addition of 60% $HClO_4$ (4 ml). The resulting solid was separated, and washed with MeOH, $CHCl_3$, and EtOH, and recrystallized from glacial acetic acid to give **2a** in 32% yield. From the first filtrate, starting material **1a** was recovered in 15% yield.

The other 1-benzothiopyrylium perchlorates (**2b** and **2c**) were similarly prepared in 30—40% yield together with the starting materials (**1b** and **1c**). **2a**(X=H): mp 225 °C; λ_{max} (acetone) 590 nm (ε 6.28×10^4); NMR(CF_3COOH)δ=3.35 (3H, s), 4.65 (3H, s), 5.78 (2H, s), and 8.20—8.90 ($\approx$9H, m); Found: C, 56.19; H, 3.70%; Calcd for $C_{21}H_{17}O_5S_2Cl$: C, 56.19; H, 3.79%. **2b**($X=OCH_3$): mp >300 °C; λ_{max} (acetone) 596 nm(ε 6.92×10^4); NMR(CF_3COOH) δ=3.20, 4.05, 4.25, 4.65, 5.55, and 7.60—8.80 (integral values could not be measured due to the poor solubility of **2b**); Found: C, 54.49; H, 4.18%; Calcd for $C_{23}H_{21}O_7S_2Cl$: C, 54.28; H, 4.13%. **2c**(X=Cl): mp>300 °C; λ_{max} (acetone) 590 nm(ε 5.22×10^4); NMR(CF_3COOH) δ=3.35 (3H, s), 4.65(3H, s), 5.75 (2H, s) and 7.80—8.90 ($\approx$7H, m); Found: C, 48.12; H, 2.73%; Calcd for $C_{21}H_{15}O_5S_2Cl_3$: C, 48.70; H, 2.90%.

*4-(1-Benzothiopyran-2-ylidenemethyl)-2-methyl-1-benzothiopyrylium Perchlorate (**3**).* A suspension of $AlCl_3$ (2.6 g) in THF (40 ml) was added to a solution of $LiAlH_4$ (0.8 g) in THF. To the resulting solution, a solution of 2-methyl(thiochromone) (3.5 g) in THF (40 ml) was added dropwise at 25—30 °C. After standing for 30 min at 30 °C, H_2O (4 ml) and then 6M-H_2SO_4 (10 ml) was added to the reaction mixture. After filtration, the filtrate was condensed and extracted with ether. To the extract 70% $HClO_4$ (5 ml) and H_2O (10 ml) were added, and the resulting solid was washed with ether and methanol to give **3**: mp 250 °C; NMR(CF_3COOH) δ=2.85 (3H, s), 5.40 (2H, s), and 7.80—8.10 ($\approx$10H, m); λ_{max} (acetone) 616 nm(ε 6.14×10^4); Found: C, 57.47; H, 3.78%; Calcd for $C_{20}H_{15}S_2O_4Cl$: C, 57.35; H, 3.58%.

*2,7-Dimethoxy-4-methyl-1-benzothiopyrylium Perchlorate (**6**).* Compound **6** was prepared from **4**[1)] by a method similar to that for compound **2a** and a reaction time of 10 h in 10% yield with the starting materials. Mp 166—168 °C; λ_{max} (acetone) 386 nm(ε 1.10×10^4); NMR(CF_3COOH) δ=3.09 (3H, s), 4.14 (3H, s), 4.60 (3H, s), 7.60—7.80 (3H, m), and 8.57 (1H, m); Found: C, 44.92; H, 4.12%; Calcd for $C_{12}H_{13}O_6SCl$: C, 44.93; H, 4.06%.

*4-Methoxy-2H-1-benzothiopyran-2-one (**7**).* Compound **7** was prepared from 4-hydroxy-2*H*-1-benzothiopyran-2-one **5**[3)] by a method similar to that for compound **2a**: yield 33%; mp 126—128 °C; ν_{CO} 1635 cm^{-1}; MS(80 eV), *m/e*(rel intensity), 192 (100), 164 (64), 149 (85), and 136 (10); NMR ($CDCl_3$)δ=4.00 (3H, s), 6.10 (1H, s), 7.40—7.50 (3H, m), and 8.15 (1H, m); Found: C, 62.58; H, 4.12%; Calcd for $C_{10}H_8O_2S$: C, 62.50; H, 4.17%.

*2,7-Dimethoxy-4-methylquinolinium Perchlorate (**11**).* Compound **10**[4)] (1.0 g) was added to dimethyl sulfate (8.4 g) with stirring. The mixture was heated at 70 °C for 4 h and after cooling, H_2O (7 ml) was added, followed by 60% $HClO_4$ (10 ml). The resulting solid was filtered after standing at room temperature for several hours. Recrystallization from EtOH gave quinolinium perchlorate **11**: yield 41%; dec 245 °C; NMR (CF_3COOH) δ=3.00 (3H, s), 4.10 (3H, s), 4.30 (3H, s), 7.20—7.55 (3H, m), and 8.30 (1H, m); Found: C, 47.15; H, 4.57; N, 4.25%; Calcd for $C_{12}H_{14}NO_6Cl$: C, 47.45; H, 4.61; N, 4.61%.

*2,7-Dimethoxy-4-methylquinoline (**12**).* Quinolinium

[†] A preliminary report of this work was presented at the 10th Congress of Heterocyclic Chemistry, Tsukuba, October 1977.

salt **11** (0.1 g) was dissolved in MeOH (5 ml), and 10% aqueous NaOH was added to this solution until the pH was 10. The resulting solid was collected and recrystallized from MeOH–H_2O solution to give 2,7-dimethoxy-4-methylquinoline **12**: mp 67—68 °C; NMR($CDCl_3$) δ=2.60 (3H, s), 3.95 (3H, s), 4.05 (3H, s), 6.63 (1H, s), and 7.20—7.80 (3H, m); Found: C, 70.68; H, 6.40; N, 6.47%; Calcd for $C_{12}H_{13}NO_2$: C, 70.94; H, 6.40; N, 6.90%.

*1,4-Dimethyl-2-methoxyquinolinium Perchlorate (**15**).* Compound **15** was prepared from **13**[5] by a method similar to that for compound **11**: yield 54%; mp 161—162 °C; NMR(CF_3COOH) δ=3.00 (3H, s), 4.30 (3H, s), 4.50 (3H, s), 7.45 (1H, s), and 7.80—8.45 (4H, m); Found: C, 50.01; H, 4.84; N, 4.73%; Calcd for $C_{12}H_{14}NO_5Cl$: C, 50.09; H, 4.87; N, 4.78%.

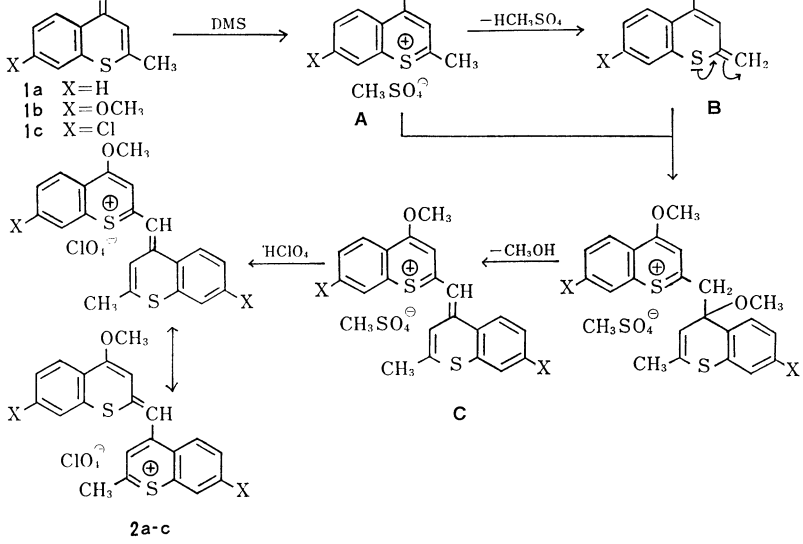
*4-Methyl-2-methoxyquinolinium Perchlorate (**16**).* Compound **14**[6] was allowed to react with DMS by a method similar to that for compound **11**. After treating with 60% $HClO_4$, the reaction mixture was allowed to stand overnight at room temperature. The resulting solid was separated by filtration, and recrystallization from MeOH afforded quinolinium perchlorate **15** (yield 11%). Another quinolinium perchlorate **16** was isolated by the evaporation of the filtrate of compound **15** and purified by repeated recrystallization from MeOH. It was found that compound **16** contained one molecule of water of crystallization by means of TG and DTA. Yield 50%; mp 157 °C; NMR(CF_3COOH) δ=3.05 (3H, s), 4.45 (3H, s) 7.45 (1H, s), and 7.70—8.40 (4H, m); Found: C, 45.79; H, 4.84; N, 5.27%; Calcd for $C_{11}H_{12}NO_5Cl\cdot H_2O$: C, 45.28; H, 4.80; N, 4.80%.

*4-Methyl-2-(methylthio)quinolinium Perchlorate (**17**) and 7-Methoxy-4-methyl-2-(methylthio)quinolinium Perchlorate (**18**).* Compound **17** was prepared by a method similar to that for compound **11** from 4-methylquinoline-2-thione:[7] yield 26%, mp 226—228 °C; NMR(CF_3COOH) δ=2.95 (6H, s) and 7.60—8.40 (5H, m); Found: C, 45.53; H, 4.30; N, 5.11%; Calcd for $C_{11}H_{12}NO_4SCl$: C, 45.60; H, 4.15; N, 4.84%. Compound **18** was similarly prepared from 7-methoxy-4-methylquinoline-2-thione (mp 240 °C; Found: C, 64.60; H, 5.44; N, 7.08%) which was obtained by the reaction of 7-methoxy-4-methyl-2-quinolone with P_2S_5 in benzene for 6 h under reflux: yield 38%; dec 250 °C; NMR (CF_3COOH) δ=2.95 (6H, s), 4.10 (3H, s), and 7.45—8.30 (4H, m); Found: C, 44.79; H, 4.46; N, 4.69%; Calcd for $C_{12}H_{14}NO_5SCl$: C, 45.07; H, 4.38; N, 4.38%.

*7-Methoxy-4-(7-methoxy-4-methylbenzopyran-2-ylidenemethyl)-2-(methylthio)benzopyrylium Perchlorate (**19**).* 7-Methoxy-4-methyl-2*H*-benzopyran-2-thione was obtained by the reaction of 7-methoxy-4-methyl(coumarin) with P_2S_5 in benzene: yield 64%; mp 135 °C; lit,[8] 136 °C. Treatment of the thiocarbonyl derivative with DMS at 70 °C and then with 60% $HClO_4$ gave a red product. Recrystallization from glacial acetic acid gave **19**: yield 23%; NMR(CF_3COOH) δ=3.10 (6H, s), 4.20 (6H, s), 5.20 (2H, s), and 7.50—8.50 ($\approx$7H, m); λ_{max}(acetone) 556 nm (ε 5.98×10^4); Found: C, 56.85; H, 4.46%; Calcd for $C_{23}H_{21}O_8SCl$: C, 56.04; H, 4.26%.

Results and Discussion

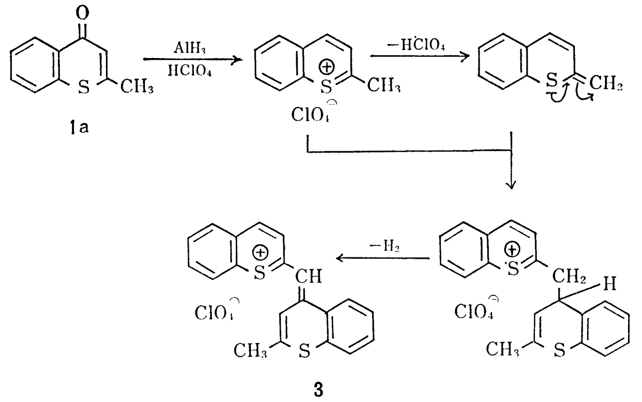
The Methylation of Thiochromones and Thiocoumarins. Traverso[9] has reported that 4-methoxythiopyrylium perchlorate, as the *O*-methylated product, was formed when 4*H*-thiopyran-4-one reacted with DMS followed by treatment with perchloric acid. In the case of 2-methyl(thiochromone) **1a**, a blue salt was found under the same conditions. The structure of this blue salt **2a** has been determined as 4-(4-methoxy-1-benzothiopyran-2-ylidenemethyl)-2-methyl-1-benzothiopyrylium perchlorate, on the basis of the NMR spectrum and elemental analyses. The structure has been also supported by ESCA.[10] The reactions of 7-methoxy-2-methyl- and 7-chloro-2-methyl(thiochromones) with DMS also gave blue 1-benzothiopyrylium salts **2b** and **2c**, respectively, with the starting materials. The blue 1-benzothiopyrylium salts have visible absorption maxima in the region 590—596 nm similar to that of a thiacyanine dye, which was prepared by the cyclodehydration of 4-(phenylthio)-2-butanone with polyphosphoric acid.[11] Tolmachev *et al.*[2] have reported that a similar 1-benzothiopyrylium salt was obtained by the reaction of 2-methyl(thiochromone) **1a** with methyl *o*-nitrobenzenesulfonate in toluene. A possible mechanism for the formation of **2a**—**c** is given in Scheme 1:



Scheme 1.

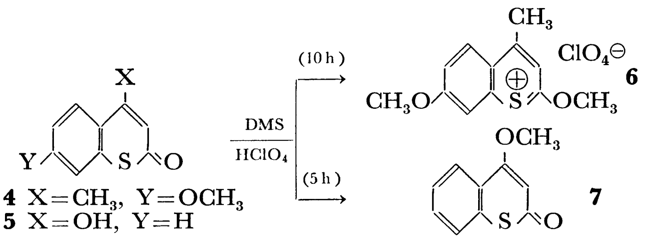
i.e. an initial attack of DMS to 2-methyl(thiochromone) derivatives leading to the *O*-methylated derivative **A**. Deprotonation could then occur to give **B**. The condensation of **B** with **A** would lead to **C**, and an anion exchange of ClO_4^- would afford the products **2a**—**c**.

Furthermore, 2-methyl(thiochromone) **1a** was reduced by aluminum hydride to 2-methyl-4*H*-1-benzothiopyran-4-ol, and the latter converted to the blue 1-benzothiopyrylium salt **3** with perchloric acid (Scheme 2). From these results, it appears that the methyl group at the 2-position of thiochromone derivatives has activated hydrogens.

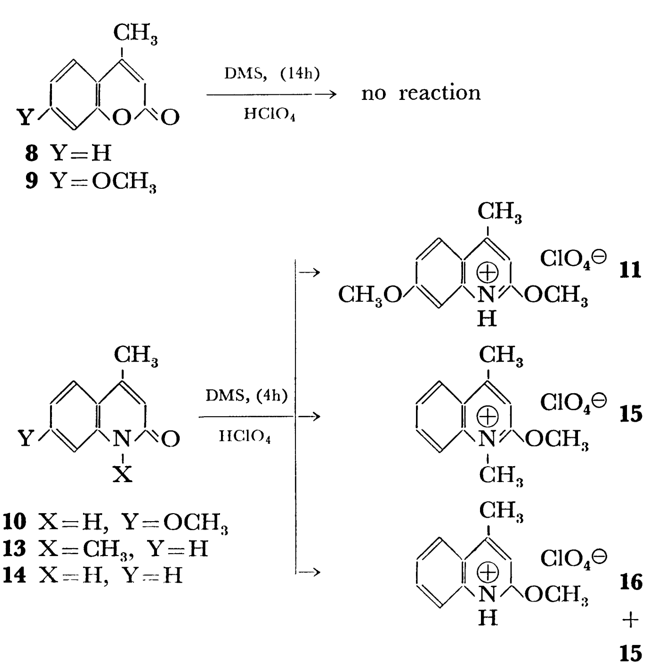


Scheme 2.

Methylation of 7-methoxy-4-methyl(thiocoumarin) **4**, the isomer of 7-methoxy-2-methyl(thiochromone) **1b**, with DMS gave a yellow salt. This yellow salt was identified with 2,7-dimethoxy-4-methyl-1-benzothiopyrylium perchlorate **6** as the *O*-methylated product of **4**. In the case of 4-hydroxy(thiocoumarin) **5**, 4-methoxy(thiocoumarin) **7** was isolated as the *O*-methylated product at the 4-position of **5** (Scheme 3). The different methylation mechanisms between 2-methyl(thiochromone) and 4-methyl(thiocoumarin) derivatives may be utilized to distinguish them.

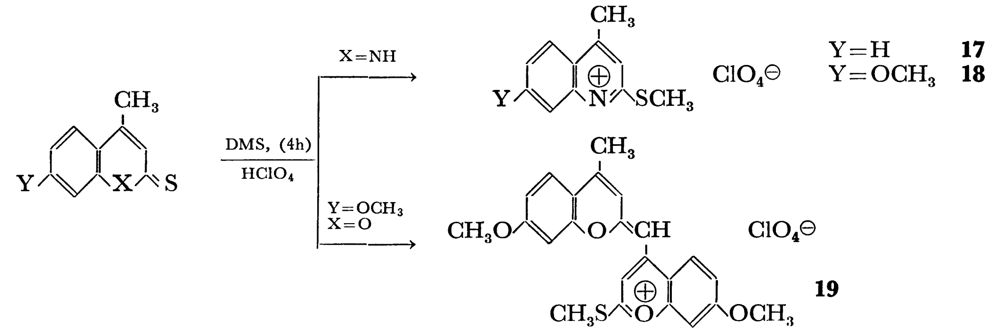


Scheme 3.



Scheme 4.

The Methylation of Oxa and Aza Analogues of Thiocoumarins with DMS. A comparison of the methylation of oxa analogues (coumarins) and aza analogues (2-quinolones) of 4-methyl(thiocoumarin) derivatives with DMS is summarized in Scheme 4. No methylation reaction occur, however, between coumarin derivatives (**8** and **9**) and DMS, even under the prolonged reaction time. In the cases of 2-quinolone derivatives (**10**, **13**, and **14**), *O*- and/or *N*-methylated products were obtained. The structures of quinolinium salts **11** and **16** could be identified by the treatment of **11** or **16** with base. For example, the 2-methoxyquinoline derivative **12** was obtained by the treatment of **11** with 10% aqueous NaOH. Similarly, 1,4-dimethyl-2-quinolone **13** gave the *O*-methylated 2-methoxy derivative **15**. In the case of 4-methyl-2-quinolone **14**, the 2-methoxy derivative **16** and the dimethylated quinolinium salt **15** were obtained. This result showed that the competitive *N*-methylation and *O*-methylation of **14** proceeded. From a comparison of the methylation of these heterocyclic compounds, it may be seen that methylation at the carbonyl group of heterocyclic compounds containing a nitrogen and/or sulfur atom readily occurs, but in the case of heterocyclic compounds containing an oxygen atom no methylation



Scheme 5.

occurs.

The Methylation of Heterocyclic Compounds Containing a Thiocarbonyl Group with DMS. Reactions of 2-quinolone and coumarin derivative(s) with phosphorus pentasulfide in benzene afforded the thiocarbonyl derivatives, which were subsequently treated with DMS (Scheme 5). In the cases of the quinoline derivatives, colorless *S*-methylated products **17** and **18** were obtained, respectively. While 7-methoxy-4-methyl-2*H*-benzopyran-2-thione afforded a red compound, 7-methoxy-4-(7-methoxy-4-methylbenzopyran-2-ylidenemethyl)-2-(methylthio)benzopyrylium salt **19**, the structure of which was assigned by analogy of **2a**—**c**, based on the NMR spectrum and elemental analyses. This observation shows that the formation of the benzopyrylium salt proceeds easier in the case of 2*H*-benzopyran-2-thione containing a thiocarbonyl group than in the case of coumarins containing a carbonyl group.

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