Synthesis of 3-Dialkylaminochromans via Thallium(III)-Induced Cyclization of Allyl Aryl Ethers

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The sulfur-containing 3-alkylaminochromans, 5-methoxy-3-[N-(2-methylthioethyl)]propylamino]-chroman (15), 5-hydroxy-3-[N-(2-methylthioethyl)]propylamino]-chroman (5) and 5-methoxy-8-methylthio-3-(dipropylamino)-chroman (6), have been prepared from 8-bromo-5-methoxy-3-chromanol (11). This precursor was synthesized from 3-allyloxy-4-bromoanisole (8), by a thallium(III)-mediated ring-closure reaction. Compound 11 also served as starting material for the synthesis of 8-bromo-3-(dipropylamino)-5-methoxychroman (7).

The finding that 2-(dipropylamino)-8-hydroxytetralin (8-OH-DPAT) (1) and 2-(dipropylamino)-8-methoxytetralin (2) are potent and selective central 5-HT 1A (5-hydroxytryptamine or serotonin) receptor agonists 1 2 has initiated further interest in the synthesis and pharmacological evaluation of structural analogs. Serotonin is thought to be involved in a variety of functions in the CNS, including blood pressure regulation, depression and anxiety. 5-HT 1A receptor agonists could have a great clinical potential for the treatment of several dysfunctions in these areas.

While this work was in progress, the preparation and pharmacological evaluation of the isosteric chroman derivatives 3 and 4 were reported. 3 4 These chroman analogs of 1 and 2 are selective 5-HT 1A agonists with high potency. In compounds related to 1 and 2, the introduction of a sulfur atom into the sidechain 5 or into the ring system 6 results in potent compounds with improved bioavailability. Based on these reports we decided to synthesize compounds 5 and 6, sulfur analogs of 3 and 4, respectively, and to evaluate them pharmacologically. The bromo derivative 7 was also included in the study, to be compared with both 6 and the debranminated methoxo compound 4.

We desired 3-chromanones as intermediates. While there is extensive literature on 4-chromanones and their derivatives, considerably less work has been devoted to 3-chromanones. 7–9 We chose the thallium(III)-mediated oxidative cyclization of easily accessible allyl aryl ethers to furnish 3-chromanols in one step, reported by Porter et al., 8 despite the fact that the yields were only low to moderate. This approach has now been applied to our systems, to furnish 3-chromanones via subsequent oxidation.

We selected 3-allyloxy-4-bromoanisole (8) as the starting material. The bromine atom serves as a blocking group in the electrophilic ring closure reaction and the bromo function could, in principle, act as a handle for the introduction of a series of functionalities in the aromatic ring via metalation, including a methylthio group, as well as a hydroxy group. The latter is of potential interest with regard to metabolic studies. 10

In an initial experiment, 3-allyloxyanisole was treated with thallium(III) sulfate in 1–1.25 M sulfuric acid at 55°C for 18 h, to yield a mixture of 9 and its isomer 10 in low yield (Scheme 1). By starting from 8 (Scheme 2), we were able to isolate 8-bromo-5-methoxy-3-chromanol (11) in 24% yield, in addition to a considerable amount of tar. The preparation of 12 by oxidation with chromium trioxide-pyridine in the presence of acetic anhydride 11 occurred smoothly in 81% yield. Reductive amination of 12 with dipropylamine and sodium cyanoborohydride afforded the target compound, 8-bromo-3-(dipropylamino)-5-methoxychroman (7), in 75% yield. Reductive amination/debromination of 12 was achieved by hydrogenation with Pd/C as catalyst to provide 4. In order to introduce the methylthio group into the aromatic ring, the bromo compound 7 was treated with butyllithium followed by dimethyl disulfide to give 6.

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Scheme 1.

Scheme 2. Reagents: a, Ti$_2$O$_2$/H$_2$SO$_4$, 8 %, 9 and 22 %, 10; b, allyl bromide, K$_2$CO$_3$, 93 %; c, Ti$_2$O$_2$/H$_2$SO$_4$, 24 %; d, pyridine/CrO$_3$, acetic anhydride, 81 %; e, dipropylamine, p-toluenesulfonic acid, H$_2$, Pd/C, 77 %; f, H$_2$, Pd/C, 90 %; g, dipropylamine, p-toluenesulfonic acid, NaBH$_4$/CN, 75 %; h, BuLi (CH$_3$)$_2$, 67 %; i, pyridine/CrO$_3$, acetic anhydride, 62 %; j, ascorbic acid, acetic acid, 2-methylthioethylamine, NaBH$_4$/CN, propionyl chloride, (Et)N, 64 %; k, LiAlH$_4$, 99 %; l, HBr (48 %), 58 %.

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5-Methoxy-3-chromanol (9)13 and 7-methoxy-3-chromanol (10). To a mixture of H$_2$SO$_4$ (50 ml) and water (58 ml) at room temperature, was added Tl$_2$O$_4$ (20.4 g, 44.7 mmol). After 30 min of stirring, more water (350 ml) was added. The temperature was raised to 60°C, 3-allyloxyanisole (14.6 g, 90.0 mmol) was added and the mixture was then stirred for 16 h. Another portion of Tl$_2$O$_4$ (10.2 g, 22.3 mmol), that had been stirred for 30 min at 20°C in H$_2$SO$_4$ (25 ml) and water (30 ml), was finally added. Stirring was continued for an additional 12 h at 60°C. The reaction was cooled and extracted with chloroform and the organic layer was washed with water and dried (MgSO$_4$). The solvent was evaporated and the crude product was chromatographed (SiO$_2$) with ether as the eluant. Compound 10 was eluted first as a pure product according to GLC analyses. The fractions enriched with 9 were further chromatographed (SiO$_2$) with light petroleum–ether (1:1) as the eluant, affording pure 9 and 10. The yields of 9 and 10 were 1.16 g (8%) and 3.19 g (22%), respectively. An analytical sample of 10 was obtained after recrystallization from a mixture of light petroleum and ether.

The use of thallium(III) nitrate, chloride or tetrafluoroborate to perform the ring-closure reaction did not improve the yields, and the isomer distribution was not altered.

5-Methoxy-3-chromanol (9).13 M.p. 96–98°C. $^1$H NMR (CDCl$_3$): δ 2.1–2.4 (s, br, 1 H), 2.7–2.8 (dd, 1 H), 2.8–2.9 (dd, 1 H), 3.8 (s, 3 H), 4.0–4.1 (s, br, 2 H), 4.2–4.3 (m, 1 H), 6.4 (d, 1 H), 6.5 (d, 1 H), 7.0–7.1 (t, 1 H). $^{13}$C NMR: δ 28.40, 55.44, 62.98, 69.30, 102.53, 108.58, 109.31, 127.26, 154.60, 158.49. MS: 180 (93, M), 136 (100), 106 (44), 137 (23), 108 (22).

Compound 9 was alternatively synthesized from 11 (400 mg, 1.54 mmol) in 90% yield by catalytic hydrogenation (Pd/C, 355 kPa) in ethanol/5 M NaOH (1000:1) for 16 h.

7-Methoxy-3-chromanol (10). M.p. 62–64°C. $^1$H NMR (CDCl$_3$): δ 1.95–2.0 (s, br, 1 H), 2.65–2.75 (dd, 1 H), 2.25–3.10 (1 H), 3.7 (s, 3 H), 4.0–4.1 (m, 2 H), 4.15–4.25 (m, 1 H), 6.4 (d, 1 H), 6.5 (d, 1 H), 6.95 (d, 1 H).

$^{13}$C NMR: δ 32.94, 51.31, 63.40, 69.75, 101.52, 108.10, 111.23, 130.86, 154.49, 159.34. MS: 180 (78, 117), 137 (79), 136 (100), 108 (61), 78 (28). Anal. C$_{16}$H$_{15}$O$_2$: C, H.

3-Allyloxy-4-bromoanisole (8). To a solution of 4-bromo-3-hydroxyanisole$^{14}$ (14.49 g, 59.3 mmol) in CH$_2$CN (200 ml), were added dry potassium carbonate (20 g) and allyl bromide (8.0 ml, 92.4 mmol). The reaction mixture was stirred and refluxed for 1 h and then cooled to room temperature, filtered and evaporated. The residue was dissolved in ether and extracted with water. The organic layer was separated and dried (Na$_2$SO$_4$). Evaporation of the solvent afforded 16.0 g (93%) of 8 as an oil. MS: 244/242 (40/40, M), 163 (100), 149 (97), 135 (62). High resolution MS with EI ionization showed M$^+$ at 241.994 (Calc. 241.994). $^1$H NMR (CDCl$_3$): δ 3.8 (s, 3 H), 4.6–4.7 (m, 2 H), 5.3–5.5 (m,
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8-Bromo-5-methoxy-3-chromanol (11). To a mixture of H$_2$SO$_4$ (6.9 ml) and water (6.1 ml) at room temperature, was added Tl$_2$O$_3$ (2.38 g, 5.22 mmol). The mixture was stirred for 30 min and water (37 ml) was added. The temperature was then raised to 60°C and 8 (2.16 g, 8.89 mmol) was added. The mixture was stirred at 60°C for 4.5 h. Another portion of Tl$_2$O$_3$ (1.0 g, 2.19 mmol), that had been stirred for 30 min at 20°C in H$_2$SO$_4$ (2.6 ml) and water (3 ml), was finally added. Stirring of the reaction mixture was continued for an additional 17 h at 60°C. After being cooled the mixture was extracted with CHCl$_3$. The organic layer was washed with water, dried (MgSO$_4$) and evaporated. The crude product was chromatographed (SiO$_2$) with ether as the eluant and 552 mg (24%) of 11 was isolated. An analytical sample of 11 was obtained after recrystallization from a mixture of light petroleum and ether, m.p. 115-117°C.

$^1$H NMR (CDCl$_3$): δ 2.0-2.1 (s, br, 1 H), 2.7-2.8 (dd, 1 H), 2.9-3.0 (dd, 1 H), 4.1 (s, 3 H), 4.8-5.0 (m, 3 H), 6.4 (d, 1 H), 6.7 (d, 1 H). $^{13}$C NMR: δ 28.65, 55.64, 62.64, 70.08, 101.85, 103.79, 110.34, 130.49, 150.75, 157.70. MS: 260/258 (100/100, M), 216 (93), 214 (91), 185 (50). Anal. C$_{10}$H$_8$Br$_3$O$_3$: C, H, N.

8-Bromo-5-methoxy-3-chroman (12). Dry pyridine (0.7 ml, 8.77 mmol) in CH$_2$Cl$_2$ (120 ml, dried over P$_2$O$_5$) was treated with CrO$_3$ (435 mg, 4.35 mmol). The mixture was stirred for 15 min and a solution of 11 (293 mg, 1.13 mmol) in dry CH$_2$Cl$_2$ (10 ml) was added immediately followed by acetic anhydride (0.41 ml, 4.35 mmol). Stirring was continued for an additional 10 min. The mixture was filtered through a short silica column (13 g, SiO$_2$) under vacuum. Fast filtration was essential to avoid decomposition. The column was washed with CH$_2$Cl$_2$ and evaporation of the solvent gave 237 mg (81%) of 12. An analytical sample of 12 was obtained after recrystallization from a mixture of light petroleum and ether, m.p. 97-100°C. Attempts to use Moffat oxidation, pyridinium chlorochromate oxidation or silica/chromium trioxide oxidation were unsuccessful.

$^1$H NMR (CDCl$_3$): δ 3.55 (s, 2 H), 3.80 (s, 3 H), 4.45 (s, 2 H), 6.5 (d, 1 H), 7.4 (d, 1 H). MS: 258/256 (64/57, M), 134 (100), 76 (11), 50 (11). Anal. C$_{10}$H$_8$Br$_3$O$_3$: C, H.

8-Bromo-3-(dipropylamino)-5-methoxycrom (7). To a solution of 12 (550 mg, 2.14 mmol) in benzene (40 ml), dipropylamine (1.8 ml, 13.2 mmol) and p-toluene sulfonic acid monohydrate (41 mg, 0.52 mmol) were added. The solution was refluxed for 5 h with a Dean-Stark apparatus under a nitrogen atmosphere. After the reaction had been cooled to room temperature, a solution of NaBH$_4$CN (2.0 g, 32 mmol) in methanol (50 ml) was added and stirring was continued overnight. Water (50 ml) and 2 M NaOH (5 ml) were added. The solution was extracted with CHCl$_3$. The organic layer was separated, washed with water and dried (Na$_2$SO$_4$). The solvent was evaporated and the residue chromatographed (SiO$_2$) with light petroleum ether (3:1) as the eluant, yielding 550 mg (75%) of 7 as an oil.

$^1$H NMR (CDCl$_3$): δ 0.6-0.9 (t, 6 H), 1.1-1.6 (m, 4 H), 2.5-3.3 (m, 8 H), 3.75 (s, 3 H), 4.2-4.5 (m, 1 H), 6.25-6.35 (d, 1 H), 7.2-7.4 (d, 1 H). MS: 343/341 (10/10, M), 314 (91), 312 (100), 241 (80).

The amine was converted into its hydrochloride with HCl-saturated ethanol. Evaporation and recrystallization from a mixture of ethanol and ether gave 7·HCl, m.p. 180-182°C. Anal. C$_{16}$H$_{25}$BrNO$_2$Cl: C, H, N.

3-(Dipropylamino)-5-methoxychrom (4). To a solution of 12 (125 mg, 0.49 mmol) in benzene (20 ml), dipropylamine (0.5 ml, 3.7 mmol) and $p$-toluenesulfonic acid monohydrate (10 mg, 0.08 mmol) were added. The solution was refluxed for 5 h in a Dean-Stark apparatus under a nitrogen atmosphere. The reaction mixture was transferred to a Parr flask, absolute EtOH was added (50 ml) and the pH was adjusted to 11 with 2 M NaOH. The product was hydrogenated overnight with Pd/C as the catalyst at 355 kPa. The catalyst was filtered off and the solvent was evaporated. The residual oil was dissolved in CH$_2$Cl$_2$ and washed with 5% aqueous Na$_2$CO$_3$. The phases were separated and the organic layer was dried (Na$_2$SO$_4$) to yield 99 mg (77%) of 4 as an oil with physical data in accordance with those reported in the literature.

3-(Dipropylamino)-5-methoxy-8-methylthiochrom (6). A solution of 7 (174 mg, 0.51 mmol) in dry ether was treated with 1.6 M butyllithium in hexane (0.6 ml, 0.96 mmol) at 0°C for 30 min under a dry argon atmosphere. Dry, distilled dimethyl disulfide was added (0.2 ml, 2.3 mmol) and the reaction mixture was stirred for 2 h at 0°C. The mixture was allowed to reach room temperature, water was added and the phases were separated. The organic layer was washed with water, separated and dried (Na$_2$SO$_4$). The solvent was evaporated and the remaining oil chromatographed (SiO$_2$) with light petroleum ether (3:1) as the eluant, yielding 105 mg (67%) of 6 as an oil. $^1$H NMR (CDCl$_3$): δ 0.7-1.1 (t, 6 H), 1.2-1.7 (m, 4 H), 2.4 (s, 3 H), 2.45-3.40 (m, 8 H), 3.9 (s, 3 H), 4.4-4.6 (m, 1 H), 6.45-6.55 (d, 1 H), 7.15-7.30 (d, 1 H). MS: 309 (41, M), 280 (99), 209 (100), 162 (26), 281 (19).

The amine was converted into its hydrochloride with HCl-saturated ethanol. Evaporation and recrystallization from a mixture of light petroleum and ether gave 6·HCl, m.p. 138-140°C. Anal. C$_{16}$H$_{25}$NO$_2$SCl·C$_7$H$_8$OH·C, H, N. Ethanol incorporation of the hydrochloride of 6 was verified by $^1$H NMR spectroscopy.

5-Methoxy-3-chromanone (13). 5-Methoxy-3-chromannone 13 was obtained from the oxidation of 9 (445 mg, 2.5 mmol), by analogy with the synthesis of 12, in 62% yield. MS: 178 (100, M), 177 (83), 135 (20), 91 (18), 43 (22).
5-Methoxy-3-[N-(2-methylthioethyl)propylamino]chroman (14). To a solution of acetic acid (400 mg, 2.27 mmol) and acetic acid (400 mg, 6.99 mmol) in absolute ethanol (10 ml) was added 13 (250 mg, 1.40 mmol), followed by 2-methylthioethylamine (0.6 ml, 6.41 mmol). The solution was stirred with 4 Å molecular sieves for 1 h 15 min. Methanol (25 ml) was added followed by NaBH₄CN (1.5 g, 23.8 mmol) dissolved in methanol (10 ml). After 30 min of stirring, water was added (50 ml) and the pH adjusted with 2 M NaOH to 11. The mixture was extracted with CH₂Cl₂. The phases were separated and the organic layer washed with water, dried (Na₂SO₄) and evaporated. The crude product was immediately propronylated with propionyl chloride (0.5 ml, 5.72 mmol) in CH₂Cl₂ (20 ml) and triethylamine (1 ml, 7.22 mmol). The reaction mixture was stirred for 30 min, washed with 5% aqueous Na₂CO₃ solution, 1 M HCl and water. The organic layer was separated and dried (MgSO₄). The solvent was evaporated and the crude product chromatographed (SiO₂) with light petroleum ether (1:1) as the eluant, yielding 276 mg (64% of 14) as an oil.

¹H NMR (CDCl₃): δ 1.1–1.3 (t, 3 H), 1.90–3.05 (m, 9 H), 3.30–3.65 (m, 2 H), 3.85 (s, 3 H), 4.05–4.40 (t, br. 2 H), 4.5–4.8 (s, br, 1 H), 6.4–6.7 (dd, 2 H), 7.05–7.3 (t, 1 H). MS: 310 (0.2, M), 192 (22), 163 (50), 162 (100), 161 (54). High resolution MS with FAB ionization showed M⁺+H at 311.141 (Calc. 311.157).

5-Methoxy-3-[N-(2-methylthioethyl)propylamino]chroman (15). A solution of 14 (207 mg, 0.70 mmol) in dry ether (10 ml) was cooled with ice and LiAlH₄ (250 mg, 6.59 mmol) was added. The mixture was stirred at 0°C for 40 min. The usual work-up gave 195 mg (99%) of 15 as an oil.

¹H NMR (CDCl₃): δ 0.80–0.95 (t, 3 H), 1.40–1.55 (m, 2 H), 2.10 (s, 3 H), 2.45–3.20 (m, 8 H), 3.70–3.90 (m, 2 H), 3.90 (2.3 H), 4.2–4.3 (m, 1 H), 6.40–6.55 (dd, 2 H), 7.0–7.1 (t, 1 H). MS: 295 (0.1, M), 235 (15), 234 (98), 164 (10), 163 (100). High resolution MS with FAB ionization showed M⁺+H at 296.165 (Calc. 296.168).

5-Hydroxy-3-[N-(2-methylthioethyl)propylamino]chroman (5). A solution of 15 (166 mg, 0.56 mmol) in 48% aqueous HBr was heated at 120°C for 30 min under a nitrogen atmosphere. The hydrobromic acid was evaporated and the residue was evaporated several times with absolute EtOH. Water was added and the pH adjusted to 11 with 10% Na₂CO₃ solution. The aqueous solution was extracted with CH₂Cl₂. The organic layer was separated, dried and the solvent was evaporated. The crude product was chromatographed (SiO₂) with light petroleum ether (3:1) as the eluant, to yield 85 mg (54%) of 5 as an oil.

¹H NMR (CDCl₃): δ 0.85–1.0 (t, 3 H), 1.4–1.8 (m, 2 H), 2.1 (s, 3 H), 2.45–3.15 (m, 9 H), 3.8–4.1 (m, br. 2 H), 4.25–4.35 (m, 1 H), 6.2–6.5 (d, 2 H), 6.9–7.0 (t, 1 H).

The amine was converted into its hydrochloride with HCl-saturated ethanol. Evaporation and recrystallization from a mixture of ethanol and ether gave 5·HCl, m.p. 125–130°C. Anal. C₁₅H₁₇NO₅SCl × C₄H₉OH: C, H, N.

Ethanol incorporation of the hydrochloride of 5 was verified by ¹H NMR spectroscopy.

References


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