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Synthesis of 2-[(3-Aminoalkyl or 3-Bromoalkyl)amino]-4H-1-Benzopyran-4-One Derivatives.

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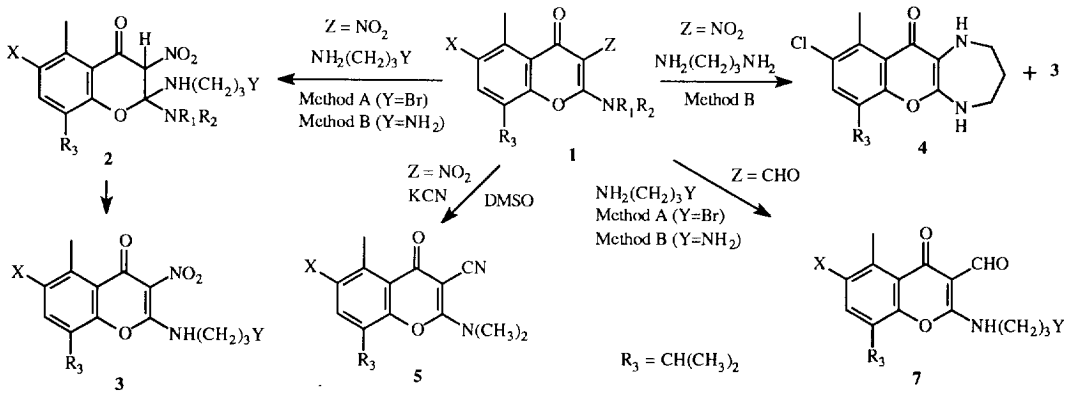
Abstract: The title compounds were advantageously synthesized from 2-(dialkylamino)chromones and 1,3-diaminopropane (or 1-amino-3-bromopropane) by amine exchange. The 3-cyano derivatives **5** were directly prepared from 2-(dimethylamino)chromones **1** and KCN by nitro displacement.

Oligonucleotides (ODN) carrying reactive groups have been developed during recent years to direct specific reactions at preselected sequences on single-stranded nucleic acids. We have recently shown[1] that α and γ-pyrones are useful stabilizing agents compared to the well established acridine derivatives. In order to find new stabilizing agents, both with more complexation ability and penetrating activity, we thought of synthesizing new chromone derivatives with either an ω-bromo or ω-aminoalkylaminogroup in position 2 because this moiety will have to be linked to the ODN and groups of biological interest such as CHO or CN, as well as NO_2 on position 3.



The first goal was achieved by extending and refining our method[2] involving amine exchange in compounds **1** (X=NO_2 or Cl)[3] by treating such γ-pyrone derivatives with amines. This behaviour, while in agreement with that of nitroenamines, is unusual in chromones in which treatment with amines generally gives rise to a ring opening of the pyrone, leading to the formation of substitute aryl systems[4a,b]. Along with the desired compounds **3**[5a,b;6], we isolated the addition compound **2**[5a,b;6], which shed light on the mechanism involved in these reactions, and the 9-chloro-2,3,4,5-tetrahydro-7-isopropyl-10-methyl-[1]benzopyrano[2, 3-b][1, 4]diazepin-11(1H)-one **4**[5a,b;6] (new heterocyclic system) resulting from further intramolecular displacement of NO_2 by the new amino substituent. Compounds **7**[5a,b;6] were obtained from **1** (Z = CHO)[7] by

the same method we prepared **3**, confirming that the nucleophilic substitution of NR_1R_2 groups occurs when there is an electronwithdrawing group in position 3, and the reaction proceeds without ring cleavage. The nature of the X and NR_1R_2 groups influenced the yields[8] but not the course of the reaction.

The second aim was accomplished by taking advantage of the reactivity of position 3 of the chromones. In particular, the 3-cyano derivatives **5**[5b,6] were directly obtained in 85% yield from **1** and KCN in DMSO at 60°C for 1h. The structure of these compounds was confirmed by comparison (IR, mixed mp) with samples obtained by a separate synthesis from **6** via the oxime derivatives **8**[9]. To our knowledge this is the first example of nucleophilic displacement of a nitro group by a cyano group in a nitroenamine system.

The nitro displacement in position 3 and the amine exchange in position 2 of our chromones **1** makes it possible to synthesise 4H-1-benzopyran-4-one derivatives not easily obtainable in other ways.

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5. a) In a typical procedure A (Y=Br), the mixture of **1** (2,8 mmol), 3-bromopropylamine (2,8 mmol) and 3 ml of triethylamine in 50ml of anhydrous ethanol was heated at 85°C for 6h. After removing the volatiles *in vacuo*, the residue was chromatographed on a silica gel column eluting first with toluene-ethyl acetate (1:1 v/v) and secondly with ethanol. The first eluted gave **3** or **7b** (X=H, Y=Br), while the second furnished **2** (if present). Typical procedure B ($Y=NH_2$): the mixture of **1** (2,5 mmol), 1,3-diaminopropane (2,5 mmol) in 50ml of toluene was heated at 110°C for 1h. As in procedure A, the residue was chromatographed on a silica gel column obtaining **3** or **7a** (X=H, $Y=NH_2$) and **4** [only from **1b** ($R_1=R_2=CH_3$, X=Cl)]. b) All compounds displayed satisfactory ^1H NMR, IR, and microanalytical data. For example, **3b** (X=Br, $Y=NO_2$) : IR (KBr) 3265 (NH), 1640 (CO) cm^{-1}. ^1H-NMR ($CDCl_3$, 60 MHz) δ 1.34 [d, 6H, $CH(\underline{CH_3})_2$], 2.38 (q, 2H, CH_2), 2.81 (s, 3H, 5-CH_3), 3.18-4.20 [m, 5H, $\underline{CH}(CH_3)_2$ + CH_2Br + $NHCH_2$], 7.82 (s, 1H, H-7), 9.95 (bs, 1H, NH, deuterium oxide exchangeable). **4**: IR (KBr) 3180b and a complex broad bands between 3200~2500 (1-NH+5-NH), 1640 (CO), 1595, 1545 cm^{-1}. ^1H-NMR ($CDCl_3$, 60 MHz) δ 1.22 [d, 6H, $CH(\underline{CH_3})_2$], 2.03 (s, 2H, CH_2), 2.79 (s, 3H, 10-CH_3), 3.15-3.70 (m, 5H, $\underline{CH}(CH_3)_2$ + $NHCH_2$), 5.90 (bs, 1H, NH, deuterium oxide exchangeable), 7.20 (s, 1H, H-8), 8.70 (bs, 1H, NH, deuterium oxide exchangeable). ESPI-MS m/z 307.7 (M^+, 100). **7b**: IR (KBr) 1666 (CHO), 1632 (CO) cm^{-1}. ^1H-NMR ($CDCl_3$, 60 MHz) δ 1.32 [d, 6H, $CH(\underline{CH_3})_2$], 2.31 (q, 2H, CH_2), 2.83 (s, 3H, 5-CH_3), 3.20-4.12 [m, 5H, $\underline{CH}(CH_3)_2$ + CH_2Br + $NHCH_2$], 7.13 (d, H-6, 1H, J=7.8 Hz), 7.44 (d, H-7, 1H, J=7.8 Hz), 10.20 (s, 1H, CHO), 10.51 (bs, 1H, NH, deuterium oxide exchangeable). **5a** and **5b**: IR (KBr) 2215 (CN) cm^{-1}.
6. Melting points: **2a** ($X=NO_2$, $Y=NH_2$) 204-5°C; **3a** ($X=NO_2$, $Y=NH_2$) 160-1°C; **3b** ($X=NO_2$, Y=Br) 211-2°C; **4**, 235°C; **5a** (X=Cl) 169-70°C; **5b** ($X=NO_2$) 194-5°C; **6b** ($X=NO_2$) 152-3°C; **7a** (X=H, Y=NH2) 215°C (dec.); **7b** (X=H, Y=BR) 131-2°C; **8a**
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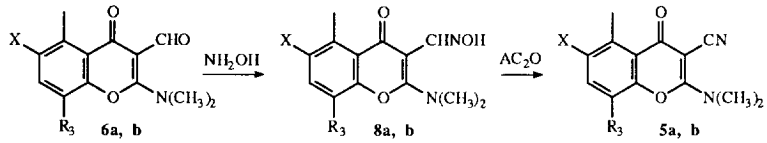
8. Example: yield of **3a** ($X=NO_2$, $Y=NH_2$): from **1a** ($R_1=R_2=CH_3$, $X=NO_2$) (40%), from **1c** ($R_1=R_2=C_2H_5$, $X=NO_2$) (25%).

9. 

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