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A Convenient Synthesis of 2-Substituted 3-Nitro-2*H*-chromene Derivatives[1)]

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Synopsis. On reaction with salicylaldehyde, ω-nitrostyrene and 4,6-dimethoxy-5-(2-nitrovinyl)pyrimidine gave a mixture of 3-nitro-4-hydroxyflavan and 3-nitro-2-phenyl-2*H*-chromene or 2-(4,6-dimethoxy-5-pyrimidinyl)-3-nitro-2*H*-chromene, respectively, whereas 4,6-dichloro-5-(2-nitrovinyl)-pyrimidine afforded substitution products: 4-chloro-6-(2-formylphenoxy)-5-(2-nitrovinyl)pyrimidine and 4,6-bis(2-formylphenoxy)-5-(2-nitrovinyl)pyrimidine.

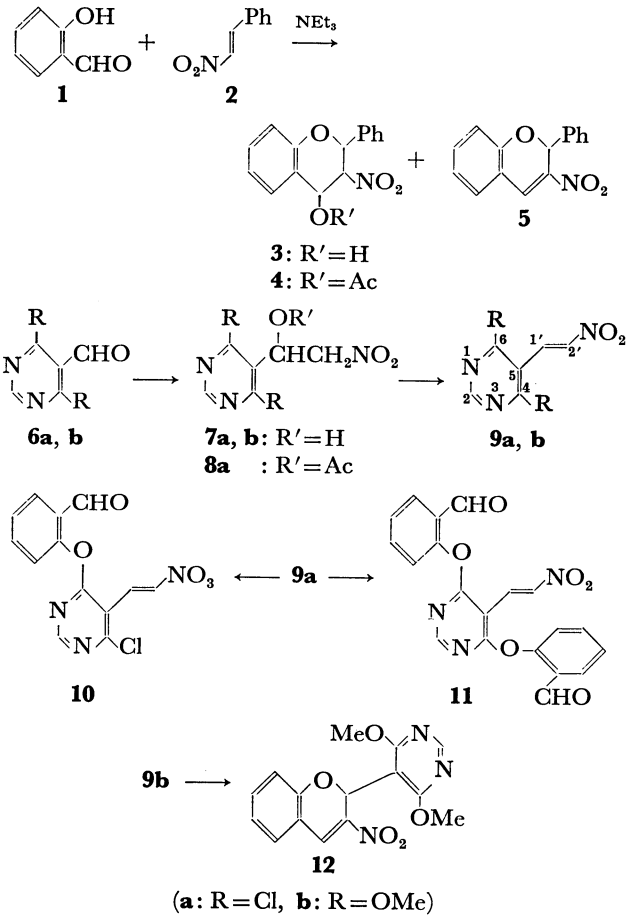
C-Nucleosides frequently have interesting biological activities, and several synthetic studies on these compounds have been reported.[2)] In a series of studies on nucleophilic addition reactions to nitro olefin derivatives, we designed the synthesis of C-nucleosides from β-hydroxy aldehyde and nitro olefins. As a preliminary examination we have carried out the reaction of (2-nitrovinyl)pyrimidine derivatives with salicylaldehyde.

Treatment of salicylaldehyde (**1**) with ω-nitrostyrene (**2**) in the presence of triethylamine afforded a mixture of two cyclic compounds, 3-nitro-4-hydroxyflavan (**3**) and 3-nitro-2-phenyl-2*H*-chromene (**5**), in a *ca.* 1:1 ratio in 69% yield. The *trans-trans* structure of the nitro alcohol **3** was determined by the NMR spectrum of its nitro acetate **4**; $J_{2,3}=10$, $J_{3,4}=8.3$ Hz. The structure of 3-nitro-2-phenyl-2*H*-chromene (**5**) was deduced from analytical, IR, and NMR data.[3)]

To extend this ring formation, (2-nitrovinyl)-pyrimidine derivatives **9a** and **9b** were prepared from the corresponding 5-formylpyrimidine **6a** and **6b**, respectively. Nitromethane condensation of 4,6-dichloro-5-formylpyrimidine **6a**[4)] in the presence of sodium or potassium hydroxide, sodium methoxide, or triethylamine as a basic catalyst failed. However, in the presence of barium hydroxide the intended nitro alcohol **7a** was isolated in 62% yield. On the other hand, 4,6-dimethoxy-5-formylpyrimidine **6b**[5)] smoothly reacted with nitromethane in the presence of triethylamine, giving the nitro alcohol **7b**. Acetylation of the nitro alcohol **7a** and **7b** with acetic anhydride-boron trifluoride etherate and subsequent elimination of acetic acid with sodium hydrogencarbonate afforded the nitro olefins **9a** and **9b**, respectively.

Treatment of the nitro olefin **9a** with equimolar salicylaldehyde under various conditions (solvents, reaction temperature, and amounts of triethylamine) resulted in a colored solution, from which no desired product was isolated. When **9a** was treated with salicylaldehyde in the presence of *ca.* 1.4 equivalents of sodium 2-formylphenoxide in DMSO, 4-chloro-6-(2-formylphenoxy)-5-(2-nitrovinyl)pyrimidine (**10**) was isolated in 65% yield. A similar treatment of **9a** with 2.1 equivalents of sodium 2-formylphenoxide yielded 4,6-bis(2-formylphenoxy)-5-(2-nitrovinyl)pyrimid ine. These results showed that the chlorine atoms were more reactive to 2-formylphenoxide than the nitro olefin moiety under the conditions employed.

Under the conditions used for preparation of the flavan **3** and chromene **5**, the reaction of **9b** with salicylaldehyde did not occur, because **9b** was immediately precipitated when triethylamine was added. But treatment of **9b** with two equivalents of salicylaldehyde in the presence of 0.1 equivalent of sodium 2-formylphenoxide in DMSO at room temperature for 24 h gave the 2*H*-chromene derivative **12** as yellow crystals in 46% yield. Its IR spectrum showed the presence of a conjugated nitro group and characteristic absorption bands due to pyrimidine and benzene ring. The NMR spectrum supports the structure of **12.**



Experimental

Melting points were taken in capillaries and are uncorrected. NMR spectra were recorded at 60 MHz on a Varian T-60 spectrometer (except compound **4**, which was analyzed at 100 MHz on a JNM-4H-100 (JEOL) spectrometer), in chloroform-*d* using tetramethylsilane as internal standard.

t-3-Nitro-c-2-phenyl-r-1-chromanol (3). To a solution of **2** (3.0 g, 20 mmol) in **1** (7.5 g, 61.5 mmol) was added 0.2 g

(2 mmol) of triethylamine. The mixture, which gradually solidified, was allowed to stand for 16 h at room temperature. The resulting crystalline solid was broken up and dissolved in hot ethanol. The solution was filtered to remove insoluble material. After evaporation of the filtrate, the residue was washed several times with carbon tetrachloride and recrystallized from ethanol to give 1.68 g (31%) of **3** as colorless crystals: mp 138.5—139.5 °C; IR 3290 (OH), 1552, and 1376 cm^{-1} (NO_2). Found: C, 66.50; H, 4.79; N, 5.27%. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16%.

t-3-Nitro-c-2-phenyl-r-1-chromanyl Acetate (4). A solution of **3** (300 mg, 1.1 mmol) in 3 ml of acetic anhydride was left at room temperature for 6 h in the presence of catalytic amounts of boron trifluoride etherate. Addition of 20 ml of water to the reaction mixture gave a precipitate (312 mg, 90.5%), which was recrystallized from ethanol to give colorless needles of **4** (87%): mp 183—184 °C; IR 1738 (C=O), 1550 and 1368 cm^{-1} (NO_2); NMR δ 2.13 (Ac), 5.39 (1H, d, $J_{2,3}$= 10 Hz, H-2), 5.15 (1H, d, $J_{3,4}$=8.3 Hz, H-3), and 6.98 (1H, d, H-4). Found: C, 65.15; H, 4.79; N, 4.50%. Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.82; N, 4.47%.

3-Nitro-2-phenyl-2H-chromene (5). The carbon tetrachloride solution obtained in the preparation of **3** was evaporated to give a yellow residue, which was recrystallized from ethanol to afford yellow crystals (1.9 g, 38%) of **5**: mp 92.5—93.5 °C (lit,[3] 87 °C); IR 1640 (C=C), 1502 and 1320 cm^{-1} (NO_2); NMR δ 6.59 (1H, s, H-2) and 8.09 (1H, s, H-4). Found: C, 70.86; H, 4.37; N, 5.73%. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.37; N, 5.53%.

4,6-Dichloro-5-(1-hydroxy-2-nitroethyl)pyrimidine (7a). To a mixture of **6a**[4] (500 mg, 2.8 mmol) and nitromethane (3.44 g, 56 mmol) in methanol (20 ml) at room temperature was added barium hydroxide octahydrate (221 mg, 0.7 mmol). The mixture was stirred for 3 h at 5 °C and then neutralized with cation-exchange resin (Mitsubishi Diaion SK 1). Evaporation of the solvent gave a solid residue, which was recrystallized from ethanol to yield colorless crystals of **7a** (419 mg, 62.4%): mp 102.5—103.5 °C; IR 3250 (OH), 1548 and 1377 cm^{-1} (NO_2). Found: C, 30.51; H, 2.09; N, 18.02%. Calcd for $C_6H_5Cl_2N_3$: C, 30.25; H, 2.10; N, 17.65%.

5-(1-Acetoxy-2-nitroethyl)-4,6-dichloropyrimidine (8a). A solution of **7a** (500 mg, 2.1 mmol) in 5 ml of acetic anhydride was allowed to stand for 6 h at room temperature in the presence of a catalytic amount of boron trifluoride etherate, and then poured into water (20 ml). The crystalline precipitate was collected and washed well with water. Recrystallization from ethanol gave colorless crystals of **8a** (511.6 mg, 87%): mp 87.5—88.5 °C; IR 1758 (C=O), 1548 and 1378 cm^{-1} (NO_2). Found: C, 34.29; H, 2.49; N, 15.24%. Calcd for $C_8H_7Cl_2N_3O_4$: C, 34.29; H, 2.50; N, 15.00%.

4,6-Dichloro-5-(2-nitrovinyl)pyrimidine (9a). To a solution of **8a** (500 mg, 1.79 mmol) in 30 ml of methanol was added solid sodium hydrogencarbonate (150 mg, 1.78 mmol). The mixture was stirred for 1 h at room temperature and then poured into 100 ml of water. The precipitate was collected and recrystallized from ethanol to give yellow crystals of **9a** (303 mg, 77%): mp 90.5—91.5 °C; IR 1642 (C=C), 1504, and 1340 cm^{-1} (NO_2); NMR δ 7.85 (1H, d, $J_{1',2'}$=14 Hz, H-2'), 8.22 (1H, d, H-1'), and 8.83 (1H, s, pyrimidine ring proton). Found: C, 33.00; H, 1.38; N, 19.31%. Calcd for $C_6H_3Cl_2N_3O_2$: C, 32.73; H, 1.36; N, 19.09%.

5-(1-Hydroxy-2-nitroethyl)-4,6-dimethoxypyrimidine (7b). To a mixture of **6b**[5] (500 mg, 2.97 mmol) and nitromethane (3.63 g, 59.5 mmol) in 50 ml of ethanol was added triethylamine (29 mg, 0.3 mmol). The mixture was allowed to stand for 4 h at room temperature and then evaporated to afford a solid residue, which was recrystallized from ethanol to give colorless crystals of **7b** (518 mg, 76%): mp 121—122 °C; IR 3200 (OH), 1550 and 1375 cm^{-1} (NO_2); NMR δ 4.45 (1H, q, J_{gem}=12.5, $J_{1a',2'}$=4 Hz, H-1a'), 4.92 (1H, q, $J_{1b',2'}$=9 Hz, H-1b'), 5.75 (1H, q, H-2'), and 8.45 (1H, s, pyrimidine ring proton). Found: C, 41.83; H, 4.95; N, 18.48%. Calcd for $C_8H_{11}N_3O_5$: C, 41.92; H, 4.84; N, 18.34%.

4,6-Dimethoxy-5-(2-nitrovinyl)pyrimidine (9b). Crude acetate obtained from **7b** (1.30 g, 5.67 mmol) under the same conditions as described above was directly treated with sodium hydrogencarbonate (510 mg, 6 mmol) in methanol at room temperature for 1 h. The mixture was evaporated to give a solid residue, which was washed completely with water and then recrystallized from ethanol to afford 791 mg (66%) of **9b** as light yellow crystals: mp 131—132 °C; IR 1620 (C=C) and 1500 cm^{-1} (NO_2); NMR δ 7.95 (1H, d, $J_{1',2'}$=14 Hz, H-2'), 8.32 (1H, d, H-1'), and 8.51 (1H, s, pyrimidine ring proton). Found: C, 45.38; H, 4.28; N, 20.04%. Calcd for $C_8H_9N_3O_4$: C, 45.50; H, 4.30; N, 19.90%.

4-Chloro-6-(2-formylphenoxy)-5-(2-nitrovinyl)pyrimidine (10). A solution of **9a** (220 mg, 1 mmol), sodium 2-formylphenoxide (196 mg, 1.36 mmol) and salicylaldehyde (1 ml) in DMSO (20 ml) was allowed to stand at room temperature for 20 h. The mixture was poured into water (50 ml) and the precipitate was collected and recrystallized from ethanol to give yellow crystals of **10** (65%): mp 126 °C; IR 1700 (C=O), 1633 (C=C), 1522 and 1340 cm^{-1} (NO_2). Found: C, 50.76; H, 2.81; N, 13.40%. Calcd for $C_{13}H_8ClN_3O_4$: C, 51.06; H, 2.62; N, 13.75%.

4,6-Bis(2-formylphenoxy)-5-(2-nitrovinyl)pyrimidine (11). A treatment of **9a** (220 mg) with sodium 2-formylphenoxide (300 mg, 2.1 mmol) similar to that described above gave yellow crystals of **11** (46%): mp 229—230 °C; IR 1692 (C=O), 1629 (C=C), and 1512 cm^{-1} (NO_2). Found: C, 60.93; H, 3.36; N, 10.64%. Calcd for $C_{20}H_{13}N_3O_6$: C, 61.38; H, 3.35; N, 10.74%.

2-(4,6-Dimethoxy-5-pyrimidinyl)-3-nitro-2H-chromene (12). To a solution of sodium 2-formylphenoxide (14.1 mg, 0.1 mmol) in DMSO (20 ml) were added **9b** (211 mg, 1 mmol) and **1** (183 mg, 1.5 mmol). The mixture was allowed to stand for 24 h at room temperature and then poured into ice-water. The precipitate was collected and recrystallized from ethanol to give 145 mg (46%) of **12** as yellow crystals: mp 143.5—144.5 °C; IR 1652 (C=C), 1502 and 1328 cm^{-1} (NO_2); NMR δ 3.82 (6H, s, 2×OMe), 7.27 (1H, s, H-2), 7.99 (1H, s, H-4), and 8.43 (1H, s, pyrimidine ring proton). Found: C, 56.97; H, 4.15; N, 13.39%. Calcd for $C_{15}H_{13}N_3O_5$: C, 57.14; H, 4.16; N, 13.33%.

References

1) T. Sakakibara, R. Sudoh, and M. Koezuka, 28 th National Meeting of the Chemical Society of Japan, Tokyo, April 1973, Abstr. p. 1731,

2) S. Hanessian and A. G. Pernet, *Adv. Carbohydr. Chem. Biochem.*, **33**, 111 (1976).

3) During our studies Rene and Royer synthesized 3-nitro-2-phenyl-2*H*-chromene (**5**) from **1** and **2** in pyridine in 34% yield; L. Rene and R. Royer, *Eur. J. Med. Chem.-Chim. Ther.*, **10**, 72 (1975).

4) H. Bredereck, G. Simchen, and A. A. Santos, *Chem. Ber.*, **100**, 1344 (1967).

5) W. Klotzer and M. Herberz, *Monatsh. Chem.*, **96**, 1573 (1965).