Notes

[Chem. Pharm. Bull. 33(5)2129—3132(1985)]

Synthesis of New Pyrimidine Derivatives from 2-Methyl-3-nitro- and 3-Amino-2-methylchromones

MASAAKI TANAKA, YUKITOSHI MURAKAMI, HIKARI MORITA and KANAME TAKAGI*

Central Research Laboratories, Zeria Pharmaceutical Co., Ltd., 2512–1, Oshikiri, Konan-mura, Osato-gun, Saitama 360–01, Japan

(Received August 27, 1984)

Reactions of 2-methyl-3-nitrochromone (**1**) with guanidine, acetamidine and benzamidine readily gave the corresponding 2-substituted-6-(2-hydroxyphenyl)-4-methyl-5-nitropyrimidine (**3a—c**) in good yields, and these were converted to 6-(2-methoxyphenyl)pyrimidines (**4a—c**) by treatment with methyl iodide and to 5-aminopyrimidines (**5a—c**) by catalytic hydrogenation. 3-Amino-2-methylchromone (**2**) reacted with guanidine, but not amidines, to give 2,5-diamino-6-(2-hydroxyphenyl)-4-methylpyrimidine (**5a**). 3-Acetamido-2-methylchromone (**6**) was converted more readily than **2** into pyrimidine derivatives (**7a, c**) by the reactions with guanidine and benzamidine, respectively.

Keywords——2-methyl-3-nitrochromone; 3-amino-2-methylchromone; 6-(2-hydroxyphenyl)-5-nitropyrimidine; 6-(2-methoxyphenyl)-5-nitropyrimidine; 5-amino-6-(2-hydroxyphenyl)pyrimidine; pyrimidine synthesis; ring transformation

In the course of a synthetic study on pyrimidines by ring transformation of oxygen heterocycles,[1] one of the authors (K.T.) earlier reported[2] that 2- or 3-alkyl (or aryl) chromones reacted with nucleophiles such as guanidine, amidines, thiourea and urea to give 2-amino-, 2-alkyl-, 2-thioxo- and 2-oxo-6-(2-hydroxyphenyl)pyrimidines, respectively. Other studies have also demonstrated[3] that pyrimidines are formed from 3-acylchromones which are more susceptible to nucleophilic attack because of the electron-withdrawing group at position 3.

Our interest in chromones as substrates for the synthesis of biologically active pyrimidines led us to study the reactions of 2-methyl-3-nitrochromone (**1**) and 3-amino-2-methylchromone (**2**) with amidines and their analogues. We now describe the synthesis of new derivatives of pyrimidine, 2-substituted-6-(2-hydroxyphenyl)-4-methyl-5-nitro and 2-substituted-5-amino-6-(2-hydroxyphenyl)-4-methylpyrimidines and their derivatives, starting from **1** and **2**.

Haas *et al.*[4] reported that 3-nitrochromone acted as an efficient Michael acceptor at position 2 for nucleophiles such as amines, enamines and enolates. We also found that the chromone **1**, prepared by the reaction of 2′-hydroxy-2-nitroacetophenone with acetic anhydride according to the method of Becket and Ellis,[5] readily reacted at position 2 wtih guanidine and amidines to give pyrimidines. Treatment of **1** with an excess (3 mol eq amount) of guanidine, acetamidine or benzamidine, in boiling anhydrous ethanol for 10 min gave the corresponding 2-substituted-6-(2-hydroxyphenyl)-4-methyl-5-nitropyrimidines (**3a—c**) in 71—94% yields (Chart 1). Analogous reaction of **1** with thiourea in the presence of sodium ethoxide yielded many unidentified products. Since the reactions of 2- or 3-alkylchromones

with amidines and their analogues to form pyrimidines required prolonged heating in the presence of sodium ethoxide,[2] the above results suggest that **1** is highly sensitive to nucleophilic attack owing to the nitro group at position 3. The structures of **3a—c** were determined on the basis of their elemental analyses and spectral data (Table I). In particular, the nuclear magnetic resonance (NMR) spectra of **3a—c** showed the signal due to the phenolic hydroxyl protons at 9.97—10.26 ppm. In fact, **3a—c** could be methylated to give the corresponding 6-(2-methoxyphenyl)pyrimidines (**4a—c**) on treatment with methyl iodide in the presence of an alkali in methanol (Chart 1). This was confirmed from the NMR spectra (Table I) where the characteristic signal of methoxyl protons appeared at 3.65—3.76 ppm with disappearance of the hydroxyl proton signal observed in the NMR spectra of **3a—c**. These observations indicate that O^1–C^2 bond cleavage of **1** was caused by attack of the nucleophiles, and consequently, provide support for the formation of the proposed pyrimidine ring system.

Compounds **3a—c** were reduced by catalytic hydrogenation with 5% Pd–C in methanol to give 2-substituted-5-amino-6-(2-hydroxyphenyl)-4-methylpyrimidines (**5a—c**) in 58—87% yields (Chart 1).

We next examined the reactions of **2** with guanidine and amidines in order to obtain the 5-amino derivatives of type **5** by ring transformation of **2**. Preparation of **2** was accomplished by catalytic hydrogenation of **1** with 5% Pd–C in methanol containing a small quantity of aqueous 36% hydrochloric acid. When **2** was heated with guanidine in anhydrous ethanol for 10 min under the same conditions as used in the reaction of **1** with guanidine, no reaction was found to occur. However, when the reaction was carried out under reflux for 24 h using a large excess of guanidine, **5a** was obtained in 22% yield. Under similar conditions, **2** did not react with acetamidine or benzamidine, and the majority of **2** was recovered. The difference of reactivity between **1** and **2** towards guanidine and amidines may be explained by the different electronic effects of the 3-nitro and 3-amino groups, which affect the susceptibility of the γ-pyrone ring to the nucleophiles.

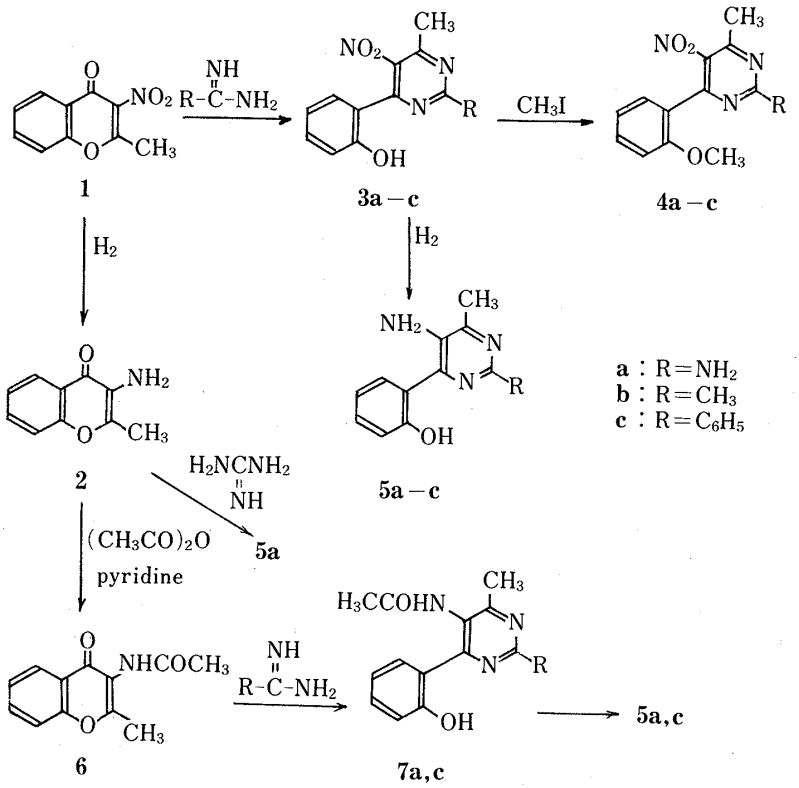

Chart 1

TABLE I. Spectral Data for 5-Nitropyrimidines **3a—c** and **4a—c**

Compd.	IR (KBr) cm^{-1}	^{1}H-NMR (DMSO-d_6) δ in ppm	MS *m/e*
3a	3500, 3400 (NH_2) 1550, 1355 (NO_2)	2.47 (3H, s, CH_3), 6.76—7.45 (4H, m, Ar-H), 7.54 (2H, s, NH_2), 9.97 (1H, s, OH)	246 (M^+), 200 ($M^+ - NO_2$), 159
3b	1535, 1355 (NO_2)	2.61 (3H, s, C_2-CH_3), 2.71 (3H, s, C_4-CH_3), 6.85—7.60 (4H, m, Ar-H), 10.22 (1H, s, OH)	245 (M^+), 199 ($M^+ - NO_2$), 158
3c	1520, 1360 (NO_2)	2.74 (3H, s, CH_3), 6.88—7.76, 8.47—8.63 (9H, m, Ar-H), 10.26 (1H, s, OH)	307 (M^+), 261 ($M^+ - NO_2$), 220
4a	3470, 3270 (NH_2) 1550, 1340 (NO_2)	2.45 (3H, s, CH_3), 3.65 (3H, s, OCH_3), 6.92—7.60 (6H, m, NH_2, Ar-H)	260 (M^+), 229, 213
4b	1530, 1335 (NO_2)	2.63 (3H, s, C_2-CH_3), 2.79 (3H, s, C_4-CH_3), 3.70 (3H, s, OCH_3), 6.84—7.68 (4H, m, Ar-H)	259 (M^+), 229, 213 ($M^+ - NO_2$)
4c	1530, 1345 (NO_2)	2.78 (3H, s, CH_3), 3.76 (3H, s, OCH_3), 6.90—7.87, 8.50—8.71 (9H, m, Ar-H)	321 (M^+), 291, 275 ($M^+ - NO_2$)

On the other hand, 3-acetamido-2-methylchromone (**6**), obtained by acetylation of **2** with acetic anhydride–pyridine in benzene, reacted more readily than **2** with guanidine and benzamidine to give 2-substituted-5-acetamido-6-(2-hydroxyphenyl)-4-methylpyrimidines (**7a, c**) in 54 and 12% yields, respectively, under the same conditions as employed for the synthesis of **5a** from **2** (Chart 1). Similar reaction of **6** with acetamidine did not afford the expected pyrimidine but **6** was recovered in 70% yield. Compounds **7a, c** gave **5a, c** by acid hydrolysis.

In conclusion, the formation of pyrimidines by the reaction of chromones with amidines and their analogues depends considerably on the electronic effect of the substituent at position 3 of the starting chromones.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. NMR spectra were measured with a JEOL C-60H spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were taken on a JEOL JMS-DX300 spectrometer. Infrared (IR) spectra were recorded on a JASCO A-102 spectrophotometer.

3-Amino-2-methylchromone (2)——A solution of **1** (1.0 g, 5 mmol) in methanol (50 ml) containing conc. HCl (5 ml) was stirred under a hydrogen atmosphere in the presence of 5% Pd–C (0.5 g). The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in water and the solution was made alkaline with $NaHCO_3$ to give a crystalline product which was recrystallized from water to yield 0.46 g (53%) of **2**, mp 121.5—123 °C. IR ν_{max}^{KBr} cm^{-1}: 3390 (NH_2), 3290 (NH_2), 1625 (CO). NMR (in DMSO-d_6) δ: 2.40 (3H, s, CH_3), 3.57 (2H, s, NH_2), 7.13—8.46 (4H, m, Ar-H). MS *m/e*: 175 (M^+). *Anal.* Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.48; H, 5.16; N, 7.95.

3-Acetamido-2-methylchromone (6)——A mixture of **2** (0.7 g, 4 mmol), pyridine (0.38 g, 4.8 mmol) and acetic anhydride (0.5 g, 4.8 mmol) in benzene (15 ml) was stirred at room temperature for 2 h. The crystals that separated were collected and recrystallized from benzene to give 0.43 g (50%) of **6**, mp 179—180 °C. IR ν_{max}^{KBr} cm^{-1}: 3250 (NH), 1680 (CO), 1625 (CO). NMR (in DMSO-d_6) δ: 2.20 (3H, s, CH_3), 2.44 (3H, s, CH_3), 7.20—8.32 (4H, m, Ar-H), 8.60 (1H, s, NH). MS *m/e*: 217 (M^+). *Anal.* Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.11; N, 6.45. Found: 66.35; H, 5.09; N, 6.50.

2-Substituted-6-(2-hydroxyphenyl)-4-methyl-5-nitropyrimidines (3a—c)——Guanidine-HCl (2.9 g, 30 mmol) was added to an ethanolic sodium ethoxide solution (0.7 g of Na in 60 ml of anhyd. ethanol) and the mixture was stirred for 5 min at room temperature. The chromone **1** (2.1 g, 10 mmol) was then added and the mixture was refluxed for 10 min. Evaporation of the solvent under reduced pressure gave a residue, which was dissolved in water. The resulting solution was acidified with aq. 10% HCl, and the precipitate was collected by filtration, washed with water and recrystallized from ethanol–water to give **3a**. In the same nanner, **3b, c** were obtained by using acetamidine-HCl and benzamidine-HCl, respectively, in place of guanidine-HCl. **3a**, mp 224—225 °C, yield, 1.75 g (71%). *Anal.* Calcd for $C_{11}H_{10}N_4O_3$: C, 53.66; H, 4.09; N, 22.76. Found: C, 53.54; H, 4.07; N, 22.79. **3b**, mp 159—160 °C, yield, 1.5 g (83%).

Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.77; H, 4.51; N, 17.19. **3c**, mp 172—173 °C, yield, 2.8 g (94.5%). *Anal.* Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67. Found: C, 66.30; H, 4.27; N, 13.70. The spectral data are given in Table I.

2-Substituted-6-(2-methoxyphenyl)-4-methyl-5-nitropyrimidines (4a—c)——A mixture of KOH (0.08 g, 1.5 mmol), a nitropyrimidine (**2a**, **b** or **c**, 1 mmol) and methyl iodide (0.7 g, 5 mmol) in methanol (20 ml) was heated under reflux for 1 h. Then, additional KOH (0.08 g in 10 ml of methanol) and methyl iodide (0.7 g) were added and the reflux was continued for 3 h. Evaporation of the solvent under reduced pressure gave a residue, which was treated with water to yield a crystalline solid. Recrystallization from benzene–ethanol afforded **4a**, **b** or **c**. **4a**, mp 240—240.5 °C, yield, 0.23 g (88%). *Anal.* Calcd for $C_{12}H_{12}N_4O_3$: C, 55.38; H, 4.65; N, 21.53. Found: C, 55.11; H, 4.59; N, 21.58. **4b**, mp 115—116 °C, yield, 0.22 g (85%). *Anal.* Calcd for $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.05; N, 16.21. Found: C, 60.23; H, 5.01; N, 16.24. **4c**, mp 227—228 °C, yield, 0.24 g (75%). *Anal.* Calcd for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.32; H, 4.72; N, 13.01. The spectral data are given in Table I.

2-Substituted-5-amino-6-(2-hydroxyphenyl)-4-methylpyrimidines (5a—c)——A solution of a nitropyrimidine (**3a**, **b** or **c**, 2 mmol) in methanol (70 ml) was stirred under a hydrogen atmosphere in the presence of 5% Pd–C (0.2 g) at room temperature. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give a crystalline solid which was recrystallized from ethanol–water to yield **5a**, **b** or **c**. **5a**, mp 211—212 °C, yield, 0.34 g (79%). IR ν_{max}^{KBr} cm^{-1}: 3350 (NH_2), 1618. MS *m/e*: 216 (M^+). *Anal.* Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.60; N, 25.91. Found: C, 60.76; H, 5.54; N, 25.71. **5b**, mp 123—124 °C, yield, 0.23 g (53%). IR ν_{max}^{KBr} cm^{-1}: 3360 (NH_2), 1632. MS *m/e*: 215 (M^+). *Anal.* Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.95; H, 6.07; N, 19.41. **5c**, mp 158—159 °C, yield, 0.46 g (83%). IR ν_{max}^{KBr} cm^{-1}: 3400 (NH_2), 1612. MS *m/e*: 277 (M^+). *Anal.* Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.56; H, 5.41; N, 15.07.

Preparation of 5a from 2——A mixture of guanidine-HCl (1.7 g, 18 mmol) and **2** (0.53 g, 3 mmol) in an ethanolic sodium ethoxide solution (0.4 g of Na and 30 ml of anhyd. ethanol) was heated under reflux for 24 h. After removal of the solvent under reduced pressure, the residue was dissolved in water and the solution was filtered to eliminate a small quantity of insoluble matter. The filtrate was acidified with aq. 10% HCl and then made alkaline by addition of anhyd. sodium carbonate. The resulting solution was extracted with ethyl acetate. The extract was worked up to give **5a**. Recrystallization from ethanol–water afforded 0.14 g (22%) of pure sample, mp 211—212 °C, which was identified by comparison of its IR spectrum with that of **5a** obtained by reduction of **3a**.

2-Substituted-5-acetamido-6-(2-hydroxyphenyl)-4-methylpyrimidines (7a, c)——A mixture of guanidine–HCl (2.0 g, 21 mmol) and **6** (0.65 g, 3 mmol) in an ethanolic sodium ethoxide solution (0.48 g of Na and 30 ml of anhyd. ethanol) was treated as described for the preparation of **5a** from **2**. Recrystallization from benzene–ethanol gave 0.42 g (54%) of **7a**, mp 241—243 °C. IR ν_{max}^{KBr} cm^{-1}: 3460, 3320 (NH_2), 3190 (NH), 1650, 1630 (CO). MS *m/e*: 258 (M^+). *Anal.* Calcd for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.69. Found: C, 60.30; H, 5.47; N, 21.63.

Similarly, treatment of **6** with benzamidine-HCl gave 0.11 g (12%) of **7c**, mp 187—189 °C. IR ν_{max}^{KBr} cm^{-1}: 3260 (NH), 1660 (CO). MS *m/e*: 319 (M^+). *Anal.* Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.42; H, 5.40; N, 13.07.

Preparation of 5a, c by Hydrolysis of 7a, c——A suspension of **7a** (0.1 g, 0.39 mmol) in a mixture of conc. HCl (1.5 ml) and ethanol (1.5 ml) was heated under reflux for 3 h. The reaction mixture was poured into water (20 ml). The resulting solution was made alkaline by addition of anhyd. sodium carbonate and extracted with ethyl acetate. The extract was worked up to give crystals, which were washed with a mixture of ethyl acetate and *n*-hexane to yield a pure sample of **5a**, mp 210—211 °C, yield, 36 mg (43%). In a similar manner, **7c** (0.10 g, 0.31 mmol) gave 77 mg (89%) of **5c**, mp 158—159 °C. These products **5a**, **c** were identical with those obtained by reduction of **3a**, **c**.

References

1) *a*) K. Takagi, *Yuki Gosei Kagaku Kyokai Shi*, **34**, 706 (1976); *b*) K. Takagi and M. Hubert-Habart, *Bull. Soc. Chim. Fr.*, **1977**, 369.
2) *a*) M. Hubert-Habart, K. Takagi and R. Royer, *Bull. Chim. Thérap.* (Paris), **1967**, 197; *b*) M. Hubert-Habart, G. Menichi, K. Takagi, A. Cheutin, M-L. Desvoye and R. Royer, *ibid.*, **1968**, 280; *c*) K. Takagi and M. Hubert-Habart, *Eur. J. Med. Chem.*, **9**, 14 (1974).
3) G. Menichi, C. Pène, M. Hubert-Habart, N. Platzer, A. Cheutin and R. Royer, *Bull. Chim. Thérap.* (Paris), **1970**, 422.
4) G. Haas, J. L. Stanton and T. Winkler, *J. Heterocycl. Chem.*, **18**, 619 (1981).
5) G. J. P. Becket and G. P. Ellis, *Tetrahedron Lett.*, **1976**, 719.