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Synthesis of 2*H*-Pyrano[2,3 − d]pyrimidine Derivatives

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Two series of 2*H*-pyrano[2,3 − d]pyrimidine-2,5(6*H*)-dione derivatives have been prepared. Thus, the reaction of 6-hydroxy-pyrimidin-4(3*H*)-ones (**1 a–c**) with bis-2,4,6-trichlorphenyl malonates (**2 a–d**) or diethyl malonates (**3 a–d**) afforded good yields of 4-hydroxy-2*H*-pyrano[2,3 − d]pyrimidine-2,5(6*H*)-diones (**4 a–l**). Application of our modified *Pechmann* reaction[9−11] using β-aminocrotonate (**5**) or β-keto esters (**6, 7**) in the presence of ammonium acetate yielded the 2*H*-pyrano[2,3 − d]pyrimidinediones **8 a–h**.

(Keywords: 2H-Pyrano[2,3 − d]pyrimidine-2,5(6H)-diones; Active malonic esters; 2,4,6-Trichlorophenyl malonates; Modified Pechmann reaction)

Synthese von 2H-Pyrano[2,3 − d]pyrimidin-Derivaten

Zwei Serien von 2*H*-Pyrano[2,3 − d]pyrimidin-2,5(6*H*)-dionen wurden hergestellt. Die Reaktion der 6-Hydroxy-pyrimidin-4(3*H*)-one (**1 a − c**) mit Malonsäure-bis-2,4,6-trichlorphenylestern (**2 a − d**) oder Malonsäurediethylestern (**3 a − d**) lieferte 4-Hydroxy-2*H*-pyrano[2,3 − d]pyrimidin-2,5(6*H*)-dione (**4 a − l**) in guten Ausbeuten. Die Anwendung unserer modifizierten *Pechmann*-Reaktion[9−11] auf **1 a − c**, unter Verwendung des β-Aminocrotonsäureesters (**5**) oder der β-Ketoester **6, 7** in Gegenwart von Ammonacetat, gab die 2*H*-Pyrano-[2,3 − d]pyrimidindione **8 a − h**.

Introduction

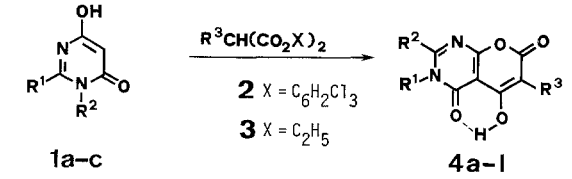
Many pyrimidines and their fused bicyclic derivatives are known to show important biological activities. Until now only a few syntheses of the 2*H*-pyrano[2,3 − d]pyrimidine ring system have been reported; for most of them barbituric acids served as starting materials and usually several

* Dedicated to Prof. Dr. *Karl Schlögl*, University of Vienna, on the occasion of his 60th birthday.

steps were needed[2–5]. In our laboratory, carbon suboxide (C_3O_2) has been used for the anellation of a pyrano ring to thiobarbituric acid[6], and amidoxime ethers were cyclized with malonyl chloride or malonic acid in the presence of acetic anhydride to yield pyrano[2,3–d]pyrimidines[7]. The present work is a continuation of our studies on the synthesis of pyrono derivatives of heterocycles[8–11], which might be considered as potential antineoplastic agents.

Results and Discussion

The dinucleophilic 6-hydroxy-4(3*H*)-pyrimidones **1a,b** used in this study were obtained by the sodium ethoxide catalyzed condensation of acetamidine and benzamidine with diethyl malonate[12]. The N-phenyl derivative **1c**, previously reported to be obtained by the reaction of N-phenylbenzamidine with carbon suboxide[13], was prepared by us more conveniently using bis-2,4,6-trichlorophenyl malonate (see Experimental Part).



1a–c

a $R^1 = CH_3$, $R^2 = H$
b $R^1 = C_6H_5$, $R^2 = H$
c $R^1 = R^2 = C_6H_5$

a $R^3 = CH_2C_6H_5$
b $R^3 = C_6H_5$
c $R^3 = C_4H_9$-n
d $R^3 = CH_3$

4a–l

R-Key see Table 1

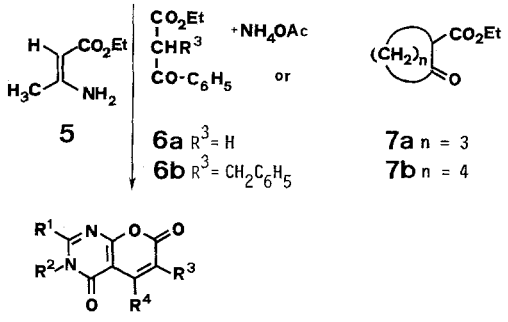
Two series of substituted 2*H*-pyrano[2,3–d]pyrimidine-2,5(6*H*)-diones were prepared: The 4-hydroxy-derivatives **4a–l** were obtained by the thermal condensation of **1a–c** with esters of malonic acid. The highest yields were observed by using the active malonic esters (*AME*'s)[14], bis-2,4,6-trichlorophenyl malonates **2a–d**, without (Method A), or with boiling 1,2-dichlorobenzene as solvent (Method B); the temperatures ranging in the "neat reaction" from 220–250 °C. However, the condensation reaction was also accomplished with the more readily available diethyl malonates **3a–d** (Method C) with less–but still satisfactory–yields (see Table 1). The products **4a–l** are pale yellow colored compounds which exhibit a greenish yellow fluorescence under UV light. They give a violet color reaction with ferric chloride solution, which is characteristic for the *cis*-fixed *β*-enol-carbonyl moiety in **4**.

Table 1. *4-Hydroxy-2H-pyrano[2,3−d]pyrimidine-2,5(6H)-diones* **4a–l**

	R^1	R^2	R^3	Method	Yield %	M. p. °C Recr. Solvent Cryst. Form	Mol. formula* (Mol. wt.)
4a	CH_3	H	$CH_2C_6H_5$	A	91	226° xylene prisms	$C_{15}H_{12}N_2O_4$ (284.1)
4b	CH_3	H	C_6H_6	A C	98 90	280° acetone/water needles	$C_{14}H_{10}N_2O_4$ (270.1)
4c	CH_3	H	C_4H_9-n	A	80	228° acetone/water needles	$C_{12}H_{14}N_2O_4$ (250.1)
4d	CH_3	H	CH_3	A	82	300° *DMF*/water needles	$C_9H_8N_2O_4$ (208.1)
4e	C_6H_5	H	$CH_2C_6H_5$	A B C	90 75 72	330° dichlorobenzene plates	$C_{20}H_{14}N_2O_4$ (346.2)
4f	C_6H_5	H	C_6H_5	A C	89 77	330° dichlorobenzene prisms	$C_{19}H_{12}N_2O_4$ (332.2)
4g	C_6H_5	H	C_4H_9-n	A B C	98 91 81	262° xylene prisms	$C_{17}H_{16}N_2O_4$ (312.1)
4h	C_6H_5	H	CH_3	A C	98 90	290° *DMF* fine prisms	$C_{14}H_{10}N_2O_4$ *(270.1)*
4i	C_6H_5	C_6H_5	$CH_2C_6H_5$	A	71	150° 1-butanol prisms	$C_{26}H_{18}N_2O_4$ (422.2)
4j	C_6H_5	C_6H_5	C_6H_5	A B C	75 69 53	130° 1-butanol fine prisms	$C_{25}H_{16}N_2O_4$ (408.2)
4k	C_6H_5	C_6H_5	C_4H_9-n	A	65	86° cyclohexane fine prisms	$C_{23}H_{20}N_2O_4$ (388.2)
4l	C_6H_5	C_6H_5	CH_3	A	65	208° benzene/ cyclohexane fine prisms	$C_{20}H_{14}N_2O_4$ (346.2)

* The C, H, N analyses were in full agreement with the molecular formulas.

Application of the modified *Pechmann* condensation[9–11], previously described for phenolic compounds[9], 4-hydroxy-2(1*H*)-pyridones[10], and 4-hydroxy-2(1*H*)-quinolones and 4-hydroxy-coumarins[11], gave also good results when applied to the hydroxy-pyrimidones **1a–c**. Thus, the reaction of **1a–c** with ethyl β-aminocrotonate (**5**), or with open chain β-keto esters (**6**) and cyclic β-keto esters (**7**) – in the presence of an excess of



8a–h R-Key see Table 2

ammonium acetate as catalyst – afforded a series of 3,4,6,7-substituted 2*H*-pyrano[2,3–d]pyrimidine-2,5(6*H*)-diones **8a–h** (Table 2). The products are insoluble in sodium carbonate solution (which allows a separation from unreacted starting material), and exhibit a blue fluorescence when irradiated with UV light.

Acknowledgement

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Experimental Part

The melting points were determined in open capillary tubes on a Büchi-Tottoli melting point apparatus, melting points above 200 °C were determined using a hot metal block and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 421 spectrophotometer using samples in potassium bromide disks. The NMR spectra were recorded with a Varian EM-360 spectrometer at 60 MHz in *DMSO-d_6* (unless otherwise indicated) with *TMS* as internal standard.

6-Hydroxy-2,3-diphenyl-pyrimidin-4(3H)-one (**1c**)

A suspension of N-phenylbenzamide (3.92 g, 20 mmol) and bis-2,4,6-trichlorophenyl malonate (9.26 g, 20 mmol) in 12 ml of bromobenzene was heated under reflux for 20 min. The reaction mixture was evaporated *in vacuo* to dryness and the oil obtained was digested with about 150 ml of ether, the produced

Table 2. *3,4,6,7-Substituted 2H-pyrano[2,3-d]pyrimidine-2,5(6H)-diones* **8a–h**

	R^1	R^2	R^3	R^4	Method	Yield %	M.p. °C Recr. Solvent Cryst. Form	Mol. formula* (Mol. wt.)
8a	CH_3	H	H	CH_3	A	84	296° methanol needles	$C_9H_8N_2O_3$ (192.1)
8b	CH_3	H	$-(CH_2)_3-$		B	61	310° dichlorobenzene fine prisms	$C_{11}H_{10}N_2O_3$ (218.1)
8c	C_6H_5	H	H	CH_3	A	98	354° dichlorobenzene plates	$C_{14}H_{10}N_2O_3$ (254.1)
8d	C_6H_5	H	H	C_6H_5	B	81	302° *DMF*/water fine prisms	$C_{19}H_{12}N_2O_3$ (316.2)
8e	C_6H_5	H	$-(CH_2)_4-$		B	91	370° *DMF*/water fine prisms	$C_{17}H_{14}N_2O_3$ (294.1)
8f	C_6H_5	H	$-(CH_2)_3-$		B	87	332° *DMF* needles	$C_{16}H_{12}N_2O_3$ *(280.1)*
8g	C_6H_5	C_6H_5	H	CH_3	A	81	264° 1-propanol needles	$C_{20}H_{14}N_2O_3$ (330.2)
8h	C_6H_5	C_6H_5	$-(CH_2)_3-$		B	80	232° 2-propanol needles	$C_{22}H_{16}N_2O_3$ (356.4)

* The C, H, N analyses were in full agreement with the molecular formulas.

precipitate was filtered and recrystallized from dioxane using charcoal. Yield 90%, pale yellow prisms, m.p. 216 °C (dioxane), lit. m.p. 212–213 °C[13].

IR: 3400–2700 m, 1645 s, 1590 s, 1550 w, 1520 cm^{-1}; NMR: 5.5 (s, 1, C-5), 7.2 (s, 10, *Ar*H).

$C_{16}H_{12}N_2O_2$ (264.1). Calcd. C 72.75 H 4.54 N 10.60.
Found. C 72.62 H 4.48 N 10.48.

4-Hydroxy-2H-pyrano[2,3-d]pyrimidine-2,5(6H)-diones (**4a–l**) (Table 1)

Method A: A mixture of **1a–c** (4 mmol) and **2a–d** (4 mmol) was heated in an oil bath adjusted to 250 °C (230 °C for compounds **4b, c, d**) for 20–30 min. The reaction mixture was cooled and quenched with a 1 : 1 mixture of diethyl ether and petroleum ether (40–60 °C); for compounds **4i–l** only 30 ml of petroleum ether was used. The residue obtained was filtered and crystallized from the specified solvent (Table 1).

Table 3. *IR and* ^{1}H-*NMR spectra of compounds* **4** *and* **8**

	IR in KBr; cm^{-1}	^{1}H-NMR in *DMSO-*d_6 (or CF_3CO_2H*); δ, ppm
4a	3300–2600 m, 1720 s, 1665 s, 1625 m, 1600 m, 1560 m	2.4 (s, 3, CH_3), 3.65 (s, 2, CH_2, 7.2 (s, 5, *Ar*H), 12.0 (s broad, 1, NH)
4b	3160–2700 m, 1725 s, 1665 s, 1595 m, 1560 s, 1535 sh w	*2,7 (s, 3, CH_3), 7.3 (s, 5, *Ar*H)
4c	3200–2760 m, 1725 sh w, 1670 s, 1600 m, 1555 m, 1510 w	0.8–1.1 (m, 3, CH_3), 1.2–1.5 (m, 4, $2CH_2$), 2.5 (s, 3, CH_3), 2.5–2.8 (m, 2, CH_2), 11.9 (s broad, 1, NH)
4d	3240–2800 m, 1705 s, 1680 s, 1620 sh w, 1610 w, 1585 sh w, 1565 m	
4e	3200–2800 w, 1730 m, 1655 s, 1610 m, 1600 sh m, 1565 m, 1540 sh w, 1515 w	
4f	3200–2900 w, 1735 s, 1650 s, 1600 s, 1560 m, 1515 w	
4g	3200–2800 m, 1735 s, 1660 s, 1600 m, 1565 m, 1510 w	0.8–1.1 (m, 3, CH_3), 1.1–1.6 (m, 4, $2CH_2$), 2.2–2.5 (m, 2, CH_2), 7.6–7.9 (m, 3, *Ar*H), 8.1–8.4 (m, 2, *Ar*H)
4h	3180–2800 m, 1730 m, 1655 s, 1610 m, 1590 sh m, 1560 m, 1535 sh w, 1510 w	* 2.1 (s, 3, CH_3), 7.5–7.8 (m, 3, *Ar*H), 7.9–8.2 (m, 2, *Ar*H)
4i	3080–2800 w, 1725 s, 1670 s, 1620 w, 1600 w, 1585 w, 1570 w, 1525 s	3.7 (s, 2, CH_2), 7.1–7.4 (m, 15, *Ar*H)

4j	3 080–2 700 w, 1 725 s, 1 665 s, 1 615 sh w, 1 570 m, 1 525 s	
4k	3 080–2 800 m, 1 725 m, 1 675 s, 1 625 w, 1 600 w, 1 570 m, 1 530 s	* 0.8–1.1 (m, 3, CH_3), 1.2–1.6 (m, 4, 2 CH_2), 2.5–2.8 (m, 2, CH_2), 7.3 (s, 10, *Ar*H)
4l	3 200–2 840 w, 1 730 s, 1 670 s, 1 620 sh m, 1 590 w, 1 565 m, 1 525 a	
8a	3 100–2 600 w, 1 740 s, 1 590 s, 1 535 m	* 2.8 (s, 3, CH_3 + dd, J = 1 Hz, 3, CH_3), 6.4 (dd, J = 1 Hz, 1, C-3)
8b	3 200–2 700 m, 1 750 sh m, 1 720 sh m, 1 690 s, 1 590 m, 1 545 sh m, 1 535 m	* 2.1–2.5 (m, 2, CH_2), 2.5–3.1 (m, 2, CH_2), 2.8 (s, 3, CH_3), 3.2–3.5 (m, 2, CH_2)
8c	3 240–2 600 m, 1 745 s, 1 650 s, 1 600 m, 1 590 sh, 1 560 sh, 1 545 s, 1 525 sh	* 2.8 (dd, J = 1 Hz, 3, CH_3), 6.4 (dd, J = 1 Hz, 1, C-3), 7.5–7.8 (m, 3, *Ar*H); 7.9–8.2 (m, 2, *Ar*H)
8d	3 220–1 700 m, 1 725 s, 1 685 sh, 1 655 s, 1 590 sh m, 1 570 w, 1 545 s, 1 525 m, 1 510 s	
8e	3 240–2 800 m, 1 720 s, 1 650 sh s, 1 640 s, 1 600 m, 1 590 w, 1 550 sh, 1 535 m, 1 515 w	* 1.7–2.0 (m, 4, 2 CH_2), 2.4–2.8 (m, 2, CH_2), 3.1–3.4 (m, 2, CH_2), 7.5–7.8 (m, 3, *Ar*H), 7.8–8.1 (m, 2, *Ar*H)
8f	3 100–2 700 w, 1 735 s, 1 650 s, 1 600 m, 1 590 sh w, 1 540 s, 1 510 m	* 2.2–2.6 (m, 2, CH_2), 2.7–3.1 (m, 2, CH_2), 3.2–3.7 (m, 2, CH_2), 7.5–7.8 (m, 3, *Ar*H), 7.8–8.2 (m, 2, *Ar*H)
8g	3 060 m, 1 730 s, 1 690 m, 1 545 m, 1 520 s	* 2.8 (dd, J = 1 Hz, 3, CH_3), 6.5 (dd, J = 1 Hz, 1, C-3), 7.1–7.5 (m, 10, *Ar*H)
8h	3 100–2 800 w, 1 750 s, 1 680 s, 1 650 sh w, 1 605 m, 1 545 sh w, 1 525 s	* 2.2–2.5 (m, 2, CH_2), 2.6–3.1 (m, 2, CH_2), 3.1–3.6 (m, 2, CH_2), 7.0–7.4 (m, 10, *Ar*H)

Method B: A suspension of **1 a–c** (4 mmol) and **2 a–d** (4 mmol) in 10 ml of 1,2-dichlorobenzene was heated under reflux for 2 h. The reaction mixture was concentrated to a small volume, cooled and treated with petroleum ether (40–60 °C). The precipitate obtained was filtered and recrystallized.

Method C: A mixture of **1 a–c** (4 mmol) and substituted diethyl malonates **3 a–d** (2,5 ml) was heated for 2 h (**3 a**), 30 min (**3 b**), or 48 h (**3 c, d**), respectively, using a short air condenser to allow the evaporation of the ethanol produced from the reaction mixture. The viscous oil obtained was digested with petroleum ether and diethyl ether and the produced precipitate was filtered and recrystallized.

3,4,6,7-Substituted 2H-Pyrano[2,3−d]pyrimidine-2,5(6H)-diones (**8 a–h**; Table 2)

Method A: A suspension of **1 a–c** (4 mmol) and ethyl *β*-aminocrotonate (**5**) in 10 ml of 1,2-dichlorobenzene was heated under reflux in an oil bath adjusted to 200 °C for 2 h (for **8 g** only 30 min were required). The solvent was removed *in vacuo*, petroleum ether was added and the precipitate obtained was filtered and recrystallized from the specified solvent.

Method B: A mixture containing **1 a–c** (4 mmol), the appropriate *β*-keto ester **6 a, b** or **7 a, b** (5 mmol) and ammonium acetate (1.54 g, 20 mmol) in 10 ml of 1,2-dichlorobenzene was heated under reflux in an oil bath adjusted to 200 °C for 2 h. Most of the solvent was evaporated *in vacuo*, petroleum ether was added, and the precipitate obtained was filtered. Any unreacted starting material should be removed before crystallization by the use of a 4% sodium bicarbonate solution. For compound **8 h** only 30 min of reflux was necessary.

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