Synthesis of 7-Substituted 5-Oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylic Acids, 2-Substituted 4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic Acids, and 2,6-Disubstituted 4-Quinolones from Meldrum's Acid Derivatives

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The title compounds are prepared from the Meldrum acid derivatives 5-[bis(methylthio)methylene]-, 5-(1-methylthioalkylidene)- and 5-(α-methylthiobenzylidene)-2,2-dimethyl-4,6-dioxo-1,3-dioxanes by reaction with 2-aminothiazole, 2-aminopyridine, or anilines, respectively.

Bis(methylthio)methylene[1] **(1)**, 1-methylthioalkylidene[2] (**2**, R = alkyl), and α-methylthiobenzylidene (**2**, R = Ph) derivatives[2] of Meldrum's acid are new synthetic intermediates of considerable utility. In previous communications, we have shown their use in novel syntheses of quinolones[3] and pyrazolones.[4] The present paper is concerned with the application of compounds **1** and **2** to the synthesis of 7-methylthio-7-alkyl-, and 7-phenyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylic acids **5**, 2-methylthio-, 2-alkyl-, and 2-phenyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids **8**, and 2-methylthio-, 2-amino-, and 2-ethoxy-4-quinolones **14, 15, 16** by reaction with 2-aminothiazole **(3)**, 2-aminopyridine **(6)**, and anilines **10**, respectively.

Upon heating in dimethylformamide or ethanol, the Meldrum acid derivatives **1** and **2** readily react with 2-aminothiazole **(3)** to give the cyclocondensation products **5** in a single step, via the intermediates **4**. This process is different from the reaction of **1** and **2** with anilines **10** in which a higher temperature is required to complete the cyclocondensation of the intermediate **11** to **14**. The analogous reaction of **1** and **2** with 2-aminopyridine **(6)** leads to the convenient formation of the 2-substituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids **8**, via the assumed intermediates **7**.

The decarboxylation of acids **5** was investigated for one example: Compound **5a** was readily decarboxylated by simple heating at 250–260 °C without solvent for 5 minutes to produce 7-methylthio-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine **(9)** in 97% yield.

As an extension of our earlier synthesis[3] of 2-alkyl- and 2-aryl-4-quinolones by reaction of anilines with compounds **2**, we now studied the reactivity of Meldrum acid derivative **1** towards anilines **10**. Thus, heating an equimolecular mixture of compounds **1** and **10** in boiling ethanol afforded 5-[anilino(methyl-

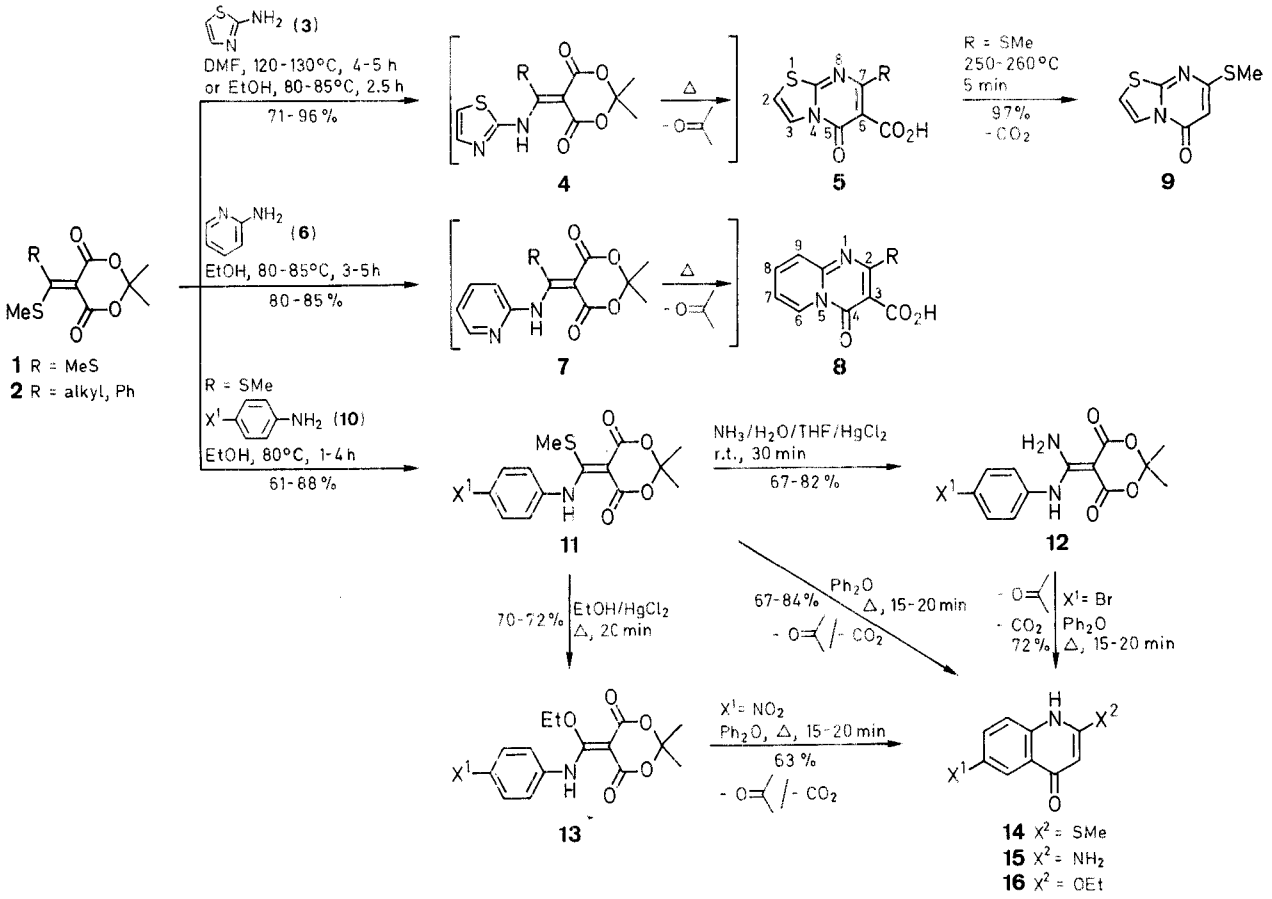

Table 1. Products **5** and **8** Prepared

Product	R	Reaction Conditions		Yield (%)	mp[a] (°C)	Molecular Formula[b]
		Solvent	Temperature (°C), Time (h)			
5a	SMe	EtOH	80–85, 2.5	96	250 (dec)	$C_8H_6N_2O_3S_2$ (242.27)
5b	Ph	DMF	120–130, 4.0	97	205–207	$C_{13}H_8N_2O_3S$ (272.27)
5c	Me	DMF	120–130, 5.0	78	221–223	$C_8H_6N_2O_3S$ (210.21)
5d	Et	DMF	120–130, 5.0	71	197–198	$C_9H_8N_2O_3S$ (224.23)
8a	SMe	EtOH	80–85, 3.0	80	262.5–263.5	$C_{10}H_8N_2O_3S$ (236.24)
8b	Ph	EtOH	80–85, 4.0	82	242.5–243.5	$C_{15}H_{10}N_2O_3$ (266.24)
8c	Me	EtOH	80–85, 5.0	85	236.5–238	$C_{10}H_8N_2O_3$ (204.18)

[a] Uncorrected.
[b] Satisfactory microanalyses: C ±0.34, N ±0.30, H ±0.11.

Table 2. Products **11**, **12**, and **13** Prepared

Product	X^1	Reaction Time (h)	Yield (%)	mp[a] (°C)	Molecular[b] Formula
11a	H	2	75	152–153	$C_{14}H_{15}NO_4S$ (293.3)
11b	Br	4	88	143–145	$C_{14}H_{14}BrNO_4S$ (372.2)
11c	Cl	1.5	69	143–144	$C_{14}H_{14}ClNO_4S$ (326.8)
11d	MeO	1	63	146–147	$C_{15}H_{17}NO_5S$ (323.3)
11e	Me	2	61	145–146	$C_{15}H_{17}NO_4S$ (307.3)
12a	H	0.5	82	156–158	$C_{13}H_{14}N_2O_4$ (262.3)
12b	Br	0.5	80	171–173	$C_{13}H_{13}BrN_2O_4$ (341.2)
12c	Cl	0.5	67	159–161	$C_{13}H_{13}ClN_2O_4$ (296.7)
12e	Me	0.5	73	139–141	$C_{14}H_{16}N_2O_4$ (277.4)
13b	Br	20 min	70	138–140	$C_{15}H_{16}BrNO_5$ (370.2)
13f	NO_2	4	72	173–174	$C_{15}H_{16}N_2O_7$ (336.3)

[a] Uncorrected.
[b] Satisfactory microanalyses: C ±0.39, N ±0.30, H ±0.21.

thio)methylene]-2,2-dimethyl-4,6-dioxo-1,3-dioxanes **11** in 61–88% yield. These Meldrum acid derivatives are versatile synthetic intermediates as they possess an active methylthio group. For example, they can be readily converted too into the amino(anilino)methylene derivatives **12** by aminolysis in the presence of mercury chloride and into the anilino(ethoxy)methylene derivatives **13** by reaction with ethanol in the presence of mercury chloride. It should be pointed out that reaction of **1** with 4-nitroaniline (**10**, X = NO_2) in ethanol directly gives the ethoxy(4-nitrophenyl)amino derivative **13b**.

In boiling diphenyl ether, compounds **11**, **12**, and **13** undergo cyclocondensation to give the 4-quinolones **14**, **15**, and **16**, respectively. This reaction can be monitored by determining the amount of carbon dioxide by absorption in a barium hydroxide solution.

Table 3. 4-Quinolones **14**, **15**, and **16** Prepared

Product	X^1	X^2	Yield (%)	mp[a] (°C)	Molecular Formula[b]
14a	H	SMe	78	220–222	$C_{10}H_9NOS$ (191.2)
14b	Br	SMe	67	274–276	C_9H_8BrNOS (270.1)
14c	Cl	SMe	68	255–257	$C_{10}H_8ClNOS$ (225.7)
14d	MeO	SMe	68	229–230	$C_{11}H_{11}NO_2S$ (218.2)
14e	Me	SMe	84	224–226	$C_{11}H_{11}NOS$ (202.2)
15b	Br	NH_2	72	344 (dec)	$C_9H_7BrN_2O$ (239.2)
16f	NO_2	OEt	63	245–246	$C_{11}H_{10}N_2O_4$ (234.2)

[a] Uncorrected.
[b] Satisfactory microanalyses: C ±0.39, N ±0.35, H ±0.29.

7-Methylthio-, 7-Alkyl-, and 7-Phenyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylic Acids 5; General Procedure:

A mixture of 5-[bis(methylthio)methylene]- (**1**), a 5-(1-methylthioalkylidene)- (**2**, R = alkyl), or 5-(α-methylthiobenzylidene)-2,2-dimethyl-4,6-dioxo-1,3-dioxane (**2**, R = C_6H_5) (2.5 mmol) and 2-aminothiazole (**3**; 0.25 g, 2.5 mmol) in DMF or EtOH (5 mL) is heated with stirring for the time given in Table 1. The solvent is then removed under reduced pressure and ice water (10 mL) is added to precipitate the product **5** which is collected by suction and purified by recrystallization from THF/petroleum ether (bp 60–90°C).

2-Methylthio-, 2-Methyl-, and 2-Phenyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic Acids 8; General Procedure:

A mixture of 5-[bis(methylthio)methylene]-(**1**), 5-(1-methylthio)ethylidene-(**2**, R = CH_3), or 5-(α-methylthiobenzylidene)-2,2-dimethyl-4,6-di-

Table 4. Spectral Data of the Compounds Prepared

Compound	IR[a] (KBr) ν (cm^{-1})	^{1}H-NMR[b] Solvent/Internal Reference	δ, J (Hz)
5a	2760, 1725, 1618, 818	CF_3CO_2H/DSS[c]	2.61 (s, 3H); 7.44 (d, 1H, J = 4.8); 8.21 (d, 1H, J = 4.8)
5b	2628, 1733, 1629, 803	CF_3CO_2H/DSS[c]	7.64 (s, 1H); 7.88 (d, 1H, J = 4.2); 8.53 (d, 1H, J = 4.2)
5c	2660, 1738, 1622, 802	$CDCl_3$/TMS	2.90 (s, 3H); 7.42 (d, 1H, J = 4.8); 8.15 (d, 1H, J = 4.8)
5d	2661, 1738, 1616, 815	$CDCl_3$/TMS	1.29 (t, 3H, J = 7.6); 3.33 (q, 2H, J = 7.6); 7.23 (d, 1H, J = 4.6); 8.07 (d, 1H, J = 4.6)
8a	2788, 1724, 1690, 774	CF_3CO_2H/DSS[c]	2.88 (s, 3H); 7.81–9.57 (m, 4H)
8b	2760, 1748, 1720, 778	CF_3CO_2H/DSS[c]	7.64 (s, 5H); 7.86–9.61 (m, 4H)
8c	2746, 1749, 1721, 778	CF_3CO_2H/DSS[c]	3.12 (s, 3H); 7.88–9.61 (m, 4H)
11a	3180, 1720, 1665, 1555, 1380	$CDCl_3$/TMS	1.76 (s, 6H); 2.27 (s, 3H); 7.41 (m, 5H); 12.81 (s, 1H)
11b	1730, 1658, 1550, 1380	$CDCl_3$/TMS	1.76 (s, 6H); 2.31 (s, 3H); 7.20 (d, 2H, J = 9.70); 7.59 (d, 2H, J = 9.70); 12.75 (s, 1H)
11c	1730, 1660, 1550, 1380	$CDCl_3$/TMS	1.74 (s, 6H); 2.28 (s, 3H); 7.25 (d, 2H, J = 9.20); 7.44 (d, 2H, J = 9.20); 12.75 (s, 1H)
11d	3180, 1720, 1665, 1560, 1375	$CDCl_3$/TMS	1.74 (s, 6H); 2.30 (s, 3H); 3.83 (s, 3H); 6.93 (d, 2H, J = 9.0); 7.23 (d, 2H, J = 9.0); 12.63 (s, 1H)
11e	3170, 1720, 1660, 1550, 1373	$CDCl_3$/TMS	1.74 (s, 6H); 2.28 (s, 3H); 2.37 (s, 3H); 7.11 (d, 2H, J = 5.4); 7.29 (d, 2H, J = 5.4); 12.63 (s, 1H)
12a	3440, 3220, 1665, 1595, 1378	$CDCl_3$/TMS	1.72 (s, 6H); 5.60 (s, 1H); 7.38 (m, 5H); 9.60 (s, 1H); 11.40 (s, 1H)
11b	3450, 3235, 1700, 1655, 1595, 1385	$CDCl_3$/TMS	1.73 (s, 6H); 5.55 (s, 1H); 7.17 (d, 2H, J = 8.6); 7.65 (d, 2H, J = 8.6); 9.66 (s, 1H); 11.42 (s, 1H)
12c	3440, 3220, 1695, 1650, 1595, 1381	$CDCl_3$/TMS	1.73 (s, 6H); 5.55 (s, 1H); 7.24 (d, 2H, J = 8.1); 7.50 (d, 2H, J = 8.1); 9.65 (s, 1H); 11.42 (s, 1H)
12e	3490, 3220, 1690, 1650, 1600, 1375	$CDCl_3$/TMS	1.72 (s, 6H); 2.37 (s, 3H); 5.54 (s, 1H); 7.05 (d, 2H, J = 9.7); 7.41 (d, 2H, J = 9.7); 9.57 (s, 1H); 11.28 (s, 1H)
13b	3220, 1720, 1670, 1605, 1380	$CDCl_3$/TMS	1.35 (t, 3H, J = 6.5); 1.76 (s, 1H); 4.65 (q, 2H, J = 6.5); 7.29 (d, 2H, J = 9.2); 7.69 (d, 2H, J = 9.2); 12.09 (s, 1H)
13f	1720, 1672, 1595, 1380	$CDCl_3$/TMS	1.40 (t, 3H, J = 8.1); 1.74 (s, 6H); 4.56 (q, 2H, J = 8.1); 7.56 (d, 2H, J = 10.8); 8.28 (d, 2H, J = 10.8); 12.45 (s, 1H)
14a	3280, 1640, 1585	DMF-d_7/TMS[d]	2.57 (s, 3H); 6.15 (s, 1H); 7.31–8.10 (m, 4H); 11.76 (s, 1H)
14b	3280, 1640, 1580	DMF-d_7/TMS[d]	2.58 (s, 3H); 6.21 (s, 1H); 7.53 (d, 1H, J = 9.7); 7.77 (dd, 1H, J = 9.7, 2.7); 8.15 (d, 1H, J = 2.7); 11.94 (s, 1H)
14c	3280, 1641, 1580	DMF-d_7/TMS[d]	2.57 (s, 3H); 6.21 (s, 1H); 7.65 (s, 2H); 8.01 (s, 1H); 12.00 (s, 1H)
14d	3240, 1640, 1580	DMF-d_7/TMS[d]	2.58 (s, 3H); 3.84 (s, 3H); 6.24 (s, 1H); 7.28 (dd, 1H, J = 9.7, 4.3); 7.44 (d, 1H, J = 4.3); 7.59 (d, 1H, J = 9.7); 11.81 (s, 1H)
14e	3265, 1643, 1580	DMF-d_7/TMS[d]	2.39 (s, 3H); 2.55 (s, 3H); 5.97 (s, 1H); 7.44 (s, 2H); 7.84 (s, 1H); 11.73 (s, 1H)
15b	3330, 3190, 1655	DMSO-d_6/TMS	5.36 (s, 1H); 6.27 (s, 2H); 7.26 (d, 1H, J = 9.8); 7.59 (dd, 1H, J = 9.8, 2.7); 8.03 (d, 1H, J = 2.7)[e]
16f	3260, 3220, 3100, 1653, 1620	DMSO-d_6/TMS	1.37 (t, 3H, J = 7.6); 4.41 (q, 2H, J = 7.6); 6.27 (s, 1H); 7.71 (d, 1H, J = 9.2); 8.34 (dd, 1H, J = 9.2, 2.5); 8.88 (d, 1H, J = 2.5); 12.18 (s, 1H)

[a] Recorded on Perkin Elmer 683 spectrophotometer.
[b] Recorded on JEOL FX 90Q spectrometer.
[c] DSS = sodium 2,2-dimethyl-2-silapentane-5-sulfonate.
[d] At 45°C.
[e] A signal of the proton at position 1 is not observed.

oxo-1,3-dioxane (**2**, R = Ph) (2.5 mmol) and 2-aminopyridine (**6**; 0.24 g, 2.5 mmol) in EtOH (5 mL) is heated with stirring for 3–5 h (see Table 1). EtOH is then evaporated and ice water (10 mL) is added. The crude product **8** is collected by suction and recrystallized from THF/petroleum ether (bp 60–90 °C).

7-Methylthio-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine (9):
7-Methylthio-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylic acid (**5a**; 0.53 g, 2.5 mmol) is heated without solvent at 250–260 °C for 5 min. The resultant product is recrystallized from THF/petroleum ether (bp 60–90 °C); yield: 0.40 g (97%); mp 110–111 °C.

$C_7H_6N_2OS_2$	calc.	C 42.40	H 3.05	N 14.13
(198.15)	found	42.10	3.02	13.99

IR (KBr): $\nu = 1673\ cm^{-1}$.

^1H-NMR ($CDCl_3$/TMS): $\delta = 2.48$ (s, 3H); 6.07 (s, 1H); 6.94 (d, $J = 5.0$ Hz, 1H); 7.92 (d, $J = 5.0$ Hz, 1H).

5-[Anilino(methylthio)methylene]-2,2-dimethyl-4,6-dioxo-1,3-dioxanes 11; General Procedure:
A mixture of 5-[bis(methylthio)methylene]-2,2-dimethyl-4,6-dioxo-1,3-dioxane (**1**; 2.482 g, 10 mmol), aniline **10** (10 mmol), and EtOH (10 mL) is heated to reflux for 1–4 h (see Table 2). The solvent is then evaporated and the residue recrystallized from THF/petroleum ether (bp 60–90 °C) to give the product **11**.

5-[Amino(anilino)methylene]-2,2-dimethyl-4,6-dioxo-1,3-dioxanes 12; General Procedure:
To a stirred solution of a 5-[anilino(methylthio)methylene]-2,2-dimethyl-4,6-dioxo-1,3-dioxane **11** (2 mmol) in THF (5 mL) is added 25–28% aqueous NH_3 (5 mL) followed by $HgCl_2$ (0.54 g, 2 mmol), and stirring is continued for 30 min. The mixture is then filtered and the filtrate extracted with CH_2Cl_2 (3 × 15 mL). The organic layer is washed with H_2O (3 × 10 mL), dried ($MgSO_4$), and evaporated. The remaining product **12** is recrystallized from THF/petroleum ether (bp 60–90 °C).

5-[4-Bromophenylamino(ethoxy)methylene]-2,2-dimethyl-4,6-dioxo-1,3-dioxane (13b):
To a solution of 5-[4-bromophenylamino(methylthio)methylene]-2,2-dimethyl-4,6-dioxo-1,3-dioxane (**11b**; 0.75 g, 2 mmol) in EtOH (5 mL) is added $HgCl_2$ (0.54 g, 2 mmol) and the mixture is heated to reflux for 20 min. The mixture is then filtered, and the filtrate evaporated. To the residue, H_2O (10 mL) is added to precipitate product **13b** which is isolated by suction and recrystallized from THF/petroleum ether (bp 60–90 °C); yield: 0.52 g (70%); mp 138–139 °C.

5-[Methylthio(4-nitrophenylamino)methylene]-2,2-dimethyl-4,6-dioxo-1,3-dioxane (13f):
A mixture of 5-[bis(methylthio)methylene]-2,2-dimethyl-4,6-dioxo-2,3-dioxane (**1**; 1.24 g, 5 mmol), 4-nitroaniline (0.70 g, 5 mmol), and EtOH (5 mL) is heated to reflux for 4 h, then allowed to cool, and H_2O (20 mL) is added. The precipitated product **13f** is isolated by suction and recrystallized from THF/petroleum ether (bp 60–90 °C); yield: 1.21 g (72%); mp 173–174 °C.

2-Methylthio-4-quinolones 14, 2-Amino-4-quinolones 15, and 2-Ethoxy-4-quinolones 16; General Procedure:
The substituted Meldrum acid derivative **11**, **12**, or **13** (2 mmol) is heated in boiling diphenyl ether (5 mL) for 15–20 min while a current of N_2 is being passed through the mixture. The CO_2 evolved during the reaction is passed into aqueous $Ba(OH)_2$. When CO_2 evolution is complete the mixture is allowed to cool and petroleum ether (bp 60–90 °C; 30 mL) is added. The precipitated product is isolated by suction and recrystallized from DMF/H_2O.

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