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Synthesis of 4-Hydroxy-2(1*H*)-pyridones from Azomethines and Substituted Dialkylmalonates

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Summary. The reaction of azomethines **4** with substituted dialkyl malonates **5** leads to the formation of 3-substituted 4-hydroxy-2(1*H*)-pyridones **6** in moderate yields. The azomethines **4** are prepared *via* arylaminopropionitriles **3** or in the conventional way by acid catalyzed condensation of ketones **1** with anilines **2**. Chlorination of pyridones **6** with sulfuryl chloride leads to compounds **8–10**.

Keywords. Azomethines; *Strecker* compounds; Dialkyl malonates; 4-Hydroxy-2(1*H*)-pyridones.

Synthese von 4-Hydroxy-2(1*H*)-pyridonen aus Azomethinen und substituierten Dialkylmalonaten

Zusammenfassung. Umsetzung der Azomethine **4** mit den substituierten Dialkylmalonaten **5** ergibt die in 3-Stellung substituierten 4-Hydroxy-2(1*H*)-pyridone **6** in mäßigen Ausbeuten. Die Azomethine **4** werden entweder über die *Strecker*-Verbindungen **3** oder konventionell über durch Säuren katalysierte Kondensation der Ketone **1** mit den Aminen **2** hergestellt. Chlorierung der Pyridone **6** mit Sulfurylchlorid führt zu den Verbindungen **8–10**.

Introduction

4-Hydroxy-2-pyridones represent an interesting class of pyridine derivatives. A number of compounds with this substitution pattern is found in natural products with biological activity, such as flavipucin [1], tenellin [2], mocimycin [3], ilicicolin [4], and sambutoxin [5]. 4-Hydroxy-2-pyridones (as deazauracil derivatives) have been used as bases for the synthesis of nucleosides [6]. Other derivatives show herbicidal activity [7]. Since 4-hydroxy-2-pyridones may also exist in their tautomeric 2-hydroxy-4-pyridone form, this aspect has found attention [8–12]. X-Ray studies [11] have confirmed earlier results of *Katritzky* [8] and *Bellamy* [9] that N-substituted 4-pyridones exhibit infrared frequencies below 1600 cm^{-1}, whereas 2-pyridones show absorption bands at 1650 cm^{-1}.

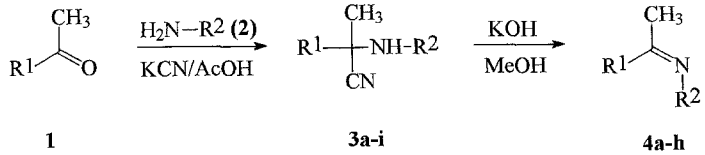
The synthesis of 4-hydroxy-2-pyridones *via* condensation of enamines or azomethines with reactive malonic acid derivatives (such as carbon suboxide, chlorocarbonyl ketenes, and *bis*-2,4,6-trichlorophenyl malonates) is well known,

and literature surveys have been recently presented [13–14]. As a general rule it has been assumed that only activated enamines – derived from β-ketoesters or 1,3-diketones with ammonia or primary amines – can be thermally condensed with substituted dialkyl malonates [15]. The present paper shows that azomethines (**4**) can also be condensed with substituted dialkyl malonates (**5**, $R^4 = CH_3$, C_2H_5) to give 4-hydroxy-2-pyridones (**6**) in moderate to good yields [16–18].

Results and Discussion

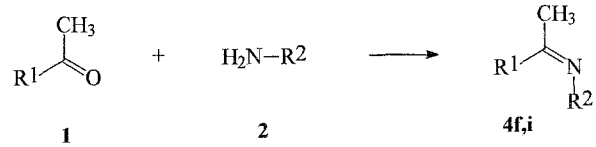
The synthesis of azomethines derived from ketones and aromatic amines as used in this work can be achieved by acid-catalyzed condensation of the two components in toluene or xylene [18, 19]. However, the yields are low due to further condensation reactions which occur also during the final distillation of the crude reaction products (even under reduced pressure). It is well known that the condensation of acetophenone and aniline yields dypnone anil in addition to acetophenone anil [18, 20]. Therefore, we have adopted another synthesis for the preparation of **4** which so far has only briefly been reported in the literature [21–23], and have used the above condensation method only in two cases (**4f,i**). The new method is a two step synthesis *via* the *Strecker* type intermediates **3** (Scheme 1). Compounds **3** are obtained in excellent yields by adding solid potassium or sodium cyanide to a cooled mixture of **1** and **2** in glacial acetic acid. The yields are usually above 90% if a two-fold excess of cyanide is used, and potassium cyanide seems to be superior to sodium cyanide (Table 1). Elimination of hydrogen cyanide from **3** to yield **4** can easily be accomplished with potassium hydroxide in refluxing methanol [22]. This method leads to pure azomethines **4** (with the exception of **4h**, see Table 3) which can be used for further reactions without distillation. The mechanism of this elimination of HCN with sodium methoxide in methanol has recently been investigated in a kinetic study [23]. It has also been reported that compounds of type **3** undergo pyrolytic elimination of HCN at 210°C to afford the azomethines **4** [24]. This fact prompted us to use *Strecker* compounds of type **3** directly for the condensation reaction with malonates. The yields of the resulting pyridones **6**, however, were much lower than those obtained starting with **4** [25].

The results of the condensation reaction of azomethines **4** with malonates **5** are presented in Table 5. In four cases (**6d,I,o,p**) "magic malonates" (*bis*-2,4,6-trichlorophenylmalonates) [14] were employed with a reaction time of 15 minutes. Under these conditions the yields were satisfactory. In all other cases, diethyl or dimethyl malonates were used. Due to the lower reactivity of alkyl malonates, reaction times had to be raised to several hours, and in some cases 4-dimethylaminopyridine was used as acylating catalyst. The yields differ between



1 **3a-i** **4a-h**

Scheme 1. For *R* of compounds **3**, see Table 1

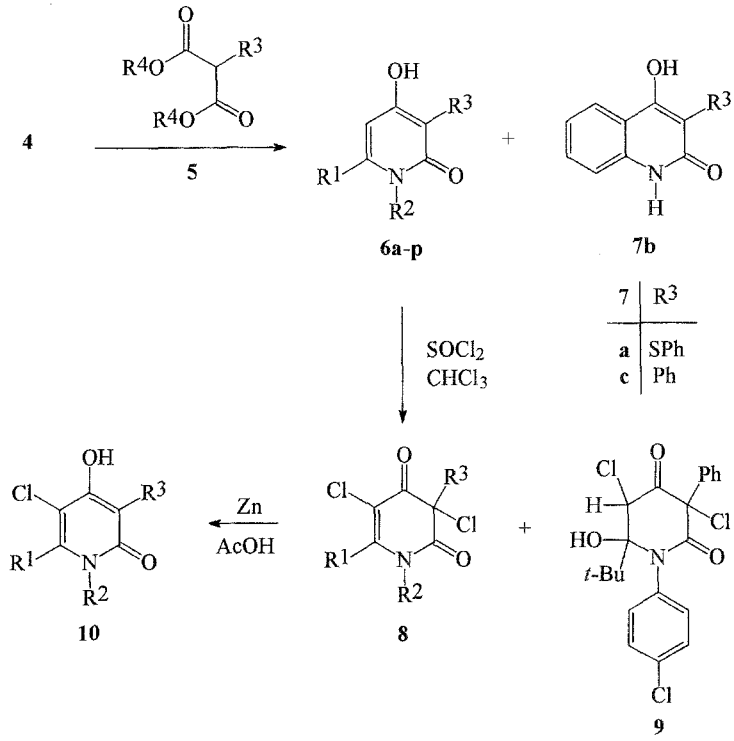


1, 2, 4	R^1	R^2
f	*o*-tolyl	Ph
i	Ph	CH_2Ph

Scheme 2

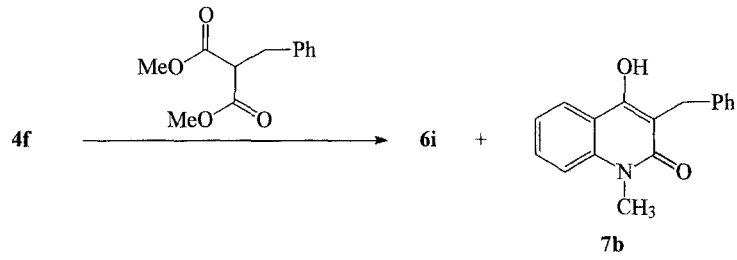
6.5 and 66%. One reason for lower yields is the formation of side products due to self condensation of the azomethines at higher temperatures as mentioned earlier. This process also liberates aniline, and in some cases the reaction products of aniline with **5** could be detected and indentified. Thus, the reaction of **4c** with **5** yielded pyridone **6d** in 32% yield, and in the mother liquor the known 4-hydroxy-3-phenylthio-2-quinolone (**7a**) [28] was found. In the crude reaction product **6n**, 4-hydroxy-3-phenyl-2-quinolone (**7c**) [29] could also be detected.

When **4f** was slowly heated with dimethyl benzylmalonate up to 260°C for a longer period of time, 3-benzyl-4-hydroxy-1-methyl-2(1*H*)-2-quinolone (**7b**) [30] could be isolated in 7.6% yield. The formation of the N-unsubstituted 3-benzyl-4-hydroxy-1-methyl-2(1*H*)-quinolone could easily be explained by the same pathway as discussed for **7a** and **7c**. The formation of **7b** can only proceed *via* N-methylation of the N-unsubstituted compound with dimethyl benzylmalonate. This



7	R^3
a	SPh
c	Ph

Scheme 3. For *R* of compounds **6** see Table 5, for *R* of compounds **8** see Table 7



Scheme 4

represents the first case of an alkylation with dialkyl malonates. Previously, we have alkylated 4-hydroxy-2-quinolones at oxygen and nitrogen in good yields with refluxing trialkyl phosphates [31], *ortho*-formates, and *orhto*-benzoates [32].

The chlorination 4-hydroxy-2-pyridones **6** with sulfuryl chloride in chloroform leads to the yellow 3,5-dichloropyridine-2,4(1*H*,3*H*)-diones **8**. This result is in agreement with previous observations on the chlorination of two 4-hydroxy-4-pyridones, unsubstituted in position 3, which resulted in the formation of 3,3-dichloro-pyridine-2,4-diones, and an additional introduction of a chloro atom in position 5 if this position was unsubstituted [33]. From the mother liquor of **8b** a second compound (which was nearly colorless) could be isolated in 24% yield, resulting from the addition of water to the highly polarized double bond between C-5 and C-6. The ^{1}H NMR analysis shows that this compound is a mixture of two diastereoisomers. Addition of HCl or Cl_2 to the C-5/C-6 double bond in a compound of type **8** has been proposed previously, but without structural assignment [33].

The reduction of the pyridinediones **8** to the 5-chloro-4-hydroxy-2-pyridones **10** is easily accomplished with zinc powder in glacial acetic acid.

Experimental

Melting points were obtained on a Gallenkamp melting point apparatus, Mod MFB-595 (open capillary tubes). IR spectra were recorded on a Perkin Elmer 298 (KBr pellets). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 instrument (*TMS* as internal standard). Microanalyses were performed on a C,H,N-Automat Carlo Erba 1106.

General procedure for the synthesis of 2-substituted 2-arylaminopropionitriles (**3**)

A stirred solution of ketone **1** (100 mmol) and aniline **2** (120 mmol) in 45 ml of glacial acetic acid was cooled in an ice bath. Solid potassium or sodium cyanide (120–180 mmol, see Table 1) was added slowly at such a rate that the temperature did not exceed 10°C.

Caution: Some hydrogen cyanide gas is liberated. The reaction must be carried out in a good working hood, and the outlet of the reaction flask should be connected directly to the exhauster!

The reaction mixture was kept at this temperature for 4–5 h and then overnight at room temperature. After dilution with ice water (100–200 ml), the product formed was filtered off, washed several times with ice water (150–200 ml), and finally with petroleum ether (at least 100 ml). Experimental data: Table 1; spectroscopic data: Table 2.

Table 1. Experimental data of 2-substituted 2-arylaminopropionitriles **3**

	R^1	R^2	Cyanide Quantity[a] (mmol)	Yield (%)	M.p. (°C) Solvent	Molecular formula[b]
3a	isopropyl	phenyl	NaCN 180	86	59–62 hexane	$C_{12}H_{16}N_2$ 188.3
3a	isopropyl	phenyl	KCN 120	82		
3b	isopropyl	4-chlorophenyl	KCN 150	90	110–112 cyclohexane	$C_{12}H_{15}ClN_2$ 227.7
3c	*t*-butyl	phenyl	NaCN 180	92	108–110 ethanol	$C_{13}H_{18}N_2$ 202.3
3c	*t*-butyl	phenyl	KCN 130	86		
3d	*t*-butyl	4-chloro-phenyl	KCN 120	78	105–107 cyclohexane	$C_{13}H_{17}ClN_2$ 236.8
3d	*t*-butyl	4-chloro-phenyl	KCN 150	91		
3e	*t*-butyl	4-fluoro-phenyl	NaCN 180	89	86–88 cyclohexane	$C_{13}H_{17}FN_2$ 220.3
3f	*o*-tolyl	phenyl	NaCN 170	78	115–116 ethanol	$C_{16}H_{16}N_2$ 236.3
3g	4-fluoro-phenyl	phenyl	NaCN 183	99	156°	$C_{15}H_{13}FN_2$ 240.3
3h	benzyl	phenyl	NaCN 180	85	77–78 cyclohexane[d]	$C_{16}H_{16}N_2$ 236.3
3i	benzyl	4-chloro-phenyl	NaCN 180	88	105–108 ethanol	$C_{16}H_{15}ClN_2$ 270.8

[a] Some experiments using smaller excesses of cyanides were carried out which afforded smaller yields of nitriles **3**; sodium cyanide afforded generally smaller yields than potassium cyanide at the same excess; [b] satisfactory microanalyses obtained within ±0.4%; [c] in Ref. [22], The same m.p. has been given for **3g**; [d] recrystallized first from ethanol and then from cyclohexane

General procedure for the preparation of N-alkylidene-arylamines (**4**) *from nitriles* **3**

A solution of potassium hydroxide (300 mmol) in methanol (120 ml) was added to a boiling solution of **3** (100 mmol) in methanol (150 ml). After refluxing for a 1 h and cooling to room temperature, the mixture was poured into ice water (250 ml) and repeatedly extracted with petroleum ether (altogether at least 250 ml). The extract was washed several times with water, and, after drying ($MgSO_4$ or Na_2SO_4) evaporated *in vacuo*. Experimental data: Table 3; Spectroscopic data: Table 4.

N-(1-(2-Methylphenyl)ethylidene)benzeneamine (**4f**) *by condensation of 2-methylacetophenone with aniline*

A solution of 2-methylacetophenone (25.05 g, 187 mmol), aniline (20.9 g, 224 mmol), and *p*-toluenesulfonic acid (0.1 g) in benzene (100 ml) was refluxed for 10 h using a *Dean-Stark* water separator. Benzene was removed *in vacuo*, and the residue was distilled.

Yield: 22.9 g (59%); yellowish liquid; b.p.: 162–168°C/1.5 kPa; Ref. [26]: b.p.: 88–90°C/1 torr (0.13 kPa).

N-(1-Phenylethylidene)benzylamine (**4i**)

A mixture of acetophenone (67 ml, 69 g, 0.57 mol), benzylamine (62 ml, 61 g, 0.57 mol), and xylene (120 ml) was refluxed for 3 h using a *Dean-Stark* trap to remove the H_2O. The fraction with a boiling range from 38–82°C/1.6 kPa was distilled off (the bath temperature should not exceed 160°C). The residue was crystallized from ethanol (100 ml).

Table 2. Spectroscopic data of the 2-substituted 2-arylaminopropionitriles **3**

	IR (KBr cm^{-1})	^1H NMR[a] (δ, ppm)
3a	3380s, 2975m, 2240m, 1607s, 1525m, 1503s	1.07 and 1.21 (*d*, *J*=7.5 Hz, 2 isopropyl-CH_3), 1.56 (s, α-CH_3), 2.26 (m, *J* =7.5 Hz, isopropyl-CH), 3.60 (s, NH), 6.85–7.0 (m, 2-H, 4-H and 6-H of phenyl), 7.26 (dd, *J* =8.5 and 1.5 Hz, 3-H and 5-H of phenyl), 7.20–7.30 (m, 3-H and 5-H of phenyl)
3b	3352s, 2972m, 1600m, 1516m, 1494s	1.06 and 1.19 (d, *J* =7 (Hz, 2 isopropyl-CH_3), 1.53 (s, α-CH_3), 2.22 (m, *J* =7 Hz, isopropyl-CH), 3.59 (s, NH), 6.86 (d, *J* = 8.5 Hz, 2-H and 6-H of chlorophenyl), 7.20 (d, *J* = 8.5 Hz, 3-H and 5-H of chlorophenyl)
3c	3400s, 2975m, 1605s, 1512m	1.18 (s, *t*-butyl), 1.50 (s, α-CH_3), 3.55 (s, NH), 6.92 (m, 4-H of phenyl), 6.95 (m, 2-H and 6-H of phenyl), 7.18–7.28 (m, 3-H and 5-H of phenyl)
3d	3420m, 2980m, 1600s, 1505m, 1495s	1.20 (s, *t*-butyl), 1.50 (s, α-CH_3), 3.57 (s, NH), 6.94 (d, *J* =8.5 Hz, 2-H and 6-H of chlorophenyl), 7.23 (d, *J* =8.5 Hz, 3-H and 5-H of chlorophenyl)
3e	3400m, 2975m, 1514s	1.21 (s, *t*-butyl), 1.44 (s, α-CH_3), 3.40 (s, NH), 6.96–7.06 (m, 4 ArH)
3f	3667m, 1996s, 1490s	2.00 (s, Ar-CH_3), 2.58 (s, α-CH_3), 4.17 (s, NH), 6.55 (dd, *J* =8.0 and 1.5 Hz 2-H and 6-H of phenylamino group), 6.75–6.85 (m, 4-H of phenylamino group), 7.05–7.30 (m, 3-H and 5-H of phenylamino group and 3-H, 4-H and 5-H of tolyl), 7.65–7.73 (m, H-6 of tolyl)
3h	3360s, 1602s, 1526m, 1500s	1.63 (s, CH_3), 3.14 and 3.31 (d, *J* =14 Hz, CH_2), 3.70 (s, NH), 6.9–7.0 (m, 2-H and 6-H of phenylaminogroup), 7.2–7.4 (m, 8 ArH); *DMSO*-d_6: 1.52 (s, CH_3), 3.19 and 3.29 (d, *J* =13 Hz, CH_2), 6.08 (s, NH), 6.71–6.81 (m, 4-H of phenylamino group) 6.95 (d, *J* =9.0+1.5 Hz, 2-H and 6-H of phenylamino group), 7.18–7.40 (m, 7 ArH)
3i	3340s, 1604m, 1525m, 1494s	1.63 (s, CH_3), 3.12 and 3.28 (d, *J* =14 Hz, CH_2), 3.67 (s, NH), 6.87 (d, *J* =9 Hz, 2-H and 6-H of chlorophenylamino group), 7.24 (d, *J* =9 Hz, 3-H and 5-H of chlorophenylamino group), 7.24–7.39 (m, 5 Arh)

[a] Measured in $CDCl_3$ if no other solvent is given

Table 3. Experimental data of N-alkylidenebenzeneamines **4** prepared from nitriles **3**

	R^1	R^2	Yield (%)	Molecular formula[a]
4a	isopropyl	phenyl	90	$C_{11}H_{15}N$ 161.2
4b	isopropyl	4-chlorophenyl	98	$C_{11}H_{14}ClN$ 195.7
4c	*t*-butyl	phenyl	96	$C_{12}H_{17}N$ 175.3
4d	*t*-butyl	4-chlorophenyl	97	$C_{12}H_{16}ClN$ 209.72
4e	*t*-butyl	4-fluorophenyl	88	$C_{12}H_{16}FN$ 193.3
4f[b]	*o*-tolyl	phenyl	92	$C_{15}H_{15}N$ 209.3
4g	4-fluorophenyl	phenyl	85[c]	$C_{14}H_{12}FN$ 213.2
4h	benzyl	phenyl	63[d]	$C_{15}H_{15}N$ 209.3

[a] Satisfactory microanalyses obtained within ±0.4%; [b] described in Ref. [26], prepared also by condensation of 2-methylacetophenone with aniline (see Experimental); [c] m.p.: 82–83°C; Ref. [22]: m.p.: 78–79°C, yield: 86%; [d] elemental analysis corresponds best of all with the mixture containing 70% of compound **4h**, 17% of substrate **3h** and 13% (w/w) of phenylacetone; this conclusion is in agreement with the ^{1}H NMR spectrum. Vacuum distillation afforded a mixture of b.p. 140°C/0.7 kPa containing 86% of compound **4h** and 14% of phenylacetone. The experiment in which hydrogen cyanide was eliminated from compound **3h** by means of sodium methoxide in methanol, without treatment of the product with water gave similar results.

Table 4. Spectroscopic data of ketimines (**4**)

	IR (KBr cm^{-1})	^{1}H NMR[a] (δ, ppm)
4a	2965s, 1660s, 1595s, 1485m	1.21 (d, J=7 Hz, 2 isopropyl-CH_3), 1.75 (s, N=C–CH_3), 2.63 (m, J =7 Hz, isopropyl-CH), 6.64–6.73 (m, 2-H and 6-H of phenyl), 6.98–7.08 (m, 4-H of phenyl), 7.24–7.34 (m, 3-H and 5-H of phenyl); *DMSO*-d_6: 1.00 and 1.15 (d, J =7.5 Hz, 2 isopropyl-CH_3), 1.72 (s, N=C–CH_3), 2.57 (m, J=7.5 Hz, isopropyl-CH), 6.63 (d, J =7.5 Hz, 2-H and 6-H of phenyl), 6.96–7.07 (m, 4-H of phenyl), 7.30 (dd, J =7.5 and 1.5 Hz, 3-H and 5-H of phenyl)
4b	2972m, 1710m, 1662s, 1488s,	1.17 (d, J =7 Hz, 2 isopropyl-CH_3), 1.73 (s, N=C–CH_3), 2.60 (m, J =7 Hz, isopropyl-CH), 6.60 (d, J =8.5 Hz, 2-H and 6-H of chlorophenyl), 7.23 (d, J =8.5 Hz, 3-H and 5-H of chlorophenyl)
4c	296m, 1651s, 1596m,	1.23 (s, *t*-butyl), 1.75 (s, N=C–CH_3), 6.65 (d, J=7.5 Hz, 2-H and 6-H of phenyl), 6.96–7.06 (m, 4-H of phenyl), 7.22–7.34 (m, 3-H and 5-H of phenyl)
4d	2968s, 1656s, 1486s, 1475s,	1.22 (s, *t*-butyl), 1.74 (s, N=C–CH_3), 6.58 (d, J =8 Hz, 2-H and 6-H of phenyl), 7.24 (d, J =8 Hz, 3-H and 5-H of phenyl)
4e	2965m, 1652s, 1500s, 1478m	1.19 (s, *t*-butyl), 1.74 (s, N=C–CH_3), 6.58 (dd, J=8.0 and 1.5 Hz, 2-H and 6-H of phenyl), 6.96 (m, 3-H and 5-H of phenyl)
4h	1658s, 1593s, 1485s	1.75 (s, CH_3), 3.76 (s, CH_2), 6.67–6.60 (m, ArH)

[a] Measured in $CDCl_3$ if no other solvent is given

Yield: 60.3 g; m.p.: 42–44°C; Concentration of the mother liquor to about half its volume *in vacuo* and cooling to 0°C yielded additional 5.0 g of m.p. 40–43°C; total yield: 65.3 g (55%); Ref. [13]: m.p.: 31°C (after distillation); Ref. [27]: m.p.: 44.5°C (ethanol).

General procedure for the synthesis of 1,3,6-trisubstituted 4-hydroxy-2(1H)-pyridones (**6**)

A mixture of the appropriate ketimine **4** (50 mmol) and diethyl or dimethyl malonate **5** was heated in an oil bath until no more alcohol was formed. For reaction temperatures and approximate reaction times, see Table 5. In some cases, the reaction was catalyzed with 4-dimethylaminopyridine (100 mg). The resulting material was digested with diethy ether and crystallized from the appropriate solvent. Experimental details and data: Tale 5; spectroscopic data: Table 6.

4-Hydroxy-3-phenylthio-2(1H)-quinolone (**7a**)

The mother liquor from the first recrystallization of crude pyridone **6b** was evaporated to dryness *in vacuo*. Repeated crystallization of this residue yielded 1.38 g (about 10%) of an enriched product **7a/6b**=78:22 (according to ^{1}H NMR).

Yellowish crystals; melting range: 198–226°C; an authentic product **7a** [28], obtained by the sulfenylation of 4-hydroxy-2(1*H*)quinolone with diphenyldisulfide, melts at 236°C; ^{1}H NMR (*DMSO*-d_6): δ =7.05–7.20 (m, 3H, ArH), 7.2–7.4 (m, 4H, ArH), 7.55–7.65 (m, 1H, ArH), 7.95 (dd, *J*= 7.5 and 1 Hz, H at C-5) ppm.

3-Benzyl-4-hydroxy-1-methyl-2(1H)-quinolone (**7b**)

A mixture of **4f** (31.39 g, 150 mmol) and dimethyl benzylmalonate (36.67 g, 165 mmol) was heated in an open flask. The temperature of the oil bath was increased from 190°C to 235°C during 1 h and held at 235–240°C for 1 h. The temperature was then increased to 250°C (1 h) and finally to 260°C for 2 h. After cooling, the product was triturated with diethyl ether and recrystallized from ethanol.

Yield: 3.0 g (7.6%); m.p.: 220–222°C (Ref. [30]: 219–220°C). IR (KBr): 3300–2800b, 1632s, 1605s cm^{-1}; ^{1}H-NMR (*DMSO*-d_6): δ =3.60 (s, 3H, CH_3), 4.00 (s, 2H, CH_2), 7.06–7.32 (m, 6H, *Ar*H), 7.48 (dd, *J*=1.5 and 7.5 Hz, 1H, *ArH*), 7.56–7.68 (m, 1H, *ArH*), 8.05 (dd, *J*=1.5 and 7.5 Hz, 1H, *ArH*), 10.4 (b, 1H, OH) ppm; MS (50eV): *m/z* (%)=266 (M^++1, 19), 265 (M^+, 100), 264 (28), 249 (6), 248 (33), 236 (4), 188 (7), 187 (6), 169 (15), 161 (19), 131 (14), 116 (5), 103 (9), 91 (24), 77 (16), 69 (14), 55 (8); $C_{17}H_{15}NO_2$ (265.3); calcd.: C 76.96, H 5.70, N 5.28; found: C 76.89, H 5.53, N 5.20.

4-Hydroxy-3-phenyl-2(1H)-quinolone (**7c**)

Detected in the reaction product **6n**, obtained from diethyl phenylmalonate (**5**) and impure **4h** (see footnote d in Table 3).

Ratio of **6n/7c**:=66:34% (by ^{1}H NMR; pure **7c** [29]: m.p.: 320°C; IR (KBr): 1640, 1620 cm^{-1}, ^{1}H NMR (*DMSO*-d_6): δ =7.00–7.60 (m, 6 ArH), 8.00 (dd, *J*=8 and 1 Hz, H at C-5) 10.1 (s, OH), 11.5 (s, NH) ppm.

General procedure for the synthesis of 1,3,6,-trisubstituted 3,5-dichloropyridine-2, 4(1H,3H)-diones (**8**)

To a stirred suspension of **6** (10 mmol) in chloroform (30 ml), sulfuryl chloride was added, leading to a yellow solution with concomitant evolution of sulfur dioxie and hydrogen chloride. The solution was evaporated *in vacuo*, and the residue was triturated with cold ethanol. The yellow crystals were isolated by filtration and recrystallized from ethanol. Experimental data: Table 7; spectroscopic data: Table 8.

Table 5. Experimental data[a] of 1,3,6-trisubstituted 4-hydroxy-2(1H)-pyridones **6**

	R^1	R^2	R^3	Reaction Temp (°C) Time (h)	Yield (%)	M.p. (°C) Solvent	Molecular formula[b]
6a	isopropyl	4-chloro-phenyl	phenyl	240–255 2.0[c]	39	320 (dec.) *DMF*-BuOH 1:1	$C_{20}H_{18}ClNO$ 339.8
6b	*t*-butyl	phenyl	phenylthio	190–245 1.25[c]	32[d]	226–229 ethanol	$C_{21}H_{21}NO_2S$ 351.5
6c	*t*-butyl	4-chloro-phenyl	phenyl	250–254 4	38	302–303 *DMF*-BuOH 1:1	$C_{21}H_{20}ClNO_2$ 353.9
6d	*t*-butyl	4-fluoro-phenyl	phenyl[e]	180–240 0.25	75	334–339[f] *DMF*-BuOH 1:1	$C_{21}H_{20}FNO_2$ 321.4
6e	*t*-butyl	4-fluoro-phenyl	phenylthio	215–228 2.25	42	221–225 ethanol	$C_{21}H_{20}FNO_2S$ 369.4
6f	*o*-tolyl	phenyl	methyl	260–228 4.25[c]	46	257–264 2-propanol	$C_{19}H_{17}NO_2$ 291.4
6g	*o*-tolyl	phenyl	ethyl	240–260 2.75[c]	46	263–266 2-propanol	$C_{20}H_{19}NO_2$ 305.4
6h	*o*-tolyl	phenyl	butyl	260–280 4.25[c]	47	250–252 ethanol	$C_{22}H_{23}NO_2$ 333.4
6i	*o*-tolyl	phenyl	benzyl	240–280 1.75[c]	7[g]	270–276 2-propanol	$C_{25}H_{21}NO_2$ 367.4
6j	*o*-tolyl	phenyl	phenyl	265–270 0.33[c]	86	340–350[h]	$C_{24}H_{19}NO_2$ 353.4
6k	4-fluoro-phenyl	phenyl	ethyl	220–260[i] 6.5[c]	6.5	300 ethanol	$C_{19}H_{16}FNO_2$ 309.3
6l	4-fluoro-phenyl	phenyl	butyl	220–260[i] 6.5[c]	6.5	285–287 ethanol	$C_{21}H_{20}FNO_2$ 337.4
6l	4-fluoro-phenyl	phenyl	butyl[e]	238 0.25	82	270–278[j]	$C_{21}H_{20}FNO_2$ 337.4
6m	4-fluoro-phenyl	phenyl	phenyl	220–240 4.5[c]	66	357–358 *DMF*-BuOH 3:1	$C_{23}H_{16}FNO_2$ 357.4
6n	benzyl	phenyl[k]	phenyl	235–245 3.0		263–273[l] *DMF*-BuOH 1:5	$C_{24}H_{19}NO_2$ 353.4
6o	phenyl	benzyl	butyl[e]	234–239 0.25	46	177–192 ethanol	$C_{22}H_{23}NO_2$ 333.4
6p	phenyl	benzyl	phenyl[e]	234–236 0.25	65	257–259[j]	$C_{24}H_{19}NO_2$ 353.4

[a] Malonates **5** were diethyl esters; crude products were triturated with diethyl ether if not given otherwise; [b] all compounds except **6n** were pure according to ^{1}H NMR and TLC; satisfactory microanalysis were obtained within ±0.4%; [c] catalyzed with 4-dimethylaminopyridine; [d] compound **7a** was found as side product in mother liquor; [e] bis (2,4,6-trichlorophenyl) ester used; [f] crude product triturated at first with petroleum ether and then with diethyl ether; Ref. [17]: m.p.: 344°C; [g] crude product triturated consecutively with petroleum ether, cyclohexane and diethyl ether; [h] crude crystalline product washed with chloroform not recrystallized; [i] 220–240°C for 5 h and 260°C for 1.5 h; [j] crude product washed first with diethyl ether and then with carbon tetrachloride, not recrystallized; [k] purity of ketimine: 70% (see Table 3, compound **4h**); [l] 3.41 g, content according to elemental analysis and ^{1}H NMR 66% (w/w) pyridone **6n** and 34% (w/w) 4-hydroxy-3-phenyl-2 (1H)-quinolone **7c**

Table 6. Spectroscopic data of 2,3,6-trisubstituted 4-hydroxy-2(1*H*)-pyridones (**6**)

	IR (KBr cm^{-1})	^1H NMR (*DMSO*-d_6, δ, ppm)
6a	3300–2000b, 1642m, 1628s, 1580m, 1545s	1.06 (d, J =6.5 Hz, 2 CH_3), 2.41 (m, J =6.5 Hz, isopropyl-CH), 6.14 (s, 5-H), 7.16–7.44 (m, 7 ArH), 7.58 (d, J = 8.5 Hz, 2 ArH), 10.49 (s, OH)
6b	3220–2420b, 1615m, 1600s, 1580s,	1.08 (s, *t*-butyl), 6.42 (s, 5-H), 7.08 (dd, J = 7.0 and 1.5 Hz, 2 ArH), 7.19–7.33 (m, 4 ArH), 7.42–7.53 (m, 3 ArH), 11.24 (s, OH)
6c	3400–2400b, 1631s, 1592s, 1548s	1.11 (s, *t*-butyl), 6.37 (s, 5-H), 7.16–7.44 9 (m, 7 ArH), 7.55 (d, J =8.5 Hz, 2 ArH), 10.48 (s, OH)
6d[a]	3080–2900b, 2680m, 1640m, 1590s,	1.10 (s, *t*-butyl), 6.35 (s, 5-H), 7.10–7.45 (m, 9 ArH)
6e	3300–2700b, 2670m, 2615m, 1621m, 1583s, 1550s	1.10 (s, *t*-butyl), 6.35 (s, 5-H), 7.02–7.14 (m, 3 ArH), 7.20–7.40 (m, 6 ArH), 11.16 (s, OH)
6f	3300–2800b, 1633s, 1599s, 1551s	1.90 (s, 3-CH_3), 2.10 (s, CH_3 of *o*-tolyl), 5.90 (s, 5H), 7.00 – 7.15 (m, 9 ArH), 10.40 (s, OH)
6g	3300–2780b, 1635s, 1600s, 1550s	1.05 (t, J =5 Hz, CH_3 of ethyl), 2.10 (s, CH_3 of *o*-tolyl), 2.45 (q, J =5 Hz, CH_2), 5.87 (s, 5-H), 6.95–7.17 (m, 9 ArH), 10.35 (s, OH)
6h	3200–2780b, 1637m, 1595m, 1548s	0.91 (t, J=7 Hz, CH_3 of butyl), 1.25–1.54 (m, 2-CH_2 and 3-CH_2 of butyl), 2.11 (s, CH_3 of *o*-tolyl), 2.46 (t, J =7 Hz, 1-CH_2 of butyl), 5.88 (s, 5-H), 6.95–7.25 (m, 9 ArH), 10.33 (s, OH)
6i	3240–2760b, 1632m, 1600m, 1550s	2.10 (s, CH_3), 3.78 (s, CH_2), 5.94 (s, 5-H), 7.0–7.3 (14 ArH), 10.60 (s, OH)
6j	3240–2750b, 1625m, 1599m, 1547s	2.20 (s, CH_3), 6.06 (s, 5-H), 7.00–7.55 (m, 14 ArH), 10.62 (s, OH)
6k	3200–2790b, 2710–2620b, 1637m, 1600m, 1550s, 1507s	1.00 (t, J =7.5 Hz, CH_3), 2.40 (q, J =7.5 Hz, CH_2), 5.95 (s, 5-H), 6.95–7.30 (m, 9 ArH), 10.38 (s, OH)
6l	3020m, 2955m, 2920m, 2860m, 2640m, 1633m, 1600s, 1582m, 1547s	0.92 (t, J =7 Hz, CH_3), 1.25–1.54 (m, 2-CH_2 and 3-CH_2 of butyl), 2.45 (t, J =7 Hz, 1-CH_2 of butyl), 6.01 (s, 5-H), 6.99–7.31 (m, 9 ArH), 10.40 (s, OH)
6m	3200–2720b, 1627m, 1600m, 1580m, 1550s	6.15 (s, 5-H), 7.0–7.5 (m, 14 ArH), 10.70 (s, OH)
6n		3.55 (s, CH_2), 5.83 (s, 5-H), 7.00–7.60 (m, 15 ArH), 10.43 (s, OH)
6o	2940m, 1630m, 1540s	0.93 (t, J =7 Hz, CH_3), 1.26–1.55 (m, 2-CH_2 and 3-CH_2 of butyl), 2.48 (t, J =7 Hz, 1-CH_2 of butyl), 5.04 (s, NCH_2), 5.89 (s, 5-H), 6.83 (d, J =7 Hz, 2 ArH), 7.15–7.50 (m, 8 ArH), 10.31 (s, OH)
6p	3320–2400b, 3050m, 3025m, 1630s, 1550s, 1495m	5.08 (s, CH_2), 6.03 (s, 5-H), 6.90 (d, J =7.5 Hz, 2 ArH), 7.15–7.58 (m, 13 ArH)

[a] Ref. [17]

6-tert-Butyl-1-(4-chlorophenyl)-3,5-dichloro-6-hydroxy-3-phenyl-5,6-dihydropyridine-2, 4(1H,3H)-dione (**9**; *mixture of two diastereoisomers*)

The mother liquor of compound **8b** was concentrated *in vacuo*; the precipitate was isolated by filtration and crystallized from 2-propanol.

Table 7. Experimental data of 1,3,6-trisubstituted 3,5-dichloropyridine-2,4(1H, 3H)-diones (**8**)

	R^1	R^2	R^3	Yield (%) Starting material	M.p. (°C)	Molecular formula[a]
8a	isopropyl	4-chloro-phenyl	phenyl	77 **6a**	153–158	$C_{20}H_{16}Cl_3NO_2$ 408.7
8b	*t*-butyl	4-chloro-phenyl	phenyl	58 **6c**	207–209	$C_{21}H_{18}Cl_3NO_2$ 422.8
8c	*o*-tolyl	phenyl	methyl	90 **6f**	172–175	$C_{19}H_{15}Cl_2NO_2$ 360.2
8d	*o*-tolyl	phenyl	butyl	69 **6h**	123–125	$C_{22}H_{21}Cl_2NO_2$ 402.3
8e	*o*-tolyl	phenyl	phenyl	49 **6j**	182–183[b]	$C_{24}H_{17}Cl_2NO_2$ 422.3

[a] Satisfactory microanalyses obtained within ±0.4%; [b] recrystallized from glacial acetic acid

Table 8. Spectroscopic data of 1,3,6-trisubstituted 3,5-dichloropyridine-2,4 (1H,3H)-diones (**8**)

	IR (KBr cm^{-1})	^1H NMR[a] (δ, ppm)
8a	1722s, 1689s, 1590s, 1580s	1.13 (*d*, *J*=7 Hz, 1 CH_3), 1.24 (d, *J* =7 Hz, 1CH_3), 2.59 (m, isopropyl-CH), 7.02 (dd, *J* =2.5 and 8.5 Hz, 2-H and 6-H of 4-chlorophenyl), 7.17 (dd, *J* =2.5 and 8.5 Hz, 3-H and 5-H of 4-chlorophenyl),7.36–7.55 (m, 5 ArH)
8b	1739s, 1705s, 1540m	0.90 (s, *t*-butyl), 7.25–7.48 (m, 9 ArH)
8c	1720s, 1680s, 1581s,	2.07 (s, CH_3 of *o*-tolyl), 2.35 (s, 3-CH_3), 6.95–7.25 (m, ArH)
8d	2970m, 2937m, 2870m, 1725s, 1686s, 1610m, 1590s	*DMSO*-d_6: 0.92 (t, *J* =6.5 Hz, butyl-CH_3), 1.3–1.5 (m, 2-CH_2 and 3-CH_2 of butyl), 2.28 (s, CH_3 of *o*-tolyl), 2.33–2.43 (m, 1-CH_2 of butyl), 7.05–7.35 (m, 9 ArH)
8e[b]	1730s, 1690s, 1575m	*DMSO*-d_6: 1.71 (s, CH_3), 2.32 (s, CH_3), 6.88–7.65 (m, 14 ArH)

[a] Measured in $CDCl_3$ if no other solvent is given; [b] signals of methyl at 1.71 and 2.32 ppm in a ratio of 3:2, doubled probably through stericaly hindered rotation of tolyl group

Table 9. Experimental data of 1,3,6-trisubstituted 5-chloro-4-hydroxy-2(1H)-pyridones (**10**)

	R^1	R^2	R^3	Yield (%) Starting material	M.p. (°C) Solvent	Molecular formula[a]
10a	isopropyl	4-chloro-phenyl	phenyl	97 **8a**	245–247	$C_{20}H_{17}Cl_2NO_2$ 347.3
10b	*t*-butyl	4-chloro-phenyl	phenyl	64 **8b**	192–194 90% AcOH	$C_{21}H_{19}Cl_2NO_2$ 388.3

[a] satisfactory microanalyses obtained within ±0.4%

Table 10. Spectroscopic data of 1,3,6-trisubstituted 5-chloro-4-hydroxy-2(1*H*)-pyridones (**10**)

	IR (KBr cm^{-1})	^1H NMR (*DMSO*-d_6, δ, ppm)
10a	3400–2600b, 1627s, 1535s, 1490m	1.30 (*d*, *J*=6 Hz, $2CH_3$), 2.76 (m, *J* =6 Hz, isopropyl-CH), 7.25–7.45 (m, 7 ArH), 7.61 (d, *J* =8 Hz, 2 ArH), 10.20 (s, OH)
10b	3400–2800b, 1620s, 1486m	1.24 (s, *t*-butyl), 7.26–7.40 (m, 7 ArH), 7.50 (d, *J* =8.5 Hz, 2 ArH), 10.24 (s, OH)

Yield: 1.06 g (24%); yellowish crystals; m.p.: 116–118°C; IR 3355s, 1751s, 1701m, 1678m, 1661s, 1599m, 1535s, 1493s cm^{-1}; ^1H NMR ($CDCl_3$: δ =1.25 (s, *t*-butyl of isomer A), 1.29 (s, *t*-butyl of isomer B), 7.20–7.57 (m, ArH of both isomers), 8.28 (s, 5H of isomer A), 8.55 (s, OH of isomer B); molar ratio of isomers A and B: approximately 2:1; $C_{21}H_{20}Cl_3NO_3$ (440.8); calcd.: C 57.22, H 4.57, Cl 24.13, N 3.18; found: C 57.02, H 4.68, Cl 24.01, N 3.08.

General procedure for the synthesis of 1,3,6-trisubstituted 5-Chloro-4-hydroxy-2(1H)-pyridones (**10**)

To a solution of **8** (15 mmol) in glacial acetic acid (150 ml), zinc powder (75 mmol) was added at 90°C in small portions. An exothermic reaction took place that caused the reaction mixture to boil. After 2 min, the excess of zinc was removed by filtration, the filtrate cooled, and diluted with water (150 ml). The precipitate was filtered off, washed with 0.5 *N* hydrochloric acid, and recrystallized. Experimental data: Table 9; spectroscopic data Table. 10.

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