80. Photooxygenation of 5-Aryl-2,4-diaminopyrimidines leading to 4-Amino-1,3,5-triazin-2-yl Ketones and, in the Presence of Sodium Borohydride, to 5,6-Dihydro-4(3*H*)-pyrimidinones

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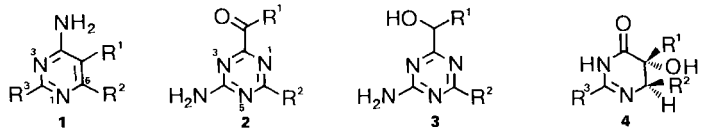
The photosensitized oxygenation of 5-aryl-2,4-diaminopyrimidines **1** in protic solvents led to the formation of the new 4-amino-1,3,5-triazin-2-yl ketones **2** in high yields. The structures of **2** were elucidated by spectroscopical means, especially by ^{13}C-NMR and UV data. Photooxygenation of 2,4-diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine **1a** under reductive conditions, *e.g.* in the presence of excess $NaBH_4$, gave 2-amino-5-(*p*-chlorophenyl)-*t*-6-ethyl-5,6-dihydro-*r*-5-hydroxy-4(3*H*)-pyrimidinone (**4a**), the structure of which was determined by X-ray analysis. In the proposed mechanisms for both types of reactions, the dipolar ion **5** is assumed to be a common intermediate. For the new efficient synthesis of 1,3,5-triazines from 2,4-diaminopyrimidines, a 5-aryl substituent seems to be essential.

1. Introduction. – Since it is known that singlet oxygen ($^1O_2$) and superoxide radical anions (O_2^-) may act as causative agents in naturally occurring oxidative reactions [1], our *in vitro* assay of the photochemical behaviour of drugs also includes their photosensitized oxygenation. With respect to the latter, we now bring into focus the antimalarial pyrimethamine **1a** which by $^1O_2$ was transformed into the corresponding 1,3,5-triazin-2-yl ketone **2a**. To recognize scope and limitations of this new type of reaction, we also extended our study to the related compounds **1b–h**.



	R¹	R²	R³
a	*p*-ClC$_6$H$_4$	Et	NH_2
b	C_6H_5	H	NH_2
c	C_6H_5	Me	NH_2

	R¹	R²	R³
d	C_6H_5	C_6H_5	NH_2
e	adamantyl	Me	NH_2
f	COOEt	H	NH_2

	R¹	R²	R³
g	*p*-ClC$_6$H$_4$	Et	NHAc
h	C_6H_5	Me	Me

2. Results. – Using VIS light, the irradiation of the compounds **1a–d** in the presence of air and hematoporphyrin or rose bengal in MeOH or EtOH led to the formation of the 1,3,5-triazin-2-yl ketones **2a–d** in good to excellent yields (see *Exper. Part*). In contrast, hematoporphyrin-sensitized photooxygenation of **1e** in EtOH caused its complete decomposition yielding not yet identified polar products. On the other hand, no reaction of the compounds **1f–h** with $^1O_2$ could be detected applying the reaction conditions mentioned above.

Photooxygenation of **1a** under reductive conditions, *e.g.* in the presence of 6 mol-equiv. of $NaBH_4$, gave no 1,3,5-triazine but the 5,6-dihydropyrimidinone **4a** as a 1:1 mixture of diastereoisomers which, during the acidic workup, were transformed into the corresponding hydrochlorides.

Spectroscopic data were used to elucidate the structures of the new 1,3,5-triazinyl ketones **2a–d**. The results were supported by reduction of **2a** and **2d** to the corresponding secondary alcohols **3a** and **3d** using $NaBH_4$. Relevant ^{13}C-NMR signals of **2a–d** as well as those of **3a** and **3d** are compared in *Fig. 1* with respect to the different substituents R^1 and R^2.

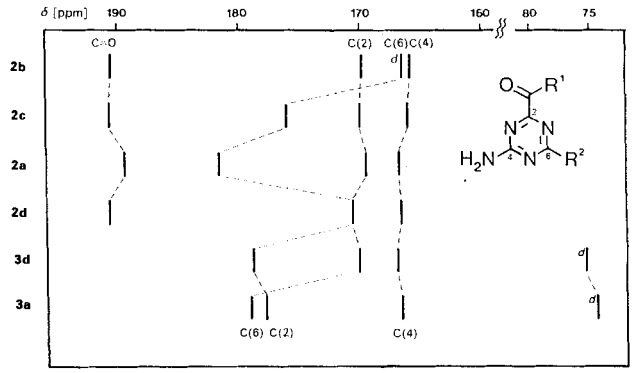


Fig. 1. *Dependence of relevant ^{13}C-NMR chemical shifts of* **2** *and* **3** *upon their substitution pattern*

In agreement with [2], the *d* at 166.58 ppm exhibited by **2b** must be assigned to C(6) and the high field *s* at 165.83 ppm to C(4) which bears the NH_2 group. Then, the *s* at 169.88 and 190.47 ppm correspond to C(2) and to C=O, respectively. Compared to the ketones **2a** and **2d**, the alcohols **3a** and **3d** show a considerable downfield shift of the signal assigned to the ring C-atom C(2) and in addition a *d* which is characteristic for the C-atom of the exocyclic secondary-alcohol function. Also the negative inductive effect of $R^1 = p\text{-}ClC_6H_4$ can be recognized as a slight upfield shift ($\Delta\delta = -(0.5–1.2)$ppm) of the signals assigned to C=O and to the C-atom of the secondary-alcohol function as well as to C(2) of the 1,3,5-triazinyl moiety of **2a** and **3a**.

Additionally, the UV spectra of **2** and **3** show a shoulder in the region of 215–230 nm and absorption maxima between 252 and 263 nm. Analogous data for unsubstituted 1,3,5-triazines are 221 and 268 nm, respectively [3]. The

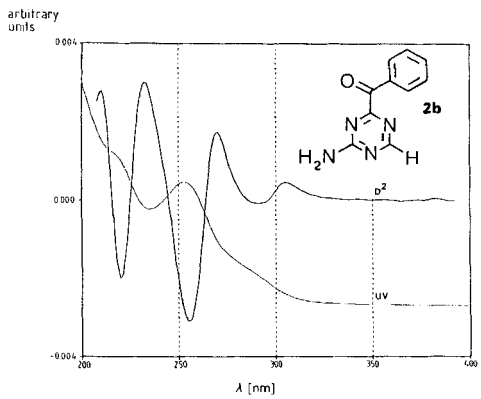


Fig. 2. *UV spectrum of* **2b** *and the corresponding second-derivative (D^2) spectrum*

shoulder at 291 nm in *Fig. 2* corresponds to the C=O group of **2b** and disappears when **2b** is reduced to the alcohol **3b**. In general, substituents scarcely change the position of the absorption maxima of **2** and **3**. Only their intensity is increased considerably by aryl substituents at C(6) (see the corresponding absorption coefficients of **2d** and **3d** in the *Exper. Part*). The small differences in the UV spectra of 1,3,5-triazines due to the substitution pattern can be enhanced using the spectral second-derivative (D^2) technique [4] which is exemplified in *Fig. 2*.

Since the steric arrangement of the substituents at C(5) and C(6) of the pyrimidinone **4a** could not be elucidated by a ^{1}H- and ^{13}C-NMR study including nuclear *Overhauser* experiments, the structure of **4a** was unambiguously determined by an X-ray analysis (see *Fig. 3* and *Exper. Part*). This analysis revealed the *cis* configuration of the *p*-chlorophenyl and Et group.

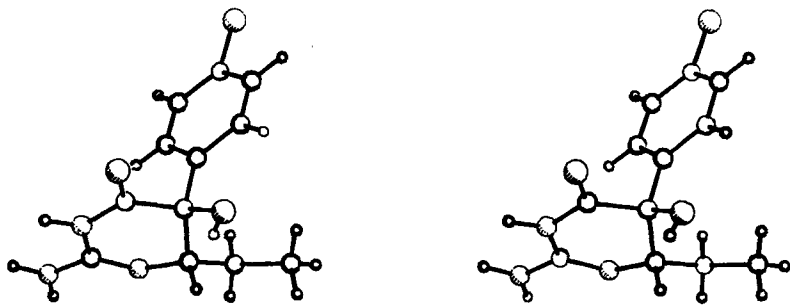


Fig. 3. *Stereoprojection of* **4a**

To substantiate the mechanism concerning the formation of 1,3,5-triazines from 2,4-diaminopyrimidines by photooxygenation, the following experiments were performed. In the presence of 2.2 mol-equiv. of 1,4-diazabicyclo[2.2.2]octane (DABCO), a known $^1O_2$ quencher [5], the photooxidative transformation of **1a** into **2a** was effectively suppressed. In AcOH with methylene blue as sensitizer, the reaction was completely inhibited. Finally, beside unidentified polar decomposition products, only traces of **2a** could be detected using CH_2Cl_2 or THF as solvents *(Table)*.

Table. *Sensitized Photooxygenation of 2,4-Diaminopyrimidines* **1** *under Different Reaction Conditions*

Substrate	Solvent	Sensitizer[a])	Irradiation time [h]	Yield [%]
1a	EtOH	HP	6–7	81 (**2a**)
1b	EtOH	HP	5	46 (**2b**)
1c	EtOH	HP	5	83 (**2c**)
1d	EtOH	HP	5	75 (**2d**)
1a	EtOH	RB	2	56.6 (**2a**)[c])
1a	EtOH	RB, DABCO[b])	2	12.2 (**2a**)[c])
1a	AcOH	MB	7	no reaction
1a	CH_2Cl_2	TPP	1.5	decomposition
1a	THF	RB	4	decomposition

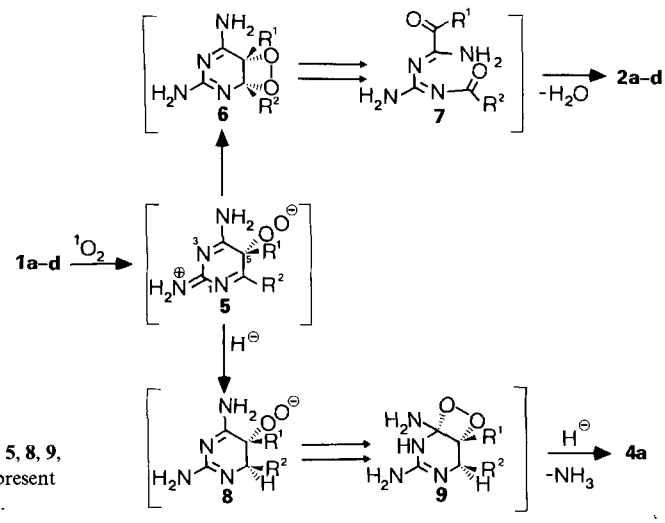
[a]) HP = hematoporphyrin, RB = rose bengal, DABCO = 1,4-diazabicyclo[2.2.2]octane, MB = methylene blue, TPP = tetraphenylporphyrin.

[b]) $3.57 \cdot 10^{-2}$ M DABCO with $1.62 \cdot 10^{-2}$ M **1a**.

[c]) Determined by GLC.

3. Discussion. – It is known that unstable endoperoxides are formed in aprotic solvents upon reaction of $^1O_2$ with pyrimidines exhibiting a substitution pattern like Me at C(2), Me or EtO at C(4), H at C(5), and EtO at C(6) [6]. This corresponds with our results concerning the decomposition of photooxygenation products derived from **1a** in aprotic solvents *(Table)*. On the contrary, in protic solvents 2,4-diaminopyrimidines with aryl substituents at C(5) and/or C(6) react with $^1O_2$ presumably to give the intermediate dioxetanes **6** *(Scheme)*, whereas the electron-deficient pyrimidines **1f–h** are not attacked by $^1O_2$ (see above).

Scheme[a])



[a]) Formulae **5**, **8**, **9**, and **4a** represent racemates.

In our study, the dipolar ion **5** seems to be a key intermediate. Attack by the peroxide anion upon C(6) leads to the expected dioxetane **6** [7] which then undergoes the usual spontaneous cleavage yielding a dicarbonyl compound. By protonation/deprotonation-assisted rotation, the former 4-amino group acquires a position suitable for a condensation (see **7**) which yields the 1,3,5-triazines **2a–d** *(Scheme)*.

In the presence of excess $NaBH_4$, the sterical hindrance exerted by R^1 and R^2 in **5** forces the bulky $NaBH_4$ to attack C(6) stereospecifically from the same side as the peroxide anion does in the absence of $NaBH_4$. Now the peroxide anion of the resulting intermediate **8** may only form a dioxetane with C(4), hereby shifting its negative charge to N(3) where it is neutralized by protonation (→**9**; *Scheme*). Reaction of $NaBH_4$ with the dioxetane O-atom at C(5) splits the O–O bond of **9** forming HO–C(5) and an O-atom at C(4) bearing a negative charge. This unstable intermediate eliminates NH_3 to give **4a**. The two reaction sequences shown in the *Scheme* proceed in protic solvents only.

The authors are indebted to Prof. *W. Adam* for helpful discussions and to Prof. *H.-J. Hansen* for encouraging this work. Furthermore, they thank Mr. *A. Ritter* for performing the large-scale photooxygenation, Dr. *W. Arnold* (NMR), Mr. *W. Meister* (MS), and Dr. *M. Grosjean* (IR) for the spectroscopic data, and our microanalytical laboratory directed by Dr. *A. Dirscherl* for the elemental analyses.

Experimental Part

1. *General.* X-Ray analysis: data collection on a *Nicolet R3m* four-circle diffractometer filled with a graphite monochromator and *LT1* cooling apparatus. UV and second derivative D^2 (MeCN): *Perkin-Elmer Lambda 9* and *Kontron Uvikon 860*, λ (nm). IR (cm^{-1}): in KBr; *Nicolet FT/IR 719*. ^{1}H- and ^{13}C-NMR ((D_6)DMSO): *Bruker-Spectrospin WM 250* (250 MHz) and *WM 400* (100.6 MHz), respectively; δ in ppm and J in Hz. MS: *MS 9* from *AEI*, Manchester, updated with *ZAB* console and data system *3000*, *m/z* (rel. %).

2. *General Procedure.* Irradiations were performed with a high-pressure Hg-lamp *TQ 150* or, for scaling up [8], with the medium-pressure Hg-lamps *TQ 2020* and *TQ 4024* (*Heraeus*, Hanau, FRG) with light $\lambda \geqslant 400$ nm using a liquid cut-off filter [9] with external cooling. Concentrations of the substrates and sensitizers in EtOH solns. were $1.0–2.0 \cdot 10^{-2}$ M **1**, $1.0 \cdot 10^{-3}$ M HP, $1.0 \cdot 10^{-4}$ M RB, $1.25 \cdot 10^{-4}$ M MB. As oxidant, air was bubbled through the solns. Reaction control by TLC (THF/hexane 1:1). Solvents, the photosensitizers, and the quencher DABCO (see *Table*) were used as obtained from *Fluka*.

Starting materials: **1a**[1]), **1e**[2]); additionally synthesized, according to the literature, were **1b–d** and **1h** [10], **1f** [11], and **1g** [12].

Workup: evaporation of the solvent at 35°. Flash chromatography or radial chromatography (*Harrison Research Chromatotron 7924 T*) on silica gel (THF/hexane 1:1). Recrystallization.

3. *Ketones* **2** *and Alcohols* **3**. *4-Amino-6-ethyl-1,3,5-triazin-2-yl* p-*Chlorophenyl Ketone* (**2a**). Yield 81%. M.p. 140–142° (cyclohexane). UV: 214.8 (11739), 263.0 (7271). IR: 3497, 3400, 3322, 3204, 2979, 2942, 1696, 1661, 1564, 1236, 824. ^{1}H-NMR: 7.90 (br. *s*, 2 H); 7.94, 7.65 (*m* centres, *AA'*, *BB'*, 4 H); 2.64 (*q*, 2 H); 1.21 (*t*, 3 H). ^{13}C-NMR: 189.47 (*s*); 181.72 (*s*); 169.51 (*s*); 166.88 (*s*); 140.80 (*s*); 132.61 (*s*); 132.19 (*d*); 128.91 (*d*); 32.13 (*t*); 11.51 (*q*). MS: 262 (70, M^+), 234 (11), 233 (11), 227 (6), 139 (100), 123 (1), 111 (59), 29 (7). Anal. calc. for $C_{12}H_{11}ClN_4O$ (262.70): C 54.87, H 4.22, Cl 13.50, N 21.33; found: C 54.67, H 4.35, Cl 13.19, N 21.06.

4-Amino-1,3,5-triazin-2-yl Phenyl Ketone (**2b**). Yield 46%. M.p. 233–234° (*i*-PrOH). UV: 217.0 (14944), 253.2 (12039). IR: 3297, 3214, 3055, 1707, 1676, 1644, 1587, 1523, 759, 741, 690. ^{1}H-NMR: 8.69 (*s*, 1 H); 8.05 (br. *s*, 2 H); 7.93 (*d*, J = 7.5, 2 H); 7.74 (*t*, J = 7.5, 1 H); 7.58 (*t*, J = 7.5, 2 H). ^{13}C-NMR: 190.47 (*s*); 169.88 (*s*); 166.58 (*d*); 165.83 (*s*); 134.38 (*d*); 133.55 (*s*); 130.04 (*d*); 128.78 (*d*). MS: 200 (53, M^+), 172 (10), 105 (100), 77 (92). Anal. calc. for $C_{10}H_8N_4O$ (200.20): C 59.99, H 4.03, N 27.99; found: C 60.08, H 4.14, N 27.80.

4-Amino-6-methyl-1,3,5-triazin-2-yl Phenyl Ketone (**2c**). Yield 83%. M.p. 180.5–181.5° (*i*-PrOH). UV: 217.0 (15805), 252.2 (12702). IR: 3319, 3174, 3061, 1677, 1651, 1595, 1569, 1527, 739, 697. ^{1}H-NMR: 7.90 (*d*, J = 8.5, 2 H); 7.89 (br. *s*, 2 H); 7.73 (*t*, J = 7.4, 1 H); 7.58 (*t*, J = 7.8, 2 H); 2.38 (*s*, 3 H). ^{13}C-NMR: 190.70 (*s*); 176.06 (*s*); 170.05 (*s*); 166.12 (*s*); 134.34 (*d*); 133.66 (*s*); 129.99 (*d*); 128.80 (*d*); 25.03 (*q*). MS: 214 (67, M^+), 186 (10), 105 (100), 77 (80). Anal. calc. for $C_{11}H_{10}N_4O$ (214.23): C 61.67, H 4.71, N 26.15; found: C 61.35, H 4.75, N 26.09.

4-Amino-6-phenyl-1,3,5-triazin-2-yl Phenyl Ketone (**2d**). Yield 75%. M.p. 159.5–160.5° (*i*-PrOH). UV: 230.3 (14759), 255.2 (21701). IR: 3289, 3170, 3058, 2932, 1696, 1648, 1599, 1588, 1551, 1525, 746, 702, 682. ^{1}H-NMR: 8.37 (*d*, J = 7.5, 2 H); 8.11 (br. *s*, 2 H); 8.02 (*d*, J = 7.8, 2 H); 7.76 (*t*, J = 7.6, 1 H); 7.64–7.53 (*m*, 5 H). ^{13}C-NMR: 190.77 (*s*); 170.69 (2*s*); 166.73 (*s*); 135.40 (*s*); 134.45 (*d*); 133.74 (*s*); 132.40 (*d*); 130.17 (*d*); 128.89 (*d*); 128.62 (*d*); 128.14 (*d*). MS: 276 (86, M^+), 248 (9), 105 (100), 77 (99). Anal. calc. for $C_{16}H_{12}N_4O$ (276.30): C 69.55, H 4.38, N 20.28; found: C 69.53, H 4.49, N 20.18.

4-Amino-α-(p-*chlorophenyl)-6-ethyl-1,3,5-triazine-2-methanol* (**3a**). Yield 80%. M.p. 148°. UV: 222.0 (22899), 255.0 (2979). IR: 3322, 3208, 2985, 2941, 2911, 1646, 1542, 1491, 1092, 823. ^{1}H-NMR: 7.50 (br. *s*, 2 H); 7.46, 7.37 (*m*, centres, *AA'*, *BB'*, 4 H); 5.83 (*d*, J = 4.9, OH; D_2O-exchangeable); 5.37 (*d*, J = 4.9, 1 H); 2.54 (*q*, 2 H); 1.16 (*t*, 3 H). ^{13}C-NMR: 179.19 (*s*); 177.89 (*s*); 166.65 (*s*); 141.13 (*s*); 131.82 (*s*); 128.40 (*d*); 127.88 (*d*); 74.47 (*d*); 31.13 (*t*); 11.37 (*q*). MS: 264 (42, M^+), 247 (4), 153 (42), 124 (100). Anal. calc. for $C_{12}H_{13}ClN_4O$ (264.72): C 54.45, H 4.95, Cl 13.39, N 21.17; found: C 54.44, H 5.01, Cl 13.13, N 20.99.

4-Amino-α-6-diphenyl-1,3,5-triazine-2-methanol (**3d**). Yield 75%. M.p. 160–161°. UV: 228.4 (20026), 255.0 (21552). IR: 3449, 3310, 3172, 3118, 3065, 2925, 1649, 1592, 1555, 1536, 720, 695. ^{1}H-NMR: 8.42–8.38 (*m*, 2 H); 7.72, 7.68 (br. *s*, 2 H); 7.59–7.50 (*m*, 5 H); 7.37–7.25 (*m*, 3 H); 5.87 (*d*, J = 5.2, 1 H); 5.52 (*d*, J = 5.3, 1 H). ^{13}C-NMR: 178.92 (*s*); 170.22 (*s*); 167.02 (*s*); 142.21 (*s*); 135.84 (*s*); 131.93 (*d*); 128.40 (*d*); 128.04 (*d*); 127.95 (*d*); 127.26 (*d*); 126.65 (*d*); 75.40 (*d*). MS: 278 (100, M^+), 201 (63), 172 (76), 104 (60), 77 (48), 69 (46). Anal. calc. for $C_{16}H_{14}N_4O$ (278.32): C 69.05, H 5.07, N 20.13; found: C 68.92, H 5.49, N 20.10.

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[1]) Generic name: *Pyrimethamine* (component of *Fansidar® Roche*).

[2]) Generously donated by Dr. *J. Kompis* from our Pharma Division.

4. *2-Amino-5-(*p*-chlorophenyl)-*t*-6-ethyl-5,6-dihydro-*r*-5-hydroxy-4(3*H*)-pyrimidinone* (**4a**). A soln. of 2.0 g (8.04 mmol) of **1a**, 1.8 g (47.6 mmol) of $NaBH_4$, and 10 mg of RB in 600 ml of EtOH was irradiated for 24 h (*TQ*, *150*, $\lambda \geq 400$ nm). After concentration, the pale orange precipitate obtained at −18° was recrystallized from $EtOH/H_2O$ 1:1: 0.83 g (39%) of **4a**. Acidic workup of the mixture by adding 50 ml of conc. HCl soln. gave a precipitate which recrystallized from EtOH yielding 1.15 g (47%) of **4a**·HCl. **4a:** M.p. 245.5–247.0° ($MeOH/H_2O$ 1:1). IR: 3600–3000, 3333, 3102, 2994, 2975, 2941, 2883, 1640, 1593, 1506, 1492, 1118, 749, 686. ^{1}H-NMR: 7.43 (br. *s*, 1 H); 7.40, 7.30 (*m* centres, *AA'*, *BB'*, 4 H); 6.87 (br. *s*, 2 H); 5.43 (br. *s*, 1 H); 3.37 (*dd*, 1 H); 1.60–1.50 (*m*, 1 H); 0.88 (*t*, 3 H); 0.82–0.71 (*m*, 1 H). ^{13}C-NMR: 179.11 (*s*); 161.93 (*s*); 138.25 (*s*); 131.88 (*s*); 127.91 (*d*); 127.55 (*d*); 72.52 (*s*); 59.37 (*d*); 21.52 (*t*); 10.35 (*q*). MS: 267 (8, M^+), 210 (3), 167 (5), 139 (21), 111 (13), 100 (100), 86 (72), 58 (83), 43 (19). Anal. calc. for $C_{12}H_{14}ClN_3O_2$ (267.72): C 53.84, H 5.27, Cl 13.24, N 15.70; found: C 53.63, H 5.32, Cl 13.00, N 15.49.

X-Ray Analysis of **4a**. *Crystal data:* triclinic $P\bar{1}$; $a = 6.543$ (2), $b = 6.669$ (2), $c = 15.016$ (4) Å; $\alpha = 83.11$ (2), $\beta = 84.40$ (3), $\gamma = 69.26$ (3); density: $D = 1.46$ Mg/m^3, $Z = 2$. *Data collection:* crystal size 0.08 × 0.25 × 0.33 mm^3, temp. 170 K; wavelength: 0.71069 Å; $\theta_{min}/\theta_{max}$: 0/25°; peak/background ratio 5:1; total data measured 2325 excluding standards; total data observed 1619; rejection criterion: $I > 2.5 \times \sigma(I)$; number of parameters 167. The refinement was performed using the *SHELXTL* package of the *R3m* system[3]). $R = 0.0805$.

*2-Amino-5-(*p*-chlorophenyl)-*t*-6-ethyl-5,6-dihydro-*r*-5-hydroxy-4(3*H*)-pyrimidinone Hydrochloride* (**4a**·HCl). M.p. 226.0–227.0° (EtOH). IR: 3260, 3108, 2991, 2967, 2935, 2879, 2801, 2729, 1722, 1685, 1620, 1566, 1258, 1103, 835. ^{1}H-NMR: 12.23–11.94 (br. *s*, 1 H); 9.70 (*s*, 1 H); 8.67–8.12 (br. *s*, 2 H); 7.52, 7.35 (*m* centres, *AA'*, *BB'*, 4 H); 7.09 (*s*, 1 H); 3.78–3.64 (*m*, 1 H); 1.62–1.38 (*m*, 1 H); 1.08–0.85 (*m*, 4 H). ^{13}C-NMR: 169.58 (*s*); 153.98 (*s*); 135.56 (*s*); 133.15 (*s*); 128.13 (*d*); 128.01 (*d*); 73.79 (*s*); 59.26 (*d*); 21.02 (*t*); 10.37 (*q*). MS: 267 (6, M^+), 210 (3), 167 (3), 139 (17), 111 (10), 100 (100), 86 (55), 58 (58), 43 (17), 36 (10). Anal. calc. for $C_{12}H_{14}ClN_3O_2$·HCl (304.18): C 47.38, H 4.97, Cl 23.31, N 13.81; found: C 47.35, H 4.97, Cl 23.47, N 13.92.

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[3]) Coordinates and thermal parameters have been deposited at the *Cambridge Crystallographic Data Centre.*