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4-Aminouracils and Pyrimido[4,5-b]indolediones from 4-Azidouracils**

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Azidouracils (**3**), which are obtained from barbituric acids (**1**), can easily be cyclized to pyrimido[4,5-b]indoles (**4**) or converted into 4-aminouracils (**6**).

(Keywords: 4-Azidouracil; 1H-Pyrimido[4,5-b]indole-2,4(3H,9H)-dione; 4-Aminouracil; 4-Phosphoranylideneaminouracil; Cyclodehydrogenation; Thermolysis)

4-Aminouracile und Pyrimido[4,5-b]indoldione aus 4-Azidouracilen

Azidouracile (**3**), die aus den entsprechenden Barbitursäuren (**1**) hergestellt werden, können leicht zu den Pyrimido[4,5-b]indolen (**4**) cyclisiert oder in die 4-Aminouracile (**6**) überführt werden.

Introduction

Heterocyclic azides have caused growing interest during the least years because of their versatility in organic syntheses [2–4]. Recently we have used azidoquinolones and azidocoumarins as synthons for ring closure reactions or introduction of other substituents [1, 5–7]. The present work extends these synthetic applications to barbituric acids in order to develop a new synthetic route to 4-aminouracils, which have potential biological reactivity [8] and furthermore to study the thermal ring closure reactions to 9*H*-pyrimido[4,5-b]indole-2,4-diones, a class of compounds, of which several substituted representatives have been prepared by other methods [9–13].

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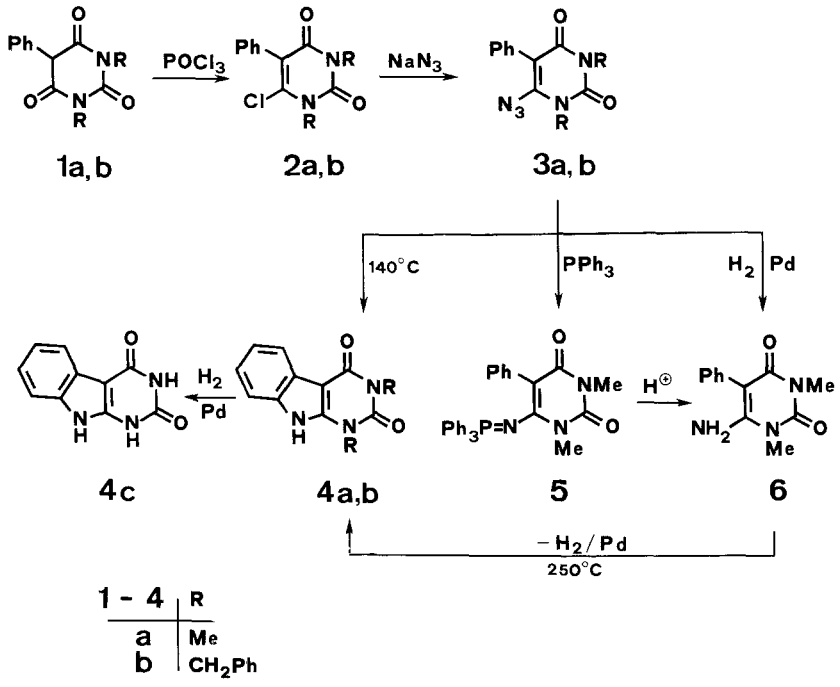
** Dedicated to Prof. Dr. *E. Ziegler* on the occasion of his 75th birthday.

Results and Discussion

1,3-Disubstituted barbituric acids (**1 a, b**) can easily be converted with phosphorylchloride to the 4-chlorouracils **2 a, b** using known methods [14, 15]. The introduction of the azido-group was achieved in the same way as shown in the quinoline series [1, 5–7] by reaction of the chlorouracils **2** with sodium azide in dimethylformamide.



On thermolysis of the azidouracils **3** in boiling xylene the formation of the fused pyrimido[4,5-b]indoles (**4**) took place in excellent yields. While in the methyl series all intermediate compounds could be obtained as crystalline substances, in the benzyl series the chloro(**2 b**)- and the azidouracil (**3**) could be isolated only as oil. There were also difficulties to get the dibenzyl barbituric acid **1 b** in crystalline form. Therefore it seemed useful to develop a synthesis of the pyrimido-indoles **4** without isolating any intermediate compound. Actually it was possible, starting from the commercially available diethyl phenylmalonate, to isolate the desired pyrimido-indoles **4** in an overall yield of appr. 50%. Hydrogenolytic debenzylation of the dibenzyl indole **4 b** afforded the unsubstituted and hitherto unknown pyrimido[4,5-b]indoledione **4 c**.

Reaction of the azide **3a** with triphenylphosphane leads to the iminophosphorane **5**, which on hydrolyzation gave the aminouracil **6**. The amine **6** could also be obtained by catalytic reduction of the azide **3a**.

Aminouracils **6** offer another possibility to achieve the indole ring closure to pyrimido[4,5-b]indolediones **4**: cyclodehydrogenation of the amine in boiling diphenylether in the presence of palladium on charcoal as catalyst [17] affords the pyrimido-indole **4a**.

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Experimental

Melting Points were determined on a Gallenkamp Melting Point Apparatus Mod. MFB-595. ^{1}H-NMR spectra were obtained on a Varian EM 360 (*TMS* as internal standard), IR-spectra on a Perkin-Elmer 298 (KBr-pellets), mass spectra on a Finnigan mass spectrometer 4500 (EI: 70 eV, CI: 120 eV, methane) and elemental analyses on a C,H,N-automat Carlo Erba 1106.

1,3-Dimethyl-5-phenyl-pyrimidine-2,4,6(1H, 3H, 5H)-trione (**1a**)

From N,N'-dimethylurea (2.2 g, 0.025 mol) and phenyl malonic acid (5.04 g, 0.028 mol) using the method as described for **1b**. Yield: 4.35 g (75%); lit. yield 42–49% [15, 18], m.p. 139–140 °C, lit. m.p. 140–143 °C [15, 18].

1,3-Dibenzyl-5-phenyl-pyrimidine-2,4-6(1H, 3H, 5H)-trione (**1b**)

1,3-Dibenzyl urea (7.2 g, 0.03 mol) and phenyl malonic acid (5.4 g, 0.03 mol) are dissolved in 70 ml of chloroform and 5.5 ml of glacial acetic acid. The mixture is warmed to 70 °C. After addition of 11 ml of acetic anhydride and 0.5 ml of trifluoro acetic acid the temperature is raised to 80 °C. Afterwards the mixture is stirred for 4 h and the solvents are then removed *in vacuo*. The resulting oil is allowed to crystallize and is recrystallized from ethanol-water. Yield: 8.2 g (72%), m.p. 144–146 °C from ethanol. IR: 3340 sh, 3320 s, 3100–2920 w, 1680 sh, 1670 m, 1620 s, 1590 w, 1570 m cm^{-1}. ^{1}H-NMR (*DMSO-d$_6$*): δ = 4.2 (s, 2 CH_2), 5.05 (s, H at C-5), 7.1–7.5 (m, 15 aromat. H).

$C_{24}H_{20}N_2O_3$ (384.4). Calcd.: C 74.98 H 5.24 N 7.29.
Found: C 75.31 H 5.19 N 7.34.

6-Chloro-1,3-dimethyl-5-phenyl-pyrimidine-2,4(1H, 3H)-dione (**2a**)

The preparation was accomplished as described in Ref. [15]. IR: 3060–2950 w, 1705 sh, 1700 s, 1650 s, 1635 sh, 1610 s cm^{-1}. ^{1}H-NMR (*DMSO-d$_6$*): δ = 3.2 and 3.4 (2 s, 2 *Me*), 7.35 (s, 5 aromatic protons).

1,3-Dibenzyl-6-chloro-5-phenyl-pyrimidine-2,4(1H, 3H)-dione (**2b**)

Dibenzylbarbituric acid **1b** (3.8 g, 0.01 mol) and 50 ml of phosphorylchloride were refluxed for 8 h, then the solvent was evaporated and the resulting oil washed

with water and ethanol-water. Yield: 3.65 g (91%) yellowish oil. IR: 1700 s, 1650 s, 1615 w, 1595 w cm^{-1}.

6-Azido-1,3-dimethyl-5-phenyl-pyrimidine-2,4(1H, 3H)-dione (**3a**)

A suspension of the chloro-uracil **2a** (5.0 g, 0.02 mol) and sodium azide (5.2 g, 0.08 mol) in 20 ml of dimethylformamide is stirred for 12 h at room temperature. The mixture is diluted with 200 ml of water and the resulting precipitate collected by filtration. Yield: 4.1 g (80%), light yellowish prisms from ethanol, decomp. above 162 °C. IR: 2960 w, 2140 s, 1690 s, 1630 s, 1605 m, 1595 m cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): δ = 3.2 and 3.35 (2 s, 2 *Me*), 7.4 (s, 5 aromat. protons).

$C_{12}H_{11}N_5O_2$ (257.3). Calcd.: C 56.03 H 4.31 N 27.22.
Found: C 56.13 H 4.51 N 27.42.

6-Azido-1,3-dibenzyl-5-phenyl-pyrimidine-2,4(1H, 3H)-dione (**3b**)

The chloro-uracil **2b** (4.1 g, 0.01 mol) was treated with sodium azide as described at **3a**. The resulting oil was separated and washed with ethanol-water. Yield: 2.9 g (71%) yellowish oil. IR: 2960 w, 2140 s, 1690 s, 1630 s, 1600 m cm^{-1}.

1,3-Dimethyl-1H-pyrimido[4,5-b]indole-2,4(3H, 9H)-dione (**4a**)

a) *From* **3a**: A solution of the azidouracil **3a** (2.6 g, 0.01 mol) in 100 ml of xylene is heated under reflux for 30 min. The resulting precipitate is filtered. Yield: 2.1 g (91%).

b) *One-pot synthesis starting from diethyl phenylmalonate:* Diethyl phenyl malonate (23.6 g, 0.1 mol) and a solution of sodium hydroxide in ethanol, which is prepared from sodium (6.9 g, 0.3 mol) in 250 ml of 95% ethanol is stirred rigorously, then 15 ml of water are added. After 4 h refluxing on a water bath, the precipitate is filtered after cooling and dissolved in 30 ml of water. To this solution 30 ml of benzene-diethylether (1 : 1) is added and after cooling on 5–7 °C the sodium salt of the phenyl malonic acid is acidified with 40 ml of conc. hydrochloric acid during 10 min (the temperature must not exceed 10 °C). The organic layer is separated and the water layer washed with 2 portions of 50 ml benzene-diethylether (1 : 1). After drying with sodium sulfate the organic solvent is removed *in vacuo*. To this crude product (about 15 g) N,N'-dimethylurea (7.9 g, 0.09 mol) is added and the reaction sequence **1** → **2** → **3** → **4** is executed without isolating the single products, only by evaporating the excess of solvents. Yield: 8.9 g (47%) of **4a**, based on dimethyl urea.

c) *Cyclodehydrogenation of the amine* **6**: A solution of 0.5 g of the aminouracil **6** in 20 ml of diphenylether is refluxed for 12 h in the presence of 0.1 g of palladium on charcoal (10%). During this time air is bubbled slowly through the reaction mixture. The catalyst is filtered off from the hot solution and the solvent is removed *in vacuo*. The residue is digested with methanol. Yield: 0.34 g (79%) colorless needles, m.p. 362–364 °C from ethanol (lit. m.p. > 300 °C [12, 13]). IR: 3260–2900 m, 1685 s, 1625 s, 1610 s, 1540 m cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): δ = 3.25 and 3.5 (2 s, 2 *Me*), 7.0–7.4 (m, 3 aromat. H), 7.6–7.8 (m, 2 arom. H). MS (EI): *m/e* (%) = 230 (11), 229 (100, M^+), 181 (61), 172 (85, M − *Me*NCO), 171 (31), 161 (10), 157 (34, M − *Me*NCO − *Me*), 144 (67), 130 (11), 116 (M − 2 *Me*−N=C=O), 102 (26), 89 (20), 76 (16).

$C_{12}H_{11}N_3O_2$ (229.2). Calcd.: C 62.87 H 4.84 N 18.33.
Found: C 62.66 H 4.73 N 18.21.

1,3-Dibenzyl-1H-pyrimido[4,5-b]indole-2,4(3H, 9H)-dione (**4b**)

A solution of the benzyl-azide **3b** (4.1 g, 0.01 mol) is cyclized in xylene as described for **4a**, method a. Yield: 3.3 g (87%) colorless prisms, m.p. 284–286 °C from ethanol. Using method b, the yield is 42%. IR: 3280–3120 m, 1690 s, 1620 m, 1600 m, 1580 sh cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): **6** = 5.1 and 5.25 (2 s, 2 benzyl-CH_2), 6.7–7.9 (m, 14 aromat. protons), 12.1 (s, broad, NH). MS (EI): *m*/e = 381 (14, M^+), 247 (9, $M - PhCH_2$—NCO), 185 (12), 158 (5), 91 (100, $PhCH_2$).

$C_{24}H_{19}N_3O_2$ (381.4). Calcd.: C 75.57 H 5.02 N 11.02.
Found: C 75.20 H 4.96 N 10.92.

1H-Pyrimido[4,5-b]indole-2,4(3H, 9H)-dione (**4c**)

A solution of the benzyl pyrimido-indole **4b** (0.38 g, 0.001 mol) in 40 ml of glacial acetic acid-dimethylformamide (5 : 1) is hydrogenated under reflux for 5 h in the presence of 0.1 g of palladium on charcoal (10%) as catalyst. The hot mixture is filtered and the solvent removed *in vacuo*. The residue is digested with ethanol and filtered. Yield: 0.18 g (89%) colorless prisms from dimethylformamide-water, dec. > 340 °C. IR: 3160 s, 3100 m, 2929 w, 1695 s, 1685 s, 1635 s, 1615 sh cm^{-1}. MS (EI): *m*/e (%) = 201 (7, M^+), 185 (21), 172 (8), 158 (100, M − HNCO), 130 (22), 103 (54).

$C_{10}H_7N_3O_2$ (201.2). Calcd.: C 59.70 H 3.51 N 20.89.
Found: C 60.56 H 3.82 N 20.61.

1,3-Dimethyl-6-triphenylphosphoranylideneamino-5-phenyl-pyrimidine-2,4(1H, 3H)-dione (**5**)

A solution of the azidouracil **3a** (2.6 g, 0.01 mol) and triphenylphosphane (2.6 g, 0.01 mol) in 50 ml of benzene is refluxed for 2 h, then the solvent is removed *in vacuo* and the resulting residue is digested with hot petroleum ether (b.p. 60–80 °C). The insoluble white crystals are collected by filtration. Yield 4.4 g (90%) colorless prisms, m.p. 186–188 °C from methanol-water. IR: 3050 w, 1670 m, 1615 s, 1580 sh, 1560 s cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): δ = 3.1 and 3.3 (2 s, 2 *Me*), 6.6–7.8 (m, 20 aromat. protons).

$C_{30}H_{26}N_3O_2P$ (491.5). Calcd.: C 73.31 H 5.33 N 8.55.
Found: C 73.55 H 5.36 N 8.49.

6-Amino-1,3-dimethyl-5-phenyl-pyrimidine-2,4(1H, 3H)-dione (**6**)

a) A solution of the iminophosphorane **5** (4.9 g, 0.01 mol) in 60 ml of glacial acetic acid, containing 1 ml of trifluoro acetic acid, and 10 ml of water is refluxed for 2 h. After cooling 70 ml of water are added and triphenyl phosphinoxide is extracted with 3 portions of 5 ml of benzene. The acetic acid-water layer is evaporated and the residue digested with 1 ml of ethanol. Yield: 1.4 g (61%).

b) A solution of the azidouracil **3a** (1.0 g) in 50 ml of methanol is hydrogenated at room temperature for 4 h in the presence of 0.1 g of palladium on charcoal (10%). The warmed solution is filtered from the catalyst and evaporated *in vacuo* and the residue obtained is digested with ethanol. Yield: 0.7 g (77%). Colorless prisms, m.p. 229–231 °C from ethanol (lit. m.p. 233 °C [8]). IR: 3340 m, 3220 m, 1685 s, 1630 m, 1595 s, 1580 s cm^{-1}. ^{1}H-NMR (*DMSO-d_6*): δ = 3.1 and 3.25 (2 s, 2 *Me*), 6.1 (s, broad, NH), 7.25 (s, 5 aromat. protons).

$C_{12}H_{13}N_3O_2$ (231.3). Calcd.: C 62.33 H 5.67 N 18.17.
Found: C 32.37 H 5.50 N 18.07.

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