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Reactions of Uracils, 7[1]

Synthesis and Novel Consecutive Thermal [1,5]-Sigmatropic Rearrangements of 6-(Alkylamino)-5-ethenyluracils

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Additional 6-(alkylamino)-5-ethenyluracils (**2d**, **7**) have been prepared for investigating substituent effects in thermal reactions. Like **2a**, upon heating in Dowtherm® A **2d** and **7** afford after saponification 6-amino-5-(ethoxycarbonyl[phenyl]ethyl)uracils **4** and **8**, respectively. After refluxing in xylene the intermediary imines **11** and **12** can be isolated. Deuteration experiments reveal consecutive thermal [1,5]H-migrations (**2a**-D_1 → **4**-D_1 and **4**-D_2; **2a'**-D_2 → **4'**-D_1). The mechanism is discussed.

Reaktionen von Uracilen, 7[1]

Synthese und eine neue Sequenz thermischer [1,5]-sigmatroper Umlagerungen von 6-(Alkylamino)-5-ethenyluracilen

Neue 6-(Alkylamino)-5-ethenyluracile (**2d** und **7**) werden dargestellt, um Substituenteneffekte bei thermischen Reaktionen zu untersuchen. Ähnlich **2a** werden **2d** und **7** beim Erhitzen in Dowtherm® A und nach anschließender Verseifung in die 6-Amino-5-(ethoxycarbonyl[phenyl]ethyl)uracile **4** bzw. **8** übergeführt. Erhitzen in Xylol liefert die intermediären Imine **11** und **12**. Deuterierungsexperimente belegen aufeinanderfolgende thermische [1,5]-H-Wanderungen (**2a**-D_1 → **4**-D_1 und **4**-D_2; **2a'**-D_2 → **4'**-D_1). Die Mechanismen werden diskutiert.

Interest in the investigation of uracils containing a lipophilic substituent at 5-position has increased considerably because of the significant biological activity of those compounds[4]. Recently, the synthesis of *N*-6-substituted 6-amino-1,3-dimethyl-5-uracilacrylic esters **2a–c** *via* aminolysis of **1** has been reported; under basic conditions **2a,b** could be cyclized to the pyrido[2,3-*d*]pyrimidines **3a,b**, while the thermal reaction of **2a** resulted in the formation of the rearranged and desalkylated 6-amino-1,3-dimethyl-5-uracilpropionic ester **4**[5].

Now, we want to describe a mechanistic study of the rearrangement reaction **2** → **4**. In order to investigate the role and effect of the 6-amino and 5-side chain substituents **2d** and **7** were prepared; **7** is obtained smoothly from 6-chloro-5-formyl-1,3-dimethyluracil (**5**)[6] in two steps, by Wittig reaction with benzyltriphenylphosphonium chloride and subsequent nucleophilic exchange of the 6-chloro substituent by *n*-butylamine (cf. Scheme 2).

Similarly to **2a**, after heating of **2d** and **7** in Dowtherm® A at 200°C, chromatography on silica gel affords the rearrangement products, **4** and **8**, respectively,

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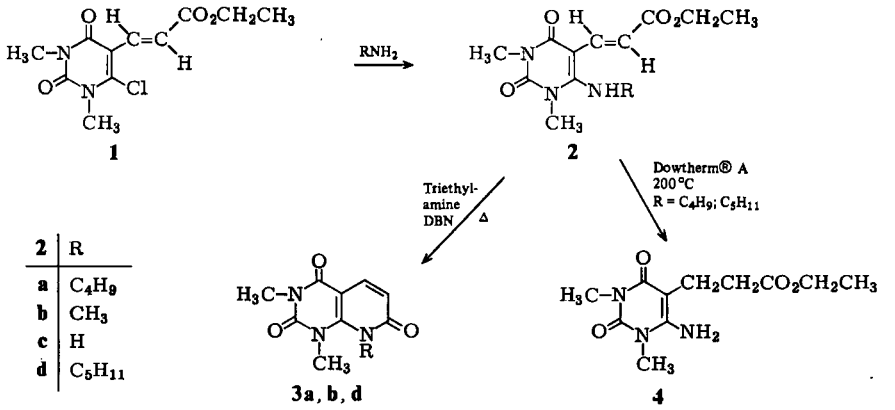
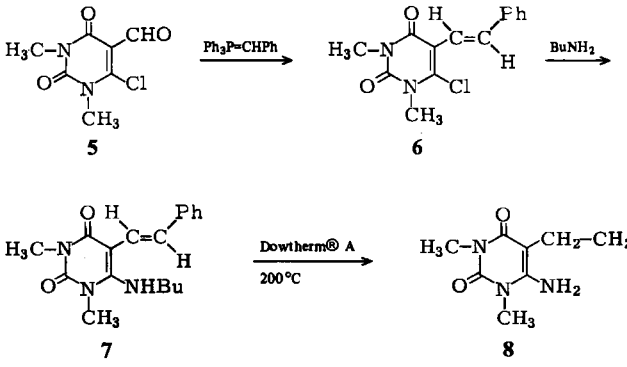
are isolated. However, refluxing of **2d** in triethylamine with catalytic amounts of 1,5-diazabicyclo[4.3.0]non-5-ene („DBN") leads to **3d** in high yield. Furthermore, when **2a** and **7** are refluxed in absol. xylene for a long time, the 6-(butylideneamino)uracils **11** and **12** are obtained, respectively.

Scheme 1

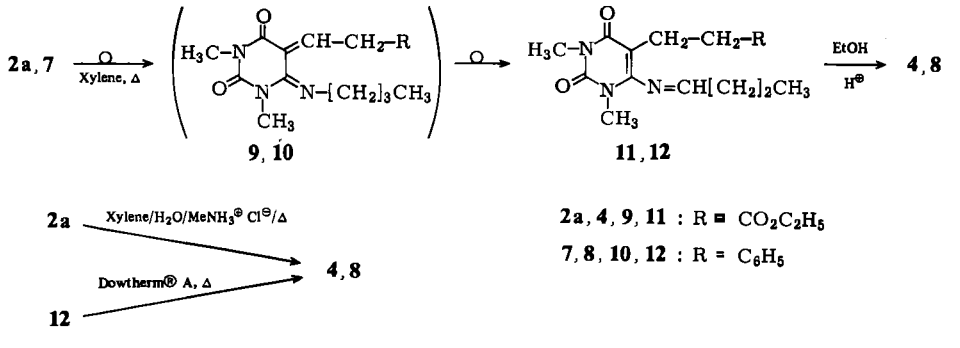


2	R
a	C_4H_9
b	CH_3
c	H
d	C_5H_{11}

Scheme 2



Scheme 3



2a, 4, 9, 11 : R = $CO_2C_2H_5$

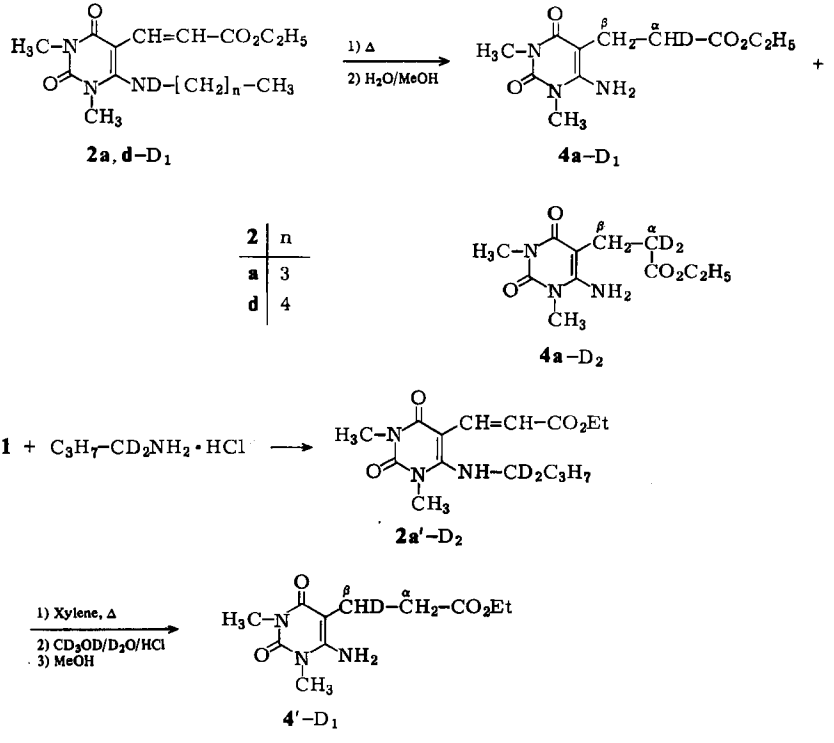
7, 8, 10, 12 : R = C_6H_5

The constitutions of **11** and **12** are unambigously established based on their spectroscopic data. Thus, the presence of a triplet (intensity: 1 H) centered at δ = 7.87 in **11**, and δ = 6.93 in **12**, and in addition well resolved AA'BB'-pattern for the $-CH_2-CH_2-R$ side chain in **12** (in **11** overlap occurs of the signals with the $N=CH-CH_2$ protons) rule out alternative structures, such as **9** and **10**. The upfield shifts of the $N=CH-CH_2-CH_2-R$ protons in **12** (compared to **11**) are explained by the anisotropic effect of the adjacent phenyl ring.

The fact that in an independent experiment in Dowtherm® A (containing 600 mg H_2O/l, according to our analysis) at 200°C **12** gives **8**, may also support the intermediate role of **12** in the direct conversion of **7** to **8**. Mild hydrolysis of both **11** and **12** affords **4** and **8**, respectively. When the reaction of **2a** in xylene is carried out in the presence of water and methylammonium chloride, **4** is likewise formed during this reaction (cf. Scheme 3).

To elucidate the rearrangement mechanisms in detail, the deuterated compounds **2a**-D_1 and **2a'**-D_2 were prepared by repeated treatment of **2a** with CH_3OD or by direct synthesis starting from **1** and 2,2-dideuterio-*n*-butylamine hydrochloride, made according to lit.[7].

Scheme 4



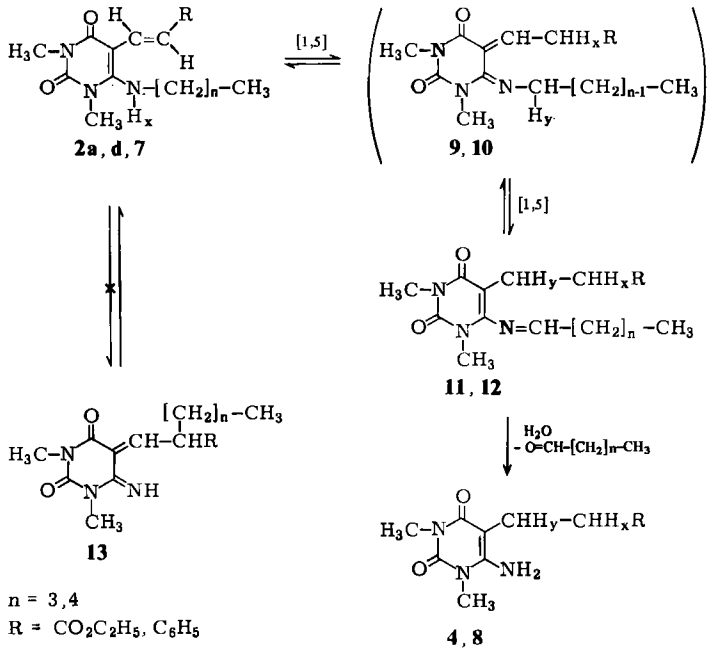
The subsequent thermal rearrangement of **2a**-D_1 employing the usual conditions followed by hydrolysis afforded a mixture of undeuterated, mono- and dideuter-

ated **4**-D_1 and **4**-D_2. The formation of the dideuterated derivative is explained by the reversibility of the rearrangement reaction.

The position of the deuterium α to the C=O group was revealed unambigously by MS. Thus, in **4** the fragmentation leading to the base peak at m/z = 168 $(C_7H_{10}N_3O_2)^+$ originates from the loss of the $CH_2CO_2C_2H_5$ side chain by vinylogeous α-cleavage. In the labelled compounds **4**-D_1 and **4**-D_2 this peak is not shifted, i.e. in this fragmentation process all deuterium atoms are lost.

In addition, the marked compound **2a'**-D_2 (6% D_1; 94% D_2) after rearrangement and hydrolysis with CH_3OH gave **4'**-D_1 (2% D_0; 98% D_1); whose base peak in the MS was quantitatively shifted to m/z = 169, thus, proving that the deuterium had migrated to the carbon atom next to the 5-position of the uracil ring.

Scheme 5



Upon consideration of the foremention results and the fact of a thermal [1,5]H-migration with *suprafacial* geometry being an allowed concerted process[8], we discuss for the conversion **2a,d**→**4**, and **7**→**8** consecutive thermal [1,5]-sigmatropic rearrangements followed by a hydrolysis. In our case, the required *cisoid* configuration of the two double bonds is met by the ring structure. The formation of the theoretically also possible β-alkyl derivatives **13** (formed e.g. *via* [1,5]alkyl migration) could not be detected; most obviously due to the considerably high activation energy difference between an [1,5]H- and [1,5]alkyl shift. As a matter of fact, the activation energy for a methyl migration is approximately 20 kcal/mol higher than that of a similar [1,5]H-migration[9] (cf. Scheme 5).

To our knowledge, the forementioned reactions represent the first examples for [1,5]H-shifts involving the uracil moiety and its substituents. Moreover, this reaction scheme might initiate a novel route for the synthesis of 5-alkyluracils.

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Experimental Part

IR spectra: Perkin-Elmer 157-G. – ^{1}H NMR spectra: Varian EM-360 and Bruker WH-90 (TMS as internal standard). – MS: Kratos MS-50 and MS-30 (AEI). – Melting points: not corrected. – Elemental analyses: Analytical Laboratory of the Institute and Mikroanalytisches Laboratorium Dr. *F. Pascher*, Bonn.

The uracils **2a–c** and the pyrido[2,3-*d*]pyrimidines **3a,b** habe been prepared according to lit.[5].

Ethyl (E)-1,3-Dimethyl-6-(pentylamino)-5-uracilacrylate (**2d**): To a stirred suspension of 1.19 g (4.4 mmol) of 6-chloro-5-uracilacrylic ester **1**[5] in 5 ml of isopropyl alcohol 4.8 ml of *n*-pentylamine are added. After a slightly exothermic reaction took place, the mixture is stirred at ambient temperature for 40 min. Then the solvent and excess of pentylamine are evaporated in vacuo (< 40°C) and the crude product recrystallized from isopropyl alcohol, yield 0.86 g (60%); m.p. 109–110°C. – IR (KBr): 3300 (NH), 1710, 1670 cm^{-1} (CO). – ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, CH_3, *J* = 6.5 Hz), 1.30 (t, OCH_2CH_3, *J* = 7 Hz), ≈ 1.3 (m, $CH_2CH_2CH_3$), 1.62 (qi, $NHCH_2CH_2$, *J* = 6 Hz), 3.3 (m, $NHCH_2$), 3.35 (s, 1-CH_3), 3.47 (s, 3-CH_3), 4.14 (q, OCH_2, *J* = 7 Hz), 4.67 (t, NH, *J* = 5 Hz), 6.85 (d, $CH-CO_2$, *J* = 15 Hz), 7.47 (d, $C-CH=$, *J* = 15 Hz). – MS: *m/z* = 323 (M^+).

$C_{16}H_{25}N_3O_4$ (323.4) Calcd. C 59.42 H 7.79 N 12.99 Found C 59.39 H 7.89 N 12.98

1,3-Dimethyl-8-pentylpyrido[2,3-d]pyrimidine-2,4,7(1H,3H,8H)-trione (**3d**): A mixture of 0.16 g (0.5 mmol) of **2d**, 2 ml of triethylamine and 2 drops of DBN are refluxed for 2 h. After evaporation of the solvent, the residue is washed with ether, then cooled to –15°C. The solid is filtered and washed with ether; yield 0.10 g (73%), m.p. 115–116°C. – IR (KBr): 1720, 1660 cm^{-1} (CO). – ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, CH_2CH_3, *J* = 6 Hz), 1.1–1.4 (m, $CH_2CH_2CH_3$), 1.78 (qi, NCH_2CH_2, *J* = 7 Hz), 3.42 (s, 1-CH_3), 3.60 (s, 3-CH_3), 4.20 (t, NCH_2, *J* = 7 Hz), 6.40 (d, 6-H, *J* = 9 Hz), 7.96 ppm (d, 5-H, *J* = 9 Hz). – MS: *m/z* = 277 (M^+).

$C_{14}H_{19}N_3O_3$ (227.3) Calcd. C 60.23 H 6.91 Found C 60.21 H 6.82

Ethyl 6-Amino-1,3-dimethyl-5-uracilpropionate (**4**)[5]: *Method A:* A mixture of 0.5 g (1.6 mmol) of **2a**, 0.10 g (1.5 mmol) of methylammonium chloride and 10 ml of xylene is refluxed for 12 h. Then, after cooling, 0.1 g (5.5 mmol) of water are added and the reflux is continued for 6 h (TLC). The solid is collected by filtration, washed with water, and recrystallized from isopropyl alcohol; yield 0.22 g (53%), m.p. 173–175°C.

Method B: A mixture of 0.10 g (0.3 mmol) of **11**, 5 ml of ethanol, and 0.05 ml of conc. hydrochloric acid is stirred overnight. The precipitate is filtered; yield 0.04 g (52%), m.p. 172–174°C. The IR spectra of the products formed by methods A and B agree with that of an authentic sample[5].

Method C: 0.70 g (2.2 mmol) of **2d** is refluxed with MeOD for 10 min, then the solvent is removed. This process is repeated two times. Then 6 ml of Dowtherm®A are added and the solution is heated to 185°C for 3.5 h, and then to 200°C for 4 h. After chromatography on silica gel (systems: petroleum ether, petroleum ether/chloroform, chloroform, chloroform/methanol) a mixture of mono- and dideuterated (and undeuterated) **4**, **4**-D_1, and **4**-D_2 was obtained; yield 0.33 g (54%), m.p. 159–163°C, after recrystallization of an analytical sample from isopropyl alcohol m.p. 174–175°C (D_0 = 11.5%, D_1 = 45%, D_2 = 43.5%; MS).

Ethyl 6-Amino-β-deuterio-1,3-dimethyl-5-uracilpropionate (**4'**-D_1): The dideuterated compound **2a'**-D_2 needed for the thermal rearrangement is obtained from 0.27 g (1 mmol) of 6-chloro-5-uracilacrylate **1** and 0.225 g (3 mmol) of 2,2-dideuterio-*n*-butylamine generated *in situ* by treatment of the hydrochloride[7] with 3 mmol of $NaOC_2H_5$. According to lit.[5] the reaction mixture is stirred 60 h at ambient temperature. After evaporation of all volatile material, the residue is washed with water and extracted with ethanol. After removal of the solvent 0.216 g (70%) of **2a'**-D_2 are obtained.

320 mg (1 mmol) of the latter **2a'**-D_2 are then refluxed in 10 ml absol. xylene for 13 h (TLC). The reaction mixture is evaporated and the residue suspended in petroleum ether (60/90), and again evaporated to dryness. The residue is then treated at room temperature with 3 ml of CH_3OD and 3 ml of D_2O, 3 drops of 2 N HCl, and then 10 ml of ether are added. After stirring for 3 h the ethereal phase containing the butyraldehyde is removed, the aqueous layer concentrated to dryness, and the residue suspended and washed with cold ether; it is then solved in 10 ml of methanol; after removal of the solvent 0.15 g (65%) of **4'**-D_1 are isolated; m.p. 172–173°C.

(E)-6-Chloro-1,3-dimethyl-5-(2-phenylethenyl)uracil (**6**): To a stirred suspension of 12.0 g (30.1 mmol) of benzyltriphenylphosphonium chloride and 120 ml of absol. dimethoxyethan 20.6 ml (ca. 48 mmol) of butyllithium in 15% hexan solution is added dropwise between −15 and −20°C. After stirring at ambient temperature for 100 min, 8.0 g (39.5 mmol) of 6-chloro-5-formyl-1,3-dimethyluracil (**5**) is added and the mixture stirred for 1 h. After standing overnight, the precipitated solid is filtered off, the filtrate being evaporated under vacuum. The oily residue is purified by chromatography on silica gel (system: benzene-methanol 1:1). Yield 3.70 g (34%), m.p. 152–153°C. – IR (KBr): 1705, 1655 cm^{-1} (CO). – ^1H NMR ($CDCl_3$): δ = 3.42 (s, 1-CH_3), 3.64 (s, 3-CH_3), 6.97 (d, C*H*Ph, *J* = 16.0 Hz), 7.22–7.58 (m, H_{ar}), 7.94 (d, *CH*=CHPh, *J* = 16.0 Hz). – MS: *m/z* = 276 (M^+).

$C_{14}H_{13}ClN_2O_2$ (276.7) Calcd. C 60.76 H 4.73 N 10.12 Found C 60.73 H 4.83 N 10.12

(E)-6-(Butylamino)-1,3-dimethyl-5-(2-phenylethenyl)uracil (**7**): 15 ml of butylamine are added to a mixture of 1.5 g (5.4 mmol) of **6** and 15 ml of isopropyl alcohol. After slight exothermal reaction the mixture is stirred at room temperature for 2 h. Then, the solvent and the excess butylamine are removed in vacuo, and after addition of 20 ml of water, the solution is extracted with 3 × 50 ml of ether. The combined organic layers are dried over $MgSO_4$. After evaporation of the solvent, the oily rest is kept at −15°C and suspended in a mixture of isopropyl alcohol-ether, and filtered. Yield 0.74 g (44%); m.p. 77–78°C. – IR (KBr): 3400 (NH), 1675 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 0.87 (m, CH_2CH_3), 1.16–1.76 (m, $CH_2CH_2CH_3$), 3.15 (m, NH–CH_2), 3.27 (s, 1-CH_3), 3.37 (s, 3-CH_3), 4.3 (br., NH), 6.69 (d, *CH*–Ph, *J* = 16.0 Hz), 7.18–7.47 (m, H_{ar}), ≈7.4 (d, *CH*=CHPh, *J* = 16.0 Hz). – MS: *m/z* = 313 (M^+).

$C_{18}H_{23}N_3O_2$ (313.4) Calcd. C 68.98 H 7.40 N 13.41 Found C 68.78 H 7.54 N 13.26

6-Amino-1,3-dimethyl-5-(2-phenylethyl)uracil (**8**): *Method A:* A mixture of 0.55 g (1.8 mmol) of **7** and 5 ml of Dowtherm®A is stirred at 200°C for 1.5 h. Then, after cooling down

15 ml of ether are added and the solution was stirred at room temperature. After standing overnight the precipitate is filtered off and washed with ether; recrystallization from isopropyl alcohol; yield 0.15 g (32%), m.p. 232–233°C. – IR (KBr): 3240–3430 (NH), 1670 cm^{-1} (CO). – ^1H NMR ($CDCl_3$): δ = 2.58–2.93 (m, CH_2CH_2), 3.34 (s, 1-CH_3), 3.36 (s, 3-CH_3), 3.84 (s, NH_2), 7.24 ppm (s, H_{ar}). – MS: *m/z* = 259 (M^+).

$C_{14}H_{17}N_3O_2$ (259.3) Calcd. C 64.84 H 6.61 N 16.21 Found C 65.08 H 6.50 N 16.27

Method B: A mixture of 0.15 g (0.98 mmol) of **12** and 2 ml of Dowtherm®A is heated at 200°C for about 2 h. After cooling down, ether was added and the precipitate was filtered off. Yield 0.04 g (27%); m.p. 232–233°C.

Method C: To a stirred solution of 20 mg (0.06 mmol) of **12** and 5 ml of ethanol 2 drops of conc. hydrochloric acid are added. After stirring at room temperature overnight, the solvent is evaporated in vacuo, and the residue suspended in ether and filtered; yield 9 mg (55%); m.p. 230–231°C.

Ethyl 6-(Butylideneamino)-1,3-dimethyl-5-uracilpropionate (**11**): 0.70 g (2.1 mmol) of **2a** are suspended in 10 ml of absol. xylene and then refluxed for 20 h. After evaporation of the solvent, the oily residue is dried at 0.5 torr at room temperature for several h. The solid is washed with hexan and dried; yield: 0.51 g (73%), m.p. 64–65°C. – IR (KBr): 1730, 1700 (CO), 1630 cm^{-1} (C=N). – ^1H NMR ($CDCl_3$): δ = 1.04 (t, $CH_2CH_2CH_3$, *J* = 7 Hz), 1.26 (t, OCH_2CH_3, *J* = 7 Hz), 1.71 (sx, $CH_2CH_2CH_3$, *J* = 7 Hz), 2.50 (br. s, $CH_2CH_2CO_2$ + $N{=}CHCH_2$), 3.20 (s, 1-CH_3), 3.31 (s, 3-CH_3), 4.06 (q, OCH_2CH_3, *J* = 7 Hz), 7.87 ppm (t, N=CH, *J* = 4.5 Hz). – MS: *m/z* = 309 (M^+).

$C_{15}H_{23}N_3O_4$ (309.4) Calcd. N 13.58 Found N 13.42

6-(Butylideneamino)-1,3-dimethyl-5-(2-phenylethyl)uracil (**12**): 0.62 g (2 mmol) of **7** are refluxed for 30 min in 6.2 ml of absol. xylene. After evaporation of the solvent the residue is separated by chromatography with chloroform on silica gel; yield 0.32 g (52%), m.p. 56–57°C.

$C_{18}H_{23}N_3O_2$ (313.4) Calcd. C 68.98 H 7.40 Found C 69.00 H 7.50

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[171/85]