REACTIONS OF URACILS 9.[1]

SYNTHESIS AND REACTIONS OF 6-SUBSTITUTED BENZYLAMINO-5-(2-ETHOXYCARBONYLETHENYL)-1,3-DIMETHYLURACILS

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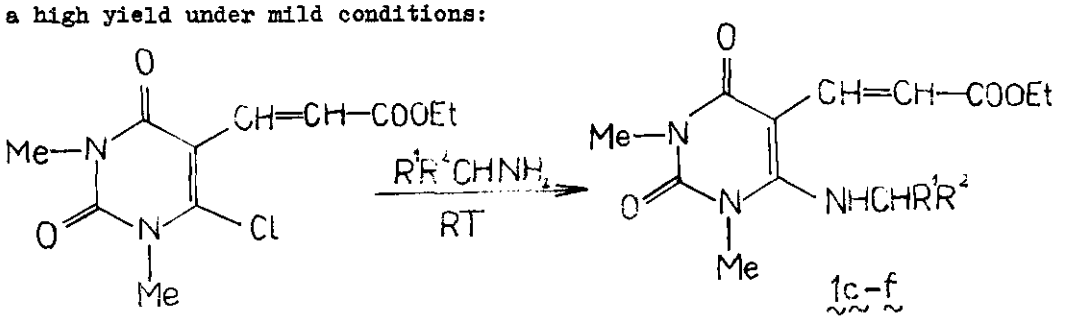
Abstract - Starting from 6-chloro-5-(2-ethoxycarbonylethenyl)-1,3-dimethyluracil the novel 6-substituted benzylamino derivatives 1c-f were synthesized which gave either 2,4,7-trioxopyrido[2,3-d]pyrimidines 2c-e or the 6-substituted benzylidenamino analogues 3c-f depending on the reaction conditions. A kinetic study was also carried out.

In our previous papers[3,4] we reported that under basic conditions 6-alkylamino-5-(2-ethoxycarbonylethenyl)-1,3-dimethyluracils 1a,b reacted to give pyrido-[2,3-d]pyrimidines 2a,b, while in thermal reactions 3a,b (Scheme 1) were obtained. It was shown by deuteriation[4] that the thermal isomerisation proceeds via consecutive intramolecular sigmatropic [1,5] hydrogen shifts.
An investigation has been undertaken to explore the scope and limitation of these reactions, as well as to study the influence of reaction conditions. According to our method[3], starting from 6-chloro-5-(2-ethoxycarbonylethenyl)-1,3-dimethyl-uracil the 6-substituted benzylamino derivatives were prepared in a high yield under mild conditions:



Refluxing of 1c-f in a mixture of triethylamine and dimethylformamide in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) yielded exclusively the new 8-substituted benzylpyrido[2,3-d]pyrimidines 2c-e. The cyclization could also be achieved by heating the amines in acetic acid for several hours. However, boiling of 1c-f in abs. xylene or nitrobenzene at 130 or 140 °C led to the formation of 5-(2-ethoxycarbonylethyl)-uracil derivatives 3c-f. Similarly, 3c was also formed when 1c was melted at 185 °C for a short period of time.
All of these results point out the decisive role of reaction conditions with respect to yield different type of products. Thus, either increasing the nucleophilicity of the 6-amino nitrogen or the electrophilicity of the carbonyl carbon in the side chain by base or acid catalysis, resp., favoured the intramolecular aminolysis, i.e. the cyclization. On the other hand, [1,5] rearrangements were preferred under neutral conditions by thermal activation.
In the case of 1c a kinetic study of the isomerisation was carried out.
The fundamental characteristic feature of the isomerisation at 130 and 140 °C in the case of 1c is that the 3e isomer was only detected after two rapid virtually irreversible steps (Scheme 2).
The rate constant for the first step (k_1) was determined at two different temperatures in abs. xylene by a computed non-linear regressional analysis using Marquardt method.[5,6] As expected for an unimolecular process, the reaction is of first order, i.e.

$$[A] = [A]_o e^{-k_1 t}$$

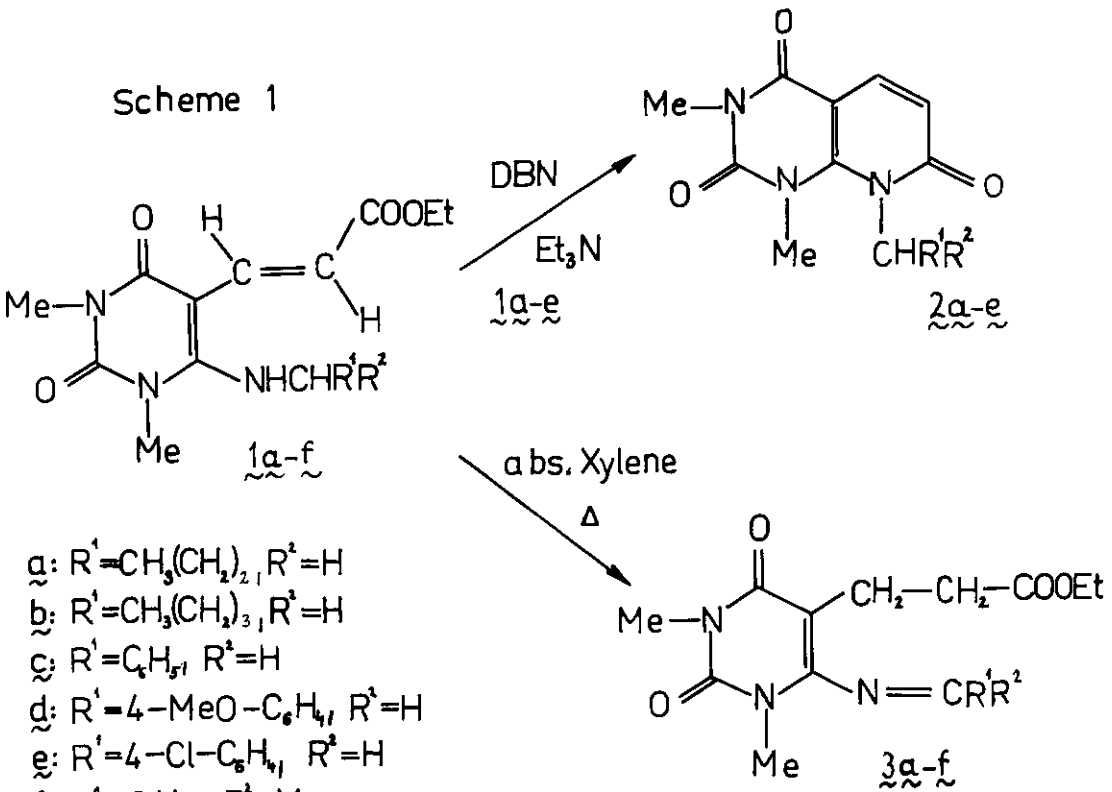
where [A] means the actual concentration for 1c.

The following data were obtained:

Temp. (°C)	130	140
k_1 (s^{-1})	9.02×10^{-5}	$1,95 \times 10^{-4}$
corr.coeff. (r)	0,991	0,999
st. deviation	3.97×10^{-6}	3.55×10^{-6}

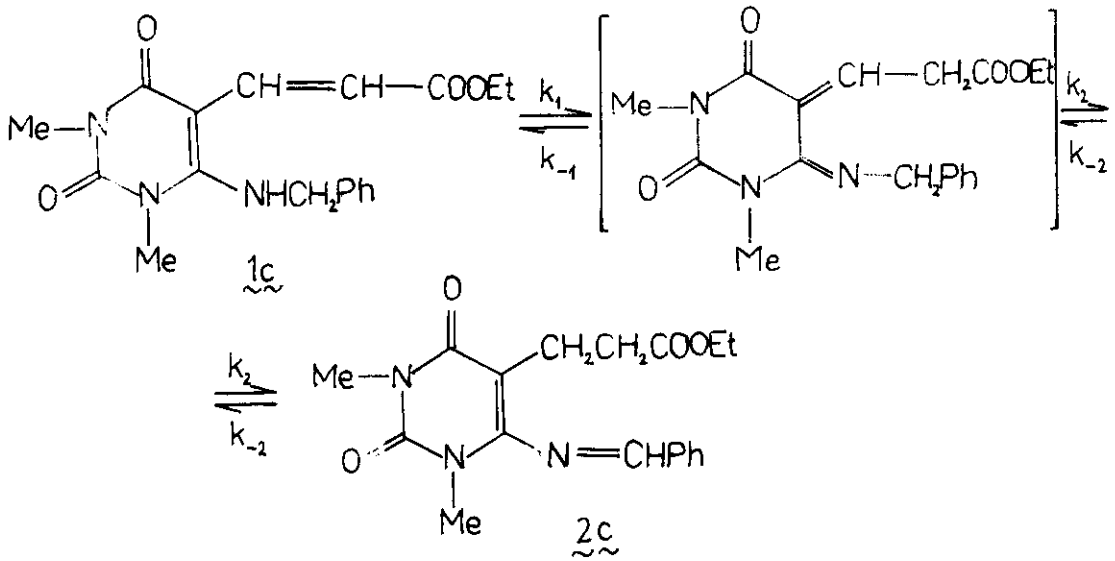
These values are quite similar to those obtained for the first step of isomerization of cyclic conjugated diene systems.[7]
The most attractive feature of our results originates from the fact that uracils of type 1 - considering their easy availability may serve not only

Scheme 1



a: $R^1=CH_3(CH_2)_2$, $R^2=H$
b: $R^1=CH_3(CH_2)_3$, $R^2=H$
c: $R^1=C_6H_5$, $R^2=H$
d: $R^1=4-MeO-C_6H_4$, $R^2=H$
e: $R^1=4-Cl-C_6H_4$, $R^2=H$
f: $R^1=C_6H_5$, $R^2=Me$

Scheme 2



as model compounds for investigation of [1,5] sigmatropic rearrangements but also as a valuable tool for converting labelled primary and secondary amines into otherwise hardly available labelled carbonyl compounds by a consecutive [1,5] hydrogen shifts followed by a hydrolytic splitting.[8]

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and are uncorrected. Infrared spectra were recorded in potassium bromide pellets on a Bruker IFS 85 spectrometer; ^{1}H nmr spectra on a JEOL 60HL at 60 MHz, at room temperature, using TMS as internal standard. The compounds prepared in this study are summerized in Tables 1 and 2.

Kinetic measurments

The actual concentrations of 1c were determined by UV spectroscopy. The absorption maxima for 1c and 3c in abs. xylene (n_D^{20} = 1.4969) differ significantly from each other (1c: λ_{max} = 324 nm (ε = 20465), 3c: λ_{max} = 343 nm (ε = 2895)). In a mixture of 1c and 3c at 324 nm the absorption originates practically exclusively from 1c while at 380 nm from 3c. (As a control, the compositions of a series of solutions containing known amounts of 1c and 3c were determined by ε, observed at the above wavelengths. These data showed a good agreement with the expected values). Minimum three parallel experiments were carried out at 130 and 140 °C to evaluate k_1. During the reactions the sum of the concentrations of 1c and 3c remained practically constant.

Preparation of E-6-substituted benzylamino-5-(2-ethoxycarbonylethenyl)-1,3-dimethyluracils (1c-f). General procedure.

The appropriately substituted benzylamine (15 mmol) was added during 5 min to a stirred suspension of 6-chloro-5-(2-ethoxycarbonylethenyl)-1,3-dimethyluracil[3] (5 mmol) in abs. ethanol (10 ml) at 15-20 °C. After ca.1 h (TLC) the mixture was cooled at 0 °C and the precipitate was filtered, washed with water (3 x 15 ml) and dried. The yields of crude products were practically quantitative.

Preparation of 8-substituted benzylamino-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4,7(1H,3H,8H)-triones (2a-e). General procedure.

A mixture of 1c-e (1.5 mmol), 1,5-diazabicyclo[4.3.0]non-5-ene (1-2 drops), triethylamine (10 ml) and dimethylformamide (1 ml) was heated for several

Table 1. List of compounds 1c-f, 2c-e and 3c-f[+]

Compd.	Solvent of Cryst.	M p (°C)	Yield (%)	Molecular Formula
1c	ethanol	174-175	78	$C_{18}H_{21}N_3O_4$
1d	ethanol	141-142	76	$C_{19}H_{23}N_3O_5$
1e	ethanol	177-178	79	$C_{18}H_{20}ClN_3O_4$
1f	ethanol	122-124	69	$C_{19}H_{23}N_3O_4$
2c	ethanol	223-224	71	$C_{16}H_{15}N_3O_3$
2d	ethanol	158-159	77	$C_{17}H_{17}N_3O_4$
2e	ethanol-dimethylformamide	192-194	90	$C_{16}H_{13}ClN_3O_3$
3c	isopropanol	126-127	88	$C_{18}H_{21}N_3O_4$
3d	isopropanol	139-140	83	$C_{19}H_{23}N_3O_5$
3e	ethanol	148-149	83	$C_{18}H_{20}ClN_3O_4$
3f	petrolether	88-90	85	$C_{19}H_{23}N_3O_4$

[+]Satisfactory elemental analyses (C,H,N) were obtained for all the newly synthesized compounds.

hours (TLC). After cooling at -10 °C the precipitate formed was filtered and recrystallized.

Preparation of 6-substituted benzylidenamino-5-(2-ethoxycarbonylethyl)-1,3-dimethyluracils (3c-f). General procedure.

A solution of 1c-f (5 mmol) in abs.xylene (25 ml) (n_D^{20} = 1.4969) was heated at 130 or 140 °C for several hours (TLC). The xylene was evaporated in vacuo, the solidal residue was either suspended in ether or recrystallized from the given solvent.

Table 2. IR and ^{1}H NMR data of compounds 1c-f, 2c-e and 3c-f

Comp.	IR (KBr, (cm^{-1}))	^{1}H NMR ($CDCl_3$, δ (ppm))
1c	3314 (NH), 1699 (CO), 1666 (CO);	1.27(t(J=7Hz),3H,$CH_2\underline{CH_3}$),3.34(s,3H,1-N-CH_3),3.47(s,3H,3-N-CH_3),4.15(q,2H,$\underline{CH_2}CH_3$),4.48(d(6),2H,NH-$\underline{CH_2}$),5.30(t,1H,NH),6.92(d(15),1H,8-CH),7.33(5H,Ph),7.57(d(15),1H,7-CH);
1d	3337 (NH), 1695 (CO), 1664 (CO);	1.22(t(7),3H,$CH_2\underline{CH_3}$),3.27(s,3H,1-N-CH_3),3.43(s,3H,3-N-CH_3),3.74(s,3H,OCH_3),4.10(q,2H,($\underline{CH_2}CH_3$),4.40(d(6.5),2H,NH-$\underline{CH_2}$),5.38(t,1H,NH), 6.87(d(15),1H,8-CH)$^+$,6.82(d(7),2H,Ph-3,5H)$^+$,7.17(d(7),2H,Ph-2,6H),7.37(d(15),1H,7-CH);
1e	3331 (NH), 1701 (CO), 1664 (CO);	1.20(t(7),3H,$CH_2\underline{CH_3}$),3.27(s,3H,1-N-CH_3),3.40(s,3H,3-N-CH_3),4.07(q,2H,$\underline{CH_2}CH_3$),4.37(d(6),2H,NH-$\underline{CH_2}$),5.10(t,1H,NH),6.75(d(15),1H,8-CH),7.22(m,4H,Ph-H),7.43(d(15),1H,7-CH);
1f	3370 (NH), 1705 (CO), 1665 (CO);	1.30(t(7),3H,$CH_2\underline{CH_3}$),1.70(d(6),3H,CH-$\underline{CH_3}$),3.33(s,1H,1-N-CH_3),3.40(s,1H,3-N-CH_3),4.17(q,2H,$\underline{CH_2}CH_3$),4.63(m,2H,NH+NH-$\underline{CH}$),6.93(d(15),1H,8-CH),7.30(m,5H,Ph-H)$^+$,7.43(d(15),1H,7-CH)$^+$;
2c^{++}	1710 (CO), 1660 (broad,CO);	3.27(s,3H,1-N-CH_3),3.40(s,3H,3-N-CH_3),5.37(s,2H,CH_2),6.37(d(9),1H,6-CH),7.28(m,5H,Ph-H),7.97(d(9),1H,5-CH);
2d^{++}	1707 (CO), 1659 (broad,CO);	3.20(s,3H,1-N-CH_3),3.27(s,3H,3-N-CH_3),3.70(s,3H,OCH_3),5.23(s,2H,CH_2),6.28(d(9),1H,6-CH),6.83(d(8),2H,Ph-3,5H),7.07(d(8),2H,Ph-2,6H),7.90(d(9),1H,5-CH);
2e	1711 (CO), 1663 (CO);	3.38(s,3H,1-N-CH_3)3.41(s,3H,3-N-CH_3),5.27(s,2H,CH_2),6.40(d(9),1H,6-CH),7.20(m,4H,Ph-H),8.05(d(9),1H,5-CH);
3c	1725 (CO), 1690 (CO);	1.16(t(7),3H,$CH_2\underline{CH_3}$),2.53(s,4H,CH_2CH_2),3.23(s,3H,1-N-CH_3),3.33(s,3H,3-N-CH_3),4.00(q(7),2H,$\underline{CH_2}CH_3$),7.51(m,3H,Ph-2,4,6H),7.83(m,2H,Ph-3,5H),8.30

Table 2. - Continued

Comp.	IR (KBr,(cm^{-1}))	^{1}H NMR ($CDCl_3$, δ (ppm))
		(s,1H,N=CH);
3d	1715 (CO), 1697 (CO);	1.17(t(7),3H,$CH_2\underline{CH_3}$),2.53(s,4H,CH_2CH_2),3.27(s,1H, 1-N-CH_3),3.37(s,1H,3-N-CH_3),3.87(s,3H,OCH_3)$^+$,4.03 (q,2H,$\underline{CH_2}CH_3$)$^+$,7.03(d(9),2H,Ph-3,5H),7.87(d(9),2H, Ph-2,6H),8.23(s,1H,N=CH);
3e	1711 (CO);	1.17(t(7),3H,$CH_2\underline{CH_3}$),2.57(s,4H,CH_2CH_2),3.27(s,3H, 1-N-CH_3),3.40(s,3H,3-N-CH_3),4.03(q,2H,$\underline{CH_2}CH_3$),7.30 (d(9),2H,Ph-3,5H)7.83(d(9),2H,Ph-2,6H),8.33(s,1H, N=CH);
3f	1722 (CO), 1695 (CO);	1.17(t(7),3H,$CH_2\underline{CH_3}$),2.38(m,7H,CH_2CH_2+C-CH_3),3.22 (s,3H,1-N-CH_3),3.40(s,3H,3-N-CH_3),4.03(q,2H,$\underline{CH_2}CH_3$), 7.50(m,3H,Ph-2,4,6H),8.00(m,2H,Ph-3,5H).

$^+$ superimposed signals

$^{++}$^{1}H NMR spectrum in (D_6)DMSO solution

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REFERENCES AND NOTES

1. Part 8: P. Mátyus and H. Wamhoff, Chem.-Ztg. accepted for publication.
2. Alexander von Humboldt Fellow in Bonn 1982/83.
3. P. Mátyus, P. Sohár and H. Wamhoff, Heterocycles, 1984, 22, 513.
4. P. Mátyus, G. Eckhardt, G. Zólyomi and H. Wamhoff, Chem. Ber., in preparation.
5. D. W. Marquardt, J. Soc. Ind. Appl. Math., 1963, 2, 431.
6. The program (REKINET, a program-member of LABSWARE) was kindly given by Z. Gabányi (COMPUDRUG LTD.).
7. a/ A. P. ter Borg and H. Kloosterziel, Rec. Trav. Chim., 1963, 82, 741;
   b/ A. P. ter Borg, H. Kloosterziel and Y. L. Westphal, Rec. Trav. Chim., 1967, 86, 474 and references therein.
8. G. Zólyomi, P. Mátyus and H. Wamhoff, J. Labelled Compd., in preparation.

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