CYCLIZATION DICHOTOMY OF ESTERS OF 3-UREIDO-2-CYANO-2-PROPENOIC AND 3-UREIDO-2-ACYL-2-PROPENOIC ACIDS

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The preparation of *E* and *Z* isomers of 3-ureido-2-cyano-2-propenoates *Ia – Id* and their base-catalyzed isomerization and cyclization to 5-carboxycytosine derivatives *IIa – IIf* and 5-cyanouracil derivatives *IIIa* and *IIIb* is described. Also described is the preparation of 3-ureido-2-acyl-2-propenoates *Va – Vd* and their base-catalyzed cyclization to 5-carboxy-2(1*H*)-pyrimidone derivatives *VIa – VIc* and 5-acyluracils *VIIa – VIIc*.

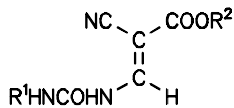
Some time ago we described[1,2] *E* and *Z* isomers of *N′*-substituted methyl 3-ureido-2-methyl-2-propenoates and their isomerization and cyclization to 3-substituted 5-methyluracils. We also described *E* and *Z* isomers of *N′*-susbtituted methyl 3-sulfamido-2-methyl-2-propenoates and their isomerization and cyclization to derivatives of 4-methyl-2*H*-1,2,6-thiadiazin-3(6*H*)-one 1,1-dioxide, a structural analog of thymine. The present communication concerns the configuration on the C=C bond in, and cyclization reactions of, esters of 3-ureido-2-cyano-2-propenoic acids *Ia – Id* and of 3-ureido-2-acyl-2-propenoic acids *Va – Vd*, and their utilization in the synthesis of 5-cyanouracil and 5-acyluracils. Our interest was aroused by a paper[3] reporting antiviral effects of 1-(2-deoxy-β-D-*erythro*-pentofuranosyl) derivatives of some 5-substituted uracils.

The base-catalyzed cyclization of ethyl 3-ureido-2-cyano-2-propenoate (*Ia*) and its *N′*-substituted derivatives represents a currently used approach to derivatives of 5-carboxycytosine *IIf* (refs[4–6]). Upon treatment with sodium ethoxide, ethyl 3-ureido-2-acetyl-2-propenoate (*Va*) is cyclized to 5-ethoxycarbonyl-4-methylpyrimidin-2(1*H*)-one (*VIa*) whereas in aqueous potassium hydroxide affords 5-acetyluracil (*VIIa*) in a low yield (25%) (refs[7,8]). The starting ureido derivatives *Ia – Id* and *Va – Vd* are well accessible by Whitehead synthesis[4,5,9,10], i.e. reaction of *N*,*N′*-bis(*N*-alkylcarbamoyl)formamidines, or directly by condensation of ureas and ethyl orthoformate with compounds containing an active CH_2 group (derivatives of malonic acid, ethyl acetoacetate or ethyl nitroacetate).

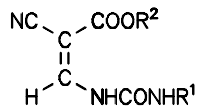
In the reaction of urea and ethyl orthoformate with ethyl cyanoacetate we obtained the *E* isomer (*E*)-*Ia* as the sole product. The same reaction with methyl cyanoacetate

gave a mixture of isomers (*E*)-*Ib* and (*Z*)-*Ib* in the ratio 5 : 2. *N*-Methylurea and ethyl orthoformate reacted with ethyl cyanoacetate to give a 5 : 9 mixture of isomers (*E*)-*Ic* and (*Z*)-*Ic*, which was separated by chromatography on silica gel. Under the same conditions, the reaction with methyl cyanoacetate gave only the isomer (*Z*)-*Id*.

In comparison with *N′*-substituted methyl 3-ureido-2-methyl-2-propenoates and methyl 3-sulfamido-2-methyl-2-propenoates, compounds *Ia* – *Id* are configurationally less stable and rapidly isomerize in solution when heated or treated with base. In boiling water, after 30 min, the isomer (*E*)-*Ia* afforded a mixture of *E* and *Z* isomers (5 : 4); after 30 min at 100 °C in 50% aqueous methanol isomer (*Z*)-*Id* gave a 1 : 1

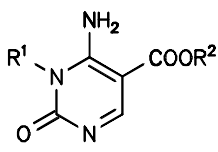


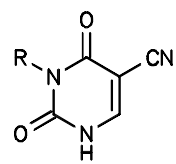
(*E*)–*I*



(*Z*)–*I*

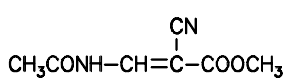
Ia, R^1 = H; R^2 = C_2H_5
Ib, R^1 = H; R^2 = CH_3
Ic, R^1 = CH_3; R^2 = C_2H_5
Id, R^1 = CH_3; R^2 = CH_3





IIa, R^1 = H; R^2 = C_2H_5
IIb, R^1 = H; R^2 = CH_3
IIc, R^1 = CH_3; R^2 = C_2H_5
IId, R^1 = CH_3; R^2 = CH_3
IIe, R^1 = H; R^2 = $(CH_3)_2CHCH_2CH_2$
IIf, R^1 = H; R^2 = H

IIIa, R = H
IIIb, R = CH_3



IV

mixture of (*E*)-*Id* and (*Z*)-*Id*. Treatment of (*E*)-*Ic* with 2 M ethanolic sodium ethoxide at room temperature for 1 min gave also a 1 : 1 mixture of (*E*)-*Ic* and (*Z*)-*Ic*.

The configuration at the C=C double bond in compounds *Ia – Id* was determined on the basis of chemical shifts of vinyl protons and the proton of the nonterminal NH group, similarly as in the case of methyl 3-(*N'*-alkylureido)-2-methyl-2-propenoates described by us[1]. The *E* : *Z* isomer ratio in the mixtures was determined by integration of vinyl proton signals after exchange of interacting NH protons in deuterium oxide. The ^{1}H NMR spectra of compounds *Ia – Id* are given in Table I.

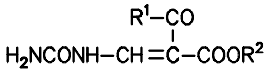
Taking into account the proven base-catalyzed *E*/*Z* isomerization of compounds *Ia – Id*, we may expect that configuration at the C=C bond will not affect the direction of the cyclization and that the decisive factor will be only the difference in reactivity of the nitrile and alkoxycarbonyl groups. In accord with the literature[4], we observed that cyclization of ethyl ester (*E*)-*Ia* in boiling 2 M solution of sodium ethoxide afforded only the cytosine derivative *IIa*. Also ethyl ester (*Z*)-*Ic* on treatment with 2 M sodium ethoxide at room temperature gave cytosine derivative *IIc* as the sole product. On the other hand, cyclization of the above-mentioned isomeric mixture of methyl esters (*E*)-*Ib* and (*Z*)-*Ib* in 2 M sodium methoxide at reflux furnished a mixture of cytosine derivative *IIb* and uracil derivative *IIIa* in the ratio 5 : 3; under the same conditions, methyl ester (*Z*)-*Id* afforded a mixture of cytosine derivative *IId* and uracil derivative *IIIb* in the ratio 15 : 1. Reaction of a mixture of methyl esters (*E*)-*Ib* and (*Z*)-*Ib* with sodium 3-methylbutoxide in boiling 3-methylbutanol led only to the cytosine derivative *IIe*. We assume that in

TABLE I
^{1}H NMR parameters of compounds *Ia – Id*, for conditions see Experimental

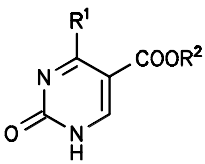
Compound	Chemical shifts, ppm				Coupling constants, Hz	
	CH=	CONHCH	RNHCO	CH_3NH	*J*(CH=,NH)	*J*(NH,CH_3)
E-*Ia*[a]	8.51 d	10.10 d	6.90 s[i]	–	13.0	–
Z-*Ia*[b]	8.11 d	10.63 d	6.90 s[i]	–	13.0	–
E-*Ib*[c]	8.44 d	10.22 d	7.40 s[i]	–	13.0	–
Z-*Ib*[d]	8.08 d	10.53 d	7.40 s[i]	–	13.0	–
E-*Ic*[e]	8.58 d	9.93 d	6.96 m	2.86 d	13.0	4.6
Z-*Ic*[f]	8.17 d	10.62 d	7.81 m	2.83 d	13.0	4.6
E-*Id*[g]	8.62 d	9.96 d	6.93 m	2.83 d	13.0	4.6
Z-*Id*[h]	8.15 d	10.62 d	7.89 m	2.81 d	13.0	4.6

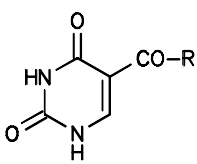
Other signals: [a] 1.31 t, 3 H, *J* = 7.0 ($C\mathbf{H}_3CH_2O$); 4.24 q, 2 H, *J* = 7.0 ($CH_3C\mathbf{H}_2O$). [b] 1.35 t, 3 H, *J* = 7.0 ($C\mathbf{H}_3CH_2O$); 4.29 q, 2 H, *J* = 7.0 ($CH_3C\mathbf{H}_2O$). [c] 3.74 s, 3 H (CH_3O). [d] 3.78 s, 3 H (CH_3O). [e] 1.34 t, 3 H, *J* = 7.0 ($C\mathbf{H}_3CH_2O$); 4.26 q, 2 H, *J* = 7.0 ($CH_3C\mathbf{H}_2O$). [f] 1.35 t, 3 H, *J* = 7.0 ($C\mathbf{H}_3CH_2O$); 4.28 q, 2 H, *J* = 7.0 ($CH_3C\mathbf{H}_2O$). [g] 3.78 s, 3 H (CH_3O). [h] 3.82 s, 3 H (CH_3O). [i] 2 H.

the first reaction step the methyl ester *Ib* is transesterified into the 3-methylbutyl ester which then is unequivocally cyclized to give compound *IIe*. In connection with the described[11,12] cyclization of ethyl 3-(*S*-ethylthioureido)-2-cyano-2-propenoate to 2-ethylthio-5-cyano-4(3*H*)-pyrimidone and of ethyl 3-acetamidino-2-cyano-2-propenoate to 5-cyano-2-methyl-4(3*H*)-pyrimidone by treatment with aqueous sodium hydroxide, we performed under comparable conditions cyclization of ethyl ester (*E*)-*Ia*. Reaction of compound (*E*)-*Ia* in boiling 0.1 M NaOH gave 51% of complex of uracil derivative *IIIa* with one molecule of urea, together with 5% of cytosine derivative *IIf*. The uracil derivative *IIIa* was liberated from the complex by treatment with Dowex 1 in the carbonate form. We prepared the same complex from an equimolecular mixture of compound *IIIa* and urea by crystallization from water. Attempted cyclization of a mixture of (*E*)-*Ib* and (*Z*)-*Ib* by sodium acetate in boiling acetic anhydride afforded a mixture of *E* and *Z* isomers of *IV* in the ratio 6 : 5. A similar cleavage was observed with methyl glyoxylate semicarbazone[13].



Va, $R^1 = CH_3$; $R^2 = C_2H_5$
Vb, $R^1 = CH_3$; $R^2 = CH_3$
Vc, $R^1 = C_2H_5$; $R^2 = C_2H_5$
Vd, $R^1 = CH_2{=}CHCH_2CH_2$; $R^2 = C_2H_5$





VIa, $R^1 = CH_3$; $R^2 = C_2H_5$
VIb, $R^1 = C_2H_5$; $R^2 = C_2H_5$
VIc, $R^1 = CH_2{=}CHCH_2CH_2$; $R^2 = C_2H_5$

VIIa, $R = CH_3$
VIIb, $R = C_2H_5$
VIIc, $R = CH_2{=}CHCH_2CH_2$

3-Ureido-2-acyl-2-propenoates *Va – Vd* were prepared by condensation of urea and ethyl orthoformate with the corresponding 3-keto esters (ethyl acetoacetate, methyl acetoacetate, ethyl 3-oxopentanoate and ethyl 3-oxo-6-heptenoate). We did not succeed in using ^{1}H NMR spectroscopy to determine configuration at the C=C bond in the obtained compounds *Va – Vd*. The spectra of these compounds did not exhibit doubled signals corresponding to *E*/*Z* isomer mixtures and after UV-irradiation in ethanol the spectrum of *Va* was identical with that of the unirradiated compound. Spectrum of compound *Vd* corresponds to a mixture of geometric isomers at the inner C=C bond.

Upon treatment of ethyl ester *Va* in boiling 0.1 M sodium ethoxide solution we obtained 5-acetyluracil (*VIIa*; 8%), in addition to compound *VIa* (62%) described[7] as the reaction product. In contrast with methyl 3-ureido-2-cyano-2-propenoate (*Ib*), no markedly higher yields of the uracil derivative *VIIa* (15%) were observed in the cyclization of methyl ester *Vb*. In this reaction we isolated another product whose composition ($C_{14}H_{18}N_4O_7$) corresponded to a condensation dimer of the starting compound *Vb*. We prepared the uracil derivative *VIIa* in 41% yield by cyclization of ethyl ester *Va* by treatment with Dowex 1 in the carbonate form. As the side-product we obtained compound *VIa* (10%). Cyclization of compounds *Vc* or *Vd* in 0.1 M NaOH at room temperature afforded a mixture of compound *VIb* and uracil derivative *VIIb* or a mixture of compound *VIc* and uracil derivative *VIIc* in the ratio 2 : 1.

The mentioned cyclization reactions of easily accessible alkyl 3-ureido-2-cyano-2-propenoates and 3-ureido-2-acyl-2-propenoates leading to the respective 5-cyanouracil and 5-acyluracil derivatives represent an alternative to cyclizations of 3-ethoxy-*N*-ethoxycarbonyl-2-cyano-2-propenoyl amide and 2-acyl-3-ethoxy-*N*-ethoxycarbonyl-2-propenoyl amide described by Shaw[14,15], as well as to the preparation of 5-cyanouracil by conversion of 5-cyanocytosine[10] by Sandmeyer reaction from 5-aminouracil[16], or by reaction[17] of 5-iodouracil with CuCN. Reaction of 5-bromouracil with NaCN affords predominantly 6-cyanouracil[18]. 1-Substituted 5-acyluracils can also be obtained by successive lithiation, acylation and oxidation of appropriate 5,6-dihydrouracils[19].

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. ^{1}H NMR spectra were measured on a Tesla BS-467 instrument (60 MHz) in a mixture of deuteriochloroform and hexadeuteriodimethyl sulfoxide (unless stated otherwise) with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale) and coupling constants (*J*) in Hz. The ^{1}H NMR spectra of compounds *Ia – Id* are given in Table I; the *E* : *Z* isomer ratios in the mixtures were determined from integration of vinyl proton signals after exchange of the interacting NH protons with deuterium oxide. UV spectra were recorded on a Specord UV-VIS instrument and IR spectra on a UR 10 spectrometer (both Zeiss, Jena, Germany). Wavenumbers are given in cm^{-1}. Thin-layer chromatography was performed on Silufol UV_{254} and column chromatography on silica gel Silpearl (both Kavalier, Votice, The Czech Republic). Analytical samples were dried at 25 °C and 6.5 Pa for 8 h.

Ethyl (*E*)-2-Cyano-3-ureido-2-propenoate ((*E*)-*Ia*)

A mixture of urea (6.0 g, 100 mmol), ethyl cyanoacetate (12.43 g, 110 mmol) and ethyl orthoformate (16.0 g, 112 mmol) was refluxed for 8 h. After cooling, the solid reaction mixture was triturated with ethyl acetate (50 ml), the solid portion was collected on filter and washed with ethyl acetate and ether; yield 12.1 g (66%) of compound (*E*)-*Ia*. Crystallization from 80% aqueous ethanol afforded (*E*)-*Ia* (8.23 g, 45%) as the only product; m.p. 177 – 199 °C (reported[4] m.p. 215 °C for a noncrystallized product). For $C_7H_9N_3O_3$ (183.1) calculated: 45.88% C, 4.95% H, 22.94% N; found: 45.69% C, 5.12% H, 22.75% N.

Methyl 2-Cyano-3-ureido-2-propenoates ((*E*)-*Ib* and (*Z*)-*Ib*)

A mixture of urea (6.0 g, 100 mmol), methyl cyanoacetate (10.89 g, 110 mmol) and ethyl orthoformate (18 ml, 108.2 mmol) was refluxed for 8 h. The reaction mixture was worked up as described for the preparation of compound *Ia*; yield 11.05 g (65%) of compound *Ib*. Crystallization from 50% aqueous methanol afforded 7.82 g (46%) of a 5 : 2 mixture of (*E*)-*Ib* and (*Z*)-*Ib*, m.p. 179 – 201 °C (reported[4] m.p. 215 °C). For $C_6H_7N_3O_3$ (169.1) calculated: 42.58% C, 4.17% H, 24.84% N; found: 42.52% C, 4.37% H, 24.68% N.

Ethyl 2-Cyano-3-(*N'*-methylureido)-2-propenoates ((*E*)-*Ic* and (*Z*)-*Ic*)

A mixture of *N*-methylurea (3.7 g, 50 mmol), ethyl cyanoacetate (6.22 g, 55 mmol) and ethyl orthoformate (15 ml, 90.2 mmol) was refluxed for 6 h. After cooling, the solid reaction mixture was triturated with benzene (20 ml), the solid portion was collected on filter and washed with benzene; yield 5.98 g (61%) of compound *Ic*. Crystallization from ethyl acetate afforded a mixture of *E* and *Z* isomers of *Ic* (3.7 g, 37%) in the ratio 5 : 9; m.p. 145 – 159 °C (reported[6] m.p. 153 – 158 °C). The obtained mixture was separated by column chromatography on silica gel (600 g) in chloroform–ethyl acetate (3 : 1).

The UV-absorbing fraction of higher R_F value afforded 1.95 g (20%) of (*Z*)-*Ic*, m.p. 146 – 156 °C (ethyl acetate). IR spectrum (chloroform, 3 . 10^{-3} mol l^{-1}): 3 452 (N^3–H, free), 3 286 (N^1–H, intramolecularly hydrogen bonded); (chloroform, ≈ 10^{-1} mol l^{-1}): 3 451 (N^3–H, free), 3 304 (N^1–H, intramolecularly hydrogen bonded); 3 224 (N^3–H, intermolecularly hydrogen bonded); 2 239, 2 227, 2 219 (C≡N); 1 734 (amide I); 1 693 (C=O, $COOC_2H_5$, intramolecularly hydrogen bonded); 1 621 (C=C); 1 559 (amide II, N^3–H); 1 538 (N^1–H). For $C_8H_{11}N_3O_3$ (197.1) calculated: 48.70% C, 5.62% H, 21.31% N; found: 48.95% C, 5.58% H, 21.09% N.

The UV-absorbing fraction of lower R_F value afforded 1.032 g (11%) of (*E*)-*Ic*, m.p. 155 – 171 °C (ethyl acetate). IR spectrum (chloroform, 3 . 10^{-3} mol l^{-1}): 3 450 (N^3–H, free); 3 412 (N^1–H, free); 3 300 (N^3–H, bonded); (chloroform, ≈ 10^{-1} mol l^{-1}): 3 411 (N–H, free), 3 388, 3 297, 3 224 (N–H, bonded); 2 225 (C≡N); 1 741 (amide I); 1 722 (C=O, $COOC_2H_5$); 1 625 (C=C); 1 552, 1 539 (amide II). For $C_8H_{11}N_3O_3$ (197.1) calculated: 48.70% C, 5.62% H, 21.31% N; found: 48.90% C, 5.62% H, 21.08% N.

Methyl (*Z*)-2-Cyano-3-(*N'*-methylureido)-2-propenoate ((*Z*)-*Id*)

A mixture of *N*-methylurea (3.7 g, 50 mmol), methyl cyanoacetate (5.45 g, 55 mmol) and ethyl orthoformate (15 ml, 90.2 mmol) was refluxed for 6 h. The reaction mixture was worked up as described for the preparation of compound *Ic*; yield 5.21 g (55%) of product. Crystallization from ethyl acetate afforded 3.96 g (42%) of (*Z*)-*Id*, m.p. 170 – 197 °C. For $C_7H_9N_3O_3$ (183.1) calculated: 45.88% C, 4.95% H, 22.94% N; found: 46.09% C, 5.20% H, 22.65% N.

Isomerization of Ethyl (*E*)-2-Cyano-3-ureido-2-propenoate ((*E*)-*Ia*)

A solution of (*E*)-*Ia* (46 mg, 0.25 mmol) in water (5 ml) was boiled for 30 min. After cooling, the water was evaporated and the isomer ratio was determined by ^{1}H NMR spectroscopy to be (*E*)-*Ia* : (*Z*)-*Ia* = 5 : 4.

Isomerization of Methyl (*Z*)-2-Cyano-3-(*N'*-methylureido)-2-propenoate ((*Z*)-*Id*)

A solution of isomer (*Z*)-*Id* (47.3 mg, 0.25 mmol) in 50% methanol (5 ml) was heated at 100 °C for 30 min in a sealed ampoule. After cooling and opening the ampoule, the mixture was evaporated and the *E* : *Z* isomer ratio (1 : 1) was determined as in the preceding experiment.

Isomerization of Ethyl (*Z*)-2-Cyano-3-(*N'*-methylureido)-2-propenoate ((*Z*)-*Ic*)

A solution of (*Z*)-*Ic* (39.5 mg, 0.2 mmol) in ethanolic 2 M sodium ethoxide (0.2 ml, 0.4 mmol) was stirred at ambient temperature for 1 min, 10 min and 1 h. After the given time, ethanol (5 ml) was added and the solution was neutralized with Dowex 50 (acid form, 2 ml). The ion exchanger was filtered off and the filtrate was evaporated to give 36, 31 and 28 mg of a mixture of (*E*)-*Ic* and (*Z*)-*Ic*, invariably in the ratio 1 : 1. The isomer ratio was determined as in the preceding experiments.

5-Ethoxycarbonylcytosine (*IIa*)

A stirred solution of isomer (*E*)-*Ia* (1.83 g, 10 mmol) in 2 M ethanolic sodium ethoxide (10 ml, 20 mmol) was refluxed for 4 h. The solid reaction mixture was cooled, dissolved in ice-cold water (100 ml) and applied onto a column of Dowex 50 (acid form; 20 ml). After washing the column with water (200 ml), the product was eluted with 5% aqueous ammonia (200 ml) and the eluate was taken down. Crystallization of the residue (1.76 g, 96%) from pyridine–water (3 : 7) afforded 1.1 g (60%) of compound *IIa*, m.p. 270 – 283 °C (decomp.). Reported[4] m.p. 260 – 270 °C. UV spectrum (methanol): λ_{max} 226 and 277 nm (log ε 4.20 and 4.80).

5-Methoxycarbonylcytosine (*IIb*) and 5-Cyanouracil (*IIIa*)

A stirred solution of a mixture of (*E*)-*Ib* and (*Z*)-*Ib* (1.69 g, 10 mmol) in 2 M methanolic sodium methoxide (10 ml, 20 mmol) was refluxed for 4 h. The solid reaction mixture was cooled, dissolved in ice-cold water (80 ml) and applied onto a column of Dowex 50 (acid form; 20 ml). The column was washed with water (200 ml) and the solvent was evaporated. Crystallization of the residue (398 mg, 29%) from water afforded 318 mg (23%) of compound *IIIa*, m.p. 320 °C (decomp.). Reported[10] m.p. 319 – 320 °C. Its IR spectrum was identical with that of an authentic sample of compound *IIIa* (ref.[10]).

Washing the column with 5% aqueous ammonia (200 ml) and evaporation of the solvent afforded 895 mg (53%) of a residue which on crystallization from pyridine–water (3 : 7) gave 665 mg (39%) of compound *IIb*, m.p. 248 – 253 °C (decomp.). UV spectrum (methanol): λ_{max} 226 and 278 nm (log ε 4.16 and 3.80). For $C_6H_7N_3O_3$ (169.1) calculated: 42.58% C, 4.17% H, 24.84% N; found: 42.80% C, 4.43% H, 24.64% N.

5-Ethoxycarbonyl-3-methylcytosine (*IIc*)

A solution of (*Z*)-*Ic* (394 mg, 2 mmol) in ethanolic 2 M sodium ethoxide (2 ml, 4 mmol) was stirred at ambient temperature for 24 h. The solid reaction mixture was dissolved in ice-cold water (16 ml) and the solution was applied onto a column of Dowex 50 (acid form; 20 ml). The column was eluted

with water (200 ml) and the eluate was evaporated: no uracil derivative *IIIb* was detected in the residue. The product *IIc* was eluted with 5% aqueous ammonia (250 ml). Evaporation of the eluate afforded 340 mg (86%) of a residue which was crystallized from water; yield 266 mg (68%) of compound *IIc*, m.p. 230 – 235 °C (decomp.). Reported[6] m.p. 234 – 235 °C. UV spectrum (ethanol): λ_{max} 253 and 296 nm (log ε 4.08 and 4.05).

5-Methoxycarbonyl-3-methylcytosine (*IId*) and 5-Cyano-3-methyluracil (*IIIb*)

A stirred solution of (*Z*)-*Id* (916 mg, 5 mmol) in 2 M methanolic sodium methoxide (5 ml, 10 mmol) was refluxed for 8 h. The solid reaction mixture was cooled, dissolved in ice-cold water (60 ml) and applied onto a column of Dowex 50 (acid form; 50 ml). The column was washed with water (500 ml), the eluate was evaporated and the residue was extracted with ethyl acetate (2 × 2 ml). The insoluble residue (47 mg; 6%) was crystallized from ethanol to give 25 mg (3%) of compound *IIIb*, m.p. 219 – 225 °C. UV spectrum (methanol): λ_{max} 215 and 273 nm (log ε 4.02 and 4.04). IR spectrum (KBr): 3 265, 3 209 (N–H); 2 246 (C≡N); 1 729, 1 658 (C=O); 1 634 (C=C). For $C_6H_5N_3O_2$ (151.0) calculated: 47.66% C, 3.33% H, 27.80% N; found: 47.79% C, 3.61% H, 27.50% N. The product *IId* was then eluted with 5% aqueous ammonia (500 ml). Evaporation of the solvent afforded 833 mg (91%) of residue which on crystallization from water afforded 652 mg (71%) of compound *IId*, m.p. 245 °C. UV spectrum (methanol): λ_{max} 206, 250 and 295 nm (log ε 3.91, 4.24 and 4.20). For $C_7H_9N_3O_3$ (183.1) calculated: 45.88% C, 4.95% H, 22.94% N; found: 45.64% C, 5.19% H, 22.87% N.

5-(3-Methylbutoxycarbonyl)cytosine (*IIe*)

A mixture of (*E*)-*Ib* and (*Z*)-*Ib* (169 mg, 1 mmol) was dissolved in a 0.5 M solution of sodium 3-methylbutoxide in 3-methylbutanol (4 ml, 2 mmol) and refluxed for 90 min under stirring. The solid reaction mixture was cooled and dissolved in 60% ethanol (20 ml) under ice-cooling. The solution was applied onto a column of Dowex 50 (acid form; 10 ml) and the column was then washed with 60% ethanol (150 ml). The product was eluted with 5% ammonia solution in 20% ethanol (150 ml). The eluate was taken down and the residue (208 mg; 92%) was crystallized from pyridine–water (3 : 7) to give 142 mg (63%) of compound *IIe*, m.p. 300 °C (decomp.). UV spectrum (methanol): λ_{max} 226 and 277 nm (log ε 4.16 and 3.75). For $C_{10}H_{15}N_3O_3$ (225.1) calculated: 53.30% C, 6.71% H, 18.65% N; found: 53.23% C, 7.01% H, 18.94% N.

5-Carboxycytosine (*IIf*) and 5-Cyanouracil (*IIIa*)

A solution of (*E*)-*Ia* (3.63 g, 20 mmol) in 0.1 M NaOH (500 ml, 50 mmol) was refluxed for 30 min. After cooling, the solution was applied onto a column of Dowex 50 (acid form; 60 ml). The column was washed with water (500 ml), the eluate was evaporated and the residue was extracted with acetone (2 × 10 ml). The insoluble portion (998 mg; 51%) consisted of equimolecular complex of 5-cyanouracil *IIIa* and urea, m.p. 250 – 320 °C. After crystallization from water, the compound (775 mg; 39%) melted at 253 – 320 °C. UV spectrum (methanol): λ_{max} 214 and 273 nm (log ε 4.02 and 4.04). IR spectrum (dimethyl sulfoxide): 2 237 (C≡N); 1 770, 1 724, 1 689, 1 629. Both the UV and IR spectrum are identical with those of an authentic sample prepared by crystallization of an equimolar mixture of compound *IIIa* and urea from water. For $C_5H_3N_3O_2 \cdot CH_4N_2O$ (197.1) calculated: 36.53% C, 3.58% H, 35.52% N; found: 36.75% C, 3.78% H, 35.76% N.

A solution of the equimolar complex of 5-cyanouracil *IIIa* and urea (197 mg, 1 mmol) in water (10 ml) was stirred with Dowex 1 (carbonate form, 3 ml) for 20 min at room temperature. The ion exchanger was filtered off, washed with water and the filtrate was concentrated to give 60 mg

(100%) of urea. The ion exchanger was then stirred with 5% formic acid (20 ml) for 20 min, filtered and washed with 5% formic acid (30 ml). Evaporation of the filtrate afforded 136 mg (100%) of compound *IIIa*, identical (m.p., UV and IR spectrum) with an authentic sample[10].

Compound *IIf* was eluted from the column with 5% sodium hydrogen carbonate solution and precipitated from the solution by addition of concentrated acetic acid. The precipitate was centrifuged and washed with water and methanol. Yield 168 mg (5%) of compound *IIf*, m.p. 257 °C (decomp.). Reported[20] m.p. 256 °C. UV spectrum (water): λ_{max} 221 and 278 nm (log ε 4.10 and 3.96).

Methyl 3-Acetylamino-2-cyano-2-propenoate (*IV*)

Compound *Ib* (169 mg, 1 mmol) in acetic anhydride (1 ml) was refluxed for 3 h. Sodium acetate (164 mg, 2 mmol) was added and the reflux was continued for 15 min. After cooling, the mixture was poured into ice-cold water (20 ml) and the suspension was extracted with chloroform (3 × 50 ml). The organic layer was dried over anhydrous sodium sulfate, the solvent was evaporated and the residue was crystallized from benzene to give 112 mg (67%) of a mixture of *E* and *Z* isomers *IV* (5 : 6); m.p. 115 – 133 °C. ^{1}H NMR spectrum (deuteriochloroform); (*E*)-*IV*: 2.38 s, 3 H ($NCOCH_3$); 3.83 s, 3 H ($COOCH_3$); 8.64 d, 1 H, *J*(CH,NH) = 13.0 (–CH=); 10.84 d, 1 H, *J*(CH,NH) = 13.0 (NH); (*Z*)-*IV*: 2.36 s, 3 H ($NCOCH_3$); 3.86 s, 3 H ($COOCH_3$); 8.15 d, 1 H, *J*(CH,NH) = 12.0 (–CH=); 9.37 d, 1 H, *J*(CH,NH) = 12.0 (NH). For $C_7H_8N_2O_3$ (168.2) calculated: 49.98% C, 4.79% H, 16.66% N; found: 50.26% C, 5.06% H, 16.82% N.

Ethyl 2-Acetyl-3-ureido-2-propenoate (*Va*)

The title compound was prepared by the described procedure[4] and was crystallized from ethanol, m.p. 178 – 195 °C (reported[4] m.p. 194 – 195 °C). ^{1}H NMR spectrum: 1.29 t, 3 H, *J* = 7.0 ($C\mathbf{H}_3CH_2O$); 2.98 s, 3 H (CH_3CO); 4.21 q, 2 H, *J* = 7.0 ($CH_3C\mathbf{H}_2O$); 7.01 s, 2 H (NH_2); 8.58 d, 1 H, *J*(CH,NH) = 12.0 (–CH=); 11.60 d, 1 H, *J*(CH,NH) = 12.O (NH).

Methyl 2-Acetyl-3-ureido-2-propenoate (*Vb*)

A stirred mixture of urea (6.0 g, 100 mmol), methyl acetoacetate (11.6 g, 100 mmol) and ethyl orthoformate (20 ml, 120.2 mmol) was refluxed for 6 h. The mixture was cooled and the deposited compound was filtered and washed with ethyl acetate and ether; yield 10.63 g (58%). Crystallization from methanol afforded 6.65 g (36%) of compound *Vb*, m.p. 195 – 217 °C. ^{1}H NMR spectrum: 3.32 s, 3 H (CH_3CO); 3.71 s, 3 H (CH_3O); 7.25 s, 2 H (NH_2); 8.53 d, 1 H, *J*(CH,NH) = 12.5 (–CH=); 11.53 d, 1 H, *J*(CH,NH) = 12.5 (NH). For $C_7H_{10}N_2O_4$ (186.1) calculated: 45.14% C, 5.41% H, 15.04% N; found: 45.36% C, 5.61% H, 15.23% N.

Ethyl 2-Propionyl-3-ureido-2-propenoate (*Vc*)

A stirred mixture of urea (1.2 g, 20 mmol), ethyl 3-oxopentanoate (2.9 g, 20 mmol) and ethyl orthoformate (4 ml, 24.0 mmol) was refluxed and then worked up as described for the preparation of compound *Vb*. The product (1.25 g; 30%) was crystallized from ethanol to give 830 mg (20%) of compound *Vc*, m.p. 186 °C. ^{1}H NMR spectrum: 1.05 t, 3 H, *J* = 7.5 ($C\mathbf{H}_3CH_2CO$); 1.29 t, 3 H, *J* = 7.0 ($C\mathbf{H}_3CH_2O$); 2.29 q, 2 H, *J* = 7.5 ($CH_3C\mathbf{H}_2CO$); 4.20 q, 2 H, *J* = 7.0 ($CH_3C\mathbf{H}_2O$); 6.92 s, 2 H (NH_2); 8.57 d, 1 H, *J*(CH,NH) = 13.0 (–CH=); 11.67 d, 1 H, *J*(CH,NH) = 13.0 (NH). For $C_9H_{14}N_2O_4$ (214.1) calculated: 50.44% C, 6.59% H, 13.07% N; found: 50.67% C, 6.47% H, 13.34% N.

Ethyl 3-Oxo-2-ureidomethylene-6-heptenoate (*Vd*)

A stirred mixture of urea (4.8 g, 80 mmol), ethyl 3-oxo-6-heptenoate (13.6 g, 80 mmol) and ethyl orthoformate (16 ml, 96.2 mmol) was refluxed for 6 h and then worked up as described for the preparation of compound *Vb*. The product (6.0 g; 31%) was crystallized from ethyl acetate to give 4.59 g (24%) of compound *Vd*, m.p. 139 – 161 °C. ^{1}H NMR spectrum (mixture of geometric isomers): 1.26 m, 6 H (2 × C**H**$_3$CH$_2$O); 2.28 m, 4 H (2 × CH$_2$); 2.95 m, 4 H (2 × CH$_2$CO); 4.19 m, 4 H (2 × CH$_3$C**H**$_2$O); 5.22 m, 4 H (2 × C**H**$_2$=CH–); 6.03 m, 2 H (2 × CH$_2$=C**H**–); 7.51 s, 4 H (2 × NH$_2$); 8.39 d, 1 H and 8.47 d, 1 H, *J*(CH,NH) = 7.0 (–CH=); 10.21 d, 1 H and 11.45 d, *J*(CH,NH) = 7.0 (NH). For $C_{11}H_{16}N_2O_4$ (240.1) calculated: 54.97% C, 6.71% H, 11.66% N; found: 54.76% C, 6.62% H, 11.64% N.

5-Ethoxycarbonyl-4-methylpyrimidin-2(1*H*)-one (*VIa*) and 5-Acetyluracil (*VIIa*)

A. Compound *Va* (1 g, 5 mmol) in 1 M ethanolic sodium ethoxide (10 ml, 10 mmol) was refluxed with stirring for 30 min. After cooling, the stirred mixture was mixed with cold water (70 ml) and neutralized with concentrated acetic acid. The separated product was filtered, washed with water and dried. Crystallization from 80% ethanol afforded 560 mg (62%) of compound *VIa*, m.p. 257 °C (decomp.). Reported[7] m.p. 248 – 250 °C. UV spectrum (ethanol–0.1 M HCl, 1 : 1): λ_{max} 240 and 303 nm (log ε 4.34 and 3.70); (ethanol–0.1 M NaOH, 1 : 1): λ_{max} 260 nm (log ε 4.35).

The mother liquors after separation of compound *VIa* were poured on a column of Dowex 50 (acid form; 20 ml). Elution with water (150 ml) and evaporation of the eluate afforded 58 mg (8%) of product which on crystallization from water gave 45 mg (6%) of compound *VIIa*, m.p. 276 – 293 °C (decomp.). Reported[7] m.p. 294 °C. UV spectrum (ethanol–0.1 M HCl, 1 : 1): λ_{max} 227 and 282 nm (log ε 4.09 and 4.11); (ethanol–0.1 M NaOH, 1 : 1): λ_{max} 249 and 310 nm (log ε 4.06 and 4.29).

B. A solution of compound *Va* (1.0 g, 5 mmol) in 80% ethanol (200 ml) was pumped in a closed cycle through a column of Dowex 1 (carbonate form; 20 ml) until the starting compound *Va* disappeared. The reaction was monitored by thin-layer chromatography on silica gel in ethyl acetate–acetone–ethanol–water (40 : 2 : 2 : 1). The ion exchanger was stirred with 5% formic acid (100 ml), filtered off, washed with 5% formic acid (100 ml) and the filtrate was concentrated. The residue was extracted with boiling water (3 × 5 ml) and the insoluble material was washed with ethanol and dried. Yield 209 mg (22%) of compound decomposing above 210 °C; its elemental composition corresponded to the condensation dimer of the starting compound *Va*. For $C_{16}H_{22}N_4O_7$ (382.4) calculated: 50.23% C, 5.80% H, 14.65% N; found: 50.51% C, 5.55% H, 14.94% N.

The combined extracts were applied onto a column of Dowex 50 (acid form; 15 ml) and the product was eluted with water (200 ml). Evaporation of the eluate and crystallization of the residue (318 mg; 41%) from water afforded 271 mg (35%) of compound *VIIa*, identical (m.p. and UV spectrum) with the compound prepared by procedure *A*.

Elution of the column with 5% solution of pyridine (200 ml) and evaporation of the eluate gave 88 mg (10%) of compound *VIa*, identical (m.p. and UV spectrum) with the compound prepared by procedure *A*.

5-Acetyluracil (*VIIa*)

A solution of compound *Vb* (930 mg, 5 mmol) in 0.1 M methanolic sodium methoxide (10 ml, 10 mmol) was refluxed for 1 h. After cooling, the mixture was stirred with ice-cold water (70 ml), neutralized with concentrated acetic acid and set aside at 3 °C overnight. The separated product was filtered and washed with water (163 mg) and the mother liquors were applied onto a column of Dowex 50 (acid form; 20 ml). Elution of the column with water (150 ml), evaporation of the solvent

and crystallization of the residue (118 mg, 15%) from water afforded 68 mg (9%) of compound *VIIa*, identical (m.p. and UV spectrum) with the compound *VIIa* prepared in the preceding experiments.

Elution of the column with 5% aqueous pyridine (150 ml) and evaporation of the eluate gave 140 mg of material which was combined with the product deposited from the reaction mixture after the neutralization with acetic acid. The combined portions (303 mg) were dissolved in 80% ethanol, the solution was mixed with silica gel (500 mg) and after evaporation chromatographed on a column of silica gel (50 g) in ethyl acetate–acetone–ethanol–water (40 : 2 : 2 :1). The obtained crystalline material (171 mg, 19%) decomposed above 210 °C and its elemental composition corresponded to that of the condensation dimer of the starting compound *Vb*. For $C_{14}H_{18}N_4O_7$ (354.1) calculated: 47.43% C, 5.12% H, 15.81% N; found: 47.21% C, 5.37% H, 15.94% N.

5-Ethoxycarbonyl-4-ethylpyrimidin-2(1*H*)-one (*VIb*) and 5-Propionyluracil (*VIIb*)

A mixture of compound *Vc* (865 mg, 4.12 mmol) and 0.1 M NaOH (80 ml, 8 mmol) was shaken at room temperature for 30 min and then neutralized with concentrated acetic acid. The precipitated product was filtered, washed with water, dried (382 mg, 47%) and crystallized from ethanol to give 324 mg (40%) of compound *VIb*, m.p. 207 °C. UV spectrum (ethanol–0.1 M HCl, 1 : 1): λ_{max} 239 and 303 nm (log ε 4.39 and 3.70); (ethanol–0.1 M NaOH, 1 : 1): λ_{max} 267 (log ε 4.39). For $C_9H_{12}N_2O_3$ (196.1) calculated: 55.07% C, 6.16% H, 14.28% N; found: 54.78% C, 6.07% H, 14.07% N.

The mother liquors were applied onto a column of Dowex 50 (acid form; 20 ml). Elution with water (200 ml), evaporation of the eluate and crystallization of the residue (200 mg, 30%) from water afforded 153 mg (22%) of compound *VIIb*, m.p. 247 °C. UV spectrum (ethanol–0.1 M HCl, 1 : 1): λ_{max} 227 and 281 nm (log ε 4.04 and 4.09); (ethanol–0.1 M NaOH, 1 : 1): λ_{max} 247 and 310 nm (log ε 4.11 and 4.36). For $C_7H_8N_2O_3$ (168.1) calculated: 49.98% C, 4.79% H, 16.66% N; found: 50.03% C, 4.77% H, 16.58% N.

Washing the column with 5% aqueous ammonia (150 ml) and crystallization from ethanol gave another 95 mg (12%) of compound *VIb*.

4-(3-Butenyl)-5-ethoxycarbonylpyrimidin-2(1*H*)-one (*VIc*) and 5-(4-Pentenoyl)uracil (*VIIc*)

A mixture of compound *Vd* (720 mg, 3 mmol) and 0.1 M NaOH (60 ml, 6 mmol) was shaken at room temperature for 30 min, neutralized with concentrated acetic acid and set aside at room temperature overnight. The deposited product was filtered, washed with water and dried; yield 186 mg (28%) of compound *VIc*. The mother liquors were applied onto a column of Dowex 50 (acid form; 20 ml). The column was washed with water (250 ml) and the eluate was concentrated. The crystalline residue (172 mg, 30%) was crystallized from water; m.p. 235 °C. UV spectrum (ethanol–0.1 M HCl, 1 : 1): λ_{max} 227 and 282 nm (log ε 4.11 and 4.13); (ethanol–0.1 M NaOH, 1 : 1): λ_{max} 249 and 311 nm (log ε 4.07 and 4.29). For $C_9H_{10}N_2O_3$ (194.1) calculated: 55.64% C, 5.19% H, 14.42% N; found: 55.57% C, 5.38% H, 14.69% N.

The column was then washed with 5% aqueous ammonia (200 ml) and the eluate was taken down. Chromatography of the sirupy residue on a silica gel column (20 g) in ethyl acetate–acetone–ethanol–water (40 : 2 : 2 : 1) afforded further amount (197 mg; 30%) of compound *VIc*. Crystallization of the combined portions of compound *VIc* (383 mg) from ethyl acetate–light petroleum gave 233 mg (35%) of *VIc*, m.p. 106 – 108 °C. UV spectrum (ethanol–0.1 M HCl, 1 : 1): λ_{max} 244 and 304 nm (log ε 4.28 and 3.70); (ethanol–0.1 M NaOH, 1 : 1): λ_{max} 262 nm (log ε 4.41). For $C_{11}H_{14}N_2O_3$ (222.1) calculated: 59.42% C, 6.35% H, 12.60% N; found: 59.35% C, 6.33% H, 12.48% N.

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