SYNTHESIS OF METHYL 3-(N'-ALKYLUREIDO)-2-METHYL--2-PROPENOATES AND THEIR CYCLIZATION TO 3-ALKYL-5-METHYLURACILS

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Received May 11th, 1981

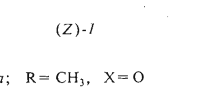
Stereoisomeric methyl 3-(N'-alkylureido)-2-methyl-2-propenoates (*Ia*—*Id*) were prepared by acid-catalyzed reaction of N-alkylureas (R = methyl, benzyl, isopropyl and tert-butyl) with methyl 3-methoxy-2-methyl-2-propenoate (*III*). Reaction of the ester *III* with N-tert-butylthiourea afforded the thioureides (*E*)-*Ie* and (*Z*)-*Ie*. On treatment with sodium methoxide in methanol, compounds *Ia*—*Ic* cyclized to the corresponding 3-alkyl-5-methyluracils *IIa*—*IIc* whereas compounds *Id* and *Ie* underwent only a base-catalyzed *E*/*Z* isomerization with (*E*)-isomers predominating.

Acid-catalyzed reaction of β-keto acid esters with substituted ureas leads to β-ureido--2-propenoic acid derivatives, useful intermediates in synthesis of 3,6-disubstituted uracils[1,2]. Only little attention has been paid to analogous reactions of β-aldehydo acid esters, which represent suitable compounds for preparation of 3,5-disubstituted uracils. Sweet and Fissekis[3] have found that reaction of methyl 3-oxopropanoate with N-alkylureas leads to 3,4-dihydro-1*H*-pyrimidin-2-one derivatives instead of the expected 3-(N'-alkylureido)-2-propenoates. This anomalous reaction course is caused by aldol autocondensation of methyl 3-oxopropanoate to dimethyl 2-formyl--3-hydroxy-1,5-pentanedioate. Such complication, however, does not occur in the reaction of methyl 2-formylpropanote in an acidic medium. Acid-catalyzed reaction of N-substituted thioureas with methyl 2-formylpropanoate afforded the corresponding thioureides which were directly cyclized in an alkaline medium to give 3-substituted 5-methyl-2-thiouracils[4]. Fissekis and Creegan[5] described several ureides, prepared by reaction of 2-formyl-γ-butyrolactones with N-alkylureas in an acidic medium.

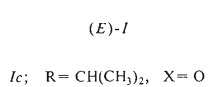
In the present communication we describe several methyl 3-(N'-alkylureido)--2-methyl-2-propenoates (*Ia*—*Id*) and their attempted cyclization into the corresponding 3-alkyl-5-methyluracils.

For our synthesis of the ureides *Ia*—*Id* we required methyl 2-formylpropanoate. Since the ester, obtained by the usual procedure, was of doubtful purity, the compound was generated by acid hydrolysis of methyl 3-methoxy-2-methyl-2-propenoate (*III*) and used *in situ* in the reaction with urea and its derivatives. Reaction of the

ester *III* with urea in 5M-HCl afforded methyl 3,3'-ureylenebis(2-methyl-2-propenoate) (*IVa*). Even in the presence of a large excess of urea, no unsymmetrical ureido derivative was detected in the reaction mixture. Thiourea reacted with the ester *III* in an analogous manner, giving methyl 3,3'-thioureylenebis(2-methyl-2-propenoate) (*IVb*). Reaction of the ester *III* with N-alkylureas gave mixtures of (*E*)- and (*Z*)-isomers of *Ia*–*Id* which were easily separable by means of chromatography. The thioureides (*E*)-*Ie* and (*Z*)-*Ie* were prepared analogously by reaction of the ester *III* with N-tert-butylthiourea. *Ia*–*Ie* are configurationally stable both in the solid state and



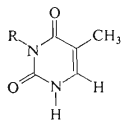
(*Z*)-*I*



(*E*)-*I*

Ia; R = CH_3, X = O
Ib; R = $CH_2C_6H_5$, X = O
Ic; R = $CH(CH_3)_2$, X = O
Id; R = $C(CH_3)_3$, X = O
Ie; R = $C(CH_3)_3$, X = S

in solution at room temperature, compounds (*E*)- and (*Z*)-*Id* were even sublimed *in vacuo* at 140°C without any detectable contamination with the other isomer. On the other hand, treatment of the (*E*)- or (*Z*)-isomers of *Ic*–*Ie* with 0·5M-CH_3ONa at 30°C for 24 h led to equilibrium mixtures containing predominantly the (*E*)-isomers (Table I, Fig. 1). (In the equilibrium mixtures of 3-(N-alkyl)-2-propenoates the *E*/*Z* ratio is reversed, probably as the result of strong hydrogen bonding in the (*Z*)-isomers[6].) Under the above-mentioned conditions, the (*Z*)-isomers of *Ia* and *Ib* cyclized to the corresponding 3-alkyl-5-methyluracils (*IIa* and *IIb*). The corresponding (*E*)-isomer occurred in the initial stage of the reaction and its concentration decreased with proceeding reaction (Fig. 2). The cyclization of (*E*)-isomers exhibited a similar time dependence, however, 50% conversion into the cyclic product required a significantly longer time than the reaction of the (*Z*)-isomers (for the (*Z*)-isomers of *Ia* and *Ib* 1·4 h and 4·0 h, for the (*E*)-isomers of *Ia* and *Ib* 4 h and 6 h, respectively)



IIa; R = CH_3 *IIb*; R = $CH_2C_6H_5$ *IIc*; R = $CH(CH_3)_2$

(Fig. 3). Substantially higher differences in the cyclization rates were found by Berá-nek and coworkers[7] for (*E*)- and (*Z*)-semicarbazones of glyoxylic acid esters. Compounds *Ic*—*Ie* did not cyclize at 30°C and we tried to convert them into uracil derivatives by treatment with 1M-CH_3ONa at 100°C. Under these conditions we prepared only the uracil derivative *IIc* in 30% yield. With longer reaction time and higher temperature (120°C) the concentration of compounds *Id* and *Ie* decreased but in the reaction mixture we did not find even traces of compounds absorbing in the region 260—280 nm.

TABLE I

Isomerization of (*E*)- and (*Z*)-isomer of *Ic*—*Ie* in 0·5M-$NaOCH_3$ at 30·0 ± 0·05°C. The *E*/*Z* ratio was determined chromatographically after 20 h of reaction

Starting compound	*E*/*Z*	Starting compound	*E*/*Z*
E-*Ic*	80/20	*Z*-*Ic*	77/23
E-*Id*	79/21	*Z*-*Id*	79/21
E-*Ie*[a]	95/5	*Z*-*Ia*[a]	93/7

[a] Measured after 24 h.

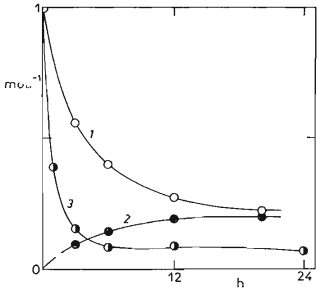


FIG. 1

Kinetics of *E*/*Z*-isomerization, expressed by time dependence of the concentration *c* (mol l^{-1}) of the corresponding (*Z*)-isomer. Starting compounds: *1* (*Z*)-*Ic*; *2* (*E*)-*Ic*; *3* (*Z*)-*Ie*

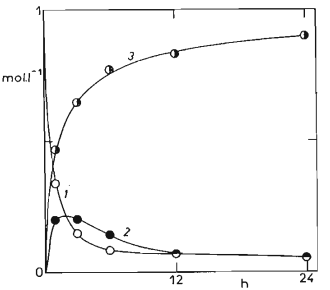


FIG. 2

Kinetics of cyclization of (*Z*)-*Ia*, expressed by time dependence of the concentration *c* (mol l^{-1}) of the reaction components. *1* (*Z*)-*Ia*; *2* (*E*)-*Ia*; *3* uracil derivative *IIa*

In an acidic medium the compounds *Ia–Id* underwent hydrolysis into methyl 2-formylpropanoate and N-alkylurea. The rate constant of hydrolysis, k_1, in 1M-HCl at 25°C is only little affected by the character of the alkyl moiety or configuration at the double bond (Table II). It is remarkable that the rate constant k_1 of compounds *Ia–Id* is by two orders of magnitude lower than the rate constant of ethyl 3-ureido-2-butenoate[8] in 0·01M-HCl at the same temperature ($k_1 = 2 \cdot 10^{-2}\ s^{-1}$). This comparison indicates that ureido derivatives derived from esters of β-aldehydo acids are much more stable toward hydrolysis than the analogous derivatives of β-keto acids. The reversibility of reaction of methyl 2-formylpropanoate with N-alkylureas is probably the cause of the very different yields of reaction of the ester *III* with N-alkylureas. The mentioned reaction afforded satisfactory yields only in cases when the products separated during the reaction.

The ^{1}H NMR spectra of the isomeric pairs of compounds *Ia–Ie* (Tables III and IV) show significant differences in chemical shifts of vinyl and non-terminal NH

TABLE II

Acid hydrolysis of compounds *Ia–Id* in 1M-HCl at 24·95 ± 0·05°C. Accuracy of k_1 values ±5%

Compound	$k_1 \cdot 10^4\ s^{-1}$	Compound	$k_1 \cdot 10^4\ s^{-1}$
E-Ia	6·93	*E-Ic*	6·28
Z-Ia	6·62	*Z-Ic*	5·99
E-Ib	4·02	*E-Id*	6·99
Z-Ib	3·60	*Z-Id*	6·32

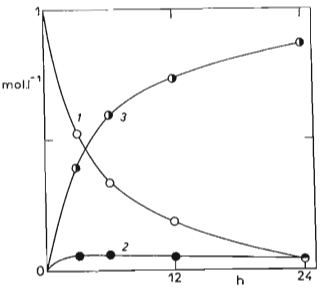


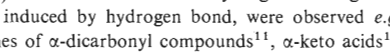
FIG. 3

Kinetics of cyclization of (*E*)-*Ia*, expressed by time dependence of the concentration *c* (mol l^{-1}) of the reaction components. *1* (*E*)-*Ia*; *2* (*Z*)-*Ia*; *3* uracil derivative *IIa*

protons. The isomers with downfield shift of the vinyl proton were assigned the (*E*)--configuration because we assume that the shift is due to the diamagnetic anisotropy of the methoxycarbonyl group. This effect of carbonyl group was recently used for configurational assignment to 1,3-diphenyl-2-buten-1-ones[9]. Downfield chemical shifts of the $H_{(3)}$ protons were observed for methyl (*E*)-(N'-alkylamino)-2-propenoates[10] whose configuration was determined on the basis of coupling constants of the $H_{(2)}$ and $H_{(3)}$ protons. The marked downfield shift of the non-terminal NH protons in the spectra of (*Z*)-isomers *Ia*–*Ie* is due to hydrogen bonding to the methoxycarbonyl group. Shifts, induced by hydrogen bond, were observed *e.g.* for (*Z*)-isomers of phenylhydrazones of α-dicarbonyl compounds[11], α-keto acids[12] or some heterocyclic ketones[13]. Since the signals of non-terminal NH protons in the ^{1}H NMR spectra of (*E*)-*Ia*–*Id* in deuteriochloroform coincided with the vinylic proton signals, the spectra of compounds *Ib*–*Id* were measured in hexadeuteriodimethyl

TABLE III

^{1}H NMR spectra of compounds *Ia*–*Ie* in deuteriochloroform (chemical shifts in ppm, coupling constants in Hz)



Compound	$H_{(A)}$	$H_{(B)}$	$H_{(C)}$	3 $H_{(D)}$	3 $H_{(E)}$	J_{AB}	J_{AD}
E-*Ia*[a]	8·01 s	8·01 s	6·22 m	1·74 s	3·67 s	—	—
Z-*Ia*[b]	7·40 dd	9·84 d	5·68 m	1·76 d	3·66 s	12·0	1·0
E-*Ib*[c]	8·05 s	8·19 s	6·83 t	1·73 s	3·65 s	—	—
Z-*Ib*[d]	7·34 dd	9·90 d	6·01 t	1·74 s	3·59 s	11·0	1·0
E-*Ic*[e]	7·98 s	7·98 s	6·14 d	1·68 s	3·70 s	—	—
Z-*Ic*[f]	7·43 dd	9·78 d	5·42 d	1·80 d	3·66 s	11·0	1·0
E-*Id*[g]	8·06 s	8·06 s	6·32 s	1·65 s	3·66 s	—	—
Z-*Id*[h]	7·36 dd	9·66 d	4·86 s	1·78 d	3·71 s	12·0	1·0
E-*Ie*[i]	8·42 dd	7·93 d	6·92 s	1·74 d	3·79 s	12·0	1·0
Z-*Ie*[j]	8·00 dd	10·92 d	6·58 s	1·83 d	3·76 s	11·0	1·0

[a] 2·79 (d, 3 H, CH_3, $J(CH_3, NH) = 5·0$ Hz). [b] 2·81 (d, 3 H, CH_3, $J(CH_3, NH) = 5·0$ Hz). [c] 4·37 (d, 2 H, Ar—CH_2, $J(CH_2, NH) = 6·0$ Hz); 7·29 (m, 5 H, H_{Ar}). [d] 4·38 (d, 2 H, Ar—CH_2, $J(CH_2, NH) = 6·0$ Hz); 7·27 (m, 5 H, H_{Ar}). [e] 1·14 (d, 6 H, $CH(CH_3)_2$, $J(CH_3, CH) = 6·5$ Hz); 3·96 (m, 1 H, $CH(CH_3)_2$). [f] 1·18 (d, 6 H, $CH(CH_3)_2$, $J(CH_3, CH) = 7·6$ Hz); 3·90 (m, 1 H, $CH(CH_3)_2$). [g] 1·33 (s, 9 H, $C(CH_3)_3$). [h] 1·35 (s, 9 H, $C(CH_3)_3$). [i] 1·53 (s, 9 H, $C(CH_3)_3$). [j] 1·49 (s, 9 H, $C(CH_3)_3$).

sulfoxide in which both the signals are separated thanks to the intermolecular hydrogen bond between the NH group and the solvent.

III *IVa*; X = O *IVb*; X = S

The presence of intramolecularly bonded hydrogen of non-terminal NH groups in the (*Z*)-isomers *Ia*–*Ie* was proved also by the IR spectral band at 3 330 cm^{-1}. The position of bands due to the carbonyl (ester and amide I in the region 1 725 to 1 690 cm^{-1} and amide II in the region 1 570–1 515 cm^{-1}), vinyl (1 670–1 630 cm^{-1}) or methyl (1 387–1 390 cm^{-1}) groups is not significantly influenced by the double bond configuration; on the other hand, the unidentified bands in the region 1 350 to to 1 020 cm^{-1} differ significantly for the isomeric pairs (Table V). Electronic spectra of (*Z*)-isomers *Ia*–*Id* exhibit a bathochromic shift (10 nm) relative to the (*E*)-isomers; this corresponds to the results found for the isomeric pairs of vinylogous urethanes[11,14,15] (Table VI).

TABLE IV

^{1}H NMR spectra of compounds *Ib*–*Id* in hexadeuteriodimethyl sulfoxide (chemical shifts in ppm, coupling constants in Hz)

(C) (B) (A) (E)

Compound	$H_{(A)}$	$H_{(B)}$	$H_{(C)}$	3 $H_{(D)}$	3 $H_{(E)}$	J_{AB}	J_{AD}
E-*Ib*[a]	7·78 dd	8·61 d	6·93 t	1·64 d	3·56 s	12·0	1·0
Z-*Ib*[b]	7·26 dd	9·61 d	8·03 t	1·69 d	3·60 s	12·0	1·0
E-*Ic*[c]	7·74 dd	8·43 d	6·44 d	1·61 d	3·51 s	12·0	1·0
Z-*Ic*[d]	7·21 dd	9·44 dd	7·44 d	1·67 d	3·60 s	12·0	1·0
E-*Id*[e]	7·73 dd	8·34 d	6·47 s	1·60 d	3·54 s	12·0	1·0
Z-*Id*[f]	7·21 dd	9·43 d	7·37 s	1·67 d	3·59 s	12·0	1·0

[a] 4·28 (d, 2 H, Ar—CH_2, $J(CH_2, NH)$ = 6·0 Hz); 7·23 (s, 5 H, H_{Ar}). [b] 4·24 (d, 2 H, Ar—CH_2, $J(CH_2, NH)$ = 6·0 Hz); 7·22 (s, 5 H, A_{Ar}). [c] 1·03 (d, 6 H, $CH(CH_3)_2$, $J(CH_3, CH)$ = 6·5 Hz); 3·61 (m, 1 H, $CH(CH_3)_2$). [d] 0·99 (d, 6 H, $CH(CH_3)_2$, $J(CH_3, CH)$ = 6·5 Hz); 3·62 (m, 1 H, $CH(CH_3)_2$). [e] 1·20 (s, 9 H, $(CH_3)_3C$). [f] 1·19 (s, 9 H, $(CH_3)_3C$).

TABLE V

IR spectra of ureides and thioureides *Ia*—*Ie* measured in 2% chloroform solutions in 0·1 cm cells. The NH bands were obtained in $3 \cdot 10^{-3}$M chloroform solutions in 1 cm cells. Band positions in cm^{-1}

E-Ia 3 458, 3 440 (NH); 1 711, 1 694 (C=O, amide I and ester); 1 657 (C=C); 1 570, 1 558 sh (C=O, amide II); 1 390 (CH_3); 1 136.

Z-Ia 3 457, 3 333 (NH); 1 726 sh, 1 698, 1 681 sh (C=O amide I and ester); 1 631 (C=C); 1 558, 1 538 sh (C=O, amide II); 1 387 (CH_3); 1 351, 1 149, 1 018.

E-Ib 3 446, 3 396 sh (NH); 1 695 (C=O, amide I and ester); 1 651 (C=C); 1 559, 1 539 sh (C=O, amide II); 1 504 sh, 1 439, 1 078, 1 031 sh (arom. ring); 1 390 (CH_3); 1 277, 1 137.

Z-Ib 3 445, 3 330 (NH); 1 692 (C=O, amide I and ester); 1 632 (C=C); 1 559, 1 540 sh, 1 533 (amide II); 1 505 sh, 1 440, 1 077, 1 030, 1 004 (arom. ring); 1 388 (CH_3); 1 346, 1 151, 1 016.

E-Ic 3 440 (NH); 1 681 sh, 1 713 sh, 1 693 (C=O, amide I and ester); 1 646 (C=C); 1 556 (amide II); 1 439, 1 390, 1 370 (CH_3); 1 320, 1 277, 1 243, 1 133.

Z-Ic 3 433, 3 327 (NH); 1 715 sh, 1 694, 1 682 sh (C=O, amide I and ester); 1 631 (C=C); 1 531 (C=O, amide II); 1 440, 1 389 (CH_3); 1 356, 1 170, 1 019.

E-Id[a] 3 444, 3 380 (NH); 1 725 sh, 1 704 (C=O, amide I and ester); 1 651 (C=C); 1 563, 1 557, 1 540 sh (C=O, amide II); 1 393, 1 366, (CH_3 and $C(CH_3)_3$); 1 273, 1 251, 1 130.

Z-Id[a] 3 448, 3 346, 3 314 (NH); 1 715, 1 688 (C=O, amide I and ester); 1 631 (C=C); 1 553, 1 515 (C=O, amide II); 1 390, 1 364 sh (CH_3 and $C(CH_3)_3$); 1 348, 1 149, 1 017.

E-Ie 3 450, 3 406, 3 390 sh (NH); 1 698 (C=O, ester); 1 657 (C=C); 1 535, (C=S, thioamide I); 1 361, 1 397 (CH_3 and $C(CH_3)_3$); 1 288, 1 245, 1 169, 1 125.

Z-Ie 3 489 sh, 3 407, 3 301, 3 261 (NH); 1 681 (C=O, ester); 1 643 (C=C); 1 591 (C=S, thioamide I); 1 363, 1 402 (CH_3 and $C(CH_3)_3$); 1 277, 1 136, 1 021, 823.

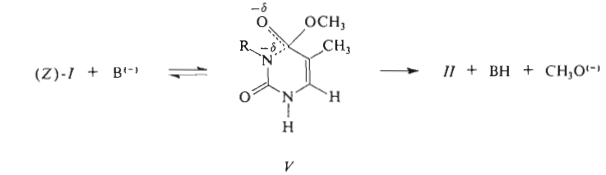
[a] Measured in tetrachloromethane.

TABLE VI

UV spectra of compounds *Ia*—*Ie* measured in 50% ethanol. Values of λ_{max} in nm

Compound	λ_{max}	log ε	Compound	λ_{max}	log ε
E-Ia	267	4·46	*Z-Ic*	279	4·33
Z-Ia	279	4·29	*E-Id*	270	4·44
E-Ib	269	4·51	*Z-Id*	280	4·31
Z-Ib	279	4·36	*E-Ie*	264, 298	4·39, 4·40
E-Ic	269	4·47	*Z-Ie*	274, 306	4·19, 4·36

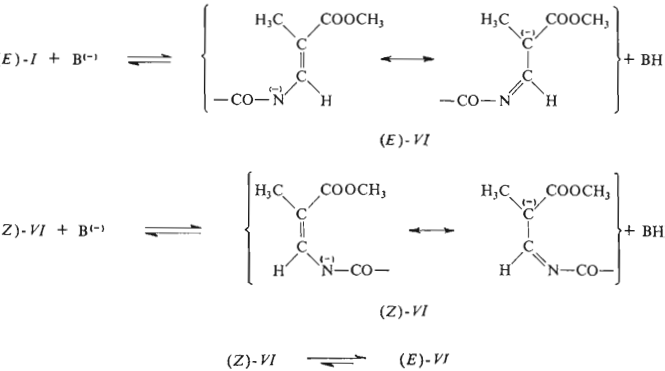
In order to identify the cyclization product of compounds *Ia* we prepared an authentic sample of 3,5-dimethyluracil by reaction of 1-acetyl-5-methyluracil with diazomethane, followed by hydrolysis of the acetyl group. This compound was already prepared by Guyot and coworkers[16] by another procedure.



V

SCHEME 1

Cyclization of ethyl 3-(N'-alkylureido)-2-butenoates was suggested to involve deprotonation of the terminal NH group, nucleophilic attack of the ethoxycarbonyl electrophilic center by the amide anion and loss of the ethoxide anion[2]. This mechanism (involving the transition state *V*) can be visualized also for the base-catalyzed cyclization of the ureides *Ia*–*Ic* of the (*Z*)-configuration (Scheme 1). The (*E*)-isomers of *Ia*–*Ic* can cyclize only after the isomerization which is probably initiated by deprotonation of the non-terminal NH group under formation of the mesomeric anion (*E*)-*VI* (Scheme 2).



SCHEME 2

Decrease in the $C_{(2)}$—$C_{(3)}$ bond order facilitates the configurational inversion leading to an equilibrium mixture of the (*E*)- and (*Z*)-anions *VI*. Since the proton transfer at the NH group is very fast[17] we can assume that the inversion around the C—C bond is the rate determining step of the isomerization and thus of the transformation of the (*E*)-isomers into uracil derivatives. The difficult cyclization of compounds *Ic* and *Id* can be explained by a steric effect of the isopropyl and tert-butyl groups. However, a tert-butyl group may not necessarily hinder the cyclization mechanism, as shown by the described[8] cyclization of ethyl 3-(N′-tert-butylureido)-2-butenoate to the corresponding substituted uracil. The non-reactivity of thioureides in alkaline medium is surprising because, by analogy with the cyclization of ethyl 2-thioureido-2-butenoate[18], the product might well be 2-tert-butylamino-5-methyl-6-oxo-1,3-thiazine whose formation should not be affected by steric effect of the tert-butyl group.

TABLE VII

Yields, melting points and elemental analyses of compounds *Ia*—*Ie*

Compound	Yield, %	M.p., °C	Formula (mol.wt.)	Calculated/Found		
				% C	% H	% N
E-Ia	3·2	177—182[a]	$C_7H_{12}N_2O_3$	48·83	7·03	16·27
			(172·2)	49·17	7·21	16·28
Z-Ia	3·5	87—92[b]	—	48·44	7·09	16·15
E-Ib	58·7	170—171[c]	$C_{13}H_{16}N_2O_3$	62·89	6·50	11·28
			(248·3)	62·90	5·56	11·30
Z-Ib	40·3	112[c]	—	62·72	6·55	11·32
E-Ic	41·7	153—156[d]	$C_9H_{16}N_2O_3$	53·98	8·06	13·99
			(200·2)	54·17	8·21	14·13
Z-Ic	5·9	96—102[e]	—	53·95	8·04	13·69
E-Id	46·5	150—159[d]	$C_{10}H_{18}N_2O_3$	56·05	8·47	13·08
			(214·3)	56·15	8·84	13·82
Z-Id	22·1	66—76[f]	—	56·63	8·68	12·87
E-Ie	13·3	181—182[a]	$C_{10}H_{18}N_2O_2S$[h]	52·12	7·88	12·17[h]
			(230·2)	51·76	7·98	12·46
Z-Ie	8·5	121—122[g]	—	52·27	7·99	12·33

[a] Ethyl acetate; [b] diethyl ether; [c] methanol; [d] toluene; [e] sublimed at 140°C/2·3 kPa; [f] sublimed at 160°C/2·3 kPa; [g] cyclohexane; [h] calculated: 13·93% S; found for (*E*)-*Ie* and (*Z*)-*Ie* 13·96% S and 13·90% S, respectively.

EXPERIMENTAL

Melting points were determined on a Kofler block. The analytical samples were dried at 25°C/6·5 Pa for 8 h. The ^{1}H NMR spectra were taken on a Tesla BS 467 (60 MHz) instrument in deuteriochloroform (internal standard tetramethylsilane) or hexadeuteriodimethyl sulfoxide (internal standard hexamethyldisiloxane); chemical shifts are given in the δ scale. UV spectra were recorded on a Specord UV VIS spectrometer, IR spectra on a UR-10 instrument (both Karl Zeiss, Jena). Thin-layer chromatography was carried out on Silufol UV_{254} sheets (Kavalier, Votice, Czechoslovakia). Analytical chromatography was performed on a high performance liquid chromatography (HPLC) instrument made in the workshops of the Institute (0·4 × 25 cm column packed with silica gel; UV detection at 254 nm, eluant n-heptane–1-propanol). N-Methyl-, N-benzyl- and N-isopropylurea were prepared by reaction of potassium cyanate with the corresponding amine hydrochlorides. N-Tert-butylurea[19] and N-tert-butylthiourea[20] were prepared by the described procedures.

Methyl 3-(N'-Alkylureido)-2-methyl-2-propenoates *Ia—Id*

Methyl 3-methoxy-2-methyl-2-propenoate[21] (2·60 g; 20 mmol) was added at room temperature to a stirred suspension of N-alkylurea (20 mmol) in 5M-HCl (15 ml). The ureides *Ib—Id* deposited as solids or oils after standing for 30 min at room temperature. After 2 h the mixture was diluted with water (15 ml) and extracted with ethyl acetate (3 × 100 ml). The organic layer was washed with a saturated solution of sodium hydrogen carbonate, dried over sodium sulfate and taken down *in vacuo*. Crystallization of the residue from methanol (*Ib*) or toluene (*Ic*, *Id*) afforded the pure (*E*)-isomer. Chromatography of the mother liquors on a column of silica gel (150 g) in benzene–ethyl acetate (2 : 1) gave the (*Z*)-isomer and another portion of the (*E*)-isomer. In the case of *Ia*, the mixture of stereosiomers was not crystallized but directly chromatographed on a silica gel column in benzene–ethyl acetate (1 : 1). The (*Z*)-isomer was isolated from the corresponding fractions by distillation at 135°C/2·4 kPa and crystallization from diethyl ether, the (*E*)-isomer of *Ia* was isolated by crystallization from ethyl acetate. For yields, melting points and elemental analyses see Table VII.

Methyl 3-(N'-Tert-butylthioureido)-2-methyl-2-propenoates (*Ie*)

Reaction of tert-butylthiourea (1·32 g; 10 mmol) with methyl 3-methoxy-2-methyl-2-propenoate (1·32 g; 10 mmol) in 5M-HCl (15 ml) according to the above-described procedure afforded a mixture of (*E*)- and (*Z*)-isomers which were separated on a column of silica gel in benzene–ethyl acetate (3 : 1). For yields, analyses and physical properties see Table VII.

Methyl 3,3'-Ureylenebis(2-methyl-2-propenoate) (*IVa*)

Methyl 3-methoxy-2-methyl-2-propenoate (2·602 g; 20 mmol) was added to a stirred solution of urea (1·201 g; 20 mmol) in 5M-HCl (10 ml) In the course of 10 min the ester dissolved and after other 10 min the product began to deposit. After standing for 12 h at room temperature the mixture was diluted with water (25 ml), the product collected on filter, washed with water and crystallized from aqueous methanol (1 : 1); yield 0·996 g (19·5%). Mother liquors afforded further portion of the product (0·114 g). According to thin-layer chromatography on silica gel in benzene–ethyl acetate (1 : 1), the product from the mother liquors contained small amount of a compound of higher mobility. M.p. 238°C (aqueous methanol). IR spectrum (in chloroform), cm^{-1}: 3 438, 3 366 (NH); 1 739, 1 705 (C=O); 1 658, sh 1 642 (C=C). UV spectrum (ethanol–0·1M-HCl,

5/95): λ_{max} 234 nm and 297 nm (log ε 4·68 and 4·54); (ethanol–0·01M-NaOH, 5/95): λ_{max} 296 nm and 334 nm (log ε 4·45 and 4·31). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 2·70 (s, CH_3—C=); 3·58 (s, CH_3O—), 7·33 (d, —CH=, J(CH, NH) = 6 Hz), 9·02 (d, NH, J(NH, CH) = 6 Hz). For $C_{11}H_{16}N_2O_5.2\,H_2O$ (292·23) calculated: 45·20%, 6·90% H, 9·58% N; found: 45·47% C, 7·05% H, 9·74% N. Drying at 100°C/6·5 Pa for 8 h afforded the anhydrous product. For $C_{11}H_{16}.N_2O_5$ (256·3) calculated: 51·56% C, 6·24% H, 10·97% N; found: 51·06% C, 6·25% H, 10·91% N.

Reaction of ester III *with excess of urea.* Methyl 3-methoxy-2-methyl-2-propenoate (1·301 g; 20 mmol) was added at room temperature in the course of 5 min to a stirred solution of urea (12·01 g; 200 mmol) in 5M-HCl (120 ml). The above-described work-up procedure afforded 1·212 g (20·7%, based on the ester) of the product, m.p. 238°C; without depression on admixture with a product prepared in the preceding experiment.

Methyl 3,3′-Thioureylenebis(2-methyl-2-propenoate) (*IVb*)

Reaction of methyl 3-methoxy-2-methyl-2-propenoate (2·602 g; 20 mmol) with thiourea (1·522 g; 20 mmol), according to the above-described procedure afforded 1·84 g (31·7%) of the *IVb* monohydrate, m.p. 229—230 °C (aqueous methanol). UV spectrum (ethanol–0·1M-HCl, 1 : 1): λ_{max} 322 nm (log ε 4·52); (in ethanol–0·1M-NaOH, 1 : 1): λ_{max} 221 nm and 358 nm (log ε 4·00 and 4·44), inflex 317 nm (log ε 4·31). IR spectrum (chloroform), cm^{-1}: 3 402, 3 358, 3 329 (NH); 1 707, sh 1 693 (C=O); 1 650 (C=C). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 1·84 (s, CH_3), 3·66 (s, CH_3O—), 7·26 (broad s, CH=); 8·41 (broad s, NH). For $C_{11}H_{16}.N_2O_4S.H_2O$ (290·34) calculated: 45·50% C, 6·25% H, 9·65% N, 11·04% S; found: 45·56% C, 6·34% H, 9·88% N, 10·71% S.

Reaction of (*E*)- and (*Z*)-Isomers in Alkaline Medium

Solutions of the compound in methanol (10^{-2}M; 200 µl) and 1M-CH_3ONa (200 µl) were pipetted into 2 ml ampoules which were sealed and kept at 30·0 ± 0·5°C. At appropriate time intervals the content was neutralized by addition of moist Dowex 50 (H^+). The filtered solution (10 µl) was then injected into an HPLC instrument. The (*E*) : (*Z*) ratios are given in Table I, kinetics of isomerization and cyclization of compounds *I* are depicted in Figs 1—3.

Acid Hydrolysis of Ureides

A $5 . 10^{-5}$M solution of the ureide in 1M-HCl was placed into a thermostated cell and kept at 24·95 ± 0·05°C. At 1 min intervals the absorbance of the solution at 270 nm was measured (Table II). In the case of compound (*E*)-*Id*, the solution was made alkaline with an equal amount of 2M-NaOH after 1 h. The alkaline solution exhibited an absorption maximum at 276 nm (absorbance 0·66) due probably to methyl 2-formylpropanoate enolate.

3,5-Dimethyluracil (*IIa*)

A solution of diazomethane in diethyl ether was added dropwise at room temperature to a stirred solution of 1-acetyl-5-methyluracil[22] (0·60 g; 3·6 mmol) in N,N-dimethylformamide (25 ml) until the evolution of nitrogen ceased. The yellowish solution was taken down *in vacuo*, the residue dissolved in methanol (15 ml) and mixed with 14% aqueous ammonia (5 ml). After evaporation, the residue was crystallized from ethanol, yielding 0·36 g (71%) of the compound *IIa*, m.p. 205°C (ethanol). UV spectrum (in 0·01M-HCl): λ_{max} 265 nm (log ε 3·86); (in 0·1M-NaOH):

λ_{max} 292 nm (log ε 4·01). ^{1}H NMR spectrum (in hexadeuteriodimethyl sulfoxide): 1·71 (d, 3 H, CH_3, $J(CH_3, 6) = 1·0$ Hz); 3·06 (s, 3 H, CH_3—N); 7·22 (q, 1 H, $H_{(6)}$, $J(6, CH_3) = 1·0$ Hz); 10·78 (br s, 1 H, $H_{(1)}$). For $C_6H_8N_2O_2$ (140·1) calculated: 51·42% C, 5·75% H, 19·99% N; found: 50·83% C, 6·61% H, 20·26% N. This product had the same chromatographic (HPLC) mobility and UV spectrum as the cyclization product from (*E*)- and (*Z*)-isomers of *Ia* in 0·5M--CH_3ONa.

3-Benzyl-5-methyluracil (*IIb*)

The (*E*)-isomer of *Ib* (0·745 g; 3 mmol) was refluxed with 0·5M-$NaOCH_3$ in methanol (40 ml) for 8 h. The mixture was neutralized with acetic acid, concentrated to one third of the original volume *in vacuo* and the concentrate diluted with the same amount of water. The product which separated on standing overnight at 0°C was crystallized from ethanol; yield 0·487 g (75%); m.p. 208—209°C (methanol). UV spectrum (in 0·01M-HCl): λ_{max} 267 nm (log ε 3·86); (in 0·1M--NaOH): λ_{max} 294 nm (log ε 4·03), IR spectrum (in KBr), cm^{-1}: 3 216, 3 174, 3 105 sh (NH); 1 712, 1 651 (C=O). ^{1}H NMR spectrum (in hexadeuteriodimethyl sulfoxide),: 1·73 (d, 3 H, CH_3, $J(CH_3, 6) = 1·0$ Hz); 4·90 (s, 2 H, CH_2—Ar); 7·24 (m, 5 H, H—Ar); 10·86 (br s, 1 H, NH). For $C_{12}H_{12}N_2O_2$ (216·3) calculated: 66·65% C, 5·59% H, 12·96% N; found: 66·56% C, 5·67% H, 13·17% N.

3-Isopropyl-5-methyluracil (*IIc*)

The (*E*)-isomer of *Ic* (0·40 g; 2 mmol) in methanolic 1M-$NaOCH_3$ (20 ml) was heated to 95°C in a sealed ampoule for 8 h. The mixture was taken down *in vacuo*, the residue dissolved in water and the product taken up in ethyl acetate. Evaporation of the solvent and crystallization from aqueous ethanol afforded 0·147 g (43·7%) of the compound *IIc*, m.p. 134—135°C. The analytical sample was sublimed at 95°C/9·3 kPa. UV spectrum (in 0·01M-HCl): λ_{max} 268 nm (log ε 3·85); (in 0·1M-NaOH): λ_{max} 294 nm (log ε 4·03). IR spectrum (in KBr), cm^{-1}: 3 330 sh, 3 220, 3 180 (NH); 1 714, 1 670 sh, 1 645 (C=O); 1 381, 1 365 (CH_3 in the isopropyl group). ^{1}H NMR spectrum (in hexadeuteriodimethyl sulfoxide): 1·30 (d, 6 H, N—$CH(CH_3)_2$, $J(CH_3, CH) = 7·0$ Hz; 1·69 (d, 3 H, CH_3, $J(CH_3, 6) = 1·0$ Hz); 4·95 (m, 1 H, N—$CH(CH_3)_2$, $J(CH, CH_3) = 7·0$ Hz); 7·15 (q, 1 H, $H_{(6)}$, $J(6, CH_3) = 1·0$ Hz); 10·57 (br s, 1 H, NH). For $C_8H_{12}N_2O_2$ (168·2) calculated: 57·13% C, 7·19% H, 16·66% N; found: 57·55% C, 7·26% H, 16·65% N.

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Translated by M. Tichý.