CONDENSATION REACTIONS OF 1,2,3,4-TETRAHYDRO-6-METHYL--2,4-DIOXO-5-PYRIMIDINECARBALDEHYDE

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Condensation reactions of 1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-5-pyrimidinecarbaldehyde with nine acid derivatives containing an active methylene group are described. The obtained products were characterized by their IR, UV, ^{1}H NMR, ^{13}C NMR and mass spectra. The stereochemistry of selected products was studied by ^{1}H and ^{13}C NMR spectroscopy.

Derivatives of 5-substituted uracil represent a large group of compounds of significant biological activity. Great attention has been paid to uracil derivatives substituted in position 5 with vinyl or other unsaturated group, particularly in connection with the synthesis of (*E*)-5-(2-bromovinyl)-2′-deoxyuridine and its antiviral properties[1,2]. Compounds of this type are often synthesized starting from 5-formyluracil[3] which is converted into the desired compounds by Wittig[4–7] and condensation reactions[8].

Isolation of sparsomycin[9] and discovery of its antitumor properties[10,11] have aroused interest in 6-methyl-5-substituted uracil derivatives. These are accessible by synthesis starting from 1,2,3,4-tetrahydro-6-methyl-2,4-dioxopyrimidine which is hydroxymethylated with formaldehyde[12] and the obtained 5-hydroxymethyl derivative *I* is subsequently oxidized[13] to give 1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-5-pyrimidinecarbaldehyde (*II*).

The approach published so far[13–15] makes use of the Wittig reaction. In this paper we study the synthesis of 6-methyl-5-vinyluracil derivatives under conditions of a classical Knoevenagel condensation which does not require alkyl substitution of the uracil nitrogen atoms.

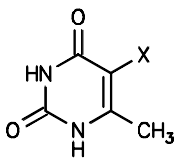
We have found that 1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-5-pyrimidinecarbaldehyde (*II*) reacts only with reactive CH-acids, i.e. derivatives of cyanoacetic acid, propanedinitrile and 2,2-disubstituted 1,3-dioxane-4,6-diones. Although the Knoevenagel condensation is carried out mostly in an anhydrous medium, its advantage consists in that it can be performed also in water, the products being deposited directly from the

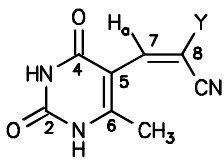
reaction mixture. Using this method, we prepared nine new substituted ethylene derivatives *III* in high yields.

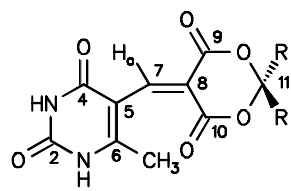
The structure of the synthesized compounds has been confirmed by elemental analyses (Table I) and spectral data (IR and UV spectra, ^1H and ^{13}C NMR spectra, mass spectra).

Infrared spectra of compounds *IIIa* – *IIIf* (Table II) exhibited characteristic but weak absorption bands in the region 2 207 – 2 243 cm^{-1} due to stretching vibrations ν(C≡N). All the studied derivatives displayed strong bands in the region 1 651 – 1 757 cm^{-1} characteristic of ν(C=O) stretching vibrations, and in the region 3 127 – 3 237 cm^{-1} due to ν(N–H) vibrations.

In the UV spectra (Table II) of the compounds we observed two absorption bands. One, relatively constant, band appeared at 264 – 267 nm (log ε ≈ 2.80 $m^2\ mol^{-1}$) and the second, more variable, at 310 – 355 nm (log ε > 3.00 $m^2\ mol^{-1}$). Comparison of UV spectra of unsubstituted 6-methyluracil with those of compounds *I* and *II* shows that introduction of the polar vinyl moiety results in marked bathochromic shift, which confirms its coplanarity with the uracil skeleton.







I, X = CH_2OH
II, X = CHO

	Y	R
IIIa	CN	–
IIIb	COOH	–
IIIc	$COOCH_3$	–
IIId	$COOCH_2CH_3$	–
IIIe	$CONH_2$	–
IIIf	$CONHNH_2$	–
IIIg	–	CH_3
IIIh	–	$-(CH_2)_4-$
IIIi	–	$-(CH_2)_5-$

The ^{13}C NMR signals were assigned on the basis of chemical shifts, direct coupling constants $^{1}J(C,H)$ and characteristic splitting due to long-range coupling. Some signals (C-2, C-8) were assigned using comparison with the literature data[16,17].

The presence of only one ^{1}H NMR signal of H_a observed for all the compounds indicates that only one geometric isomer has been formed.

The stereochemistry of the products was determined by ^{13}C NMR spectroscopy making use of the fact that the vicinal coupling constant $^{3}J(CN,H_a)$ is higer for the (*E*) than for the (*Z*) arrangement of the interacting nuclei. The found value of this coupling constant (13.3 Hz for *IIIb*, 13.8 Hz for *IIIc* and 13.4 Hz for *IIIf*) proves that the nitrile

TABLE I
Characteristic data of synthesized compounds *IIIa – IIIi*

Compound	M.p., °C Yield, %	Formula (M.w.)	Calculated/Found		
			% C	% H	% N
IIIa	246 – 247	$C_9H_6N_4O_2$	53.47	2.99	27.71
	89	(202.2)	53.52	2.91	27.58
IIIb	242 – 243	$C_9H_7N_3O_4$	48.88	3.19	19.00
	61	(221.2)	48.67	3.15	19.06
IIIc	260 – 261	$C_{10}H_9N_3O_4$	51.07	3.86	17.87
	91	(235.2)	51.01	3.91	17.94
IIId	235 – 236	$C_{11}H_{11}N_3O_4$	53.01	4.45	16.86
	87	(249.2)	52.93	4.37	16.73
IIIe	243 – 244	$C_9H_8N_4O_3$	49.09	3.66	25.45
	78	(220.2)	49.12	3.73	25.38
IIIf	269 – 270	$C_9H_8N_4O_3$	45.96	3.86	29.78
	81	(235.2)	46.11	3.81	29.74
IIIg	270 – 271	$C_{12}H_{12}N_2O_6$	51.43	4.32	10.00
	89	(280.2)	51.58	4.39	9.96
IIIh	241 – 242	$C_{14}H_{14}N_2O_6$	54.90	4.61	9.15
	84	(306.3)	54.85	4.70	9.10
IIIi	239 – 240	$C_{15}H_{16}N_2O_6$	56.25	5.04	8.75
	87	(320.3)	56.13	5.12	8.79

group and the olefinic proton H_a are in the *trans* relation and thus all the compounds are (*E*)-isomers. The *s-cis* arrangement of the multiple bond of the pyrimidinedione nucleus and the ethylenic bond follows unequivocally from the values of ^3J(C-4,H_a) (6.9 Hz for *IIIa*, 4.0 Hz for *IIIb*, 5.2 Hz for *IIIc* and 6.0 for *IIIh*). The *s-trans* arrangement is excluded also by the great steric interaction between the substituents on the ethylenic bond and the carbonyl group C(4)=O. The ^{1}H and ^{13}C NMR spectral data are given in Tables III and IV.

Mass spectra of all the compounds (Table V) displayed molecular peaks ($M^{+\bullet}$) of relative intensity 2.7 to 65%. Spectra of derivatives *IIIb* – *IIIe* exhibited intense fragment ions *m*/*z* 176 arising by loss of the carboxyl group. Compounds *IIIg*, *IIIh* and *IIIi* showed an ion *m*/*z* 222 formed by loss of the corresponding ketone (2-propanone from compound *IIIg*, cyclopentanone from *IIIh* and cyclohexanone from *IIIi*), and also fragments *m*/*z* 178 and 150 arising by subsequent decomposition of the 1,3-dioxane-4,6-dione residues.

TABLE II
UV and IR spectral data of compounds *I* – *III*

Compound	UV spectrum[a] λ_{max}, nm (log ε, m^2 mol^{-1})		ν_{max}(CN)[b], cm^{-1}
[c]	206 (2.93)	259 (2.97)	–
I	211 (2.82)	265 (2.84)	–
II	231 (2.90)	289 (3.05)	–
IIIa	265 (2.64)	339 (3.25)	2 224
IIIb	264 (2.80)	324 (3.16)	2 230
IIIc	265 (2.80)	330 (3.24)	2 232
IIId	264 (2.79)	329 (3.24)	2 230
IIIe	265 (2.82)	324 (3.17)	2 207
IIIf	255 (2.79)	310 (3.07)	2 243
IIIg	267 (2.70)	353 (3.06)	–
IIIh	266 (2.80)	355 (3.14)	–
IIIi	265 (2.79)	353 (3.11)	–

[a] Ethanol; [b] KBr; [c] 6-methyluracil.

TABLE III
^{1}H NMR chemical shifts of synthesized compounds *IIIa* – *IIIi* (δ, ppm)

Compound	CH_3	H_a	NH	Y	R
IIIa	2.36 s	7.93 s	11.65 bs, 12.03 bs	–	–
IIIb	2.30 s	7.92 s	11.51 bs, 11.63 bs	–	–
IIIc	2.27 s	7.96 s	11.55 bs, 11.78 bs	3.81 s	–
IIId	2.26 s	7.97 s	11.54 bs, 11.76 bs	1.28 t	–
IIIe	2.20 s	7.79 s	11.46 bs, 11.59 bs	4.27 q	–
IIIf	2.19 s	7.80 s	11.43 bs, 11.61 bs	–	–
IIIg	2.27 s	7.92 s	11.42 bs, 11.72 bs	–	1.74 s
IIIh	2.29 s	7.88 s	11.44 bs, 11.77 bs	–	1.73 – 2.14 m
IIIi	2.27 s	7.89 s	11.44 bs, 11.73 bs	–	1.35 – 2.19 m

TABLE IV
^{13}C NMR chemical shifts of synthesized compounds *IIIa* – *IIIi* (δ, ppm)

Compound	CH_3	C-2	C-4	C-5	C-6	C-7	C-8	Other signals
IIIa	17.6	149.5	160.3	104.5	162.1	152.5	80.1	115.9 (CN), 113.1 (CN)
IIIb	18.0	149.9	160.8	104.5	157.2	147.8	104.5	115.6 (CN), 188.5 (COO)
IIIc	18.0	149.9	160.7	104.3	158.3	148.4	104.5	115.0 (CN), 162.8 (COO), 53.1 (OCH_3)
IIId	18.1	149.9	160.7	104.4	158.1	148.4	105.0	115.0 (CN), 162.2 (COO), 62.1 (OCH_2), 14.1 (CH_2**CH**$_3$)
IIIe	17.9	150.1	161.1	104.5	155.8	144.0	110.3	115.9 (CN), 162.2 ($CONH_2$)
IIIf	18.6	150.1	163.4	103.1	153.9	140.7	116.2	115.8 (CN), 164.3 (CONH)
IIIg	17.6	149.9	160.3	104.5	157.9	145.4	106.0	159.7 (COO), 162.2 (COO), 116.8 (C-11), 26.8 (CH_3)
IIIh	17.6	149.8	160.3	105.8	158.4	144.9	117.2	160.4 (COO), 162.8 (COO), 113.3 (C-11), 37.6 (C-12), 22.9 (C-13)
IIIi	17.6	149.9	160.4	105.0	157.8	144.9	106.0	159.7 (COO), 162.1 (COO), 117.3 (C-11), 35.3 (C-12), 23.5 (C-13), 22.0 (C-14)

EXPERIMENTAL

Apparatus

Infrared spectra were recorded on an FTIR PU 9802/25 Philips spectrometer using the KBr technique, UV spectra were taken on a Specord M 40 instrument (Zeiss, Jena) in ethanol, concentration $1 \cdot 10^{-4} - 1 \cdot 10^{-5}$ mol dm^{-3}. Proton NMR spectra were obtained with a BS 587A Tesla (80 MHz) and an FT NMR Varian VXR-300 (300 MHz) spectrometer in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. ^{13}C NMR spectra were measured on a Varian VXR-300 spectrometer (at 75.43 MHz) in hexadeuteriodimethyl sulfoxide. In addition to the fully decoupled carbon spectra ^{13}C–(^{1}H), for compounds *IIIa – IIIc*, *IIIf* and *IIIh* we applied also the APT technique and gated decoupling with NOE in which all interactions J(C,H) are preserved; we also made use of a selective INEPT experiment[18] in order to assign unequivocally some of the carbon signals.

Mass spectra were taken on an MS 902-S instrument (AEI Manchester); direct inlet, ionizing electron energy 70 eV, 100 μA, ion source temperature 160 – 220 °C.

1,2,3,4-Tetrahydro-6-methyl-2,4-dioxo-5-hydroxymethylpyrimidine (*I*) was synthesized according to the literature[12] in 72% yield; m.p. 310 – 312 °C (reported[12] m.p. 305 – 310 °C). 1,2,3,4-Tetrahydro-6-methyl-2,4-dioxo-5-pyrimidincarbaldehyde (*II*) was prepared in 69% yield as described[13]; m.p. 297 – 299 °C (reported[13] m.p. >200 °C).

TABLE V
Mass spectral data of compounds *IIIa – IIIi*

Compound	*m/z* (relative abundance)[a]
IIIa	202 ($M^{+\bullet}$, 65), 175 (14), 159 (45), 134 (17), 133 (13), 132 (23), 118 (16), 89 (11), 44 (73), 42 (100), 28 (66)
IIIb	221 ($M^{+\bullet}$, 6.6), 177 (47), 176 (19), 150 (20), 134 (18), 106 (34), 105 (25), 93 (17), 64 (12), 44 (100), 42 (60), 28 (32)
IIIc	235 ($M^{+\bullet}$, 25), 203 (88), 176 (100), 161 (10), 160 (13), 133 (30), 123 (9), 44 (58), 42 (90), 31 (48), 28 (92)
IIId	249 ($M^{+\bullet}$, 24), 204 (40), 203 (98), 177 (44), 176 (100), 133 (40), 57 (44), 55 (28), 44 (68), 42 (84), 31 (58), 28 (64)
IIIe	220 ($M^{+\bullet}$, 13), 203 (100), 176 (57), 160 (22), 123 (26), 71 (20), 69 (20), 57 (33), 55 (24), 44 (89), 42 (61), 28 (57)
IIIf	235 ($M^{+\bullet}$, 23), 195 (26), 152 (100), 151 (43), 68 (33), 55 (27), 52 (26), 45 (25), 42 (68), 31 (63), 28 (41)
IIIg	280 ($M^{+\bullet}$, 19), 222 (44), 178 (38), 150 (83), 100 (34), 81 (61), 44 (100), 43 (94), 31 (59), 28 (97)
IIIh	306 ($M^{+\bullet}$, 10), 213 (31), 212 (26), 178 (35), 150 (35), 84 (38), 56 (29), 55 (100), 44 (77), 41 (35), 28 (59)
IIIi	320 ($M^{+\bullet}$, 2.7), 222 (20), 178 (15), 150 (24), 98 (53), 69 (38), 55 (90), 44 (95), 42 (60), 32 (65), 31 (100), 28 (65)

[a] The table lists relative abundances of $M^{+\bullet}$ and 9 – 11 most intense peaks.

Derivatives of 2-Cyano-3-(1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-5-pyrimidyl)propenoic Acid (*IIIb – IIIf*)

Boiling water (20 ml) was added to a boiling solution of the cyanoacetic acid derivative (10 mmol) and β-alanine in ethanol or methanol (10 ml). To this solution a hot solution (90 – 100 °C) of 1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-5-pyrimidinecarbaldehyde (*II*; 10 mmol) in water (80 ml) was added slowly with stirring. The reaction mixture was then stirred at room temperature for 24 h, the deposited crystals were collected, washed with cold methanol and crystallized from water.

2-(1,2,3,4-Tetrahydro-6-methyl-2,4-dioxo-5-pyrimidylmethylidene)propanedinitrile (*IIIa*) and 2,2-disubstituted 5-(1,2,3, 4-tetrahydro-6-methyl-2,4-dioxo-5-pyrimidylmethylidene)-1,3-dioxane-4,6-diones (*IIIg – IIIi*) were prepared in the same manner. For elemental analyses, yields and melting points see Table I. The spectral data are given in Tables II – V.

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