

Reactivity of Nucleophilic Uracil Derivatives

Géraldine Grangier [a], David J. Aitken [a], Dominique Guillaume [a],
Alain Tomas [b], Bernard Viossat [b] and Henri-Philippe Husson [a]*

[a] Laboratoire de Chimie Thérapeutique, URA 1310 du CNRS, and [b] Laboratoire de Physique,
Faculté des Sciences Pharmaceutiques et Biologiques,
4 avenue de l'Observatoire, 75270 Paris cedex 06, France
Received May 4, 1994

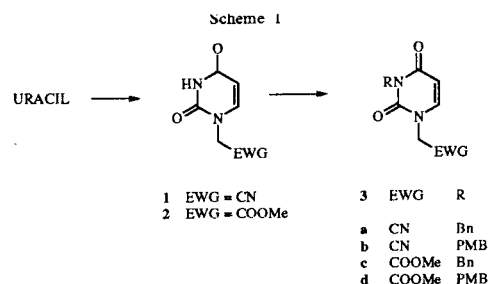
The reactivity of uracil derivatives bearing acidic methylene groups at N1 was investigated. On treatment with strong base, compounds with nitrile as the activating group underwent extensive dimerisation to give new tricyclic systems. Ester-activated compounds also produced dimers in the absence of an external electrophile, but their monomeric carbanions could be trapped by prompt addition of benzyl bromide to give normally alkylated products.

J. Heterocyclic Chem., **31**, 1707 (1994).

In recent years, the search for new chemotherapeutic agents, particularly those with anti-viral activity, has stimulated tremendous efforts in the synthesis of nucleoside analogs [1-3]. The diversity of molecular structures of interest in this field has broadened beyond the scope of sugar chemistry, and compounds in which the ribofuranose ring had been replaced by carbocyclic [4-6] or acyclic [7,8] functions have shown interesting or promising pharmacological activities. A common feature of traditional synthetic methodologies is the condensation of a nucleic base with the ribose moiety or its surrogate at a late stage in the synthetic sequence [9,10]. This approach is not always the most convenient, and in some cases the heterocyclic base has been assembled on the ready-formed sugar analog [4,11]. We have undertaken a research program investigating an original alternative strategy, in which the synthesis begins with the heterocyclic base, onto which various other carbon chains and functions are constructed progressively as required.

We have previously studied the functionalization of active aminomethylene compounds *via* deprotonation-alkylation procedures [12-14]. In this paper we report on the extension of this chemistry to the special cases of pyrimidine heterocycles. Compounds of this type give rise to synthons with dual reactivity, with nucleophilic side chain α -carbanions and electrophilic Michael acceptor centers at C6. The success of our synthetic strategy depends entirely on differentiation of these two types of reactivity. To test the system, uracils **3a-d** were selected, bearing N1 methylene groups activated by nitrile or carboxylic ester, each protected at N3 with a benzyl (Bn) or *p*-methoxybenzyl (PMB) group. These compounds were prepared conveniently *via* **1** and **2** by known procedures [15-17] or appropriate modifications thereof (Scheme 1).

Initial experiments were carried out to investigate the self-condensation reactivity of compounds **3** under



strongly basic conditions. Further experiments were performed in an attempt to trap newly formed anions with a representative external electrophile, benzyl bromide. The results of these studies are presented in Tables 1 and 2, respectively, and all product structures are shown in Scheme 2. The ^1H and ^{13}C nmr spectral data for new dimeric compounds are listed in Table 3 and Table 4 respectively.

Nitrile Series.

Treatment of **3a** and **3b** with LDA/HMPA at -70° gave

Table 1.

Products Isolated on Treatment of **3** with LDA/HMPA (Yields %)

	Recovered 3	4	5
3a	15	24	41
3b	21	10	53
3c	33	-	48
3d	24	-	62

Table 2.

Products Isolated on Treatment of **3** with LDA/HMPA then PhCH_2Br (Yields %)

	Recovered 3	4	5	6	7	8
3a	5	27	-	5	25	-
3b	8	16	12	14	6	20
3c	38	-	-	39	-	-
3d	34	-	-	48	-	-

orange/yellow anion solutions, which were left alone for 3 hours then quenched with aqueous ammonium chloride. Mixtures of unreacted starting material (15-20%) and dimeric adducts (60-70%) were obtained (Table 1). Two types of dimers were identified: single Michael-addition products **4a** and **4b**, and tricyclic structures **5a** and **5b**. In the absence of other electrophiles, anionic intermediates **I** are therefore capable of undergoing self-condensation reactions *via* **II**, **III** and/or **IV**. These reactions were incomplete after the 3 hour period, however, which suggested that alkylation of **I** with a sufficiently reactive external electrophile should be possible.

In the event, treatment of **3a** and **3b** with LDA/HMPA at -70° followed rapidly (10-15 minutes) by benzyl bromide gave only small quantities (<15%) of the desired alkylation products **6a** and **6b** (Table 2). Michael adducts **4a** and **4b** were again isolated, this time as mixtures of diastereoisomers, accompanied by small amounts of starting material (<10%). The tricyclic system was also present, in non-alkylated **5b** or mono-alkylated **7a** and **7b** forms. The mono-alkylation site (C5 of the uracil which behaved as the first Michael acceptor) suggested equilibration of intermediate **III** to **IV** before alkylation. From **3b**, a symmetrical dialkylated double-Michael adduct **8b** was isolated as a single stereoisomer.

It was noteworthy that none of the dimers was alkylated α - to a nitrile group (C7 or C7') even though intermediates **II**, **III** and **IV** were presumably still deprotonated at these carbon centers. Benzyl groups were invariably introduced α - to amide carbonyl groups, to give structures **7** and **8**. Two reactivity trends can be deduced from the product distribution: Michael condensations take place more rapidly than alkylation, and the carbanions thus formed are more readily alkylated than their α -nitrile counterparts. These combined features make control of condensation reactions difficult, resulting in poor yields of simple alkylated products **6**.

Ester Series.

Reactions of **3c** and **3d** were more straightforward. In the LDA/HMPA experiments (Table 1), only the tricyclic double-Michael products **5c** and **5d** were obtained (50-65%). As in the nitrile series, sufficient starting material was recovered (25-35%) upon quenching after 3 hours to allow some optimism for the electrophilic trapping experiments. Indeed, when freshly-generated anion **I** was treated with benzyl bromide, the desired alkylation products **6c** and **6d** were isolated in acceptable yields (40-50%), accompanied only by unreacted starting material (Table 2). None of the dimeric structures was obtained. The carboxylic ester function evidently reverses the reac-

tivity trend for the nitrile group, and allows interception of intermediate **I** before Michael condensations can take place, provided the electrophile is added rapidly to the reaction mixture.

Dimers **5** and **7** represent an original heterocyclic system for which several diastereoisomeric forms were evidenced. Structures **5a-d** were deduced from their ^{13}C nmr spectra. No olefinic pyrimidine carbon signals were present, while four CH_2 and four CH resonances were observed in the region δ 30-70 ppm in a DEPT experiment. The ^{13}C nmr spectra of compounds **7a** and **7b** in the range δ 30-70 ppm displayed similar signals to those of **5a** and **5b**, with the exception of the lack of one CH (*c.* 45 ppm) and the appearance of a new CH_2 (*c.* 41 ppm) and a quaternary carbon (*c.* 53 ppm). These modifications, together with additional resonances around δ 128-130 ppm, indicated the substitution of the tricyclic system by an extra benzyl group, which could be located at either C7 or C5'. The latter position was deduced from the ^1H - ^1H COSY spectrum which indicated an isolated geminal AB system (C7') and two isolated vicinal systems corresponding to a CH_2 - CH unit (C5-C6) and a CH - CH unit (C6'-C7).

Determination of the structure of **8b** turned out to be more problematic since its ^{13}C nmr spectrum displayed 17 resonances (6 upfield and 11 downfield) and its ^1H nmr spectrum displayed 19 different proton signals. These data might have been attributed to a benzylated monomer, but the C_i symmetrical dimeric structure **8b** was deduced by an X-ray crystallographic study (Figure 1). Lists of positional parameters (Table 5) and bond lengths and angles (Table 6) are presented. The two uracil-derived rings adopt twist chair conformations, in which the sp^3 carbons C5 and C6 lie above and below the plane defined by the four other atoms. The central six-membered ring adopts a chair conformation. Remarkably, the four substituents (two benzyls and two nitriles) borne by skeletal sp^3 carbons are in axial positions.

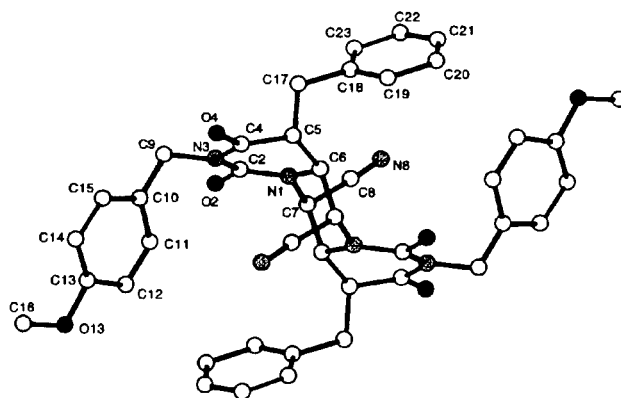


Figure 1. X-ray structure of **8b**.

Table 3 (continued)

		5c						5d							
H5	2.77	dd	16.0, 4.6	2.85	dd	15.8, 13.2	2.62	dd	15.9, 13.8	2.83	dd	15.8, 11.8	2.54	dd	15.7, 14.1
	3.13	dd	16.0, 13.7	3.02	dd	15.6, 3.7	3.10	dd	15.9, 4.0	3.00	dd	15.8, 3.9	3.04	dd	15.8, 3.9
H5'	3.53	t	7.3	3.22	dd	9.7, 6.3	3.31	dd	10.7, 3.6	3.20	dd	9.9, 5.9	3.21	dd	10.6, 3.4
H6	4.33	ddd	13.7, 7.3, 4.6	4.07	m		4.83	m		3.99	m		4.68	m	
H6'	4.19	dd	7.3, 4.6	4.29	d	6.2	4.28	dd	10.7, 7.7	4.27	d	5.9	4.21	dd	10.5, 7.7
H7	4.66	d	4.6	4.67	s		4.87*			4.65	s		4.75	d	8.1
H7'	4.06	d	18.0	4.05	d	17.8	3.64	d	17.9	4.01	d	17.8	3.57	d	17.8
	4.40	d	18.0	4.40	d	17.8	4.81	d	17.7	4.41	d	17.8	4.69	d	17.2
EWG	3.71	s		3.66	s		3.21	s		3.70	s		3.16	s	
	3.75	s		3.75	s		3.78	s		3.78	s		3.70	s	
CH ₃ O										3.72	s		3.70	s	
										3.74	s		3.71	s	
CH ₂	4.77	d	15.0	4.81	d	14.7	4.91	m		4.71	d	13.8	4.59	d	14.1
	4.95	s		4.86	d	14.5				4.78	d	13.8	4.70	d	14.3
	4.97	d	15.0	4.94	d	14.4				4.86	d	13.8	4.79	d	14.4
				5.00	d	14.2				4.92	d	13.8	4.83	d	13.8
H _{Ar}	7.26	m		7.24	m		7.32	m		6.78	d	7.9	6.74	d	8.0
										7.26	d	7.9	6.75	d	8.0
													7.25	d	8.0
													7.28	d	8.0
		7a [b]				7b				8b [c]					
H5		2.91	dd	15.5, 3.8		2.80	dd	15.3, 14.1		2.58	m				
H5'		3.27	dd	15.6, 13.8		2.98	dd	15.6, 4.0							
H6		4.86	dd	13.5, 3.3		4.57	dd	13.7, 3.9		3.27	dd	6.5, 3.7			
H6'		4.79	d	7.5		3.99	d	7.1							
H7		5.83	d	7.6		5.35	d	7.3		5.00	d	3.6			
H7'		4.29	d	17.6		3.76	d	17.1							
		4.39	d	17.7		4.03	d	17.5							
CH ₂ Ph		3.04	d	13.1		2.65	d	13.1		2.37	dd	14.1, 7.3			
		3.15	d	13.2		3.10	d	13.0		2.72	dd	14.0, 4.7			
		6.92	d	7.1		6.69	d	7.9		6.97	m				
		7.09	t	7.4		6.98	t	7.9							
		7.20	t	7.4		7.15	t	7.9							
CH ₃ O						3.72	s			3.18	s				
						3.75	s								
CH ₂		4.54	d	14.4		4.71	d	14.1		4.76	d	13.9			
		4.68	d	14.4		4.73	s			4.95	d	13.9			
		4.75	d	15.2		4.90	d	14.1							
		4.86	d	15.2											
H _{Ar}		7.32	m			6.79	t	7.9		6.71	d	8.7			
						7.29	d	7.9		7.45	d	8.7			
						7.37	d	7.9							

[a] Spectra recorded in deuteriochloroform unless otherwise indicated. Chemical shift data are followed by multiplicities and observed coupling constants when calculable. Multiple data are given for compounds for which several diastereoisomers were isolated. Resonances marked with an asterisk (*) were obscured by other signals but were detected in 2D correlation experiments. [b] Recorded in DMSO-d₆. [c] Recorded in benzene-d₆.

Table 4.
¹³C NMR Spectral Data for New Dimeric Compounds [a]

	4a		4b		5a[b]		5b	
C2	150.5	150.7	150.6	150.7	151.6	150.8	150.7	151.1
C2'	151.4	151.3	151.3	151.2	152.3	150.8	151.1	151.5
C4	161.2	160.9	160.1	160.5	166.9	164.3	165.9	164.3
C4'	165.5	165.3	165.2	165.1	169.2	167.1	166.9	167.2
C5	104.6	104.8	104.8	105.0	34.3	33.5	37.4	37.4
C5'	33.0	32.5	33.2	32.5	44.4	43.9	45.3	48.1
C6	138.5	138.1	138.2	137.8	53.3	53.0	52.8	54.4
C6'	53.6	53.3	53.5	53.3	59.6	58.7	54.6	58.4
C7	51.0	49.7	51.1	49.7	51.8	51.2	50.0	51.5

Table 4 (continued)

	4a		4b		5a[b]		5b			
C7'	36.5	35.9	36.2	35.8	37.5	36.0	35.8	35.2		
EWG	113.2	113.6	113.0	113.5	117.3	114.8	113.6	114.7		
	114.5	114.9	113.0	114.7	117.6	115.8	115.0	115.2		
	5c		5d		7a [b]		7b		8b	
C2	151.7	151.1	151.7	151.2	151.1	150.9	149.7	151.4		
C2'	151.7	152.5	151.7	152.5	151.1	152.3	151.4			
C4	165.3	164.8	166.8	167.5	166.8	169.2	167.2	167.0		
C4'	167.7	165.3	167.4	164.7	167.4	169.2	170.4			
C5	33.8	37.1	38.3	37.1	38.1	34.6	34.3	43.5		
C5'	44.3	48.6	45.1	48.6	45.0	53.2	52.6			
C6	53.6	54.0	53.8	54.0	53.7	57.5	57.1	51.3		
C6'	58.5	57.9	54.8	57.8	54.7	60.5	60.4			
C7	63.6	63.8	59.9	63.3	59.8	51.2	50.0	47.4		
C7'	48.5	47.0	48.5	46.9	48.2	37.1	35.5			
EWG	168.7	167.6	167.8	168.6	168.5	116.0	113.9	113.0		
	169.7	168.6	168.7	168.6	169.0	116.6	114.5			
	52.6	52.4	52.5	52.5	52.5					
	53.1	53.3	52.8	53.4						
CH ₂ Ph						40.6	41.3	35.1		
						128.4	128.5	127.8		
						129.1	128.8	128.6		
						130.2	129.1	129.6		
						134.7	132.3	135.0		

[a] Spectra recorded in deuteriochloroform unless otherwise indicated. Primed and non-primed data may be interchanged for C2 and C4. Multiple data are given for compounds for which several diastereoisomers were isolated and identified. All compounds **a** and **c** have the following additional resonances from each of their N3 and N3' benzyl groups: 44.4 (CH₂), several signals 127-130 (CH_{Ar}), 136.8 (C_{Ar}); all compounds **b** and **d** have the following additional resonances from each of their N3 and N3' *p*-methoxybenzyl groups: 44.2 (CH₂), 55.2 (OCH₃), 114.1 (CH_{Ar}), 128.3 (C_{Ar}), 130.9 (CH_{Ar}), 159.2 (C_{Ar}). Non-equivalent N3 and N3' functions usually produce two distinct signal sets. Figures fall in the range ± 0.5 ppm for all cases, except for spectra recorded in DMSO-d₆ in which N3 and N3' benzylic CH₂ and *ipso*-C resonances move downfield by 1.0 ppm. [b] Recorded in DMSO-d₆.

Table 5

Positional Parameters (x10⁴) and Mean Recalculated Isotropic Factors (x10³) for Non-hydrogen Atoms of Compound **8b**

Atom	X	Y	Z	U _{eq}
O2	6106 (4)	-597 (5)	5435 (1)	41 (4)
O4	7465 (4)	4818 (5)	5168 (1)	53 (4)
O13	7148 (7)	3198 (7)	7553 (2)	113 (8)
N1	8280 (5)	135 (5)	4941 (1)	28 (4)
C2	6993 (7)	467 (7)	5234 (2)	31 (6)
N3	6758 (5)	2131 (6)	5296 (1)	31 (5)
C4	7661 (6)	3416 (8)	5070 (2)	36 (6)
C5	8747 (7)	2967 (6)	4665 (2)	34 (6)
C6	9499 (6)	1361 (6)	4733 (2)	28 (5)
C7'	11158 (6)	1501 (6)	5016 (2)	31 (6)
N8'	10814 (6)	2801 (6)	5845 (2)	60 (6)
C8'	10974 (6)	2221 (7)	5489 (2)	36 (6)
C9	5386 (7)	2507 (8)	5619 (2)	41 (6)
C10	5937 (7)	2772 (8)	6127 (2)	45 (7)
C11	6808 (11)	1704 (10)	6366 (3)	86 (10)
C12	7202 (12)	1881 (12)	6835 (3)	105 (13)
C13	6697 (9)	3132 (13)	7073 (3)	80 (10)
C14	5894 (11)	4289 (13)	6856 (3)	103 (12)
C15	5485 (10)	4051 (12)	6373 (3)	87 (12)
C16	6487 (10)	4377 (15)	7840 (3)	126 (14)
C17	7607 (8)	2972 (8)	4223 (2)	48 (7)
C18	8318 (9)	2309 (8)	3785 (2)	55 (8)
C19	9834 (11)	2944 (10)	3620 (3)	81 (11)
C20	10474 (14)	2307 (17)	3206 (5)	128 (17)
C21	9584 (21)	1101 (22)	2974 (4)	152 (24)
C22	8110 (22)	451 (16)	3138 (5)	153 (24)
C23	7436 (11)	1034 (11)	3543 (3)	90 (11)

Table 6

Bond Distances (Å) and Angles (°) for Non-hydrogen Atoms of Compound **8b**

O2 -C2	1.213 (7)	C18 -C23	1.385 (11)
O4 -C4	1.209 (8)	C19 -C20	1.403 (15)
O13 -C13	1.412 (10)	C20 -C21	1.335 (21)
O13 -C16	1.406 (12)	C21 -C22	1.327 (24)
N1 -C2	1.371 (7)	C22 -C23	1.377 (17)
N1 -C6	1.456 (6)	C2 -N3	1.409 (7)
N3 -C4	1.378 (7)	N3 -C9	1.484 (7)
C4 -C5	1.509 (7)	C5 -C6	1.515 (7)
C5 -C17	1.552 (8)	C6 -C7'	1.546 (7)
C7' -C8'	1.480 (8)	N8' -C8'	1.129 (8)
C9 -C10	1.516 (8)	C10 -C11	1.355 (10)
C10 -C15	1.341 (11)	C11 -C12	1.374 (12)
C12 -C13	1.325 (13)	C13 -C14	1.347 (13)
C14 -C15	1.420 (13)	C17 -C18	1.493 (9)
C18 -C19	1.354 (11)	N1 -C7	1.464 (6)
C13 -O13 -C16	118.3 (7)	C2 -N1 -C6	125.0 (4)
O2 -C2 -N1	122.6 (5)	O2 -C2 -N3	121.1 (5)
N1 -C2 -N3	116.3 (5)	C2 -N3 -C4	125.1 (4)
C2 -N3 -C9	116.8 (4)	C4 -N3 -C9	118.0 (4)
O4 -C4 -N3	121.0 (5)	O4 -C4 -C5	122.6 (5)
N3 -C4 -C5	116.0 (5)	C4 -C5 -C6	113.8 (4)
C4 -C5 -C17	105.4 (4)	C6 -C5 -C17	112.9 (4)
N1 -C6 -C5	111.0 (4)	N1 -C6 -C7'	110.4 (4)
C5 -C6 -C7'	114.4 (4)	C6 -C7' -C8'	112.6 (4)
C7' -C8' -N8'	178.2 (6)	N3 -C9 -C10	114.0 (5)
C9 -C10 -C11	122.9 (6)	C9 -C10 -C15	120.8 (6)

Table 6 (continued)

C11 -C10 -C15	116.2 (7)	C10 -C11 -C12	123.0 (8)
C11 -C12 -C13	119.5 (9)	O13 -C13 -C12	115.2 (8)
O13 -C13 -C14	123.5 (8)	C12 -C13 -C14	121.2 (9)
C13 -C14 -C15	117.6 (8)	C10 -C15 -C14	122.4 (8)
C5 -C17 -C18	115.4 (5)	C17 -C18 -C19	120.4 (6)
C17 -C18 -C23	120.3 (7)	C19 -C18 -C23	119.3 (7)
C18 -C19 -C20	119.5 (8)	C19 -C20 -C21	120.1 (12)
C20 -C21 -C22	120.9 (15)	C21 -C22 -C23	121.0 (14)
C18 -C23 -C22	119.3 (9)	N1 -C7 -C8	110.2 (4)
N1 -C7 -C6'	108.3 (4)	C2 -N1 -C7	115.9 (4)
C6 -N1 -C7	114.9 (3)		

In conclusion, several new heterocyclic systems have been obtained by facile self-condensation reactions of **3a** and **3b**. Through use of the different methylene-activating group in **3c** and **3d**, it was possible to control the dual nucleophile-electrophile activity, permitting selective reaction with an external electrophile. Extension of this methodology may prove to be of interest for the preparation of diverse pyrimidine derivatives and nucleoside analogs.

EXPERIMENTAL

General Procedures.

Melting point determination was performed without correction using a Reichert Thermovar apparatus. The ^1H (300 MHz) and ^{13}C (75 MHz) nmr spectra were recorded on a Bruker AC 300-P spectrometer using standard Bruker software. Chemical shifts (δ) were measured relative to internal solvent residues and are reported in ppm. Coupling constants (J) are reported in Hz. The ir spectra were recorded on a Perkin-Elmer FT 1600 spectrometer (ν in cm^{-1}). Chemical ionization mass spectra were recorded on a Nermag R 10-10 spectrometer using ammonia as the ionizing agent. Elemental analyses were performed by the I.C.S.N. Microanalytical Laboratory (CNRS, Gif-sur-Yvette, France). Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). *p*-Methoxybenzyl bromide was prepared according to the literature [18] and used directly without purification. Literature methods [15,16] were used to obtain compounds **1** [89% yield, mp 229° (water)] and **2** [72% yield; mp 193° (ethanol)], each in two steps from uracil. Diisopropylamine, diisopropylethylamine, acetonitrile, dichloromethane, THF and HMPA were dried and distilled under nitrogen by standard procedures immediately before use. All other solvents and reagents were used as supplied.

3-Benzyl-1-(cyanomethyl)uracil **3a**.

Based on the procedure of Singh [15], a suspension of **1** (0.47 g, 3.1 mmol) in acetonitrile (10 ml) containing benzyl bromide (0.37 ml, 3.1 mmol), potassium fluoride (1.26 g, 21.8 mmol), and TEBA-Cl (20 mg) was heated at reflux and monitored by tlc. After completion of the reaction (8 hours) solids were removed by filtration and the solvent evaporated. The crude product was purified by flash chromatography using cyclohexane-ethyl acetate (1:1), then crystallized from acetonitrile to give **3a** as colorless needles, yield 0.71 g (95%), mp 241° (acetonitrile); ms: m/z 259 ($\text{MH} + \text{NH}_3$)⁺, 242 (MH)⁺; ir: ν 3084, 1702, 1656; ^1H -nmr (deuteriochloroform): δ 4.55 (2H, s,

CH_2CN), 5.02 (2H, s, CH_2Ph), 5.81 (1H, d, $J = 8.3$, H5), 7.10 (1H, d, $J = 8.3$, H6), 7.22-7.37 (5H, m, Ph); ^{13}C -nmr (deuteriochloroform): δ 36.3 (CH_2CN), 44.5 (CH_2Ph), 103.5 (C5), 113.8 (CN), 127.8, 128.4, 128.7, (CH_{Ar}), 136.0 (C_{Ar}), 140.2 (C6), 150.6 (C2), 162.0 (C4).

Anal. Calcd. for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.76; H, 4.57; N, 17.52.

3-(*p*-Methoxybenzyl)-1-(cyanomethyl)uracil **3b**.

Following the procedure of Ozaki [17], a solution of **1** (0.61 g, 4.0 mmol), diisopropylethylamine (0.9 ml, 5.2 mmol) and *p*-methoxybenzyl bromide (0.97 g, 4.8 mmol) in acetonitrile (5 ml) was stirred at room temperature overnight. The mixture was filtered and evaporated to dryness. The crude product was purified by flash chromatography using cyclohexane-ethyl acetate (1:1) then crystallized from acetonitrile to give **3b** as colorless needles, yield 0.59 g (54%), mp 123° (acetonitrile); ms: m/z 289 ($\text{MH} + \text{NH}_3$)⁺, 272 (MH)⁺, 121 ($\text{MeOC}_6\text{H}_4\text{CH}_2$)⁺; ir: ν 3084, 3002, 2966, 1694, 1652; ^1H -nmr (deuteriochloroform): δ 3.69 (3H, s, CH_3), 4.51 (2H, s, CH_2CN), 4.96 (2H, s, CH_2OAr), 5.76 (1H, d, $J = 8.0$, H5), 6.75 (2H, d, $J = 8.7$, 2H_{Ar}), 7.07 (1H, d, $J = 7.9$, H6), 7.33 (2H, d, $J = 8.6$, 2H_{Ar}); ^{13}C -nmr (deuteriochloroform): δ 36.2 (CH_2CN), 43.9 (NCH_2Ar), 55.1 (CH_3), 103.5 (C5), 113.6 (CN), 113.7 (CH_{Ar}), 128.2 (C_{Ar}), 130.4 (CH_{Ar}), 140.1 (C6), 150.5 (C2), 159.1 (C_{Ar}), 161.9 (C4).

Anal. Calcd. for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.82; H, 4.98; N, 15.54.

3-Benzyl-1-(methoxycarbonylmethyl)uracil **3c**.

The procedure for **3a** was repeated using **2** as starting material. Product **3c** was obtained in 99% yield. Crystallization from chloroform afforded an analytical sample, mp 76°C (chloroform); ms: m/z 292 ($\text{MH} + \text{NH}_3$)⁺, 275 (MH)⁺; ir: ν 2955, 1749, 1708, 1666; ^1H -nmr (deuteriochloroform): δ 3.77 (3H, s, CH_3), 4.43 (2H, s, CH_2COO), 5.11 (2H, s, CH_2Ph), 5.78 (1H, d, $J = 7.9$, H5), 7.05 (1H, d, $J = 7.9$, H6), 7.28-7.42 (5H, m, Ph); ^{13}C -nmr (deuteriochloroform): δ 44.1 (CH_2Ph), 49.6 (CH_2CO), 52.6 (CH_3), 101.9 (C5), 127.4, 128.2, 128.3 (CH_{Ar}), 136.3 (C_{Ar}), 142.3 (C6), 151.3 (C2), 162.5 (C4), 167.7 (COOMe).

Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_4$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.17; H, 5.12; N, 10.01.

3-(*p*-Methoxybenzyl)-1-(methoxycarbonylmethyl)uracil **3d**.

The procedure for **3b** was repeated using **2** as starting material. Product **3d** was obtained in 91% yield, as a pale oil; ms: m/z 322 ($\text{MH} + \text{NH}_3$)⁺, 305 (MH)⁺, 121 ($\text{MeOC}_6\text{H}_4\text{CH}_2$)⁺; ir: ν 1754, 1708, 1666; ^1H -nmr (deuteriochloroform): δ 3.71 (3H, s, CH_3), 3.73 (3H, s, CH_3), 4.38 (2H, s, CH_2COO), 4.99 (2H, s, NCH_2Ar), 5.76 (1H, d, $J = 7.9$, H5), 6.76 (2H, d, $J = 8.9$, 2H_{Ar}), 7.36 (1H, d, $J = 7.9$, H6), 7.40 (2H, d, $J = 8.9$, 2H_{Ar}); ^{13}C -nmr (deuteriochloroform): δ 43.9 (NCH_2Ar), 49.8 (CH_2CO), 52.9 (CH_3OCO), 55.3 (CH_3OAr), 102.4 (C5), 113.8 (CH_{Ar}), 128.8 (C_{Ar}), 130.5 (CH_{Ar}), 142.3 (C6), 151.5 (C2), 159.1 (C_{Ar}), 162.8 (C4), 168.0 (COOMe).

Anal. Calcd. for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_5$: C, 59.21; H, 5.30; N, 9.21. Found: C, 59.09; H, 5.24; N, 8.87.

General Method of Deprotonation.

An oven-dried flask was flushed with nitrogen and charged

with diisopropylamine (0.51 ml, 3.5 mmoles) and THF (15 ml). The solution was cooled to -40° and 2.5 M butyllithium-hexane (1.40 ml, 3.5 mmoles) was added by syringe. The mixture was stirred for 30 min at -40° , then cooled to -78° . A solution of **3** (3.5 mmoles) and HMPA (0.92 ml, 5.3 mmoles) in THF (5 ml) was added by syringe to the LDA solution, and the reaction mixture was stirred at -78° for 3 hours. Saturated aqueous ammonium chloride solution (15 ml) was added and the mixture was allowed to warm to room temperature then concentrated *in vacuo*. The semi-solid residue was dissolved in the minimum quantity of methanol and applied to a flash chromatography column which was eluted using cyclohexane-ethyl acetate (proportions vary from 2:3 to 1:4). Products and yields are presented in Table 1. Spectroscopic data for dimers are given in Tables 3 and 4.

General Method of Deprotonation-alkylation.

A solution of LDA was prepared and a solution of **3** added as above. The mixture was stirred at -78° for 15 minutes, then benzyl bromide (1 equivalent) was added and the mixture was stirred for a further 3 hours. Saturated aqueous ammonium chloride solution was added, and the reaction was treated as above. Products and yields are presented in Table 2. Spectroscopic data for alkylated dimers are given in Tables 3 and 4. Alkylated monomers obtained from appropriate starting materials are described below.

3-Benzyl-1-(1-cyano-2-phenylethyl)uracil **6a**.

This compound was obtained from **3a** as an oil; ms: *m/z* 349 (MH + NH₃)⁺, 332 (MH)⁺; ir: ν 3025, 2912, 1713, 1666; ¹H-nmr (deuteriochloroform): δ 3.19 (2H, d, *J* = 7.1, CCH₂Ph), 4.97 (1H, d, *J* = 13.9, NCH₂Ph), 5.07 (1H, d, *J* = 13.9, NCH₂Ph), 5.66 (1H, t, *J* = 7.0, CHCN), 5.70 (1H, d, *J* = 8.1, H5), 7.00 (1H, d, *J* = 8.1, H6), 7.08-7.40 (10H, m, 2Ph); ¹³C-nmr (deuteriochloroform): δ 38.5 (CCH₂Ph), 44.5 (NCH₂Ph), 48.9 (CHCN), 103.0 (C5), 115.6 (CN), 126.8, 127.6, 128.3, 128.5, 129.0, 129.3 (CH_{Ar}), 132.2, 135.9 (C_{Ar}), 138.1 (C6), 150.1 (C2), 161.6 (C4).

Anal. Calcd. for C₂₀H₁₇N₃O₂: C, 72.49; H, 5.17; N, 12.68. Found: C, 71.60; H, 5.69; N, 12.01.

3-(*p*-Methoxybenzyl)-1-(1-cyano-2-phenylethyl)uracil **6b**.

This compound was obtained from **3b**, mp 116° (acetonitrile); ms: *m/z* 379 (MH + NH₃)⁺, 362 (MH)⁺, 121 (MeOC₆H₄CH₂)⁺; ir: ν 3013, 2954, 2919, 2367, 2343, 1713, 1666, 1614; ¹H-nmr (deuteriochloroform): δ 3.20 (2H, d, *J* = 7.1, CCH₂Ph), 3.71 (3H, s, CH₃), 4.91 (1H, d, *J* = 14.2, NCH₂Ph), 5.13 (1H, d, *J* = 14.2, NCH₂Ph), 5.66 (1H, t, *J* = 7.1, CHCN), 5.79 (1H, d, *J* = 7.9, H5), 6.75 (2H, d, *J* = 7.9, 2H_{Ar}), 7.00 (1H, d, *J* = 7.9, H6), 7.05-7.38 (7H, m, Ph+2H_{Ar}); ¹³C-nmr (deuteriochloroform): δ 38.7 (CCH₂Ph), 44.1 (NCH₂Ph), 49.1 (CHCN), 55.2 (CH₃O), 103.2 (C5), 113.7 (C_{Ar}), 115.7 (CN), 128.3, 128.9, 129.4, 130.4 (CH_{Ar}), 130.8, 131.1 (C_{Ar}), 132.3 (CH_{Ar}), 138.2 (C6), 150.2 (C2), 159.1 (C_{Ar}), 161.8 (C4).

Anal. Calcd. for C₂₁H₁₉N₃O₃: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.12; H, 5.47; N, 11.72.

3-Benzyl-1-(1-methoxycarboxy-2-phenylethyl)uracil **6c**.

This compound was obtained from **3c**, mp 122° (cyclohexane-ethyl acetate); ms: *m/z* 365 (MH)⁺; ir: ν 3060, 3037, 2955, 2367, 2343, 1743, 1708, 1666; ¹H-nmr (deuteriochloroform): δ 3.17 (1H, dd, *J* = 14.3, 11.0, CCH₂Ph), 3.40 (1H, dd,

J = 14.4, 5.1, CCH₂Ph), 3.67 (3H, s, CH₃), 4.26 (1H, d, *J* = 14.1, NCH₂Ph), 5.04 (1H, d, *J* = 14.1, NCH₂Ph), 5.11 (1H, dd, *J* = 11.0, 5.1, CHCOO), 5.53 (1H, d, *J* = 8.0, H5), 6.91 (1H, d, *J* = 8.0, H6), 6.96 (4H, m, Ph), 7.13 (6H, m, Ph); ¹³C-nmr (deuteriochloroform): δ 35.6 (CCH₂Ph), 43.8 (NCH₂Ph), 52.5 (CH₃OCO), 61.0 (CHCOO), 101.1 (C5), 126.9, 127.0, 127.8, 128.0, 128.2, 128.5 (CH_{Ar}), 135.0, 136.2 (C_{Ar}), 141.0 (C6), 150.9 (C2), 161.9 (C4), 169.0 (COOMe).

Anal. Calcd. for C₂₁H₂₀N₂O₄: C, 69.22; H, 5.53; N, 7.69. Found: C, 68.95; H, 5.72; N, 7.61.

3-(*p*-Methoxybenzyl)-1-(1-methoxycarboxy-2-phenylethyl)uracil **6d**.

This compound was obtained from **3d**, mp 121° (cyclohexane-ethyl acetate); ms: *m/z* 395 (MH)⁺; ir: ν 3013, 2955, 2825, 1749, 1713, 1666, 1614; ¹H-nmr (deuteriochloroform): δ 3.14 (1H, dd, *J* = 14.3, 10.7, CCH₂Ph), 3.39 (1H, dd, *J* = 14.4, 5.3, CCH₂Ph), 3.71 (3H, s, CH₃), 3.72 (3H, s, CH₃), 4.86 (1H, d, *J* = 13.8, NCH₂Ar), 4.98 (1H, d, *J* = 13.8, NCH₂Ar), 5.13 (1H, dd, *J* = 10.6, 5.2, CHCOO), 5.56 (1H, d, *J* = 8.0, H5), 6.75 (2H, d, *J* = 8.7, 2H_{Ar}), 6.88 (1H, d, *J* = 8.0, H6), 6.96 (2H, m, Ph), 7.14 (3H, m, Ph), 7.21 (2H, d, *J* = 8.7, 2H_{Ar}); ¹³C-nmr (deuteriochloroform): δ 36.2 (CCH₂Ph), 43.7 (NCH₂Ph), 52.9 (CH₃OCO), 55.1 (CH₃OAr), 60.9 (CHCOOMe), 101.7 (C5), 113.6 (CH_{Ar}), 127.3 (C_{Ar} and CH_{Ar}), 128.8, 130.1 (CH_{Ar}), 135.1 (C_{Ar}), 140.7 (C6), 151.2 (C2), 158.9 (C_{Ar}), 162.2 (C4), 169.4 (COOMe).

Anal. Calcd. for C₂₂H₂₂N₂O₅: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.67; H, 5.72; N, 7.03.

X-ray Structure Analysis of **8b**.

This compound had molecular formula C₄₂H₃₈O₆N₆, *M* = 722. Intensity data were collected at room temperature on a PW 1100 Philips diffractometer; λ (Cu-K α) = 1.5418 Å, graphite monochromator. 25 reflections in the range $2 \leq 2\theta \leq 44^{\circ}$ were chosen to refine the unit cell parameters; monoclinic system, space group P2₁/c, *a* = 8.002(4), *b* = 8.212(4), *c* = 28.388(15) Å, β = 95.71(9) $^{\circ}$, *V* = 1856.2(1) Å³, *Z* = 2, μ = 6.34 mm⁻¹, *d* = 1.30 g cm⁻³, *F*(000) = 760. 3140 reflections up to $2\theta = 122^{\circ}$ were collected ($-9 \leq h \leq 9$, $0 \leq k \leq 9$, $0 \leq l \leq 32$) using flying STEPSCAN technique of which 1337 reflections with *I* > 3 σ (*I*) were considered as observed and kept in refinement calculations. The structure was solved by direct methods using SHELXS86 [19] and refined with SHELXL76 [20] by minimizing the function $\sum w(F_o - F_c)^2$. Non-hydrogen atoms were refined with anisotropic temperature factor, hydrogen atoms were located in difference Fourier map and refined with isotropic temperature factor. Convergence was reached at $R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o| = 0.0501$, $R_w = [\Sigma w(|F_o| - |F_c|)^2 / \Sigma w|F_o|^2]^{1/2} = 0.058$ for 299 parameters. The residual electron density in the final difference Fourier map was less than 0.18 eÅ⁻³ with a minimum of -0.20 eÅ⁻³. In the calculation, the complete molecule was considered as comprising two identical parts, each corresponding to one asymmetric unit, linked through the symmetry center by C6-C7' and C7-C6' bonds. The crystallographic asymmetric unit corresponds closely, but not exactly, to the monomeric uracil precursor, with C7', C8' and N8' of the former replacing respectively C7, C8 and N8 of the latter. Lists of the atomic coordinates, thermal parameters, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre, U.K.

Acknowledgements.

We thank F. Libot for recording mass spectra and the Ministère de la Recherche et de la Technologie for financial support (to G. G.).

REFERENCES AND NOTES

- [1] E. De Clercq, *Design of Anti-AIDS Drugs*, Elsevier, Amsterdam, 1990.
- [2] D. M. Huryn and M. Okabe, *Chem. Rev.*, **92**, 1745 (1992).
- [3] C. Périgaud, G. Gosselin and J.-L. Imbach, *Nucleosides Nucleotides*, **11**, 903 (1992).
- [4] A. D. Borthwick and K. Biggadike, *Tetrahedron*, **48**, 571 (1992).
- [5] V. E. Marquez and M.-I. Lim, *Med. Res. Rev.*, **6**, 1 (1986).
- [6] J. A. Montgomery, *Antiviral Res.*, **12**, 113 (1989).
- [7] C. K. Chu and S. J. Cutler, *J. Heterocyclic Chem.*, **23**, 289 (1986).
- [8] A. Holy, in *Bio-Organic Heterocycles - Synthesis, Mechanisms and Bioactivity*, H. C. van der Plas, M. Simonyi, F. C. Alderweireldt and J. A. Lepoivre, eds, Elsevier, Amsterdam, 1986, pp 91-114.
- [9] L. B. Townsend, ed, *Chemistry of Nucleosides and Nucleotides*, Vol 1, Plenum Press, New York, 1988.
- [10] E. Lukevics and A. Zabluka, *Nucleoside Synthesis: Organosilicon Methods*, Ellis Horwood, Chichester, 1991.
- [11] For recent examples, see: R. Pontikis and C. Monneret, *Nucleosides Nucleotides*, **12**, 547 (1993); S. Ahmad, G. S. Bisacchi, A. K. Field, G. A. Jacobs, A. V. Tuomari, B. McGeever-Rubin, G. D. Vite and R. Zahler, *Bioorg. Med. Chem. Letters*, **3**, 1215 (1993); B. L. Booth and P. R. Eastwood, *Tetrahedron Letters*, **34**, 5503 (1993); M. E. Jung and I. D. Trifunovich, *Tetrahedron Letters*, **33**, 2921 (1992); X. Chen, S. M. Siddiqi and S. W. Schneller, *Tetrahedron Letters*, **33**, 2249 (1992); S. D. Patil, M. Koga, S. W. Schneller, R. Snoeck and E. De Clercq, *J. Med. Chem.*, **35**, 2191 (1992); H. Boumchita, M. Legraverand, C. Huel and E. Bisagni, *J. Heterocyclic Chem.*, **27**, 1815 (1990); J. Béres, G. Sagi, I. Tömösközi, L. Gruber, E. Baitz-Gaes, L. Ötrös and E. De Clercq, *J. Med. Chem.*, **33**, 1353 (1990); A. D. Borthwick, B. E. Kirk, K. Biggadike, A. M. Exall, S. Butt, S. M. Roberts, D. J. Knight, J. A. V. Coates and D. M. Ryan, *J. Med. Chem.*, **33**, 179 (1990).
- [12] D. Guillaume, D. J. Aitken and H.-P. Husson, *Synlett*, 747 (1991).
- [13] D. Guillaume, M. Brum-Bousquet, D. J. Aitken and H.-P. Husson, *Bull. Soc. Chim. France*, **131**, 391 (1994).
- [14] J. L. Marco, J. Royer and H.-P. Husson, *Tetrahedron Letters*, **26**, 3567 (1985).
- [15] H. Singh, P. Aggarwal and S. Kumar, *Synthesis*, 520 (1990).
- [16] D. Burdi and T. P. Begley, *J. Am. Chem. Soc.*, **113**, 7768 (1991).
- [17] T. Akiyama, M. Kumegawa, Y. Takesue, H. Nishimoto and S. Ozaki, *Chem. Letters*, **339** (1990).
- [18] W. Q. Beard, Jr. and C. R. Hauser, *J. Org. Chem.*, **25**, 334 (1960).
- [19] G. M. Sheldrick, SHELXS86, Program for Crystal Structure Determination, University of Göttingen, Federal Republic of Germany, 1986.
- [20] G. M. Sheldrick, SHELX76, Program for Crystal Structure Determination, University of Cambridge, England, 1976.