SYNTHESIS AND CONFORMATION OF SOME 6-AMINOMETHYLURACIL AMIDES

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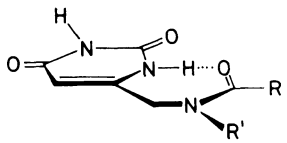
Three model amides (*I*—*III*) derived from 6-(N-alkylaminomethyl)-uracil and arylcarboxylic acids were synthesized and their conformation in solution studied. The 7-membered intramolecular hydrogen bond between amide carbonyl and H–N^1 of uracil nucleus was proved to exist in solution of all three compounds using NMR and IR spectroscopy.

Long-chain substituted amides derived from higher fatty acids and 6-aminomethyluracil moiety has recently been found to form supramolecular liquid crystals[1]. The supposed conformational rigidity of these compounds is thought to be due to intramolecular 6-membered hydrogen bonding shown in formula *I*—*III*.

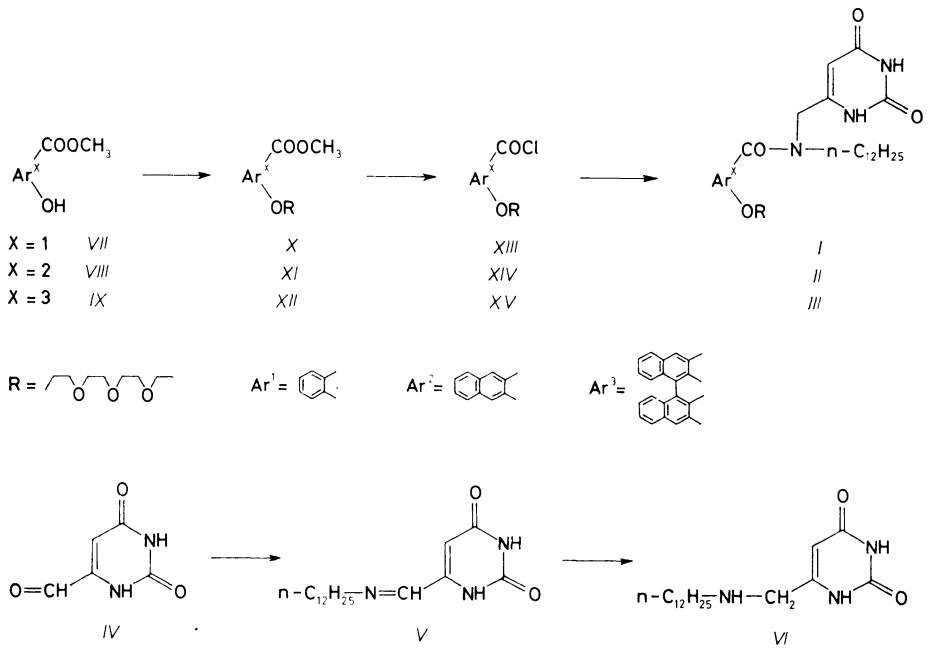


I - III

We report on the preparation of the new derivatives of the above mentioned type *I*—*III* having aromatic substituent R and dodecyl group as R′. These structures could be also considered as model compounds capable of stacking and multiple inter-nucleobase hydrogen bond interactions with biopolymers[2,3]. The monoethyl--triethyleneglycol derivatization of phenolic hydroxyl group was used in the hope to bring about better solubilities of resulting structures in organic solvnts than many binaphthyl as well as uracil derivatives usually show, and indeed all compounds studied were fairly soluble in common organic solvents.

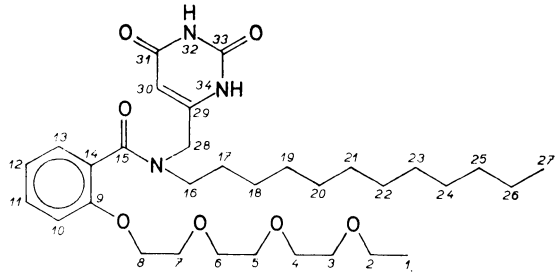
The starting secondary amine *VI* was prepared from 6-formyluracil (*IV*)[4,5] in analogy with the described procedure used for 5-substituted analogues[6]. Either commercial (*VII*, *VIII*) or known[7,8] (*IX*) esters were used for preparation of title compounds *I*—*III* using standard side-chain elaboration. Esters were first alkylated

with appropriate bromide yielding alkylated esters *X*–*XII*, these were hydrolyzed by treatment with sodium hydroxide in diluted alcohol, and acids thus obtained were transformed without isolation to corresponding acid chlorides *XIII*–*XV*. The subsequent reaction with amine *VI* furnished desired amides *I*–*III*. Structures and yields are summarized in Scheme 1.



SCHEME 1

The assigned ^{1}H NMR and ^{13}C NMR shifts for *I* are summarized in Table I.



The most remarkable point is the extraordinary high difference between shifts of

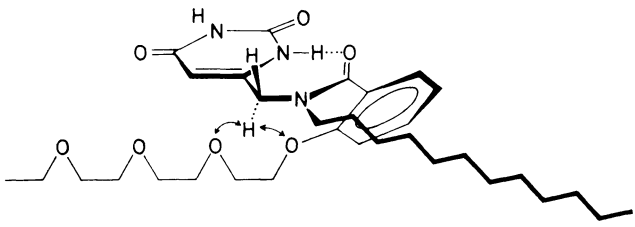
methylene protons in allylic position to uracil nucleus (position 28 in Table I), the phenomenon completely absent if aliphatic carboxylic portion of amide was used[1].

TABLE I

^{1}H and ^{13}C NMR shifts of *I* ($CDCl_3$, δ in ppm relative to TMS; *J* in Hz)

Position	^{1}H NMR	^{13}C NMR
1	1·20 t (7·1, 7·1)	15·05
2	3·52 q (7·1, 7·1, 7·1)	66·54
3	3·55–3·69 m	67·97
4	3·55–3·69 m	69·13
5	3·55–3·69 m	69·72
6	3·55–3·69 m	69·72
7	3·55–3·69 m	72·52
8	3·55–3·69 m	72·52
9	3·55–3·69 m	154·17
10	6·96 dd (0·9, 8·5)	112·16
11	7·37 ddd (1·5, 7·4, 8·5)	130·94
12	7·03 ddd (0·9, 7·4, 7·4)	127·88
13	7·26 dd (1·8, 7·4)	121·28
14	—	124·88
15	—	171·99
15	—	171·19
16	4·22 t (4·8, 4·8)	45·80
17	3·20 m	28·17
18	1·03–1·32 m	26·22
19	1·03–1·32 m	26·22
19	1·03–1·32 m	29·25
20	1·03–1·32 m	29·29
21	1·03–1·32 m	29·42
22	1·03–1·32 m	29·52
23	1·03–1·32 m	29·52
24	1·03–1·32 m	28·86
25	1·03–1·32 m	31·84
26	1·03–1·32 m	22·61
27	0·88 t (6·6, 6·6)	14·06
28	4·10 bd (15·6)	
	4·85 bd (15·6)	49·39
29	—	151·13
30	5·68 bs	99·60
31	—	164·06
32	9·49 bs	—
33	—	151·98
34	9·39 bs	—

The inspection of CPK models has led us to conclusion, that it is the triethyleneglycol monoethylether moiety hydrogen that is, in turn strongly deshielded. The rigidity, caused by intramolecular hydrogen bonding is the necessary prerequisite for this effect (see formula *I*).



I

This feature was further proved by IR spectroscopy. The results of standard dilution technique are summarized in Table II.

The intramolecular associated N^1—H frequencies found in all three amides studied are considered as independent and unambiguous proof of rigid 7-memberred intramolecular hydrogen bonding. The two distinct N^1—H vibrations observed in case of *I* and *II* are attributed to two possible conformations of 7-membered ring. Only one of them is apparently present in *III* due to sterical hindrance connected with 1,1'-binaphthyl system.

In summary, it is very likely, that amides derived from 6-aminomethyluracil possess in general some extent of conformational rigidity due to intramolecular 7-membered hydrogen bond between N^1—H of uracil nucleus and amide carbonyl groups.

TABLE II

IR bands ($\tilde{\nu}$ NH) of uracil nucleus in CCl_4 (in cm^{-1})

Compound	Conc.	N^3–H		N^1–H assoc.[b]
		free	assoc.[a]	
I	3	3 412 m	3 207 m	3 306 m, 3 280 m
	0·15	3 412 m	3 216 w	3 315 w, 3 294 w
II	3	3 412 m	3 203 m	3 312 m, 3 280 m
	0·15	3 411 m	3 216 w	3 313 w, 3 285 w
III	2	3 412 w	3 200 s	3 261 s
	0·08	3 412 w	3 204 m	3 268 m

[a] Intermolecular hydrogen bond; [b] intramolecular hydrogen bond.

This fact is hoped to open up the new possibilities for design of molecules capable interact with oligo- and polynucleotides by means of multiple hydrogen bonding and intercalation.

EXPERIMENTAL

The IR spectra were recorded on a Perkin–Elmer 580 apparatus. NMR spectra were measured on FT NMR spectrometer Varian XL-200 (^{1}H and ^{13}C at 200 MHz and 50·3 MHz, respectively) and Tesla BS-497·0 (^{1}H at 100 MHz in CD_3Cl) if not otherwise stated. Mass spectra were measured on VG ZAB-EQ mass spectrometer using 70 eV for EI and glycerol matrix, Cs^+ and 15 kV as accelerating voltage for primary ions in SIMS.

Amides *I*—*III*: General Procedure

Hydrochloride of *VI* (350 mg, 0·001 mol) was treated with 0·6 ml of triethylamine in 2 ml of dimethylsulfoxide and 20 ml of dry toluene at ambient temperature with stirring for 30 min. A solution of 0·001M (0·0005M in case of *XV*) of appropriate acid chloride in 30 ml of dry toluene was added dropwise during 30 min and stirred for next 24 hours. The reaction was monitored using TLC (5% methanol in chloroform). The reaction mixture was diluted with 200 ml of toluene, washed with water, diluted (1 : 10) hydrochloric acid and again with water (100 ml of each), evaporated in vacuo and pure products were isolated by flash chromatography (silica, 2% methanol in chloroform).

N-(1-*Dodecyl*)-N-(*uracil*-6-*methylene*)-2-(1,4,7,10-*tetraoxadodecyl*)-*benzamide* (I). For $C_{32}H_{51}N_3O_7$ (589·8) calculated: 65·17% C, 8·72% H; found: 65·01% C, 8·65% H. SIMS-MS (*m/z*, %): 590 $[M + 1]^+$ (100); 466 (42); 308 (26).

N-(1-*Dodecyl*)-N-(*uracil*-6-*methylene*)-3-(1,4,7,10-*tetraoxydodecyl*)-*naphthalene*-2-*carboxamide* (II). For $C_{36}H_{53}N_3O_7$ (639·8) calculated: 67·58% C, 8·35% H; found: 67·72% C, 8·20% H. SIMS-MS (*m/z*, %): 640 $[M + 1]^+$ (78); 516 (31); 506 (20); 404 (30); 336 (25); 320 (34); 308 (55); 215 (100).

N,N′-*Bis*(1-*dodecyl*)-N,N′-*bis*(*uracil*-6-*methylene*)-3,3′-*bis*(1,4,7,10-*tetraoxadodecyl*)-1,1′-*binaphthol*-2,2′-*dicarboxamide* (III). For $C_{72}H_{104}N_6O_{14}$ (1 277·7) calculated: 67·69% C, 8·20% H; found 67·50% C, 8·66% H. SIMS-MS (*m/z*, %): 1 278 $[M + 1]^+$ (3); 1 042 (5); 805 (40); 778 (16); 543 (20); 451 (75); 396 (82); 310 (100).

Shiff Base *V*

Formyluracile *IV* (140 mg, 0·001 mol), 1-dodecylamine (185 mg, 0·001 mol) in 50 ml of 96% ethanol was heated to reflux for 4 hours. Pure product was collected by filtration from cool reaction mixture. After drying in vacuo, 250 mg (81%) of *V* was obtained. For $C_{17}H_{29}N_3O_2$ (307·4) calculated: 66·42% C, 9·51% H; found: 66·30% C, 9·40% H. ^{1}H NMR spectrum (CD_3SOCD_3): 0·85 t, 3 H (CH_3); 1·35 m, 26 H (CH_2); 1·65 bt, 2 H (CH_2–CH_2–N); 3·65 t, 2 H (CH_2–N); 6·00 s, 1 H (H-5); 8·2 s, 1 H (CH=N); 10·5 bs, 1 H (H-1); 11·3 bs, 1 H (H-3). MS-EI (*m/z*, %): 307 $[M^+]$ (98); 222 (10); 208 (15); 194 (100); 180 (10); 154 (32); 140 (27); 109 (14).

N-(1-Dodecyl)-N-(uracil-6-methylene) Amine Hydrochloride (*VI*.HCl)

Schiff base *V* (200 mg, 0·6 mmol) suspended in 40 ml of 80% aqueous ethanol was treated with 150 mg (4 mmol) of natriumborohydride ahd heated to reflux for 4 hours. The reaction mixture

was evaporated in vacuo and treated with 20 ml of diluted (1 : 10) hydrochloric acid. Pure product (185 mg, 82%) was obtained by filtration of cool mixture and crystallization from 80% aqueous ethanol. For $C_{17}H_{32}ClN_3O_2$ (345·9) calculated: 59·03% C, 9·32% H; found: 58·86% C, 9·07% H. ^{1}H NMR spectrum (CD_3SOCD_3): 0·85 t, 3 H (CH_3); 1·35 m, 26 H (CH_2); 1·70 bt, 2 H (CH_2–CH_2–N); 3·00 bt, 2 H (CH_2–N); 3·95 s, 2 H (CH_2-allylic); 5·80 s, 1 H (H-5); 9·70 bs, 2 H (NH_2); 11·2 bs, 1 H (H-1); 11·4 bs, 1 H (H-3).

Methyl 2-(1,4,7,10-Tetraoxadodec-1-yl)-benzoate (*X*) and
Methyl 3-(1,4,7,10-Tetraoxadodec-1-yl)-2-naphthoate (*XI*)

Sodium hydride 1·25 g (0·04 mol) as 80% dispersion in mineral oil was added to 0·04 mol of hydroxyester (*VII* or *VIII*) in 150 ml of anhydrous tetrahydrofuran and the mixture was refluxed with stirring for 30 min under argon. 4,7,10-Trioxadodecylbromide (12 g, 0·05 mol) was added and the mixture was refluxed for 36 hours while after each 12 hours 0·77 g of sodium hydride and 6 g of bromide were added. The mixture was evaporated in vacuo, 200 ml of water and 200 ml of toluene were added. Toluene phase was separated, aqueous phase was extracted with toluene (2 × 200 ml), combined organic phases were washed with 2% aq. sodium hydroxide and water (100 ml of each), dried with magnesium sulfate, evaporated in vacuo and isolated using flash chromatography (silica–$CHCl_3$).

Benzoate X: yield 11·0 g (88%). For $C_{16}H_{24}O_6$ (312·4) calculated: 61·52% C, 7·74% H; found: 61·68% C, 7·90% H. ^{1}H NMR spectrum: 1·19 t, 3 H (CH_3); 3·52 q, 2 H (CH_2–CH_3); 3·62–3·90 m, 13 H (CH_2–O, CH_3–O); 4·20 m, 2 H (Ar–O–C*H*$_a$); 6·87–7·82 m, 4 H (aromatic).

Naphthoate XI: yield 10·9 g (76%). For $C_{20}H_{26}O_6$ (362·4) calculated: 66·28H C, 7·23% H; found: 66·40% C, 7·15% H. ^{1}H NMR spectrum: 1·19 t, 3 H (CH_3); 3·53 q, 2 H (CH_2–CH_3); 3·61–3·96 m, 13 H (O–CH_2, O–CH_3); 4·30 m, 2 H (Ar–O–CH_2); 7·22–8·29 m, 6 H (aromatic).

Dimethyl 2,2′-Bis(1,4,7,10-tetraoxadodecyl)-1,1′-binaphthalene-3,3′-dicarboxylate (*XII*)

Hydroxyester *IX* (20·1 g, 0·05 mol) was dissolved in mixture of 20 ml of dimethylsulfoxide and 500 ml of dry dioxane and treated with 2·7 g (0·11 mol) of natrium hydride (80% oil suspension) and heated to 80°C for 1 hour with stirring under argon. 3,6,9,-Trioxaundecylbromide (24 g, 0·1 mol) was added and the mixture was heated to reflux for total of 48 hours while 1·25 g of sodium hydride suspension and 10 g of bromide were added after each 12 hours. Reaction mixture was evaporated in vacuo, partitioned between 500 ml of ether and 300 ml of water, phases were separated, aqueous phase was extracted with ether (2 × 200 ml), organic phases were combined, washed with water (100 ml), dried with magnesium sulfate, evaporated in vacuo and after flash chromatography (silica–1% methanol in chloroform) 12 g (33%) of *XII* were isolated as pale yellow oil. For $C_{40}H_{50}O_{12}$ (722·8) calculated: 66·47% C, 6·97% H; found: 66·64% C, 6·97% H. ^{1}H NMR spectrum: 1·18 t and 1·20 t, 6 H (CH_2–CH_3); 3·49 s, 6 H (OCH_3); 2·85–4·05 m, 28 H (O–CH_2); 6·95–8·05 m, 8 H (aromatic); 8·51 s, 2 H (H-4, H-4′).

Acid Chlorides *XIII*, *XIV*, *XV*: General Procedure

Alkylated ester (0·01 mol) was treated with the solution of 0·8 g sodium hydroxide in 50 ml of 50% ethanol (the amounts are doubled in case of *XII*) with stirring at ambient temperaturel The reaction was monitored using TLC (silica, 3% methanol in chloroform) and was complete within 2 hours. The reaction mixture was then acidified with cooling, extracted with dichloromethane (3 × 200 ml), combined organic phases were washed with water (100 ml), evaporated in vacuo, coevaporated twice with 200 ml of dry toluene, crude acid thus obtained was dis-

solved in dry toluene (200 ml) and treated with fourfold amount of commercial oxalyl chloride in the presence of trace of pyridine at ambient temperature with stirring for 48 hours. The sufficiently pure chlorides were isolated by evaporation of volatiles in vacuo (finally 12 hours, 100 Pa, ambient temperature).

Chloride XIII (79%). For $C_{15}H_{21}ClO_5$ (318·8) calculated: 56·87% C, 6·68% H; found: 56·60% C, 6·74% H. ^{1}H NMR spectrum: 1·20 t, 3 H (CH_3): 3·51 q, 2 H ($\mathbf{CH_2}$–CH_3); 3·62 m, 4 H ($\mathbf{CH_2}$–$\mathbf{CH_2}$–OEt); 3·73 m, 4 H ($\mathbf{OCH_2}$–$\mathbf{CH_2O}$); 3·90 m, 2 H (Ar–O–CH_2–$\mathbf{CH}\alpha$); 4·23 m, 2 H (ArO–$\mathbf{CH}\alpha$); 6·97—7·17 m, 2 H (H-4, H-5); 7·56 m, 1 H (H-3); 8·06 m, 1 H (H-6).

Chloride XIV (72%). For $C_{19}H_{23}ClO_5$ (366·9) calculated: 62·21% C, 6·32% H; found: 62·45% C, 6·30% H. ^{1}H NMR spectrum: 1·20 t, 3 H (CH_3); 3·52 q, 2 H ($\mathbf{CH_2}$–CH_3); 3·63 m, 4 H ($\mathbf{CH_2}$–$\mathbf{CH_2}$–OEt); 3·73 m, 4 H (OCH_2–CH_2); 3·97 m, 2 H (ArO–CH_2–$\mathbf{CH_2}$); 4·31 m, 2 H (ArO–CH_2); 7·20—7·90 m, 5 H (aromatic); 8·61 s, 1 H (H-1).

Chloride XV (94%). For $C_{38}H_{44}Cl_2O_{10}$ (731·7) calculated: 62·38% C, 6·06% H; found: 62·45% C, 6·10% H. ^{1}H NMR spectrum: 1·19 t and 1·21 t, 6 H (CH_3); 3·31 m, 12 H ($\mathbf{CH_3}$–$\mathbf{CH_2}$–O–$\mathbf{CH_2}$–$\mathbf{CH_2}$); 3·59 bs, 8 H (OCH_2–CH_2); 3·83 m, 4 H (Ar–CH_2–$\mathbf{CH_2}$); 4·46 m, 4 H (ArO–CH_2); 7·05—8·15 m, 8 H (aromatic); 8·83 s, 2 H (H-4, 4′).

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