N_1-(2-FUROYLMETHYL) AND N_1-(5-NITRO-2-FUROYLMETHYL) DERIVATIVES OF URACIL AND ITS 5-SUBSTITUTED DERIVATIVES

S. A. Giller, A. Ya. Perkone,
I. N. Getsova, A. B. Rozenblit, and V. E. Golender

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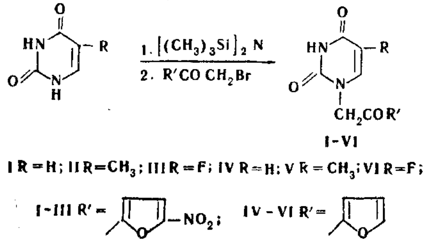
The corresponding N_1-(2-furoylmethyl) and N_1-(5-nitro-2-furoylmethyl) derivatives of uracil and its 5-substituted derivatives were obtained by the reaction of 2-bromo- and 5-nitro-2-bromoacetylfurans with uracil, 5-fluorouracil, and thymine. The structures of these compounds as N_1-substituted uracils were proved by a study of the UV spectra at various pH values. The computational method of expanding the UV spectra into individual bands was used.

A study of pyrimidine derivatives, especially fluoro-substituted pyrimidines, is of interest in connection with the high antitumorigenic activity of these compounds [1,2]. Pyrimidines that contain furan and 5-nitrofuran groupings as substituents have antibacterial, antitumorigenic, fungicidal, and antiviral properties and are highly active compounds with a broad spectrum of action [3-5].

We have synthesized N_1-(2-furoylmethyl) and N_1-(5-nitro-2-furoylmethyl) derivatives of uracil and its 5-substituted derivatives (I-VI) by the reaction of 2-bromoacetylfuran and 5-nitrobromoacetylfuran with the appropriate uracils. The "silyl method" [6, 7] was used for the condensation. Compounds I-VI are light-yellow substances (Table 1) that are only slightly soluble in the usual organic solvents.



The structures of IV-VI as N_1-substituted uracils were proved by the absence of a shift in the maximum of the pyrimidine ring as the pH of the medium changed [8] (Table 2).

TABLE 1. N_1-(2-Furoylmethyl) and N_1-(5-Nitro-2-furoylmethyl) Derivatives of Uracil and Its 5-Substituted Derivatives

Comp.	mp, °C	Crystallization solvent	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
I	237—238	Acetone	$C_{10}H_7N_3O_6$	45,09	2,74	16,01	45,29	2,66	15,85	72
II	247—248	Alcohol	$C_{11}H_9N_3O_6$	47,32	3,20	15,07	47,32	3,25	15,05	77
III	176—178	Ethyl acetate	$C_{10}H_6FN_3O_6$	42,20	2,36	14,88	42,41	2,14	14,84	16
IV	278—279	Acetone - H_2O	$C_{10}H_8N_2O_4$	54,45	3,56	12,95	54,55	3,66	12,72	50
V	276—277	Acetone	$C_{11}H_{10}N_2O_4$	56,24	4,40	12,12	56,41	4,30	11,96	56
VI	279	Acetone	$C_{10}H_7FN_2O_4$	50,68	3,08	11,98	50,43	2,96	11,76	42

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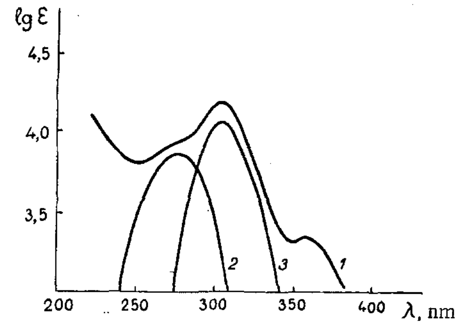

Fig. 1. UV spectra: 1) N_1-(5-nitro-2-furoylmethyl)thymine (I) (pH 9-11); 2) absorption band of thymine calculated with a computer for the spectrum of I with λ_{max} 275 nm; 3) absorption band of 5-nitroacetylfuran calculated with a computer from the spectrum of I with λ_{max} 302 nm.

TABLE 2. UV Spectra of IV-VI

Compound	λ_{max}, nm (lg e)	
	at pH 2—3	at pH 9—31
IV	273 (4,51)	273 (4,38)
V	276 (4,43)	273 (4,35)
VI	277 (4,38)	275 (4,18)

The UV spectra of I-III, which contain a 5-nitrofuran grouping, proved to be extremely complex: the absorption band characteristic for the pyrimidine ring (λ_{max} 270-280 nm) is close to the absorption of nitrofuran derivatives (λ_{max} 300-310 nm) [9], as a result of which both bands are overlapped. The intensity of the absorption of pyrimidine in alkaline media is lower than in acidic media, and the shoulder at ~270 nm, which was observed at pH 2-3, disappeared at pH 9-11. Expansion of the spectra into individual bands by means of computational methods [10] therefore became necessary.

The individual bands were approximated by Gaussian curves, and the parameters of the curves were selected in such a way as to minimize the functional

$$\Phi = \sum_{k=1}^{m} \Big[y(\lambda_k) - \sum_{i=1}^{n} c_{i1} \exp\left(c_{i2}(c_{i3} - \lambda_k)^2\right) \Big] ,$$

where $y(\lambda_k)$ is the absorption measured at wavelength λ_k, n is the number of bands, c_{i1}, c_{i2}, and c_{i3} are the parameters of the i-th band, and m is the number of experimental points.

The method of linearized least squares with optimization of the pace and the method of configurations [11] were used to minimize Φ.

The computations were initially performed with a Nairi computer. However, it became clear that, because of the complex "ravine" character of the minimizing function, the convergence of the iterations was very slow, and the computations required great expenditures of machine time. The computations were subsequently performed with a GE-415 high-speed computer. The programs were composed in FORTRAN ASA language. The time required to expand the spectrum into four bands averaged 7 min.

Expansion of the absorption curve (Fig. 1) proved that the spectrum of N_1-(5-nitro-2-furoylmethyl) thymine consists of absorption bands of the pyrimidine and 5-nitrofuran rings, and it was shown that the characteristic maximum of the pyrimidine ring is not shifted when the pH of the medium is changed. The results confirm the structures of I-III as N_1-substituted uracils.

EXPERIMENTAL

N_1-(5-Nitro-2-furoylmethyl)uracil (I). A mixture of 2.24 g (0.02 mole) of uracil, 20 ml of hexamethyldisilazane, and 0.5 ml of trimethylchlorosilane was heated at 150-170° for 2 h (until the uracil had completely dissolved). The excess hexamethyldisilazane was removed by distillation at reduced pressure at a bath temperature no higher than 60°, and the reaction mixture was cooled to room temperature and dissolved in 20 ml of dry benzene. A solution of 4.6 g (0.02 mole) of 5-nitro-2-bromoacetylfuran in 30 ml of dry benzene was added gradually with vigorous stirring. The temperature was raised slowly to 60° and held there for 1 h; the mixture was then cooled to room temperature, 10 ml of ethanol was added, and the mixture was allowed to stand overnight. The precipitate was removed by filtration, washed with ethanol, dried, and refluxed with 60 ml of chloroform. Evaporation of the chloroform solution gave unchanged 5-nitro-2-bromoacetylfuran. The chloroform-insoluble solid was 3.83 g (72%) of I with mp 237-238° (from acetone).

Compounds II-VI were similarly obtained.

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