

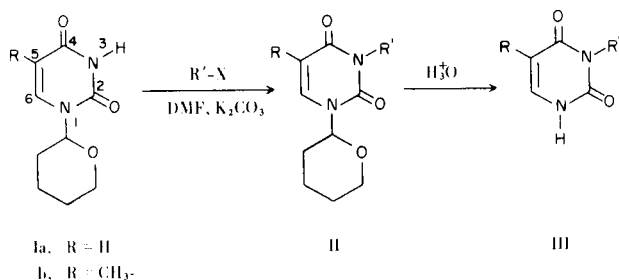
Synthesis of Some 3-Alkyluracils and 3-Alkylthymines

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The preparation of 3-alkyluracils by direct alkylation of uracils is usually not possible (1). Even under the most favorable conditions, a mixture containing both *N*-1 and *N*-3 monoalkylated products and *N*-1, *N*-3 dialkylated product is obtained (2). The ratio of the three products is variable and is known to be influenced by substituents at the 5 and 6 positions and the ratio of alkylating agent to the uracil (2-4).



To circumvent this problem the tetrahydropyran-2-yl moiety was employed as a blocking group for the *N*-1 position of uracil and thymine. Alkylation at *N*-3 without competition from *N*-1, followed by hydrolytic removal of the blocking group, led to good yields of *N*-3 alkylated products. The use of the tetrahydropyran-2-yl moiety as a blocking group in this sequence was suggested by its previous use as a protecting group for the *N*-9 imidazole nitrogen in the synthesis of 6-substituted purines (5) and the ready availability of the 1-tetrahydropyran-2-yl derivatives of uracil (Ia) and thymine (Ib) (6). The present method is thus limited to those uracils which, after conversion to suitable 2,4-dialkoxy derivatives, will undergo the Hilbert-Johnson reaction (7) with 2-chlorotetrahydropyran to form the necessary *N*-1 blocked derivatives.

No special effort was made to maximize the yields reported in Table I. Most of the 3-alkyl-1-(tetrahydropyran-

TABLE I

Summary of 3-Alkyluracil and Thymine Preparations

Compound	R	R'	M.p., C°	Yield, %	Calculated			Found		
					C	H	N	C	H	N
IIa	H	<i>n</i> -C ₃ H ₇	Oil	93	60.48	7.61	11.76	60.11	7.59	12.11
IIb	H	<i>n</i> -C ₈ H ₁₇	Oil	98	66.20	9.15	9.08	66.02	9.49	8.47
IIc	H	allyl	Oil	99	61.00	6.83	11.86	60.80	6.68	12.14
IId	CH ₃	allyl	87-89	78	62.38	7.25	11.19	62.24	7.40	11.27
IIf	H	-CH ₂ C ₆ H ₅	103-104	66	67.11	6.34	9.78	67.00	6.19	9.68
IIIa	H	<i>n</i> -C ₃ H ₇	157-158 (a)	68	54.53	6.54	8.17	54.80	6.62	8.28
IIIb	H	<i>n</i> -C ₈ H ₁₇	144-146	77	64.25	8.99	12.49	64.18	8.69	12.58
IIIc	H	allyl	133-134	46	55.25	5.30	18.41	54.96	5.24	18.17
IIId	CH ₃	allyl	175-177	83	57.82	6.07	16.86	57.90	6.07	17.12
IIIe	H	-CH ₂ C ₆ H ₅	180-181 (b)	76	65.33	4.98	13.86	65.37	5.29	13.55
IIIf	H	-CH ₂ C ₆ F ₅	200-202	82	45.22	1.73	9.59	45.20	1.94	9.85

(a) Prepared previously by E. Falch, *Acta Chem. Scand.*, **24**, 137 (1970). (b) A value of 180-182° has been reported by A. Novacek, *Collect. Czech. Chem. Commun.*, **36**, 4066 (1971), who prepared the compound by benzylation of 1-(2-cyanoethyl)uracil followed by alkaline decyanoethylation.

pyran-2-yl)uracils were obtained as pure compounds. In the one case (IIIb) where impurities were detected, no effort was made at purification since the pure 3-alkyluracil (IIIb) resulted from its hydrolysis. Evidence for the position of alkylation was obtained from ultra-violet spectra. All alkylated uracils and thymines reported here (IIIa-IIIf) showed a bathochromic shift of 24-28 nm in neutral vs. 0.1 N sodium hydroxide solution. Only *N*-3 alkylated uracils show such shifts to longer wavelengths (8). The expected shifts for the *N*-1 isomers are less than 2 nm.

EXPERIMENTAL (9)

3-Alkyl-1-(tetrahydropyran-2-yl)uracils and Thymines (IIa-f).

The general procedure used to prepare these compounds is illustrated by the synthesis of 3-*n*-propyl-1-(tetrahydropyran-2-yl)uracil (IIa). A mixture of 13.7 g. (0.07 mole) of 1-tetrahydropyran-2-yl)uracil, 12.3 g. (0.1 mole) of *n*-propyl bromide, and 13.8 g. (0.1 mole) of anhydrous potassium carbonate in 150 ml. of dimethylformamide was heated overnight on a steam bath. The reaction mixture was poured into 300 ml. of water and extracted three times with 150 ml. portions of chloroform. The combined chloroform extracts were washed twice with 100 ml. portions of water, dried over anhydrous magnesium sulfate, and the chloroform removed *in vacuo* to give 15.5 g. (93%) of 3-*n*-propyl-1-(tetrahydropyran-2-yl)uracil as a light yellow oil, λ max (methanol) 261 nm (log ϵ , 3.94); nmr (DMSO- d_6) δ 0.93 (3H, t, $J = 7.0$ Hz, -CH₃) 3.92 (2H, t, $J = 7.0$ Hz, >N-CH₂-), 5.77 (1H, d, $J = 8.0$ Hz, uracil 5-H), 7.40 (1H, d, $J = 8.0$ Hz, uracil 6-H).

3-Alkyluracils and Thymines (IIIa-f).

The general procedure used to prepare these compounds is illustrated by the synthesis of 3-*n*-propyluracil (IIIa). A solution of 10.8 g. (0.045 mole) of 3-*n*-propyl-1-(tetrahydropyran-2-yl)uracil (IIa) in 120 ml. of 8:3:1 methanol-concentrated hydrochloric acid-water was refluxed overnight. After cooling, the hydrolysis mixture was neutralized with saturated sodium bicar-

bonate solution, extracted three times with 150 ml. portions of chloroform and the combined extracts dried over anhydrous magnesium sulfate. The chloroform was removed *in vacuo* and the residue triturated with ether to furnish 4.75 g. (68%) of 3-*n*-propyluracil, m.p. 157-158°; λ max (methanol) 259 nm (log ϵ , 3.86), λ max (0.1N sodium hydroxide) 284 nm (log ϵ , 4.09); nmr (DMSO- d_6) δ 0.85 (3H, t, $J = 7.0$ Hz, -CH₃), 1.55 (2H, m, -CH₂CH₂CH₃), 3.75 (2H, t, $J = 7.0$ Hz, >N-CH₂-), 5.60 (1H, d, $J = 8.0$ Hz, uracil 5-H), 7.43 (1H, d, $J = 8.0$ Hz, uracil 6-H).

REFERENCES

- (1) A facile synthesis of 3-alkyl-5-nitrouracils has been reported by H. U. Blank and J. J. Fox, *J. Heterocyclic Chem.*, **7**, 735 (1970), by direct alkylation of the dianion of 5-nitrouracil. This unique method takes advantage of a substantial difference in the nucleophilicity of the dianion at positions *N*-3 and *N*-1 that permits preferential alkylation.
- (2) B. R. Baker, M. Kawazu, D. V. Santi, and T. J. Schwan, *J. Med. Chem.*, **10**, 304 (1967).
- (3) B. R. Baker and G. B. Chheda, *J. Pharm. Sci.*, **54**, 25 (1965).
- (4) B. R. Baker and T. J. Schwan, *J. Med. Chem.*, **9**, 76 (1966).
- (5) R. K. Robins, E. F. Godefroi, E. C. Taylor, L. R. Lewis, and A. Jackson, *J. Am. Chem. Soc.*, **83**, 2574 (1961).
- (6) Prepared from 2-chlorotetrahydropyran and the commercially available 2,4-dimethoxypyrimidines, C. W. Noell and C. C. Cheng, *J. Heterocyclic Chem.*, **3**, 5 (1966).
- (7) For a review of the Hilbert-Johnston reaction and its synthetic limitations see J. Pliml and M. Prystas in "Advances in Heterocyclic Chemistry," Vol. 8, A. R. Katritzky and A. J. Boulton, Eds., Academic Press, Inc., New York, N. Y., 1967, p. 115.
- (8) D. Shugar and J. J. Fox, *Biochem. Biophys. Acta*, **9**, 199 (1952).
- (9) Melting points (uncorrected) were taken on a Fisher-Johns melting point block. Uv and nmr spectra were recorded with a Beckman Dk-2 and a Varian Model A-60 spectrometer. Chemical shifts are reported in ppm downfield from tetramethylsilane as the internal standard. Coupling constants are accurate to ± 0.5 Hz.