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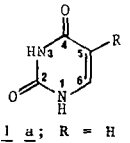
THE BENZOYLATION OF URACIL AND THYMINE

Kenneth A. Cruickshank, Josef Jiricny, and Colin B. Reese*

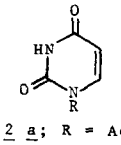
Department of Chemistry, King's College, Strand, London WC2R 2LS, England

Summary: Uracil and thymine react with benzoyl chloride in acetonitrile-pyridine solution at room temperature to give first their 1-N-benzoyl (2b and 3b) and then their 1-N, 3-N-dibenzoyl derivatives (4a and 4b, respectively); the latter compounds are converted into the corresponding 3-N-benzoyl derivatives (5a and 6a) under mild conditions of basic hydrolysis.

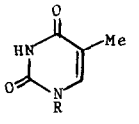
While it seems clear from the literature that both uracil (1a) and thymine (1b) react[1] with acetic anhydride to give their 1-N-acetyl derivatives (2a and 3a, respectively), the benzoylation of uracil and thymine does not appear to have been thoroughly investigated. It has been reported[2] that uracil reacts with benzoyl chloride in pyridine to give a mixture of 1- and 3-N-benzoyluracils (2b and 5a, respectively) but the evidence presented was not conclusive. However, Nováček *et al.* have shown[3] that when uracil (1a) or thymine (1b) is heated with an excess of benzoyl chloride in dioxan-pyridine, the corresponding 1-N, 3-N-dibenzoyl derivative[4] (4a or 4b) is obtained; these workers have also shown[3] that 1-N, 3-N-dibenzoyluracil (4a) decomposes during chromatography on alumina to give 3-N-benzoyluracil (5a) in good yield.



1 a; R = H
b; R = Me



2 a; R = Ac
b; R = Bz
c; R = Me



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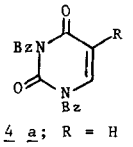
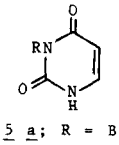
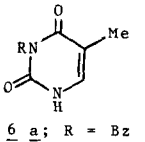


4 a; R = H
b; R = Me



5 a; R = Bz
b; R = Me



6 a; R = Bz
b; R = Me

We now report that when uracil (1a) was allowed to react with a slight excess of benzoyl chloride in acetonitrile-pyridine (5:1 v/v) at room temperature for 2.5 hr, 1-N-benzoyluracil (2b) was obtained as a crystalline solid, m.p. 167-168.5°C, in 89% isolated yield[9]. The

structure of 2b is based on its conversion [(i) CH_2N_2/acetone-ether, (ii) $MeNH_2$/ethanol] into 3-N-methyluracil (5b) in 60% isolated yield. Under similar conditions, thymine (1b) reacted with benzoyl chloride[10] to give 1-N-benzoylthymine (3b) in 85% isolated yield and uracil (1a) reacted with *p*-anisoyl chloride to give 1-N-(*p*-anisoyl)uracil (2; R = 4-$MeOC_6H_4CO$) in 68% isolated yield. The latter compounds (3b and 2; R = 4-$MeOC_6H_4CO$) were also characterized by converting them to the corresponding 3-N-methyl derivatives (6b and 5b, respectively).

When uracil (1a) and thymine (1b) were each stirred with a larger excess (2.2 mol. equiv.) of benzoyl chloride in acetonitrile-pyridine (5:2 v/v) at room temperature for 16 hr, they were converted into their 1-N, 3-N-dibenzoyl derivatives[3] (4a and 4b, respectively). The latter compounds were isolated as pure crystalline solids in 65 and 77% isolated yields, respectively. When 4a and 4b were treated with 0.25*M* potassium carbonate in dioxan-water (1:1 v/v), they were converted into 3-N-benzoyluracil (5a; 65%, m.p. 148-149°C) and 3-N-benzoylthymine (6a, 77%, m.p. 150-152°C)[11], respectively. Treatment of uracil (1a) with a twofold excess of *p*-nitrobenzoyl chloride in acetonitrile-pyridine at room temperature, followed by treatment of the products with ice-cold aqueous sodium hydrogen carbonate gave 3-N-(*p*-nitrobenzoyl)uracil (5; R = 4-$O_2NC_6H_4CO$) as a crystalline solid in 71% isolated yield. It did not prove possible to isolate the putative intermediate 1-N, 3-N-di-(*p*-nitrobenzoyl) derivative.

TABLE 1. ^1H and ^{13}C N.m.r. Spectroscopic Data[a]

Entry No.	Compound	NH	C(5)
1	Uracil (1a)		100.23
2	1-N-Benzoyluracil (2b)	11.59s	103.65
3	3-N-Benzoyluracil (5a)	~11.6 br	100.08
4	1-N, 3-N-Dibenzoyluracil (4a)	-	103.32
5	1-N-(*p*-Anisoyl)uracil (2; R = 4-$MeOC_6H_4CO$)	11.56s	103.12
6	3-N-(*p*-Nitrobenzoyl)uracil (5; R = 4-$O_2NC_6H_4CO$)	~11.7 br	100.07
7	Thymine (1b)		107.78
8	1-N-Benzoylthymine (3b)	11.62s	111.45
9	3-N-Benzoylthymine (6a)	~11.2 br	107.87
10	1-N, 3-N-Dibenzoylthymine (4b)	-	111.33

[a] ^1H N.m.r. spectra were measured at 250 MHz and ^{13}C n.m.r. spectra at 22.62 or 62.9 MHz. Anhydrous $(CD_3)_2SO$ was used as solvent. Chemical shifts are given in p.p.m. downfield from tetramethylsilane.

The-3-N-benzoyl derivatives of uracil and thymine (5a and 6a, respectively) and 3-N-(*p*-nitrobenzoyl)uracil (5; R = 4-$O_2NC_6H_4CO$) were characterized by converting them, by the two step process indicated above, into the corresponding 1-N-methyl derivatives (2c and 3c). However, an examination of the ^1H and ^{13}C n.m.r. spectra of the acyl-uracils and -thymines described above reveals that 1-N- and 3-N-acyl derivatives can be distinguished[12] (Table 1) on the basis of their exchangeable (NH) proton resonance signals and also on the basis of the chemical shifts of their C(5) carbon resonances. Thus, the H(3) proton resonances of 1-N-acyl derivatives [2b, 2(R = 4-$MeOC_6H_4CO$), and 3b; Table 1, entry nos. 2, 5, and 8] are observed as relatively sharp singlets at δ *ca.* 11.6 while the H(1) proton resonances of 3-N-

acyl derivatives [5a, 5(R = 4-$O_2NC_6H_4CO$), and 6a; entry nos. 3, 6, and 9] are observed as very broad signals over a wider chemical shift range. It can further be seen from Table 1 that the C(5) resonance signals of uracil and thymine are shifted significantly downfield (by > 3 p.p.m.) by the introduction of a 1-N-acyl substituent [Table 1, entry nos. 2, 4, 5, 8, and 10] but that 3-N-acylation [entry nos. 3, 6, and 9] has a much smaller effect.

TABLE 2. Deacylation of Monoacyl Derivatives of Uracil and Thymine

Entry No.	Compound	$t_{\frac{1}{2}}$ (min)[a]	t_{∞} (min)[a]
1	1-N-Benzoyluracil (2b)	-	<0.33
2	1-N-(*p*-Anisoyl)uracil (2; R = 4-$MeOC_6H_4CO$)	-	<0.33
3	1-N-Benzoylthymine (3b)	-	<0.33
4	3-N-Benzoyluracil (5a)	250	2250
5	3-N-(*p*-nitrobenzoyl)uracil (5; R = 4-$O_2NC_6H_4CO$)	6	45
6	3-N-Benzoylthymine (6a)	150	1200

[a]The experiments were carried out by adding concentrated aqueous ammonia (*d* 0.88, 0.1 ml) to a stirred suspension of substrate (0.005g) in methanol (0.9 ml) at 20°C. Thus the deacylation medium is *ca.* 1.5*M*-ammonia in methanol-water. The reactions were monitored by t.l.c.: $t_{\frac{1}{2}}$ and t_{∞} represent the approximate times for the half-completion and completion of the reactions.

The observation that it is possible to prepare both 1-N- and 3-N-benzoyl derivatives of uracil and thymine in relatively good yields is clearly of practical importance. The latter monoacyl derivatives can be regarded as protected intermediates which are potentially of synthetic value. Thus, as indicated above, 1-N- and 3-N-methyluracils (2c and 5b) were easily obtained, in satisfactory yields, by deacylating the methylation products of 3-N- and 1-N-benzoyluracils (5a and 2b), respectively. In order to investigate the suitability of aroyl groups for the protection of uracil and thymine residues, we attempted to measure the relative rates of deacylation of the above monoacyl derivatives. The deacylating agent used was *ca.* 1.5*M*-ammonia in wet methanol. The results obtained [Table 2] indicate that 1-N-acyl derivatives [entry nos. 1-3] undergo deacylation at rates which may be as much as four orders of magnitude faster than the rates for the corresponding 3-N-acyl derivatives [entry nos. 4-6]. Indeed, deacylation of the 1-N-acyl derivatives was too fast to measure accurately. As expected, 3-N-(*p*-nitrobenzoyl)uracil (5; R = 4-$O_2NC_6H_4CO$) [entry no. 5] underwent ammonolysis appreciably faster than 3-N-benzoyluracil (5a) [entry no. 4]. Thus, it is hardly surprising in the light of these deacylation studies, that attempts to isolate 1-N-(*p*-nitrobenzoyl)uracil (2; R = 4-$O_2NC_6H_4CO$) and 1-N, 3-N-di-(*p*-nitrobenzoyl)uracil (see above) were not successful. It may be concluded from the data in Table 2 that benzoyl and other aroyl groups are likely to be useful for the 3-N-protection of uracil, thymine and related pyrimidines but that they are likely to be only of limited use for the 1-N protection of these systems.

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REFERENCES AND FOOTNOTES

[1] L.B. Spector and E.B. Keller, *J. Biol. Chem.*, 232, 185 (1958).

[2] R.W. Chambers, *Biochemistry*, 4, 219 (1965).

[3] A. Nováček, D. Hesoun, and J. Gut, *Collection Czechoslov. Chem. Commun.*, 30, 1890 (1965).

[4] Notwithstanding the evidence in the literature that 2-acetoxy- and 2-benzoyloxy-pyridines are, respectively, the principal acetylation[5] and benzoylation[6] products of 2-pyridone, it has been tacitly assumed by previous workers[7] that uracil and thymine undergo acylation on N-1 and N-3 rather than on O-2 and O-4. While it is difficult to support this assumption on the basis of n.m.r. and i.r. spectroscopic evidence [for example, 1-N, 3-N-dibenzoylthymine (4b) and 3-N-benzoyluracil (5a) have ν_{max}^{KBr} 1750 and 1765 cm^{-1}, respectively], a recent X-ray crystal structure determination has established[8] that 1-N, 3-N-dibenzoylthymine (4b) has indeed been assigned the correct structure.

[5] A. McKillop and M.J. Zelesko, *Tetrahedron Lett.*, 4945 (1968).

[6] D.Y. Curtin and L.L. Miller, *J. Am. Chem. Soc.*, 89, 637 (1967); P.A. Singgih and M.J. Janssen, *Tetrahedron Lett.*, 4223 (1971).

[7] See, for example, refs. 1-3.

[8] S. Neidle, A. Aggarwal, B. Chaudhuri, and C.B. Reese, unpublished observations.

[9] Satisfactory microanalytical and spectroscopic data were obtained for all new compounds described.

[10] Benzoyl chloride (1.39 ml, 12.0 mmol) was added in one portion to a magnetically stirred suspension of powdered thymine (1.261g, 10.0 mmol) in acetonitrile (10 ml) and pyridine (2 ml) at room temperature. The reaction mixture remained heterogeneous throughout. After 2 hr, the products were filtered and the crystalline residue was washed with acetonitrile and then dried *in vacuo* at room temperature for 24 hr. 1-N-Benzoylthymine (3b) was thereby obtained as a colourless crystalline solid, m.p. 212-213°C; yield, 1.968g (85%); R_F 0.55 [$CHCl_3$-MeOH (9:1 v/v)]; ν_{max}^{KBr} 1735, 1700, 1675, 1650(sh), 1600 cm^{-1}; δ_H [$(CD_3)_2SO$, 250 MHz] 1.90 (3H, s), 7.54 (2H, m), 7.69 (1H, m), 7.85 (3H, m), 11.62 (1H, s).

[11] If 1-N, 3-N-dibenzoylthymine (4b) is not isolated as an intermediate, 3-N-benzoylthymine (6a) can be prepared from thymine (1b) in 80% overall yield.

[12] Isomeric 1-N- and 3-N-benzoyl derivatives of uracil and thymine can also be easily distinguished by t.l.c. [Merck silica gel 60 F_{254} plates, developed in $CHCl_3$-MeOH (9:1 v/v)]. Thus, the R_F's of the 1-N-benzoyl derivatives (2b and 3b) were found to be higher than the R_F's of the corresponding 3-N-benzoyl isomers (5a and 6a, respectively). As expected, the R_F's of the 1-N, 3-N-dibenzoyl derivatives (4a and 4b) were found to be higher still.

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