JOURNAL
OF
THE CHEMICAL SOCIETY

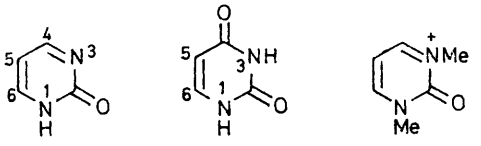
SECTION B
Physical Organic Chemistry

Kinetics and Mechanism of Electrophilic Substitution of Heteroaromatic Compounds. Part XXII.[1] The Nitration of Pyrimidinones

By **C. D. Johnson, A. R. Katritzky, M. Kingsland, and E. F. V. Scriven,** School of Chemical Sciences, University of East Anglia, Norwich NOR 88C

Pyrimidin-2(1*H*)-one and pyrimidin-2(1*H*),4(3*H*)-dione (uracil) and their *N*-methyl derivatives are nitrated in sulphuric acid as the oxo- (or dioxo-) tautomeric forms of the free base species. Rate constants are compared with those for other heterocycles and the influence of the ring NH and CO groups is discussed.

A RECENT comparison of the acid-catalysed hydrogen exchange of pyrimidinones[2] with earlier data for pyridones[3] indicated a significant effect of covalent hydration in the pyrimidinones. We now report on the nitration of pyrimidinones which represents an extension of our general investigation of the nitration of heterocycles.



(I) (II) (III)

The preparative nitrations of pyrimidin-2(1*H*)-one (I) and its 1-methyl derivative were described by Fox *et al.*,[4] and we find that these reactions can be followed kinetically by the usual u.v. technique. However, our attempts to nitrate pyrimidin-4(1*H*)-one failed, both at the preparative and kinetic levels. The nitration of uracil (II) is well known:[5] this reaction and those of the corresponding 6-methyl and 1,3-dimethyl derivatives proceeded smoothly under kinetic conditions. However, the nitration of 2,4-dimethoxypyrimidine could only be followed kinetically over the first 20% of reaction in 98% sulphuric acid, and not at all at lower acidities because of concomitant hydrolysis. The nitration of 6-chlorouracil was accompanied by fast hydrolysis to nitrobarbituric acid.

EXPERIMENTAL

Materials.—Nitric acid and sulphuric acid were AnalaR grade; the acids used for kinetic runs were prepared by diluting the sulphuric acid with deionized water, and standardized by titration. Uracil, 1,3-dimethyluracil, and 6-methyluracil were recrystallized commercial samples with m.p.s agreeing with literature values. The following compounds were prepared by the literature methods quoted: 5-nitrouracil,[5] m.p. 278—280° (decomp.); 2,4-dimethoxypyrimidine, b.p. 90—95°/10 mm. (lit.,[6] 202°/760 mm.); 2,4-dimethoxy-5-nitropyrimidine, m.p. 93° (lit.,[7] 92—93°); 1,3-dimethyl-5-nitrouracil, m.p. 157° (lit.,[8] 155°); 6-methyl-5-nitrouracil,[9] m.p. 285° (lit.,[10a] 290°); 6-chlorouracil, m.p. 298° (decomp.) (lit.,[11] 300° decomp.): 6-chloro-5-nitro-uracil, m.p. 200—205° (lit.,[11] 220—222°); pyrimidin-2(1*H*)-one, m.p. 160—161° (lit.,[12] 179—181°); 5-nitropyrimidin-2(1*H*)-one, m.p. 199—200° (lit.,[4] 200—202°); 1-methylpyrimidin-2(1*H*)-one, m.p. 125—126° (lit.,[13] 125—

[1] Part XXI, P. J. Brignell, P. E. Jones, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1970, 117.
[2] A. R. Katritzky, M. Kingsland, and O. S. Tee, *J. Chem. Soc.* (*B*), 1968, 1484.
[3] P. Bellingham, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1967, 1226.
[4] J. J. Fox and L. M. Stempel, Report of A. C. S. Meeting, New York, 1963.
[5] D. J. Brown, *J. Appl. Chem.*, 1952, **2**, 239.
[6] G. E. Hilbert and T. B. Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 2001.
[7] D. J. Brown, *J. Appl. Chem.*, 1957, **7**, 109.
[8] D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.*, 1955, 211.
[9] R. K. Robins, F. W. Furcht, A. D. Grauer, and J. W. Jones, *J. Amer. Chem. Soc.*, 1956, **78**, 2418.
[10] D. J. Brown, 'The Pyrimidines,' 'The Chemistry of Heterocyclic Compounds,' ed. A. Weissberger, vol. 16, 1962, (*a*) p. 606; (*b*) p. 522.
[11] R. M. Cresswell and H. C. S. Wood, *J. Chem. Soc.*, 1960, 4768.
[12] R. R. Hunt, J. F. W. McOmie, and E. R. Sayer, *J. Chem. Soc.*, 1959, 525.
[13] J. J. Fox and D. Van Praag, *J. Amer. Chem. Soc.*, 1960, **82**, 486.

TABLE 1

pK_a Values of pyrimidines and wavelengths for measurements of nitration products

Compound	λ/nm (pK_a)	H_0 [a] (half-protonation)	n [a]	pK_a	λ/nm [b] (kinetic)	log ε [c] (product)
Uracil	258	−3·50 [d]	1·89 [d]	−1·85 [e]	300	3·76
1,3-Dimethyluracil	265	−3·25 [d]	1·76 [d]	−1·85 [e]	310	3·93
6-Methyluracil	280	−2·48	1·75	−1·42 [e]	300	3·51
2,4-Dimethoxypyrimidine				*f*	300	2·97
Pyrimidin-2(1*H*)-one				2·24 [g]	350	3·50
1-Methylpyrimidin-2(1*H*)-one				2·50 [h]	350	3·58

[a] Calculated from equation $H_0 = H_0(\text{half-protonation}) - n \log [BH^+]/[B]$. [b] For appearance of nitro-compound; in all cases nitration occurred at the 5-position. [c] In all cases, log ε (substrate) <0·01. [d] A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 1962, 1540. [e] Calculated assuming H_A acidity behaviour ($n = 1·67$). [f] Unable to be determined owing to rapid hydrolysis. [g] Determined potentiometrically (A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 1951, 414). [h] Determined potentiometrically, taken from ref. 8.

TABLE 2

Nitrations at high acidities

H_2SO_4/%	$-H_0$ [a]	10^3k_2 (obs) / (l mol^{-1} s^{-1})	log k_2 (obs) + 4	log k_2(fb) [b] + 1
		Uracil at 50 °C		
97·3	10·27	0·63	0·797	2·30
95·6	9·96	1·54	1·188	2·06
93·2	9·54	3·72	1·570	2·20
91·1	9·08	4·88	1·689	2·03
89·0	8·75	7·32	1·864	2·00
87·0	8·45	5·80	1·763	1·73
85·6	8·19	3·17	1·501	1·31
83·6	7·91	1·03	1·041	0·68
		1,3-Dimethyluracil at 50 °C		
96·9	10·20	3·72	1·57	2·73
93·6	9·61	8·51	1·93	2·74
91·8	9·25	16·2	2·21	2·80
90·5	8·97	26·3	2·42	2·85
88·4	8·67	20·0	2·30	2·55
85·0	8·15	12·3	2·09	2·03
80·4	7·39	1·74	1·24	0·72
		6-Methyluracil at 40 °C		
97·3	10·27	1·62	1·208	2·88
95·5	9·95	5·85	1·385	2·86
93·7	9·62	7·17	1·855	3·12
91·5	9·18	12·3	2·091	3·11
89·8	8·86	12·6	2·100	2·92
88·9	8·74	10·6	2·025	2·77
87·3	8·40	8·14	1·911	2·45
81·5	7·58	3·13	0·495	0·54
		Pyrimidin-2(1*H*)-one at 115 °C		
96·1	10·04	0·121	0·082	10·36
94·2	9·71	0·224	0·350	9·30
91·9	9·26	0·433	0·636	9·14
89·8	8·87	0·425	0·628	8·74
89·2	8·78	0·296	0·471	8·49
86·4	8·36	0·023	−0·640	6·96
		1-Methylpyrimidin-2(1*H*)-one at 115 °C		
98·2	10·46	0·229	0·360	10·32
95·5	9·94	0·621	0·418	9·86
91·9	9·27	0·960	0·982	9·75
89·8	8·88	1·10	1·042	9·42
86·8	8·42	0·357	0·553	8·47
86·3	8·34	0·177	0·249	8·09

[a] Taken from M. J. Jorgenson and D. R. Harrter, *J. Amer. Chem. Soc.*, 1963, **85**, 985. [b] Calculated assuming $n = 1·67$.

126°); 1-methyl-5-nitropyrimidin-2(1*H*)-one, m.p. 169—170° (lit.,[13] 170—171°); pyrimidin-4(1*H*)-one, m.p. 164° (lit.,[10b] 163—165°); a sample of 1,3-dimethyl-2(1*H*)-oxopyrimidinium hydrogen sulphate was kindly supplied by Dr. O. S. Tee. All the above compounds that were used for kinetic studies ran as one spot on t.l.c. plates.

Kinetic Procedures.—Rate measurements were carried out under pseudo-first-order conditions as previously described.[14] pK_a Values [15] and the wavelengths at which the kinetics were followed are given in Table 1. The results are recorded in Table 2.

DISCUSSION

Uracil and its Methyl Derivatives.—The rate profiles for the nitration of uracil and its 1-methyl and 1,3-dimethyl derivatives both for the high (Figure 1) and

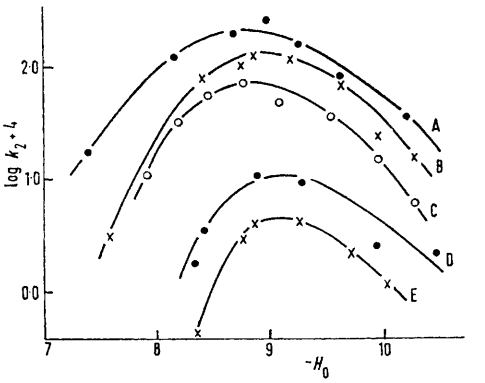


FIGURE 1 Rate profiles for the nitration of: A, 1,3-dimethyluracil at 50°; B, 6-methyluracil at 45°; C, uracil at 50°; D, 1-methylpyrimidin-2(1*H*)-one at 115°; and E, 2-pyridone at 115°

for the low acidity region (Figure 2) indicate that these compounds are all nitrated in the free-base form (Table 3). Thus, for the high acidity region, the increase in rate with H_0 at acidities lower than $H_0 = -9$ is less (and the decrease at acidities above this greater) than would be expected for the nitration of a species, the concentration of which is invariant with acidity.[16] Uracils protonate on oxygen and follow an acidity function similar to H_A;[17,18] Figure 3 shows rate profiles

[14] C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, and M. Viney, *J. Chem. Soc.* (*B*), 1967, 1204.
[15] C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, N. Shakir, and A. M. White, *Tetrahedron*, 1965, **21**, 1005.
[16] A. R. Katritzky and C. D. Johnson, *Angew. Chem.* (*Internat. Edn.*), 1967, **6**, 608.
[17] A. R. Katritzky, A. J. Waring, and K. Yates, *Tetrahedron*, 1963, **19**, 465.
[18] K. Yates, J. B. Stevens, and A. R. Katritzky, *Canad. J. Chem.*, 1964, **42**, 1957.

corrected for the variation of free base concentration with acidity; they now have the normal form. The Moodie–Schofield plots [19] for the lower acidity regions (Figure 2) have least-square slopes of 0·43 (uracil), 0·47 (1,3-dimethyluracil), and 0·40 (1-methyluracil): these values are as expected for free bases, such plots for nitrations proceeding on conjugate acids show slopes

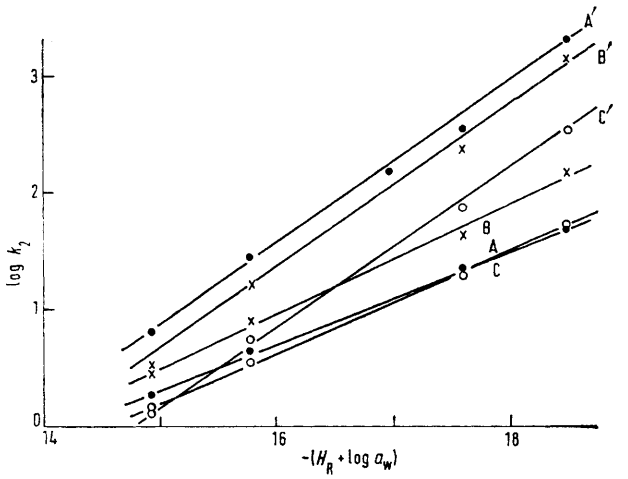


FIGURE 2 Moodie–Schofield plots of log k_2 (obs) against $-(H_R + \log a_w)$ for the nitration of: A, 6-methyluracil; B, 1,3-dimethyluracil; and C, uracil, all at 60 °C. A′, B′, and C′ are corresponding plots of log k_2(fb) against $-(H_R + \log a_w)$

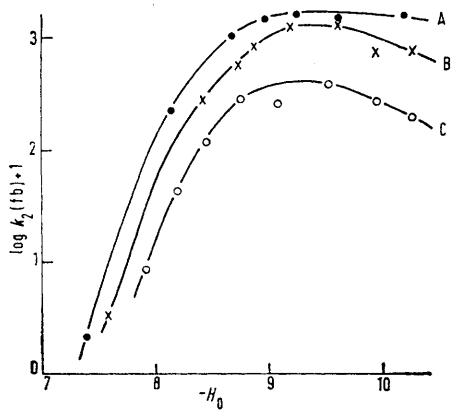


FIGURE 3 Rate profiles for the nitration of: A, 1,3-dimethyluracil at 50°; B, 6-methyluracil at 40°; C, uracil at 50 °C; rate constants are for reaction on the free base species, the concentration of which is calculated by use of H_A

of *ca.* unity. Similar plots of log k_2(fb) against $-(H_R + \log a_w)$, also shown in Figure 2, have slopes of *ca.* 0·7 (w = H_2O).

The Arrhenius parameters (Table 4) also support reaction as the free base species: the activation energies (E_a) are all *ca.* 24 kcal mol^{-1} with log A values of 13·7—14·9. A wide variety [20] of electrophilic nitration reactions *via* free base species have E_a = *ca.* 22 kcal mol^{-1} whereas many nitrations of conjugate acids have E_a = *ca.* 17 kcal mol^{-1} in the 90—98% sulphuric acid region.

TABLE 3

Nitrations at low acidities at 60 °C

H_2SO_4/%	$-(H_R + \log a_w)$	$\frac{\log k_2 \text{ (obs)} + 4}{(\text{l mol}^{-1}\text{ s}^{-1})}$	log k_2(fb) [a] + 2
		Uracil	
76·2	14·93	0·156	0·10
78·7	15·78	0·563	0·74
83·0	17·59	1·294	1·88
85·3	18·48	1·729	2·54
		1,3-Dimethyluracil	
76·2	14·93	0·454	0·53
78·7	15·78	0·905	1·23
83·0	17·59	1·642	2·38
85·3	18·48	2·194	3·15
		6-Methyluracil	
76·2	14·93	0·275	0·81
78·7	15·78	0·665	1·45
81·5	16·96	1·144	2·19
83·0	17·59	1·359	2·56
85·3	18·48	1·704	3·12

[a] Calculated assuming H_A behaviour (n = 1·67).

The similarity in rate between the three compounds indicates that uracil and 1-methyluracil are undergoing nitration in the dioxo-form rather than *via* any of the minor tautomeric species. This is confirmed by the appreciably lower rate found for 2,4-dimethoxypyrimidine (a factor of *ca.* 1·6 × 10^{-4} compared with uracil at 25 °C and $-H_0$ 10·26). Unfortunately rate profiles could not be determined for the dimethoxy-compound because of hydrolysis at lower acidities; however, the Arrhenius parameters (Table 4) suggest [20] reaction on the conjugate acid.

TABLE 4

Temperature-dependence of rates of nitration

H_2SO_4/%	Temp./°C	$-\log k_2$ (obs)	E_a	log A
		Uracil		
91·2	29·4	3·115	23·14	13·71
	38·7	2·836		
	45·2	2·252		
		1,3-Dimethyluracil		
91·2	33·8	2·618	24·03	14·46
	45·3	1·874		
	50·4	1·778		
		6-Methyluracil		
90·2	29·4	2·315	24·09	14·91
	34·5	2·036		
	45·2	1·452		
		2,4-Dimethoxypyrimidine		
97·5	50·3	3·18	16·42	7·93
	55·6	3·03		
	61·8	2·81		
	65·7	2·68		

Pyrimidin-2(1H)-one and its 1-Methyl Derivative.—The shapes of the high acidity rate profiles (Figure 1)

[19] K. Schofield, R. B. Moodie, and M. J. Williamson, 'Nitro-compounds,' Proceedings of the International Symposium, Warsaw, September 1963.

[20] C. D. Johnson, A. R. Katritzky, and E. F. V. Scriven, unpublished work.

indicate that the compounds are also nitrated as free bases. This is confirmed by the unreactivity of the cationic species (III) to nitration under comparable conditions.

In conclusion, in connection with the calculation of partial rate factors, we note the important observation made by Moodie and Schofield [21] that realistic comparisons of deactivated aromatic compounds with benzene can only be made in acidities of less than 68% aqueous sulphuric acid. A detailed consideration of partial rate factors for these compounds is therefore deferred for a general review: [20] it can be seen qualitatively however that the introduction of a second nitrogen atom into pyridone somewhat *decreases* the reactivity towards nitration as expected, although direct comparison is difficult because of temperature differences; *cf.* pyrimidin-2(1*H*)-one at 115 °C in 89·8% H_2SO_4, log k_2(fb) = 7·74; 3-methyl-2-pyridone at 31° in 90·07% H_2SO_4, log k_2(fb) = 5·32.[22]

[9/1943 *Received*, *November* 13*th*, 1970]

[21] R. G. Coombes, R. B. Moodie, and K. Schofield, *J. Chem. Soc.* (*B*), 1968, 800.

[22] P. J. Brignell, A. R. Katritzky, and H. O. Tarhan, *J. Chem. Soc.* (*B*), 1968, 1477.