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Selective Oxidative Halogenation of Uracils

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A variety of *N*-substituted uracils has been selectively brominated to the corresponding 5-bromouracils in high yield by $CHBr_3$–O_2. Both oxidative bromination and chlorination of *N*-substituted uracils can be performed by means of a combination of haloalkane solvents with *m*-chloroperbenzoic acid, magnesium monoperoxyphthalate, *tert*-butyl hydroperoxide or iodosylbenzene. Intermediates along the reaction path leading to the 5-halouracils have been identified; the intermediates depend on the oxidant used. Mechanistic aspects of the halogenation reactions and the reactive intermediates are discussed.

Selective oxidative halogenation of organic substrates in a simplified manner has received considerable interest in recent years.[1] One way to accomplish oxidative halogenation is the combination of a halide, an oxidant and a catalyst, and this procedure has, e.g. been related to the study of the action of enzymes which can catalyse halogenation.[2] Another approach to halogenation has been introduced by Barton *et al.*, who have been able to brominate unactivated C–H bonds, using bromoalkanes and the $GoAgg^{III}$-system ($FeCl_3 \cdot 6\,H_2O$, picolinic acid, H_2O_2 in pyridine–acetic acid) as the catalyst.[3]

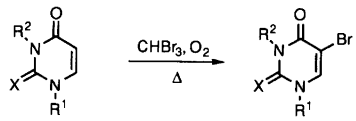
Uracil is a fundamental building block in the nucleic acids,[4] and halogenation of both uracil and *N*-substituted uracils has received considerable attention because of the importance of these reactions in relation to changes in cells, and because halogenated uracils may have favourable therapeutic effects.[5] Fluorouracils have found use in cancer treatment,[6] chlorouracils[7] and bromouracils[8] may induce cancer, whereas iodouracils may have potential application in the treatment of herpes and AIDS.[5]

The introduction of a halogen in uracil and *N*-substituted uracils using a halide/halogen donor system and an oxidant, with or without a catalyst is another way of performing halogenation of these systems. This approach is important in relation to the interaction of the uracil with the reactive intermediates formed by an oxidant and a halide/halogen donor system. The oxidative halogenation of uracils catalysed by enzymes,[9] and a halide in combination with an oxidant,[10] has only briefly been studied.

This paper describes a new approach towards oxidative halogenation of *N*-substituted uracils and *N*-substituted-5,6-dihydrouracils (*i*) using $CHBr_3$ in combination with O_2, (*ii*) with *m*-chloroperbenzoic acid, magnesium monoperoxyphthalate, *tert*-butyl hydroperoxide or iodosylbenzene in combination with a haloalkane solvent and (*iii*) halogenation with haloalkanes initiated by radical initiators.

Results and discussion

N-Substituted uracils, **1**, form the 5-bromo analogue **2** on being heated in $CHBr_3$ saturated with O_2 at 90°C (Table 1). No reaction was observed in the absence of oxygen.



1 **2**

The results in Table 1 show that a selective bromination of **1** takes place, as only the corresponding 5-bromo analogue, **2**, is formed. 1,3-dimethyl-2-thiouracil (**1b**, entry 2) gave mainly 5-bromo-1,3-dimethyl-2-thiouracil, (**2b**, 83%), with 5-bromo-1,3-dimethyluracil as a by-

Table 1. Selective bromination of **1a–h** using $CHBr_3$–O_2 at 90°C.

Entry	1	R^1	R^2	X	Reac. time/h	Yield of **2** (%)[a]
1	**a**	CH_3	CH_3	O	11	91
2	**b**	CH_3	CH_3	S	16	83 6 (X=O)
3	**c**	C_2H_5	H	O	5	86
4	**d**	$CH(CH_3)_2$	H	O	5	95
5	**e**	C_3H_7	H	O	13	95
6	**f**	C_6H_5	H	O	16	93
7	**g**	*p*-Cl–C_6H_4	H	O	24	95
8	**h**	C_6H_5	CH_3	O	5	89

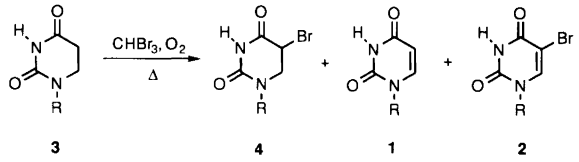
[a] Isolated yield.

Table 2. Bromination of **3d, f** using $CHBr_3$–O_2 at 90°C.

Entry	3	R	Reac. time/h	Yield of **4** (%)	Yield of **1** (%)	Yield of **2** (%)
1	**d**	$CH(CH_3)_2$	5	8	0	22
2	**f**	C_6H_5	1	≈2	7	24
3	**f**	C_6H_5	5	34	0	29

product (6%). The latter is formed by a subsequent >C=S to >C=O transformation, which can be observed for the reaction of thiouracils with soft electrophiles.[11] It should be noted that the $CHBr_3$–O_2-bromination in the phenyl derivatives was selective for the uracil ring (**1f, h**, entries 6, 8).

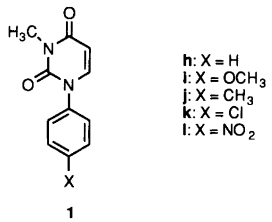
Bromination of *N*-substituted-5,6-dihydrouracils, **3**, using $CHBr_3$–O_2 gave **4** and **2** as the major products (Table 2).



3 **4** **1** **2**

Based on the product distribution in Table 2 it is suggested that the first product formed is the 5-bromo-5,6-dihydrouracil derivative, **4**, which eliminates HBr to the uracil, **1**, which is subsequently brominated (**2**). It has been found that **4f** eliminates HBr with formation of **1f** under these reaction conditions supporting this reaction sequence.

The reaction rate for the bromination of **1h–l** using $CHBr_3$–O_2 shows no general tendency, and no significant difference in reaction rate for the substrates is observed. The only notable difference for the disappearance of **1h–l** is that **1i** is more reactive than **1l**.

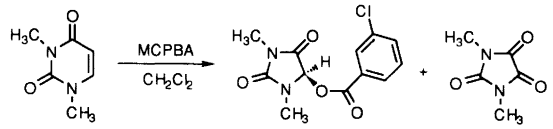


1

h: X = H
i: X = OCH_3
j: X = CH_3
k: X = Cl
l: X = NO_2

The use of $CHBr_3$–O_2 in the presence of a radical trap, e.g., 2-methyl-*N*-(phenylmethylene)-2-propylamine *N*-oxide, gave no bromination, indicating that radicals might be present along the reaction path.

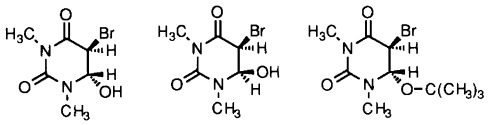
The oxidative chlorination and bromination of **1a** using MCPBA (*m*-chloroperbenzoic acid), MMPP (magnesium monoperoxyphthalate), TBHP (*tert*-butyl hydroperoxide) or iodosylbenzene (PhIO) and haloalkanes as the halogen donor have also been investigated. To the best of our knowledge the only reaction previously reported in this field has been an attempt to oxidise **1a** with MCPBA in CH_2Cl_2 which besides 5-chloro-1,3-dimethyluracil, gave **5** and **6**, in low yield.[10a,d]



1a **5** **6**

The results for oxidative bromination of **1a** using various oxidation reagents and $CHBr_3$ are presented in Table 3.

Use of MCPBA at 25°C gave **2a** as the major product and a minor amount of **5** (Table 3, entry 1). Two initial intermediates are also formed, which gradually disappear as the reaction proceeds. Independent syntheses have confirmed the structures as *trans*-5-bromo-1,3-dimethyl-6-hydroxyuracil, **7**, and *cis*-5-bromo-1,3-dimethyl-6-hydroxyuracil, **8**.



7 **8** **9**

With oxidation reagent TBHP the reaction proceeds readily at 90°C, not at 25°C (Table 3, entries 2, 3) (**2a**, 72%) with a minor amount of 5-bromo-6-*tert*-butoxy-1,3-dimethyluracil, **9**. Compound **9** is also an intermediate

Table 3. Oxidative bromination of 1,3-dimethyluracil, **1a**, in $CHBr_3$ with different oxidants.

Entry	Oxidant	*T*/°C	Reac. time/h	Yield of **2a** (%)	Other products Yield (%)
1	MCPBA	25	8	78	**5** (≈2), **7,8**[a]
2	TBHP	25	24	<2	—
3	TBHP	90	6	72	**9** (4)[a]
4	PhIO	90	12.5	88	**7,8**[a]

[a] See the text.

Table 4. Oxidative chlorination of 1,3-dimethyluracil, **1a**, in CH_2Cl_2 or $Cl_2CHCHCl_2$ using different oxidants.

Entry	Oxidant	*T*/°C	Reac. time/h	Yield of **10a** (%)	Other products Yield (%)
1	MCPBA[a]	25	5	<2	**11**[c] (35)
2	MMPP[a]	61	72	25	—
3	TBHP[b]	90	5	33	—
4	PhIO[b,d]	90	5	71	**12**[c] (5)

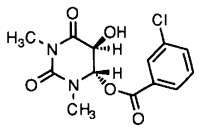
[a] $CHCl_3$ as the chlorine donor. [b] $Cl_2CHCHCl_2$ as the chlorine donor. [c] See the text. [d] Iodosylbenzene : **1a** = 3 : 1.

in this reaction. The reagent PhIO, which in recent years has been used mainly as a terminal oxidant in transition-metal catalysed oxidations,[12] can effect bromination of **1a** to **2b** (88%) in $CHBr_3$, with traces of the intermediates **7** and **8**.

MCPBA and PhIO in $CHBr_3$ probably react with **1a** to give first **7** and **8**, followed by elimination of H_2O to produce **2a**. Independent synthesis of **7** and **8** by reaction of **1a** with Br_2–H_2O followed by heating of **7** and **8** to the reaction temperature for the MCPBA and the PhIO reactions, leads to elimination of H_2O to produce **2a**. For the formation of the minor product, **5**, the C(5)–C(6) bond in the uracil ring is broken, followed by a nucleophilic attack of N(1) at C(5) and an elimination of a C=O fragment and addition of *m*-chlorobenzoate. Changing the oxidant to TBHP also leads to the formation of **2a** as the main product and the reaction proceeds probably via an intermediate related to that observed for the MCPBA and PhIO reactions, but with *tert*-butoxide replacing the hydroxide group.

The different oxidation reagents, in combination with chloroalkanes, can effect chlorination of **1a** to 5-chloro-1,3-dimethyluracil, **10a** (Table 4).

The reagent MCPBA in $CHCl_3$ cannot chlorinate **1a** at 25°C and the only product detected is **11** (Table 4, entry 1). Changing the oxidation reagent to MMPP in $CHCl_3$ at 61°C leads to the formation of **10a** in 25% yield (Table 4, entry 2). The reagent TBHP in $Cl_2CHCHCl_2$ at 90°C chlorinates **1a** in 33% yield (Table 4, entry 3), but PhIO is the most reactive reagent, as 71% of **10a** is obtained in $Cl_2CHCHCl_2$, with a minor amount of **12** (Table 4, entry 4).



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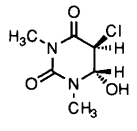

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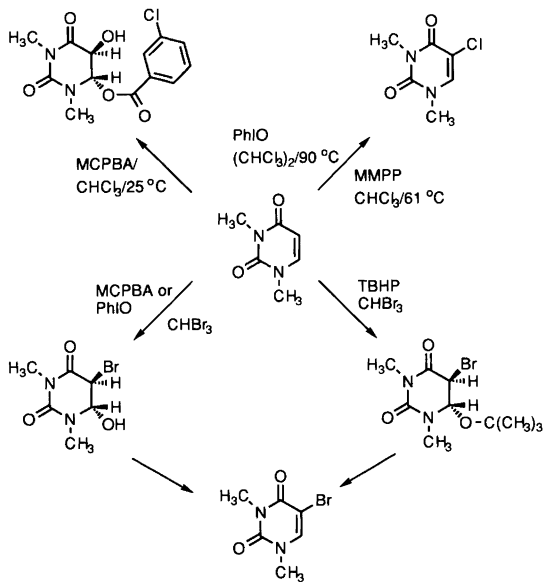
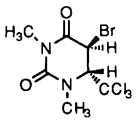
The main reaction paths for the oxidative halogenation of **1a** with haloalkane solvents are summarised in Scheme 1.

The bromination of **1a** can also be achieved with radical initiators such as azoisobutyronitrile (AIBN) and benzoyl peroxide (BPO) in $CHBr_3$. The results are presented in Table 5, where the reactions with AIBN were carried out at 90°C, while the reactions with BPO were performed at 65°C.



Scheme 1.

A 1 : 1 ratio between the substrate and the radical initiator is necessary for the reaction to proceed in high yield; BPO was observed to be a better initiator than AIBN (Table 5, entries 1 and 4). No 'Kharasch-addition' by-products of $CHBr_3$[13] were observed in these radical-initiated reactions. However, changing the halogen donor to $CBrCl_3$ with BPO as the radical initiator leads to the formation of the 'Kharasch-addition' products **13** and **14**, in addition to the expected **2a**.



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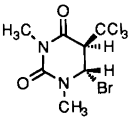

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Table 5. Reaction of 1,3-dimethyluracil, **1a**, in $CHBr_3$ in the presence of radical initiators azoisobutyronitrile (AIBN) and benzoyl peroxide (BPO).

Entry	Initiator	Reac. time/h	In: **1a**	Yield of **2a** (%)
1	AIBN	11.5	1 : 1	81
2	AIBN	11.5	1 : 10	24
3	AIBN	46.5	1 : 10	28
4	PBO	5	1 : 1	98
5	PBO	6	1 : 5	32

To achieve bromination with $CHBr_3$ it is necessary to bubble O_2 through $CHBr_3$ (in the present experiments we found that bubbling for 2 h leads to an active $CHBr_3$ solution). Freshly distilled $CHBr_3$ cannot brominate the uracil derivatives. It has also been found that the addition of Br_2 does not accelerate the bromination. This is probably due to equilibrium (1)[14]

$$CHBr_3 + Br_2 \rightleftharpoons CBr_4 + HBr$$

and the fact that Br_2 shifts the equilibrium to the right. An analysis of the $CHBr_3$–O_2 solution shows that, besides $CHBr_3$, which is the major component, CH_2Br_2 and $COBr_2$ were also identified, the former by ^1H NMR and MS and the latter by MS. It is known that $CHBr_3$ can be oxidised to $COBr_2$,[15,16] and that it can decay to CO and Br_2. The Br_2 formed can then react with the substrate, and this principle has been used in the von Braun reaction.[17] The $CHBr_3$–O_2 combination seems thus to be a mild and selective bromination reagent like NBS and tribromide salts.

The bromination of uracils with Br_2–H_2O is a classical reaction,[18] but proceeds via a complex set of mechanisms depending on the reaction conditions.[19] NBS can achieve selective bromination of uracils in the 5-position under both ionic and radical conditions.[20] The combination of the bromide ion and an oxidant for the bromination of uracils has only been described for a few cases: KBr–$Na_2S_2O_8$ in acetic acid,[10e] HBr–MCPBA in DMF[10d] and LiBr–cerium(IV) ammonium nitrate (CAN) in CH_3CN or CH_3OH.[10g] A comparison of these methods with that described here reveals that the latter is both easy and convenient to use for bromination of the substituted uracils. The present method can, e.g., be compared with the CAN procedure[10g] where a stoichiometric amount of oxidation reagent is necessary, whereas the present method only requires bubbling of O_2 through $CHBr_3$.

The combination of the oxidants MCPBA, MMPP, TBHP and PhIO and haloalkanes leads to a system which can perform bromination and chlorination, with the former as the most feasible reaction. But the oxidant/haloalkane leads to various by-products depending on the system used, and is therefore not comparable to the $CHBr_3$–O_2 method. The radical-initiated bromination of using AIBN and BPO also leads to bromination of the 5-position in the uracils, showing that this position is the most reactive position for halogenation under the different reaction conditions studied.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Varian 200 MHz Gemini spectrometer. Deuteriochloroform or dimethyl sulfoxide was used as the solvent and reported δ values are relative to tetramethylsilane (TMS). Mass spectra were recorded on a Micromass 7070F mass spectrometer and GLC–MS on a Trio-2 spectrometer.

Materials. CH_2Cl_2, $CHCl_3$, $Cl_2CHCHCl_2$ and $CHBr_3$ were purified according to the standard methods and distilled before use. To 'activate' $CHBr_3$, O_2 was bubbled through a commercially available sample for about 2 h. Uracil is commercially available and was used without further purification. The other uracil derivatives were prepared according to the literature.[21] MCPBA, MMPP and TBHP are commercially available; PhIO was synthesised according to the literature.[22]

General procedure for bromination of **1** *and* **3** *with* $CHBr_3$–O_2. Compound **1** or **3** (0.5 mmol) was dissolved in 5 ml $CHBr_3$ which had been activated with O_2 as described above, at 90°C and stirred for the reaction times given in Tables 1 and 2. The $CHBr_3$ was evaporated off and the product was recrystallised and analysed by spectroscopic means. The data for some of the compounds are given below.

Kinetic experiments. The general procedure was used and samples of the reaction mixture was taken every 0.5–2 h. The solvent was evaporated off and the reaction mixture was analysed by NMR spectroscopy.

Oxidative halogenation of 1,3-dimethyluracil, **1a**, *with haloalkanes and an oxidant.* Compound **1a** (0.5 mmol) and 0.5 mmol of the oxidant (MCPBA, MMPP, TBHP or PhIO) were mixed in 2 ml of the haloalkane solvent. The reaction times and temperatures are given in Tables 3 and 4. After the reaction had finished the solvent was evaporated off and the reaction mixture was separated by column chromatography (silica gel, MeOH–CH_2Cl_2 = 1 : 1). The products were analysed by NMR spectroscopy and the data for some of them are given below.

Bromination of 1,3-dimethyluracil, **1a**, *with radical initiators in* $CHBr_3$. Compound **1a** (0.5 mmol) was dissolved in 5 ml of freshly distilled $CHBr_3$ and the radical initiator (AIBN or BPO) was added. The reaction times and temperatures are given in Table 5. When the reaction had finished the solvent was evaporated off and the reaction mixture was analysed by NMR spectroscopy.

^1H and ^{13}C NMR data.

2c: ^1H NMR (DMSO-d_6): 1.16 (t, 3 H, J = 7.1 Hz, $-CH_3$), 3.70 (qs, 2 H, J = 7.1 Hz, $-CH_2-$), 8.22 (s, 1 H, C–H), 11.71 (s, 1 H, NH). ^{13}C NMR: 14.23 ($-CH_3$), 43.46 ($-CH_3$), 94.89 (C–Br), 145.65 (C–H), 150.64 (C=O), 160.25 (C=O). M.p. 244–245°C. MS: m/z 218, 220 (M^+).

2g: ^1H NMR (DMSO-d_6): 7.47–7.59 (m, 4 H, –Ph), 8.25 (s, 1 H, C–H), 11.96 (s, 1 H, NH). ^{13}C NMR: 96.39 (C–Br), 129.47, 133.49, 137.96 (–Ph), 145.16 (C–H), 150.31 (C=O), 160.69 (C=O). MS: m/z 268, 270 (M^+).

4f: ^1H NMR (DMSO-d_6): 2.70 [t, 2 H, J = 6.7 Hz, C(5)–H], 3.79 [t, 2 H, J = 6.7 Hz, C(6)–H], 7.2–7.4 (m, 5 H, –Ph), 10.37 (s, 1 H, NH). ^{13}C NMR: 39.0 [C(5)], 53.0 [C(6)], 126.2, 128.0, 129.9, 140.8 (–Ph), 151.0

(C=O; 166.2 C=O). M.p. 194–196°C. MS: *m/z* 190 (M^+).

5: ^{1}H NMR ($CDCl_3$): 3.03 (s, 3 H, CH_3), 3.12 (s, 3 H, CH_3), 6.37 (s, 1 H), 7.9–8.1 (m, 4 H, Ph). M.p. 159–160°C.[10a]

7: ^{1}H NMR ($CDCl_3$): 3.18 (s, 3 H, CH_3), 3.21 (s, 3 H, CH_3), 4.40 [d, 1 H, J = 2.3 Hz, C(5)–H], 5.01 [dd, 1 H, C(6)–H], 5.67 (br d, 1 H, J = 2.3 Hz, OH).

8: ^{1}H NMR ($CDCl_3$): 3.18 (s, 3 H, CH_3), 3.21 (s, 3 H, CH_3), 4.34 [d, 1 H, $J \approx 3$ Hz, C(5)–H], 5.02 [dd, 1 H, C(6)–H], 5.67 (br d, 1 H, $J \approx 3$ Hz, OH).

9: ^{1}H NMR ($CDCl_3$): 1.19 [s, 9 H, $C(CH_3)_3$], 3.19 (s, 3 H, CH_3), 3.22 (s, 3 H, CH_3), 4.63 (d, 1 H, J = 2.2 Hz, CH), 5.03 (s, 1 H, J = 2.2 Hz, CH). ^{13}C NMR ($CDCl_3$): 25.85 [$C(CH_3)_3$], 27.80 [$C(CH_3)_3$], 35.91 (CH_3), 37.91 (CH_3), 82.11 [C(5)], 90.84 [C(6)], 152.47 (C=O), 165.87 (C=O).

11: ^{1}H NMR ($CDCl_3$): 3.23 (s, 3 H, CH_3), 3.33 (s, 3 H, CH_3), 5.01 (d, 1 H, J = 4.1 Hz, CH), 5.81 (d, 1 H, J = 4.1 Hz, CH), 7.9–8.1 (m, 4 H, Ph).

12: ^{1}H NMR ($CDCl_3$): 3.19 (s, 3 H, CH_3), 3.24 (s, 3 H, CH_3), 4.37 (d, 1 H, J = 2.4 Hz, CH), 4.96 (d, 1 H, J = 2.4 Hz, CH).

References

1. See, e.g., Champers, R. and James, S. R. In: Barton, D. H. R. and Ollis, W. D., Eds., *Comprehensive Organic Chemistry*, Pergamon, Oxford 1979, p. 493.
2. See, e.g., (a) Itoh, N., Izumi, Y. and Yamada, H., *Biochemistry 26* (1987) 282; (b) Libby, R. D., Thomas, J. A., Kaiser, L. W. and Hager, L. P. *J. Biol. Chem. 57* (1982) 5030; (c) Neidleman, S. L. and Geigert, J. *Endeavour 11* (1987) 5.
3. (a) Balavoine, G., Barton, D. H. R., Bovin, J., Lecoupanec, P. and Lelandais, P. *New J. Chem. 13* (1989) 691; (b) Barton, D. H. R., Csuhai, E., Doller, D., Ozbalik, N. and Senglet, N. *Tetrahedron Lett. 31* (1990) 3097; (c) Barton, D. H. R., Csuhai, E. and Doller, D. *Tetrahedron Lett. 33* (1992) 3413; (d) Barton, D. H. R., Csuhai, E. and Doller, D. *Tetrahedron 42* (1992) 9195.
4. See, e.g., Ulbright, T. L. V. *Purines, Pyrimidines and Nucleotides*, Pergamon, London 1964.
5. See, e.g., Hobbs, J. B. In: Hansch, C., Sammes, P. G. and Taylor, J. B., Eds., *Comprehensive Medicinal Chemistry*, Pergamon, Oxford 1990, Vol. 2. p. 299.
6. (a) Anderson, R. *Am. Lab. 6* (1974) 36; (b) Filler, R. *J. Fluorine Chem. 33* (1986) 331.
7. Bernade, M. A., Snow, W. B., Olivieri, V. P. and Davidson, B. *Appl. Microbiol. 15* (1967) 257.
8. Pietrzyowska, I. *Mutat. Res. 19* (1973) 1.
9. (a) Itahara, T. and Ide, N. *Chem. Lett.* (1987) 2311; (b) Itahara, T. and Ide, N. *Bull. Chim. Soc. Jpn. 62* (1989) 3750.
10. (a) Harayama, T., Kotoji, K., Yoneda, F., Taga, T., Osaki, K. and Nagamatsu, T. *Chem. Pharm. Bull. 32* (1984) 2056; (b) Itahara, T., Tada, M. and Ide, N. *Nucleic Acids Symp. Ser. 17* (1986) 17; (c) Itahara, T., Ebihara, R., Fujii, Y. and Tada, M. *Chem. Lett.* (1986) 1319; (d) Ryu, E. K. and MacCoss, M. *J. Org. Chem. 46* (1981) 2819; (e) Itahara, T., Ebihara, R., Seto, Y., Fujii, Y. and Tada, M. *Nucleic Acids Symp. Ser. 16* (1965) 61; (f) Asakura, J. and Robbins, M. J. *J. Org. Chem. 55* (1990) 4928.
11. (a) Moriarty, R. M., Prakash, I., Clarisse, D. E., Penmasta, R. and Awasthi, A. K. *J. Chem. Soc., Chem. Commun.* (1987) 1209; (b) Mikolajczyk, M. and Luczak, J. *J. Org. Chem. 43* (1978) 2132; (c) Mikolajczyk, M. and Luczak, J. *Synthesis* (1975) 114.
12. Mansuy, D. *Chem. Rev. 92* (1992) 1411.
13. Kharasch, M. S., Jensen, E. V. and Urry, W. H. *J. Am. Chem. Soc. 69* (1947) 1100.
14. Strong, J. W. and Pease, R. N. *J. Chem. Phys. 10* (1942) 79.
15. (a) Emmerling, A. *Ber. Dtsch. Chem. Ges. 13a* (1880) 873; (b) von Bartal, A. *Ann. Chem. 345* (1906) 334; (c) Lenher, S. and Schumacher, H.-J. *Z. Phys. Chem. 135* (1928) 85; (d) Schumacher, H.-J. and Lehner, S. *Ber. Dtsch. Chem. Ges. 61* (1928) 1671; (e) Koblitz, W., Meissner, H. and Schumacher, H.-J. *Ber. Dtsch. Chem. Ges. 70* (1937) 1080.
16. (a) Stevens, J. L. and Anders, M. W. *Biochem. Pharmacol. 28* (1979) 3189; (b) Philpot, R. M., Nastainczyk, W. M., Mason, R. P. and Wolf, C. R. *Microsomes, Drug Oxidation, Chem. Carcinogen.* (1979); (c) Mico, B. A. and Pohl, L. R. *Biochem. Biophys. 225* (1983) 596.
17. Phillips, B. A., Fodor, G., Gal, J., Letourneau, F. and Ryan, J. J. *Tetrahedron 29* (1973) 3309.
18. Wheeler, H. L. and Johnson, T. B. *J. Biol. Chem. 3* (1907) 183.
19. See, e.g., Yang, S. Y., Apicella, M. and Stone, B. R. *J. Am. Chem. Soc. 78* (1956) 4180; (b) Yang, S. Y. *Nature (London) 180* (1957) 91; (c) Moore, A. M. and Anderson, S. M. *Can. J. Chem. 37* (1959) 590; (d) Banerjee, S. and Tee, O. S. *J. Chem. Soc., Chem. Commun.* (1974) 535; (e) Bakker, C. N. M. and Kaspersen, F. M. *Recl. Trav. Chim. Pays-Bas. 100* (1981) 267; (f) Rouillier, P., Delmau, J. and Nofre, C. *Bull. Soc. Chim. Fr.* (1966) 3515; (g) Tee, O. S. and Banerjee, S. *Can. J. Chem. 57* (1979) 626.
20. (a) Nishiwaki, T. *Chem. Pharm. Bull. 9* (1961) 38; (b) Celewicz, L. and Koroniak, H. *Synth. Commun. 15* (1985) 1001; (c) Nishiwaki, T. and Goto, T. *Bull. Chem. Soc. Jpn. 33* (1960) 26.
21. (a) Davidson, D. and Baudisch, O. *J. Am. Chem. Soc. 48* (1926) 2379; (b) Winkelmann, I. and Larsen, E. H. *Synthesis* (1986) 1041.
22. (a) Nappa, M. J. and Tolman, C. A. *Inorg. Chem. 24* (1986) 4711; (b) Saltzman, H. and Sharekin, J. G. *Org. Synth. Coll. Vol. 5*, Wiley, New York 1973, p. 658.

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