Photochemistry of Uracils in Halogenated Solvents

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The photochemistry of uracil and 1-substituted and 1,3-disubstituted uracils in $CHBr_3$–CH_2Cl_2 is investigated. Photolysis of uracil leads to the formation of 5,6-dibromo-5,6-dihydrouracil as the main product, with 5-bromouracil as the by-product. In contrast with this the 5-bromouracils are formed as the main products by the photolysis of 1-substituted and 1,3-disubstituted uracils, with the corresponding 5,6-dihydro- and 5-bromo-5,6-dihydrouracils as the by-products. The kinetics of the bromination reaction have also been investigated and based on these results a free radical mechanism is proposed.

The occurrence of uracil in nucleic acids[1] has stimulated much work in the chemistry of these compounds, and the photochemistry, especially of 1,3-dimethyluracil, **1**, in hydroxylic solutions has been a subject of great interest as a model system for the interaction of uracil with other biologically important molecules.[2] The photolysis of **1** in methanol gives a variety of products **2–8**.[3–6]

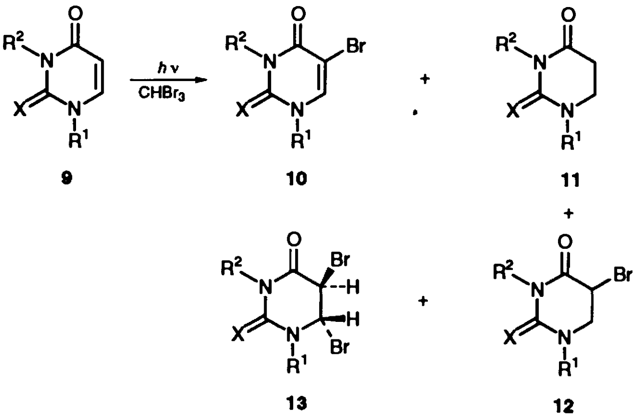
Halogenation of uracil and 1-substituted and 1,3-disubstituted uracils has been the subject of many investigations, because the products are important in the biomedical sciences.[7] For instance, fluorouracils have been used in cancer treatment,[8] while chlorouracils[9] and bromouracils[10] are thought to induce cancer, whereas iodouracils have found use in herpes and AIDS treatment.[7]

In the present investigation the photochemical reactions of uracil and 1-substituted- and 1,3-disubstituted uracils in haloalkane solvents were studied, and the purpose of this was to obtain insight into the interaction of uracils with halogenated solvents under UV light conditions.

Results and Discussion

Photolysis of uracil, **9a**, and uracil derivatives, **9b–j**, in $CHBr_3$–CH_2Cl_2 (1:20) (the notation for **a–j**, R^1, R^2 and X is given in Table 1), using an unfiltered Hanovia lamp leads to the formation of four main products, **10–13**, depending on the starting material.

The results of the photolysis of **9a–j** in $CHBr_3$–CH_2Cl_2 are given in Table 1 (see the Experimental section for further details).



It appears from Table 1 that the main product for all the 1,3-substituted and 1-substituted uracils, **9b–j**, is the corresponding 5-bromo analogue, **10b–j**, showing that the bromination reagent formed by the photolysis is a selective halogenation reagent. The highest yield is obtained with 1,3-dimethyluracil, **9b**, by which 95% of 5-bromo-1,3-dimethyluracil, **10b**, is formed (entry 2). 1,3-Dimethyl-2-thiouracil, **9c**, gives the corresponding 5-bromo-1,3-dimethyl-2-thiouracil, **10c**, as the main product in 69% yield, with 23% of 5-bromo-1,3-dimethyluracil (entry 3); for the formation of the latter product a >C=S to >C=O transformation also took place. This >C=S to >C=O transformation is probably due to dissolved molecular oxygen. It should be noted that the conversion of 2-thiouracil into uracil has recently been found for the reaction of 2-thiouracil under oxidative conditions with iodosylbenzene.[11] For some of the remaining substrates the 5,6-dihydro-, **11**, and 5-bromo-5,6-dihydro, **12**, analogues are also formed as minor by-products by the photolysis; it should be noted that for 3-methyl-1-

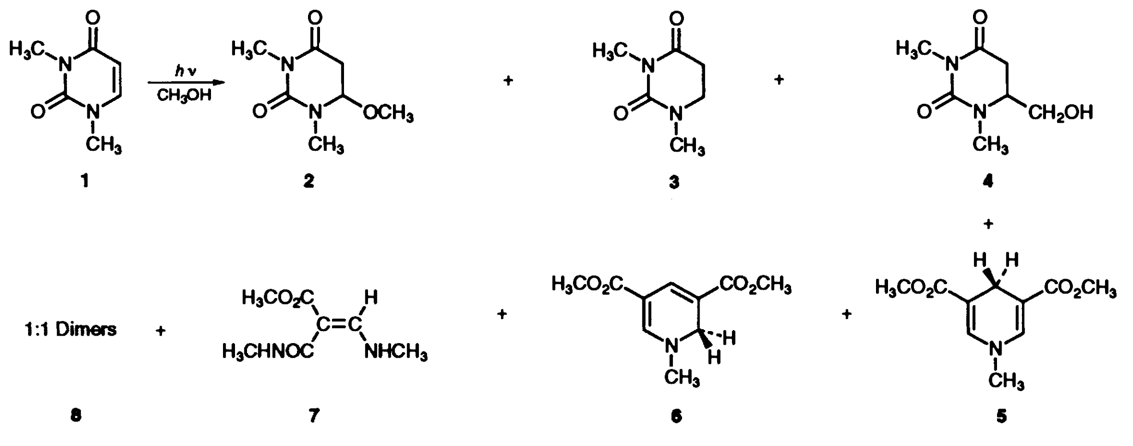


Table 1 Photolysis of uracil, **9a**, 1,3-disubstituted uracils, **9b–e** and 1-substituted uracils, **9f–j** in $CHBr_3$–CH_2Cl_2

						Yield (%)			
Entry	**9**	R^1	R^2	X	t/h	**10**	**11**	**12**	**13**
1	**a**	H	H	O	40	7	—	—	53
2	**b**	CH_3	CH_3	O	4	95	—	—	—
3	**c**	CH_3	CH_3	S	7.5	69 23 (X = O)	—	—	—
4	**d**	C_2H_5	C_2H_5	O	11	54	—	*ca.* 2	—
5	**e**	Ph	CH_3	O	19	29	*ca.* 2	15	—
6	**f**	C_2H_5	H	O	20	33	—	4	—
7	**g**	$CH(CH_3)_2$	H	O	15	70	—	—	—
8	**h**	C_3H_7	H	O	19	57	—	*ca.* 2	—
9	**i**	Ph	H	O	20	31	*ca.* 2	*ca.* 2	—
10	**j**	*p*-ClC_6H_4	H	O	6	22	—	—	—

phenyluracil, **9e**, 15% of 5-bromo-5,6-dihydro-3-methyl-1-phenyluracil, **12e**, is formed (entry 5). Uracil, **9a**, is an exception compared with the substituted uracils, as the main product formed by photolysis is 5,6-dibromo-5,6-dihydrouracil, **13a** (entry 1). The latter has been found to eliminate HBr to produce **10a**.

In the photolysis of 1-substituted uracils, **9f–j**, another by-product is also produced; its structural elucidation has not yet been achieved, but several possible structures can be excluded. It should also be emphasised that only minor amounts of the uracil dimers, **8**, are produced by the photolysis. The photolysis of uracil and the uracil derivatives in $CHBr_3$–CH_2Cl_2 does not lead to any chlorine-containing products. HBr and CH_2Br_2 are also produced during the photolysis.

A tentative proposal for the mechanism for the photolytic bromination of the uracils using $CHBr_3$ is outlined in Scheme 1.[12]

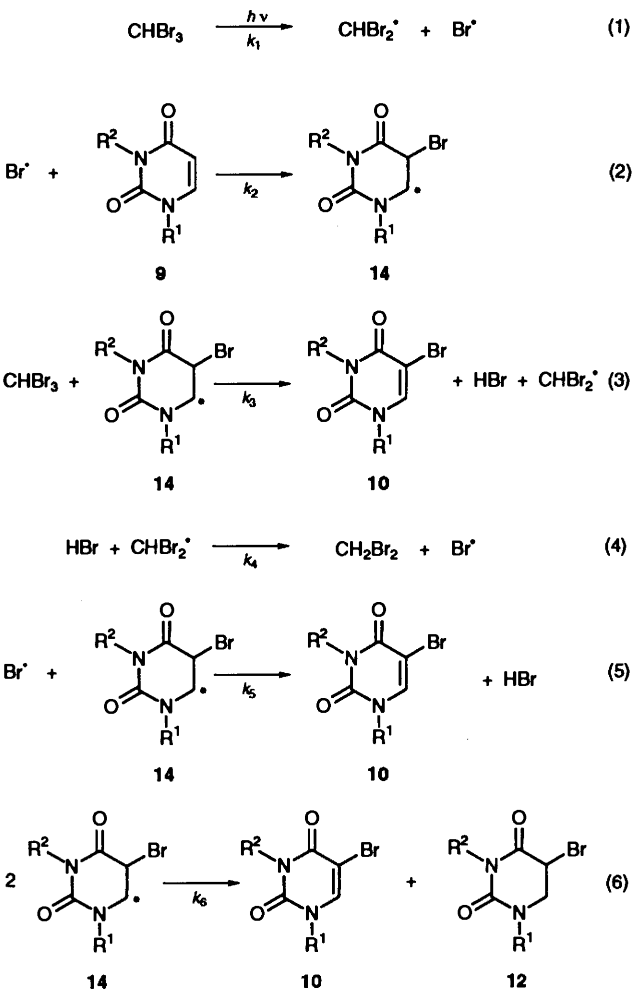
The first step in Scheme 1 is a photolytic cleavage of the C–Br bond in $CHBr_3$ producing Br and $CHBr_2$ radicals; this process requires 62.9 kcal mol^{-1}. Reaction (2) is the addition of the bromine radical at position 5 in the uracil derivative, producing the 5-bromouracil-radical derivative, **14**. It should be noted that it has recently been found that radical bromination of 1,3-dimethyluracil by *N*-bromosuccinimide produces exclusively 5-bromo-1,3-dimethyluracil.[13] The next step, reaction (3) is a hydrogen abstraction from $CHBr_3$ by **14** to give the 5-bromouracil derivative, **10**, HBr and a $CHBr_2$ radical. Reaction (4) is a reaction between the $CHBr_2$ radical and HBr to produce $Br^•$ and CH_2Br_2. The two termination steps for the reaction are suggested to be either a hydrogen abstraction from the 5-bromouracil-radical derivative, **14**, by the bromine radical leading to the 5-bromouracil derivative, **10**, and HBr [reaction (5)], or a coupling of two 5-bromouracil-radical derivatives, **14**, with the formation of the 5-bromouracil derivative, **10**, and the 5-bromo-5,6-dihydrouracil derivative, **12** [reaction (6)].

Although radical reactions can take many different rate laws that are often complicated,[14] we have tried to investigate the kinetics under pseudo-first-order conditions, *i.e.*, $[CHBr_3] \gg [\mathbf{9b}]$, assuming the change in [**9b**] to be as given in eqn. (1) where x is reaction order.

$$-\frac{d[\mathbf{9b}]}{dt} \approx k[\mathbf{9b}]^x \qquad (1)$$

The initial change in the concentration of **9b** $(-d[\mathbf{9b}]_0/dt)$ as a function of four different starting concentrations of **9b** was studied. A plot of log $(-d[\mathbf{9b}]_0/dt)$ as a function of log $[\mathbf{9b}]_0$ is shown in Fig. 1(*a*).

It appears from Fig. 1(*a*) that a straight line is found for log $(-d[\mathbf{9b}]_0/dt)$ as a function of log $[\mathbf{9b}]_0$. From the slope in Fig. 1(*a*) x was determined to be *ca.* 0.5. To support the validity of $x \approx 0.5$, $[\mathbf{9b}]^{\frac{1}{2}}$ is plotted as a function of the time, t, in Fig. 1(*b*), which gives straight lines ($|r| > 0.997$).



Scheme 1

With the mechanism for the photolytic bromination outlined in Scheme 1 and assuming that reaction (5) is the termination step, the change in the concentration of uracil, **9**, can be expressed as eqn. (2),[14] where I is the light intensity. It is

$$-\frac{d[\mathbf{9}]}{dt} = \sqrt{\frac{k_1k_2k_3I}{k_5}}[CHBr_3]\sqrt{[\mathbf{9}]} \qquad (2)$$

assumed in eqn. (2) that the concentration of the bromine radical is larger than the concentration of any more reactive radical, and that reaction (4) is fast compared with reaction (3).

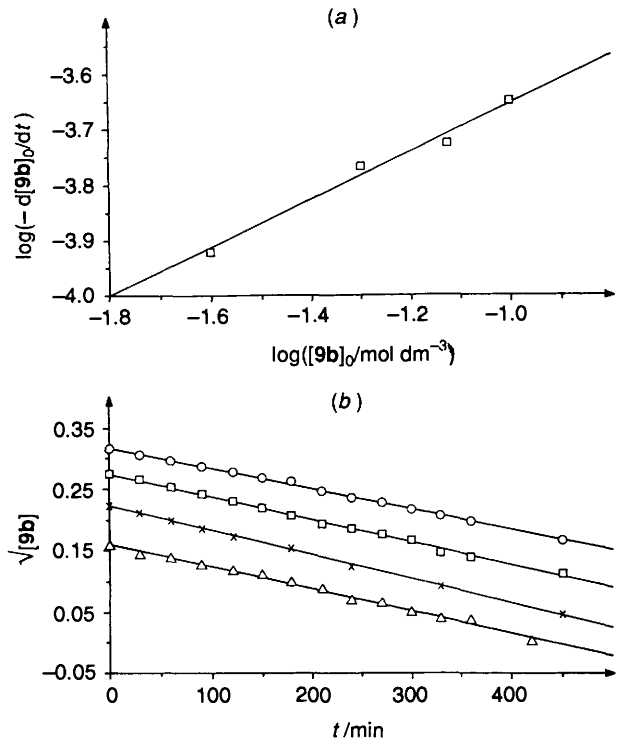


Fig. 1 (*a*) log $(-\mathrm{d}[\mathbf{9b}]_0/\mathrm{d}t)$ as a function of log $[\mathbf{9b}]_0$; (*b*) $[\mathbf{9b}]^{\frac{1}{2}}$ as a function of time, *t*

If reaction (6) is the termination step the change in concentration of uracil can be written as eqn. (3).[14]

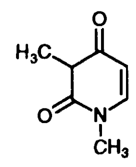
$$-\frac{\mathrm{d}[9]}{\mathrm{d}t} = k_3\sqrt{\frac{k_1 I}{2k_6}}\,[\mathrm{CHBr_3}]^{\frac{1}{2}} \qquad (3)$$

The reaction order for the disappearance of **9** in eqn. (2) is 0.5, whereas the order is zero in eqn. (3). The reaction order of 0.5 in eqn. (2) fits the results observed for the photolysis of 1,3-dimethyluracil, **9b**, and thus accounts, to a certain extent, for the mechanism outlined in Scheme 1. However, **12**, is also observed as a by-product for some substrates (**9d**, **e**, **f**, **h**, **i**) which might indicate that reaction (6) in Scheme 1 could be involved in the reaction sequence. A delicate balance between reaction (5) and (6) in Scheme 1 could operate in the photolytic bromination of *N*-substituted uracils.

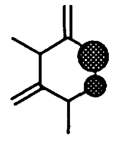
The photolytic bromination of uracil, **9a**, with $CHBr_3$ produces 5,6-dibromo-5,6-dihydrouracil, **13a**, as the main product, with only a minor amount of 5-bromouracil, **10a**. The formation of **13a** as the main product in this reaction might also be accounted for by the reaction sequences outlined in Scheme 1 as the coupling between the bromine radical and the 5-bromouracil radical, **14** [reaction (5)], whereas for the formation of 5-bromouracil, **10a**, a hydrogen abstraction by the bromine radical takes place.

The kinetics for the photolytic bromination of 1,3-dimethyluracil, **9a**, giving a reaction order of about 0.5 is consistent with the reaction orders obtained for other photoinduced free-radical chain reactions.[14]

Another mechanism might also account for the reaction pattern observed. Rather than the hydrogen abstraction in reaction (5) in Scheme 1, an addition of the bromine radical to **14** could take place with the formation of the corresponding 5,6-dibromo-5,6-dihydrouracil derivatives, **13a–j**. The observed difference in product distribution for the reaction of uracil, **9a**, and the *N*-substituted uracils, **9b–j**, could then be that the latter eliminates HBr much faster than the former, and that it is the rate of elimination which makes the difference in product distribution.



9b



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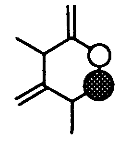

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The selectivity of the bromine radical for position 5 in the uracil skeleton can be accounted for by the frontier orbitals of the system, *e.g.*, as shown for 1,3-dimethyluracil, **9a**, where the HOMO, located at −9.66 eV, and the LUMO located at −0.18 eV, are outlined in **15** and **16**, respectively. These results were obtained using AM1 calculations.[15]

The HOMO, **15**, is mainly located at C-5, whereas the LUMO, **16**, is mainly at C-6. The bromine radical is considered to be electrophilic in nature, which accounts for the selectivity in the present photolytic bromination reactions.

The present photochemical study of uracil and 1-substituted and 1,3-disubstituted uracils in $CHBr_3$–CH_2Cl_2 has shown that a selective bromination of the substituted uracils in the 5-position is the main product, with minor products as the 5,6-dihydro and 5-bromo-5,6-dihydrouracil derivatives. Uracil reacts to give 5,6-dibromo-5,6-dihydrouracil as the major product by this photolysis. The kinetics of the reaction have shown that the reaction probably takes place by addition of a bromine radical at position 5 of the uracil skeleton.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian 200 MHz Gemini spectrometer. Deuteriochloroform or dimethyl sulfoxide were used as solvent and reported δ-values are relative to tetramethylsilane (TMS). Mass spectra were recorded on a Micromass 7070F mass spectrometer and GC–MS on a Trio-2 spectrometer. Irradiations were carried out in quartz tubes of 1 cm i.d. in a merry-go-around surrounding a 450W Hanovia lamp. Solutions of the uracils of about 5×10^{-1} mol dm^{-3} were purged with nitrogen for about 10 min prior to photolysis. The irradiation time is given in Table 1. The solutions were then concentrated and the reaction mixture was separated on a silica gel column.

Materials.—CH_2Cl_2 and $CHBr_3$ were purified according to the standard methods before use. Uracil is commercially available and was used without further purification. The other uracil derivatives were prepared according to the literature.[16]

^{1}*H and* ^{13}*C NMR data.* **10a**: $\delta_H(CDCl_3)$ 7.92 (CH), 11.25 (br, 1 H, NH) and 11.52 (br, 1 H, NH).

13a: $\delta_H(CDCl_3)$ 3.52 (dd, $J = 4$, 1 H, CH), 3.92 (m, 1 H, CH), 7.63 (s, 1 H, NH) and 10.06 (s, 1 H, NH); δ_C 164.4 (C=O), 153.3 (C=O), 49.2 (CH) and 37.2 (CH).

10b: $\delta_H(CDCl_3)$ 3.38 (s, 3 H, NCH_3), 3.40 (s, 3 H, NCH_3) and 7.53 (s, 1 H, CH); δ_C 28.57 (CH_3), 37.10 (CH_3), 95.71 (CBr), 142.57 (CH), 151.26 (C=O) and 159.72 (C=O); m.p. 181–182 °C; *m*/*z* 218 and 220 (M^+).

10c: $\delta_H(CDCl_3)$ 3.76 (s, 3 H, NCH_3), 3.79 (s, 3 H, NCH_3) and 7.74 (s, 1 H, CH); δ_C 36.18 (CH_3), 46.21 (CH_3), 100.46 (CBr), 143.28 (CH), 157.57 (C=O) and 176.70 (C=S); m.p. 228–229 °C; *m*/*z* 234 and 236 (M^+).

10d: $\delta_H(CDCl_3)$ 1.21 (t, 3 H, $J = 7.1$ Hz, CH_3), 1.31 (t, 3 H, $J = 7.2$ Hz, CH_3), 3.81 (q, 2 H, $J = 7.2$ Hz, CH_2), 4.04 (q, 2 H, $J = 6.8$ Hz, CH_2) and 7.49 (s, 1 H, CH); δ_C 12.44 (CH_3), 14.20

(CH$_3$), 37.78 (CH$_2$), 45.10 (CH$_2$), 96.18 (CBr), 141.55 (CH), 150.43 (C=O) and 159.28 (C=O); m.p. 77–78 °C; *m*/*z* 246 and 248 (M$^+$).

10e: δ_H(CDCl$_3$) 3.45 (t, 3 H, CH$_3$), 7.30–7.53 (m, 5 H, Ph) and 7.68 (s, 1 H, CH); δ_C 29.30 (CH$_3$), 98.86 (CBr), 126.51, 129.36, 129.88, 138.87 (Ph), 141.98 (CH), 150.64 (C=O) and 159.60 (C=O); m.p. 198–199 °C; *m*/*z* 280 and 282 (M$^+$).

10f: δ_H([^{2}H$_6$]DMSO) 1.16 (t, 3 H, J = 7.1 Hz, CH$_3$), 3.70 (q, 2 H, J = 7.1 Hz, CH$_2$), 8.22 (s, 1 H, CH) and 11.71 (s, 1 H, NH); δ_C 14.23 (CH$_3$), 43.46 (CH$_3$), 94.89 (CBr), 145.65 (CH), 150.64 (C=O) and 160.25 (C=O); m.p. 244–245 °C; *m*/*z* 218 and 220 (M$^+$).

10g: δ_H([^{2}H$_6$]DMSO) 1.26 [d, 6 H, J = 6.6 Hz, CH(CH_3)$_2$], 4.63 [sep, 1 H, J = 6.6 Hz, CH(CH$_3$)$_2$], 8.18 (s, 1 H, CH) and 11.69 (br, 1 H, NH); δ_C 20.72 [CH(CH$_3$)$_2$], 47.99 [CH(CH$_3$)$_2$], 95.58 (CBr), 142.13 (CH), 150.62 (C=O) and 159.73 (C=O); m.p. 213–214 °C; *m*/*z* 234 and 236 (M$^+$).

10h: δ_H 0.87 (t, 3 H, J = 7.3 Hz, CH$_3$), 1.25 (sex, 2 H, J = 7.3 Hz, CH$_2$), 1.55 (q, 2 H, J = 7.3 Hz, CH$_2$), 3.66 (t, 2 H, J = 7.2, NCH$_2$), 8.22 (s, 1 H, CH), 11.72 (br, 1 H, NH), δ_C 13.61 (CH$_3$), 19.17 (CH$_2$), 30.63 (CH$_2$), 47.84 (NCH$_2$), 94.83 (CBr), 145.84 (CH), 150.80 (C=O) and 160.18 (C=O); m.p. 177–179 °C; *m*/*z* 246 and 248 (M$^+$).

10i: δ_H(DMSO) 7.4–7.6 (m, 5 H, Ph), 8.24 (s, 1 H, CH) and 11.93 (s, 1 H, NH); δ_C 96.16 (CBr), 127.50, 128.96, 129.56, 138.88 (Ph), 145.46 (CH), 150.39 (C=O) and 160.34 (C=O); m.p. 271–273 °C; *m*/*z* 266 and 268 (M$^+$).

11i: δ_H(DMSO) 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) and 10.37 (s, 1 H, NH); δ_C 31.06 [C(5)], 44.56 [C(6)], 125.52, 126.04, 128.88, 142.36 (Ph), 152.47 (C=O) and 161.00 (C=O); m.p. 194–196 °C; *m*/*z* 190 (M$^+$).

12i: δ_H(DMSO) 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) and 10.37 (s, 1 H, NH); δ_C 39.0 [C(5)], 53.0 [C(6)], 126.2, 128.0, 129.9, 140.8 (Ph), 151.0 (C=O) and 166.2 (C=O); m.p. 194–196 °C; *m*/*z* 190 (M$^+$).

10j: δ_H(DMSO) 7.47–7.59 (m, 4 H, Ph), 8.25 (s, 1 H, CH) and 11.96 (s, 1 H, NH); δ_C 96.39 (CBr), 129.47, 133.49, 137.96 (Ph), 145.16 (CH), 150.31 (C=O) and 160.69 (C=O); *m*/*z* 268 and 270 (M$^+$).

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Paper 3/00703K
Received 4*th February* 1993
Accepted 12*th May* 1993