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PHOTOCHEMISTRY OF AROMATIC COMPOUNDS—VII[1]

THE INFLUENCE OF ALIPHATIC AMINES ON THE PHOTOCHEMISTRY OF 5-BROMOPYRIMIDINES IN METHANOL

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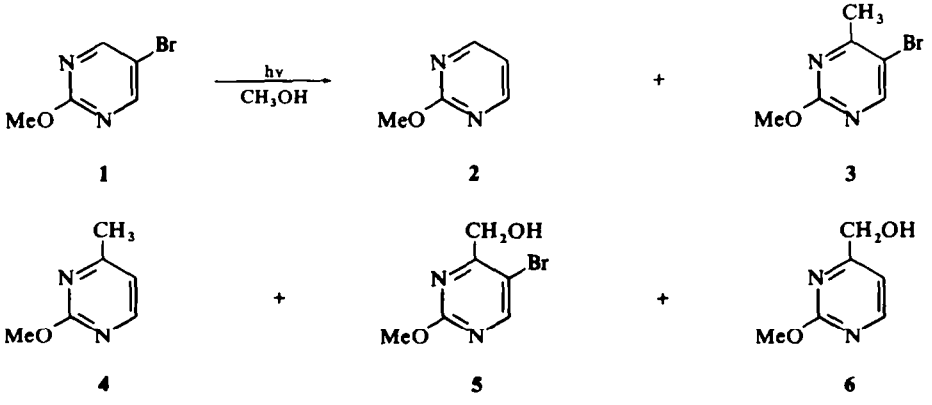
Abstract—The UV irradiation of 2-methoxy-, 2-phenyl- and 2-dimethylamino-5-bromopyrimidine in methanol yields the corresponding dehalogenated, methylated and hydroxymethylated compounds. Added diethylamine or triethylamine strongly increases the rate of dehalogenation. It is suggested that amines influence the photochemistry of these compounds by transfering an electron to the excited state of the bromopyrimidines.

ONLY little is known about the photochemistry of pyrimidines in water or in alcohols; photo-alkylations in methanol, ethanol and isopropanol are reported to give good yields.[2] Among the 5-bromopyrimidines, 5-bromouracil has been thoroughly examined under steady irradiation,[3] flash photolysis and pulse radiolysis.[4] We describe here the behaviour of 2-methoxy-, 2-phenyl- and 2-dimethylamino-5-bromopyrimidines when irradiated in methanol, and the changes induced by added aliphatic amines.

RESULTS

1. *5-Bromo-2-methoxypyrimidine*

a. *In methanol.* Irradiation of 5-bromo-2-methoxypyrimidine (**1**) in methanol gives five different products: 2-methoxypyrimidine (**2**), 5-bromo-2-methoxy-4-methylpyrimidine (**3**), 2-methoxy-4-methylpyrimidine (**4**), 5-bromo-4-hydroxymethyl-2-methoxypyrimidine (**5**) and 4-hydroxymethyl-2-methoxypyrimidine (**6**) (Chart 1).



1 **2** **3** **4** **5** **6**

CHART 1

b. *In methanol and amines.* When the photolysis is run in methanol containing 0·1 to 0·4 M diethylamine or triethylamine, the products are those of chart one, and include then also amine hydrobromide. The data of Table 1 show that the addition

TABLE 1. INFLUENCE OF AMINES ON THE PHOTOLYSIS OF 5-BROMOPYRIMIDINES IN METHANOL. PURE NITROGEN WAS BUBBLED THROUGH THE SOLUTIONS DURING THE IRRADIATIONS

Starting pyrimidine	Concentration M	Diethylamine M	Lamp[a]	Irradiation time (min)	%I[b]	%II[c]
5-Bromo-2-methoxy	$1·0 \times 10^{-2}$	—	LP	40	74	2
	$1·0 \times 10^{-2}$	0·1	LP	40	49	16
	$1·0 \times 10^{-2}$	0·4	LP	40	30	34
5-Bromo-2-dimethylamino	$0·99 \times 10^{-2}$	—	MP1	210	90	4
	$0·98 \times 10^{-2}$	0·1	MP1	210	66	12
	$0·99 \times 10^{-2}$	0·4	MP1	210	45	30
5-Bromo-2-phenyl	$0·88 \times 10^{-2}$	—	LP	55	93	1
	$0·92 \times 10^{-2}$	0·1	LP	55	58	20
	$0·92 \times 10^{-2}$	0·4	LP	55	36	29
	$0·98 \times 10^{-2}$	—	MP2	10	92	2
	$0·95 \times 10^{-2}$	0·39[d]	MP2	10	21	47

[a] LP: 9W low pressure Hanau NK6 mercury arc, quartz well; with the concentrations used, the absorption by the amine is negligible. MP1: 450W medium pressure Hanovia mercury arc, pyrex well. MP2: 125W medium pressure Philips HPK 125 mercury arc, pyrex well.

[b] Recovered starting material.

[c] Corresponding debrominated pyrimidine.

[d] Triethylamine instead of diethylamine.

of amines results in an increased yield of debrominated product **2**; it was found also that amines reduce the yields of methylated compounds **3** and **4**. The importance of hydroxymethylation seems to depend on the initial concentration of starting material (Table 2).

TABLE 2. RELATIVE YIELDS (VPC) AS A FUNCTION OF STARTING CONCENTRATION IN THE PHOTOLYSIS OF **1** IN METHANOL + 0·376 M DIETHYLAMINE*

Initial concentration (M)	Irradiation time (min)	Recovered **1**(%)	%**2**	%(**5** + **6**)
$1·0 \times 10^{-2}$	4	80·0	20·0	—
$4·0 \times 10^{-2}$	16	79·0	19·7	1·3
$8·0 \times 10^{-2}$	32	80·0	17·9	2·1

* Pure nitrogen was bubbled through the solutions before irradiation; 125W medium pressure Philips HPK 125 mercury arc, quartz well. %(**5** + **6**) is the relative yield of solvent incorporation products.

2. *2-Methoxypyrimidine*

a. *In methanol, and in methanol*/HCl. Prolonged irradiation of 2-methoxypyrimidine ($7·3 \times 10^{-2}$M) in pure methanol yields a TLC spot identified as 4-hydroxymethyl-2-

methoxypyrimidine; this spot appears only diffusely in irradiations performed with 0·1 M HCl, but instead GLC shows the presence of 2-methoxy-4-methylpyrimidine.

b. *In methanol and triethylamine.* Photolysis of 2-methoxypyrimidine in methanol containing 0·193 M triethylamine yields appreciable amounts of 4-hydroxymethyl-2-methylpyrimidine, detected by TLC and GLC.

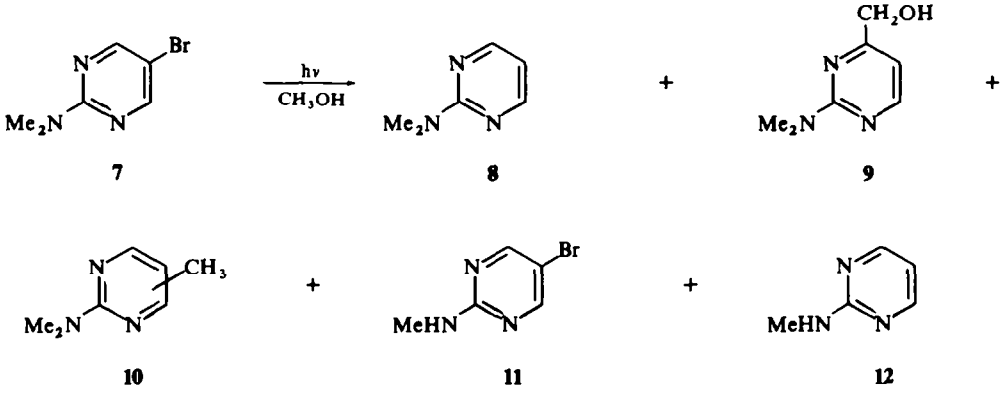
3. 5-*Bromo-2-phenylpyrimidine*

The irradiation of 5-bromo-2-phenylpyrimidine in methanol gives 2-phenylpyrimidine and 4-hydroxymethyl-2-phenylpyrimidine in an approximate ratio of 1:2 without added amine, and a 10:1 ratio in the presence of amine; here again, the amine has a very large rate-enhancing influence (Table 1).

4. 5-*Bromo-2-dimethylaminopyrimidine*

a. *In methanol.* 5-Bromo-2-dimethylaminopyrimidine (**7**) gives, after 210 min irradiation through Pyrex, 90% recovered starting material, 4% 2-dimethylaminopyrimidine (**8**), 1% 2-dimethylamino-4-hydroxymethylpyrimidine (**9**) and 2% of a partially demethylated product: 5-bromo-2-methylaminopyrimidine (**11**) (Chart 2).

b. *In methanol and amine.* 0·4 M diethylamine in methanol strongly accelerates the debromination of **7** in the same conditions, giving 30% of **8**, 5% of **9**, 2% of **11** and 45% of unchanged starting material. Prolonged irradiation allowed the identification of trace amounts of **10** (mass spectrometry only) and **12** (by comparison of mass spectrum and GLC with corresponding data of an authentic sample).



7 8 9 10 11 12

CHART 2

DISCUSSION

The data of Table 1 clearly show the accelerating effect of amines on the dehalogenation of 5-bromopyrimidines. This can be interpreted by assuming that the excited state of the heterocycle is quenched by the amine through an electron transfer,[5] resulting in a solvated ion pair as outlined in Eq. (1).

$$Ar\text{–}Br^{*} + R_3N \xrightarrow{k_q} ArBr^{\cdot-} \cdots R_3N^{\cdot+} \qquad (1)$$

The bromopyrimidine radical-anion thus formed then loses a bromide ion, as in ground-state Birch reductions[6] leaving a 5-pyrimidyl radical which abstracts an H atom from the solvent to give the dehalogenated product.

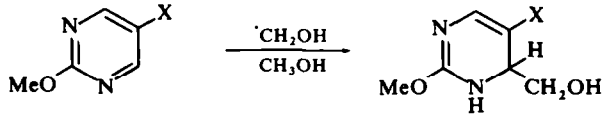
The comparison of the polarographic half-wave reduction potentials and the energy of the (estimated) 0—0 band of the lowest electronic transition for our bromopyrimidines with the corresponding values for aromatic hydrocarbons whose fluorescence is quenched by amines in a variety of solvents[8–10] suggests that an electron transfer from the amine to the excited pyrimidines is a quite reasonable process. If now the loss of bromide ion from the radical-anion, is fast compared with the back transfer of the electron to the amine cation, this leads to the observed rate enhancement.

The full mechanism of the amine-induced photoreduction in methanol must however be more complex. It appears indeed that the debromination of 5-bromo-2-methoxypyrimidine without amine is rather inefficient ($\phi \simeq 0{\cdot}1$) but that triethylamine increases the rate by a factor of 40.[7] The quantum yield of 4 (with 0·2 M triethylamine) suggests that the photo-induced electron transfer is the initiation step of a chain reduction. The reaction would then start by two ways, expressed by Eq (2) for the spontaneous photodebromination and Eq (3) for the amine-catalysed mechanism. The chain propagating radical: $^{\cdot}CH_2OH$ would then be regenerated after every reduction step.

$$Ar\text{–}Br^{*} \longrightarrow Ar^{\cdot} + Br^{\cdot} \xrightarrow{CH_3OH} ArH + HBr + 2{\cdot}CH_2OH \qquad (2)$$

$$Ar\text{–}Br^{*} + R_3N \longrightarrow ArBr^{\cdot -} + R_3N^{\cdot +} \xrightarrow{CH_3OH} ArH + R_3NH^{+}\,Br^{-} + 2{\cdot}CH_2OH \qquad (3)$$

The presence of this species would explain the formation of the methylated and hydroxymethylated compounds: the $^{\cdot}CH_2OH$ radical would attack a ground state pyrimidine molecule to give a dihydro-hydroxymethylpyrimidine such as **13**, or some isomer of it, as shown in Eq. (4).



X = H, Br

13

(4)

If the addition reaction is also a chain reaction, it would regenerate hydroxymethyl radicals; it seems however that such chains should be very short, in view of the estimated very low exothermicity of the process.

Our hypothesis about the origin of the hydroxymethylated and methylated products is supported by the observation that the formation of these compounds is always related to the production of hydroxyalkyl radicals derived from the solvent, whether they are generated by direct photolysis of the alcohol,[11] by photochemical sensitisation by ketones,[11,12] by γ radiolysis,[12] by the thermal decomposition of peroxides[12b] or, as in our case, by another photochemical reaction. The fate of the assumed dihydrohydroxymethyl intermediate **13** seems to depend on the acidity of the medium. In neutral or basic solutions, it may remain as such until work-up, when it will be air-oxidised to the hydroxymethylpyrimidine; in the presence of acid, it may dehydrate to the methylpyrimidine. Other mechanistic aspects of the photodebromination will be discussed in a forthcoming publication.

EXPERIMENTAL

1. *Syntheses.* 5-Bromo-2-methoxypyrimidine,[13,14] 2-methoxypyrimidine,[15] 2-dimethylaminopyrimidine[15] and 2-methylaminopyrimidine[15] were synthesised according to known procedures.

a. 5-Bromo-2-phenylpyrimidine[16] was made by adapting the method used to synthesise 5-chloro-2-phenylpyrimidine;[17] the condensation of bromomalondialdehyde[18] with benzamidine gave 5-bromo-2-phenylpyrimidine with a 40% yield; F: 104–105°.

b. 5-Bromo-2-dimethylaminopyrimidine was formed by refluxing 5-bromo-2-chloropyrimidine[13,14] with an excess of ethanolic solution of dimethylamine (33%), and was then recrystallised from MeOH; yield: 65%; F: 81-82°. IR(KBr pellet; cm^{-1}): 2900, 2840, 1600, 1530, 1410, 1380, 1310, 1200, 1170, 1120, 980, 950, 790, 780. UV: water, $\lambda_{max} = 335$ nm ($\varepsilon = 2000$), $\lambda_{min} = 287$ nm ($\varepsilon = 700$); methanol, $\lambda_{max} = 332$ nm ($\varepsilon = 2000$), $\lambda_{min} = 282$ nm ($\varepsilon = 600$); cyclohexane, $\lambda_{max} = 331$ nm ($\varepsilon = 2100$), $\lambda_{min} = 282$ nm ($\varepsilon = 670$). NMR (60MHz, $CDCl_3$, TMS): NMe_2, 3·13 ppm (singlet); $H_{4,6}$: 8·27 ppm (singlet).

2. *Analysis of photochemical runs*

The solns were concentrated and chromatographed through silicagel for a first crude separation. The various fractions were then submitted to one or two preparative TLC and the products isolated. Liquid products were usually trapped from the GLC (Versamid or Carbowax); even on 6 m long Versamid 900 (5%) columns, the methylated and non methylated products were poorly separated. Absolute yields are given with 5–10% errors. All compounds gave mass spectra compatible with the assumed structure.

a. *5-Bromo-2-methoxy-4-methylpyrimidine.* Liquid, NMR (Varian HA 100, $CDCl_3$, TMS): CH_3O, 4·18 ppm (singlet); CH_3, 2·76 ppm (singlet); H_6, 8·63 ppm (singlet).

b. *2-Methoxy-4-methylpyrimidine.* Liquid,[19,20] NMR (Varian HA 100, $CDCl_3$, TMS): CH_3O, 4·21 ppm (singlet); CH_3, 2·67 ppm (singlet); H_5, 6·98 ppm (doublet); H_6, 8·55 ppm (doublet), $J(H_5-H_6) = 5$Hz.

c. *5-Bromo-4-hydroxymethyl-2-methoxypyrimidine.* White solid (F: 123·5–124·5°), IR ($CHCl_3$; cm^{-1}): ~ 3460, 1570, 1470, 1370, 1060, 960; UV (MeOH): $\lambda_{max} = 282$ nm ($\varepsilon = 3450$); $\lambda_{min} = 250$ nm ($\varepsilon = 590$). NMR (Varian A60, $CDCl_3$, TMS): CH_3O, 4·08 ppm (singlet); CH_2, 4·73 ppm (doublet); OH, 3·75 ppm, $J(CH_2-OH) = 3$ Hz; H_6, 8·5 ppm (singlet).

d. *4-Hydroxymethyl-2-methoxypyrimidine.* White solid (F: 104–105°), IR ($CHCl_3$; cm^{-1}): ~ 3440, 2970, 2940, 1590, 1570, 1470, 1380, 1330, 1060, 970; NMR (Brücker 90 MHz, $CDCl_3$, TMS): CH_3O, 4·02 ppm (singlet); CH_2, 4·68 ppm (doublet); H_5, 4·29 ppm (poorly resolved triplet, further splitted by H_6); H_6, 6·88 ppm (doublet), $J(H_5-H_6) = 5$ Hz, $J(CH_2-H_5) \approx 0{\cdot}5$ Hz*.

e. *2-Dimethylamino-4-hydroxymethylpyrimidine.* Liquid, IR ($CHCl_3$: cm^{-1}): ~ 3420, 2940, 2860, 1710, 1590, 1570, 1530, 1410, 1350, 1300, 1060, 1010, 890; NMR (Varian A60, $CDCl_3$, TMS): $(CH_3)_2N$, 3·2 ppm (singlet); CH_2, 4·55 ppm (doublet); H_5, 6·33 ppm (poorly resolved triplet, further splitted by H_6); H_6, 8·23 ppm (doublet), $J(H_5-H_6) = 5$ Hz, $J(CH_2-H_5) \approx 0{\cdot}5$ Hz*.

f. *5-Bromo-2-methylaminopyrimidine.* White solid (F: 121°);[21] IR($CHCl_3$; cm^{-1}): 3470, 2960, 2920, 1600, 1570, 1540, 1410, 1380, 1130, 950; NMR (Varian A60, $CDCl_3$, TMS): CH_3N, 2·97 ppm (doublet); NH, broad band 5·1-6·3 ppm, $J(CH_3-N-H) = 5$ Hz; $H_{4,6}$, 8·28 ppm (singlet).

g. *4-Hydroxymethyl-2-phenylpyrimidine.* Liquid, IR (film; cm^{-1}): ~ 3350, 3060, 3030, 2900, 2840, 1590, 1570, 1460, 1430, 1390, 1180, 1110, 1070, 1030, 840, 750, 700. NMR (Varian A60, $CDCl_3$, TMS): CH_2,

* OH line position and couplings obscured due to adventitious moisture in the sample.

4·83 ppm (doublet); H_5, 7·17 ppm (double triplet); H_6, 8·74 ppm (doublet), $J(CH_2-H_5) \approx 0·7$ Hz, $J(H_5-H_6) = 5$ Hz; *ortho* phenyl protons, 8·5 ppm (multiplet); *meta* and *para* phenyl protons, 7·5 ppm (multiplet)*. Corresponding data for 2-methoxypyrimidine,[15,22] 2-dimethylaminopyrimidine[15] and 2-phenylpyrimidine[23] were found identical with reported values and checked with authentic samples.

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