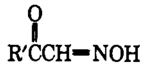
thionite gave 6-methyl-7,8-dihydropterin[9,10] (**5**, R = CH_3, 90%) which on potassium permanganate oxidation gave the known 6-methylpterin[11-13] (**6**, R = CH_3).

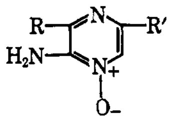
$\underset{\text{CN}}{\text{RCHNH}_2}$

1



$R'\overset{O}{\overset{\|}{C}}CH{=}NOH$

2



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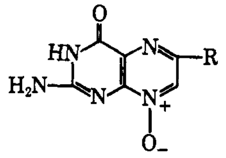

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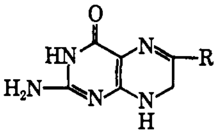

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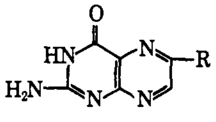
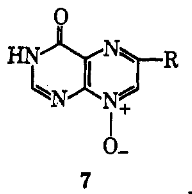


6

Similarly, **1** (R = $COOC_2H_5$) was condensed with the α-oximino ketones **2** (R′ = C_6H_5, $CH{=}CHC_6H_5$, $CH{=}C(CH_3)_2$) to give the pyrazine 1-oxides **3** (R = $COOC_2H_5$; R′ = C_6H_5, $CH{=}CHC_6H_5$, $CH{=}C(CH_3)_2$), which were condensed with guanidine to give 6-phenylpterin 8-oxide (**4**, R = C_6H_5, 60%), 6-styrylpterin 8-oxide (**4**, R = $CH{=}CHC_6H_5$, 71%), and 6-(2-methyl-1-propenyl)pterin 8-oxide (**4**, R = $CH{=}C(CH_3)_2$, 70%). Sodium dithionite reduction of **4** (R = C_6H_5), followed by potassium permanganate oxidation, gave 6-phenylpterin (**6**, R = C_6H_5, 75%), identical with an authentic sample prepared independently by an alternate, unambiguous route.[14] Appropriate functionalization of olefinic side chains such as those present in the above pteridines should permit the formation of compounds related to biopterin, neopterin, and sepiapterin.

Condensation of α-aminocyanoacetamide[15] (**1**, R = $CONH_2$) with isonitrosoacetone (**2**, R′ = CH_3) in glacial acetic acid gave 2-amino-3-carbamoyl-5-methylpyrazine 1-oxide (**3**, R = $CONH_2$; R′ = CH_3, 62%; mp 218.3°); its identity was confirmed by sodium dithionite deoxygenation to 2-amino-3-carbamoyl-5-methylpyrazine, identical in all respects with an authentic sample.[16] Similarly, condensation of **1** (R = $CONH_2$) with isonitrosoacetophenone (**2**, R′ = C_6H_5) gave 2-amino-3-carbamoyl-5-phenylpyrazine 1-oxide (**3**, R = $CONH_2$; R′ = C_6H_5, 32%; mp 281.6°). Cyclization of **3** (R = $CONH_2$; R′ = CH_3, C_6H_5) with triethyl orthoformate gave 6-methyl-4(3H)-pteridinone 8-oxide (**7**, R = CH_3, 64%) and 6-phenyl-4(3H)-pteridinone 8-oxide (**7**, R = C_6H_5, 70%), respectively.

6-Methyllumazine 8-oxide (**8**, R = CH_3, 72%) and 6-phenyllumazine 8-oxide (**8**, R = C_6H_5, 90%) were prepared from **3** (R = $CONH_2$; R′ = CH_3, C_6H_5) by reaction with ethyl chloroformate followed by cyclization of the intermediate urethans with sodium methoxide.



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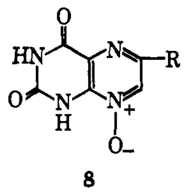

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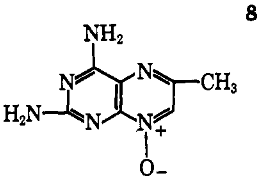

9

Finally, condensation of aminomalononitrile[17] (**1**, R = CN) with **2** (R′ = CH_3) gave 2-amino-3-cyano-5-methylpyrazine 1-oxide (**3**, R = CN; R′ = CH_3, 81%; mp 188.1°), which was cyclized with guanidine to 2,4-diamino-6-methylpteridine 8-oxide (**9**, 84%). This latter two-step sequence of reactions should provide a simple, unequivocal, and versatile route to the 8-oxides of the clinically important 2,4-diamino-6-substituted pteridines (antifolics),[18] from which the latter may be prepared by deoxygenation.

Extensions of these reactions to the preparation of the 4-amino derivatives of biopterin and related pteridine cofactors are in progress.

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(8) Few pteridine oxides have been reported. Lumazine 5-oxides, 8-oxides, and/or 5,8-dioxides have been prepared by oxidation of lumazines with performic (W. Pfleiderer and W. Hutzenlaub, *Angew. Chem.*, 77, 1136 (1965)) or pertrichloroacetic acid (H. Zondler, H. S. Forrest, and J. M. Lagowski, *J. Heterocyclic Chem.*, **4**, 124 (1967)); the nature of the product(s) formed apparently depends on steric as well as electronic factors. Direct oxidation is not, however, applicable to pteridines carrying substituent amino groups (*e.g.*, pterins). Several pteridine 5-oxides were prepared by the condensation of 5-nitroso-6-aminopyrimidines with phenacyl- or acetonylpyridinium salts (I. J. Pachter, P. E. Nemeth, and A. J. Villani, *J. Org. Chem.*, **28**, 1197 (1963)).

(9) 6-Methyl-7,8-dihydropterin has recently been shown to be a substrate for dihydrofolate reductase and has been used as a model for the naturally occurring cofactor, dihydrofolic acid (J. M. Whiteley and F. M. Huennekens, *Biochemistry*, **6**, 2620 (1967)).

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(13) S. F. Mason, "The Chemistry and Biology of Pteridines," A CIBA Symposium, G. E. W. Wolstenholme and M. P. Cameron, Ed., J. and A. Churchill, Ltd., London, 1954, pp 74–92.

(14) This method involves condensation of 2,6-diamino-5-(*p*-nitrophenylazo)-4(3H)-pyrimidinone with the morpholine enamine of phenylacetaldehyde, and will be described independently (E. C. T. and I. Sword).

(15) A. H. Cook, I. Heilbron, and E. Smith, *J. Chem. Soc.*, 1440 (1949).

(16) O. Vogl and E. C. Taylor, *J. Am. Chem. Soc.*, **81**, 2472 (1959).

(17) J. P. Ferris and L. E. Orgel, *ibid.*, **88**, 3829 (1966).

(18) (a) "Experimental Chemotherapy," Vol. IV, Part I, R. J. Schnitzer and F. Hawking, Ed., Academic Press Inc., New York, N. Y., 1966; (b) L. F. Larionov, "Cancer Chemotherapy," Pergamon Press, Ltd., Oxford, 1965; (c) F. E. Knock, "Anticancer Agents," Charles C Thomas, Publisher, Springfield, Ill., 1966.

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Systematics and Mechanism of Hot Halogen Reactions. Trends in Total Yield

Sir:

Previous work has shown that hot halogen atoms react with organic molecules by atomic replacement.[1-3]

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(1) (a) J. F. Hornig, G. Levey, and J. E. Willard, *J. Chem. Phys.*, **20**, 1556 (1952); (b) S. Goldhaber and J. E. Willard, *J. Am. Chem. Soc.*, **74**, 318 (1952); (c) R. Wolfgang, *Progr. Reaction Kinetics*, **3**, 97 (1965).

(2) (a) N. Colebourne and R. Wolfgang, *J. Chem. Phys.*, **38**, 2782 (1963); (b) N. Colebourne, J. F. J. Todd, and R. Wolfgang, "Chemical

Table I. Yields (%) of Hot Fluorine Replacement Reactions[a]

Reaction type	Reactant molecule					
	CH_4	CH_3F	CH_2F_2	CHF_3	CF_4	CH_3Cl
Replacement for F or Cl		4.7 (CH_3F)	2.6 (CH_2F_2)	1.4 (CHF_3)	2.8 (CF_4)	7.9 (CH_3F)
Replacement for H	15.8 (CH_3F)	3.4 (CH_2F_2)	0.9 (CHF_3)	1.3 (CF_4)		<0.5 (CH_2ClF)
Replacement for 2F			2.8 (CH_2FI)	3.3 (CHF_2I)	2.5 (CF_3I)	
Replacement for H and F or Cl		2.1 (CH_2FI)	2.9 (CHF_2I)	1.0 (CF_3I)		7.3 (CH_2FI)
Replacement for 2H	4.6 (CH_2FI)	0.4 (CHF_2I)	0.8 (CF_3I)			<0.5 ($CHClFl$)
Other reactions	<0.5	<0.5	<0.5	<0.5	<0.5	
Total hot yield, %	20.4	10.6	10.0	7.0	5.3	15.2–16.2
Calcd area available for reaction	1.00	0.73	0.50	0.26	0.05	0.73
Calcd hot yield, %	(20.4)	14.9	10.0	5.3	1.0	14.9

[a] Per cent of total F^{18} incorporated in product shown in parentheses.

While these processes are analogous to those of the better understood hot hydrogen, yield data and kinetic analyses indicate significant differences in mechanism.[2,3] We communicate here results of a survey of hot fluorine atom reactions sufficiently complete to establish systematic trends. The accompanying paper reports on parallel work with hot chlorine. On the basis of these data, we attempt to define the mechanistic factors controlling the reactions of fast halogen atoms.

Hot F^{18} was produced in the Bremsstrahlung beam of the 40-Mev Yale electron accelerator by the $F^{19}(\gamma,n)F^{18}$ nuclear reaction. Samples at 1 atm and 25° contained the reagent mixed with small quantities of ethylene and iodine to scavenge thermalized atoms[2] and help suppress radiation effects. In the cases of CH_4 and CH_3Cl, CF_4 was added as a source of fluorine.[3] Details of irradiation procedures and the radiogas chromatographic analysis have already been reported.[2,3]

Data on F^{18} reactions in the absence of moderator are shown in Table I. Two apparently opposing trends emerge. (1) The total hot yield decreases as the number of halogen substituents on the reagent increases. (2) When halogen atoms are present, they are replaced in preference to hydrogen. These striking trends, observed here for the first time, appear to dominate hot halogen reactions.

In attempting to find a model, we assume what is now well established for hot hydrogen reactions with saturated hydrocarbons: that reaction is direct, occurring on a time scale comparable with a bond vibration.[1c,4] It is then reasonable that replacement reactions can occur only when the hot halogen atom strikes the central carbon atom or one of the bonds uniting it with its ligands. This implies no such reactions occur when a bound halogen is struck on the side away from the carbon atom. Such an impact may result in abstraction, although even this may not be very likely, because of the weakness of the halogen–halogen bond formed.

The basic model suggests that two factors will be important in determining the reaction: steric[2] and translational inertial (the latter being discussed in the following paper). The importance of the steric factor is measured by the fraction of collisions in which the hot halogen atom strikes a bound halogen without also interacting with the central carbon. To a first approximation this corresponds to the solid angle over which the incident hot atom collides with a bound halogen. It is assumed that the hydrogen provides no hindrance to reactive approach. This is plausible, not so much because the hydrogen atoms are small, but because their vibrational relaxation times are short or comparable to the time of the collision. Thus they can adiabatically adjust to the incoming halogen atom—in other words, get out of the way.

The total probability of reaction with any given molecule can now be predicted very simply. The experimentally determined probability of reaction with the sterically unhindered methane molecule is multiplied by the estimate of the fractional solid angle of the molecule in question that is available for reaction. These calculated values are included in Table I. Comparison with the total experimental yields shows that the steric factor serves well in correlating and predicting trends of total reactivity.[5]

Acknowledgment. The authors wish to thank the staff of the Yale University linear electron accelerator for their help. This work was supported by the U. S. Atomic Energy Commission under Contract SAR/AT(30-1)1957.

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(4) M. A. El-Sayed, P. J. Estrup, and R. Wolfgang, *ibid.*, 62, 1356 (1958).

(5) Even if the steric effect were the sole factor controlling total probability of reaction on collision, there would not be exact agreement between the calculated and experimental trends. There are two reasons for this. (1) The calculation of steric hindrance is only approximate, as it considers only "head-on" collisions (events of zero impact parameter with respect to the carbon atom) and assumes normal Lennard–Jones cross sections. (2) The total yield depends not only on the average probability of reaction per collision, but on the number of collisions. The latter quantity will vary with the moderating properties of the medium (as measured by the collisional energy loss parameter α).[6] This will change somewhat between different reagent molecules. Such an effect could be eliminated by comparing not yields but rather "reactivity integrals" which are obtained by extrapolation to infinite dilution with an inert moderator and are therefore independent of the moderating properties of the reagent. We have determined a few of these reactivity integrals, and they correlate well with the calculated steric effect.

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Systematics and Mechanism of Hot Halogen Reactions. Product Distribution

Sir:

Reactions of hot chlorine atoms produced by Bremsstrahlung *via* the $Ar^{40}(\gamma,p)Cl^{39}$ process have been