**Table I**

| Halide | Product | Yield, %[a] |
|---|---|---|
| Bromobenzene | Biphenyl | 85 |
| 4-Bromoanisole | 4,4′-Dimethoxybiphenyl | 99 |
| 4-Bromotoluene | 4,4′-Dimethylbiphenyl | 91 |
| 3-Bromotoluene | 3,3′-Dimethylbiphenyl | 85 |
| 4-Bromo-o-xylene | 3,3′,4,4′-Tetramethylbiphenyl | 76 |
| 2-Bromo-6-methoxynaphthalene | 6,6′-Dimethoxy-2,2′-binaphthyl | 73 |
| 4-Bromobiphenyl | 4,4′-Quaterphenyl | 91 |
| 4-Bromochlorobenzene | 4,4′-Dichlorobiphenyl | 73[b] |
| 4-Fluorobromobenzene | 4,4′-Difluorobiphenyl | 73[c] |
| 2-Bromonaphthalene | 2,2′-Binaphthyl | 84 |
| Cyclohexyl bromide | Bicyclohexyl | 58 |
| Cyclopentyl bromide | Bicyclopentyl | 56 |
| 2-Bromopentane | 3,4-Dimethyloctane | 50 |

[a] Calculated on pure recrystallized or redistilled material. [b] Accompanied by 5% di(4-chlorophenyl)thallium(III) bromide. [c] Accompanied by 7% di(4-fluorophenyl)thallium(III) bromide.

fully investigated, however, and will be reported independently.

The above results are accommodated by the tentative reaction course of eq 1–6.

$$RMgBr + TlBr \longrightarrow RTl + MgBr_2 \quad (1)$$

$$RTl + 2TlBr \longrightarrow RTlBr_2 + 2Tl \quad (2)$$

$$2RTl \longrightarrow R\text{–}R + 2Tl \quad (3)$$

$$2RTlBr_2\ (R = \text{alkyl}) \longrightarrow R_2TlBr + TlBr_3 \quad (4)$$

$$ArTlBr_2 \xrightarrow{\text{heat}} ArBr + TlBr \quad (5)$$

$$ArTl + ArBr \longrightarrow Ar\text{–}Ar + TlBr \quad (6)$$

Equation 3 was suggested by Gilman and Jones[6] as the source of the small amount of biphenyl obtained on treatment of phenyllithium with thallium(I) chloride. The major product in this reaction was triphenylthallium, which we have not observed under our conditions. Contrary to the suggestion of Gilman and Jones,[6] we have shown that triphenylthallium does *not* disproportionate to biphenyl and thallium. The disproportionation of alkylthallium(III) dibromides (eq 4) has been observed previously in the reaction of alkyl Grignard reagents with thallium(III) bromide.[7,8] Arylthallium(III) dibromides, on the other hand, are known to be considerably more stable, although they do disproportionate on heating (eq 5).[9]

(6) H. Gilman and R. G. Jones, *J. Am. Chem. Soc.*, 68, 517 (1946).
(7) C. R. Hart and C. K. Ingold, *J. Chem. Soc.*, 4372 (1964).
(8) D. Sarrach, *Z. Anorg. Allgem. Chem.*, 319, 16 (1962).
(9) A. N. Nesmeyanov and R. A. Sokolik, "Methods of Elemento-Organic Chemistry. Vol. I. The Organic Compounds of Boron, Aluminum, Gallium, Indium and Thallium," The World Publishing Co., New York, N. Y., 1967.

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## An Unequivocal Synthesis of 6-Substituted Pteridine 8-Oxides, Pteridines, and 7,8-Dihydropteridines[1]

*Sir:*

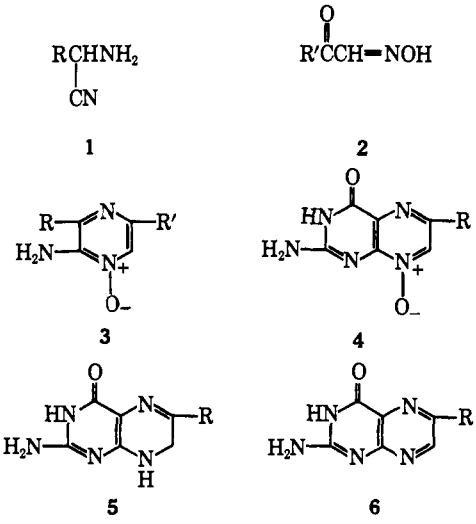
Almost all naturally occurring pteridines are 6-substituted derivatives and are unsubstituted at position 7.[2] Their unequivocal synthesis by the classical, most widely employed synthetic route to pteridines (condensation of a 4,5-diaminopyrimidine with an $\alpha,\beta$-dicarbonyl compound) is therefore not possible, since this method suffers from an unavoidable ambiguity when an unsymmetrical $\alpha,\beta$-dicarbonyl component is employed.[2,3] The mixture of isomers which results is not only extremely difficult to separate but is often undetectable by normal chromatographic techniques. One can, in principle, avoid this ambiguity by initially preparing a pyrazine intermediate with a known substitution pattern and subsequently closing the pyrimidine ring,[4] but this approach has not seen much application and has never been used for the preparation of any naturally occurring pteridines because of inaccessibility of the requisite pyrazine intermediates.

We describe in this communication a general, unequivocal synthesis of 6-substituted pteridine 8-oxides. These compounds are readily reduced to 7,8-dihydropteridines, again of unequivocal structure; subsequent mild oxidation gives 6-substituted pteridines. The procedure readily permits wide variations in substitution patterns in both the pyrimidine and pyrazine rings and appears directly applicable to the unambiguous synthesis of a variety of naturally occurring pteridines carrying different types of substituents at $C_6$.

Condensation of ethyl $\alpha$-aminocyanoacetate[5] (**1**, R = $COOC_2H_5$) with isonitrosoacetone[6] (**2**, R′ = $CH_3$) in glacial acetic acid at room temperature gave 2-amino-3-carbethoxy-5-methylpyrazine 1-oxide[7] (**3**, R = $COOC_2H_5$; R′ = $CH_3$, 60%; mp 134.8°) which upon reaction with guanidine in methanol containing sodium methoxide, followed by cyclization of the pyrazinoylguanidine intermediate by heating in DMF, gave 6-methylpterin 8-oxide (**4**, R = $CH_3$, 65%). Both the 6-methyl and the 8-oxide groupings are positioned unambiguously by this sequence of condensation reactions.[8] Reduction of **4** (R = $CH_3$) with sodium di-

(1) This work was supported by a grant (CA-02551) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.
(2) For general references on pteridine chemistry, see (a) "Pteridine Chemistry," W. Pfleiderer and E. C. Taylor, Ed., Pergamon Press, Ltd., London, 1964; (b) R. C. Elderfield and A. C. Mehta, "Heterocyclic Compounds," Vol. 9, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1967, pp 1–117; and references cited therein.
(3) See, for example (a) R. G. W. Spickett and G. M. Timmis, *J. Chem. Soc.*, 2887 (1954); (b) R. Tschesche and G. Sturm, *Chem. Ber.*, 98, 851 (1965).
(4) For examples of this route to pteridines, see (a) S. Gabriel and A. Sonn, *ibid.*, 40, 4850 (1907); (b) A. Albert, D. J. Brown, and G. W. H. Cheeseman, *J. Chem. Soc.*, 474 (1951); (c) E. C. Taylor, J. A. Carbon, and D. R. Hoff, *J. Am. Chem. Soc.*, 75, 1904 (1953); (d) E. C. Taylor, R. B. Garland, and C. F. Howell, *ibid.*, 78, 210 (1956); (e) G. P. G. Dick and H. C. S. Wood, *J. Chem. Soc.*, 1379 (1955); (f) E. C. Taylor and W. W. Paudler, *Chem. Ind.* (London), 1061 (1955); (g) W. B. Wright and J. M. Smith, *J. Am. Chem. Soc.*, 77, 3927 (1955).
(5) (a) A. H. Cook, I. Heilbron, and A. L. Levy, *J. Chem. Soc.*, 1594 (1947); (b) B. Ohta, *J. Pharm. Soc. Japan*, 68, 226 (1948); *Chem. Abstr.*, 48, 4440*g* (1954).
(6) Condensation of alkyl $\alpha$-aminonitriles with oximinomethyl ketones to give pyrazine 1-oxides (**3**, R = alkyl) was described by Sharp and Spring (W. Sharp and F. S. Spring, *J. Chem. Soc.*, 932 (1951)) during their early work on the synthesis of aspergillic acid.
(7) Satisfactory microanalytical and spectral data (ir, uv, and nmr) were obtained for all new compounds reported. Compounds for which no melting points are reported did not melt below 320°.

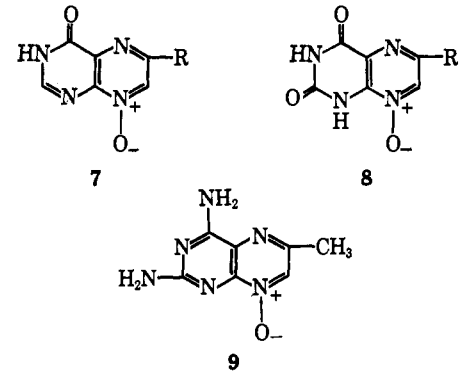
thionite gave 6-methyl-7,8-dihydropterin[9,10] (**5**, R = $CH_3$, 90%) which on potassium permanganate oxidation gave the known 6-methylpterin[11-13] (**6**, R = $CH_3$).



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.



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.

(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)).

(10) W. Pfleiderer and H. Zondler, *Chem. Ber.*, 99, 3008 (1966).

(11) J. H. Boothe, C. W. Waller, E. L. R. Stokstad, B. L. Hutchings, J. H. Mowat, R. B. Angier, J. Semb, Y. SubbaRow, D. B. Cosulich, M. J. Fahrenbach, M. E. Hultquist, E. Kuh, E. H. Northey, D. R. Seeger, J. P. Sickels, and J. M. Smith, *J. Am. Chem. Soc.*, 70, 27 (1948).

(12) W. R. Boon and T. Leigh, *J. Chem. Soc.*, 1497 (1951).

(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]

(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