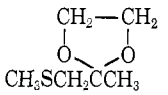
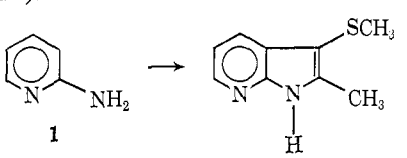
use of 2-amino-4-methylpyridine (**9**) in place of **1** led to **16** in 25% yield (46% based on unrecovered **9**): nmr ($CDCl_3$, TMS) τ 7.72 (3 H, s), 7.15 (3 H, s), 3.26 (1 H, d), 2.72 (1 H, s), 1.96 (1 H, d), and −2.34 (1 H, broad s).

A further modification of our procedure permitted the preparation of 2-substituted 7-azaindoles. Use of the ethylene glycol ketal, **17**, in place of **14**, with **1** as



17

our starting amine gave **18** in 37% overall yield: nmr ($CDCl_3$, TMS) τ 7.76 (3 H, s), 7.90 (3, H, s), 2.98 (1 H, d of d), 2.11 (1 H, d of d), 1.84 (1 H, d of d), and −2.22 (1 H, broad s).



1 **18**

In summary, we have found that certain aminopyridines can be converted in good overall yields into pyridines where the position ortho to the amino function has been alkylated. When this alkyl side chain also contains a masked carbonyl group in the β position, simple transformation into a carbonyl group leads to condensation with the nitrogen and azaindole formation. In view of the efficiency with which this process works on aminopyridines, we anticipate that this procedure should find wide applicability in the substitution of other amino heteroaromatics. We are continuing to investigate such applications.

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Pteridines. XXX. A Facile Synthesis of Xanthopterin[1]

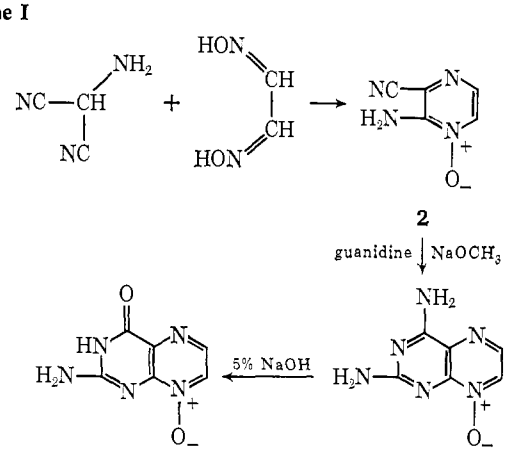
Sir:

Xanthopterin (**1**) is historically one of the most important of the naturally occurring pteridines. Along with leucopterin (7-hydroxyxanthopterin), it was the first of the pteridine butterfly wing pigments to be isolated, characterized, and synthesized.[2] It has since been found widely distributed in insects and in animals,[3] and is a normal constituent of human urine.[4] Interest in this apparently esoteric pigment has recently been rekindled as a result of a report that it exhibits tumor inhibitory properties.[5] However, although first synthesized in 1940,[2] and since prepared by a number of alternative procedures,[6] **1** remains a relatively inaccessible material of sometimes questionable purity.

We have recently developed a new, general synthetic approach to pteridines which employs the condensation of α-aminonitriles with α-oximinocarbonyl compounds to give pyrazine 1-oxides which are subsequently converted to pteridines and pterins by a variety of pathways.[7-10] A major advantage of this new synthesis lies in the unambiguous positioning of substituents in the pyrazine ring, thus permitting unequivocal syntheses of the 6-substituted pteridine natural products. In all previously described exploitations of this synthetic principle, the *N*-oxide grouping (which arises in the initial cyclization reaction by participation of the oximino grouping as a nucleophile) served no subsequent synthetic purpose and was removed at the pyrazine or pteridine stage by reduction. However, the well known utility of *N*-oxides as intermediates for the functionalization of heterocycles[11] prompted us to examine the chemistry of these pteridine 8-oxides, and we describe herein a simple, extremely efficient synthesis of **1** based upon an unusual *N*-oxide rearrangement. This reaction constitutes the first exploitation of the pteridine 8-oxide grouping in synthesis and makes pure **1** readily available.

The immediate precursor to **1** was pterin 8-oxide (**4**), which was prepared as follows. Condensation of aminomalononitrile tosylate with glyoxime in aqueous solution gave 2-amino-3-cyanopyrazine 1-oxide (**2**), which reacted with guanidine in methanolic sodium methoxide to give 2,4-diaminopteridine 8-oxide (**3**) (91%). Compound **4** was then obtained from **3** by alkaline hydrolysis of the 4-amino grouping (98%) (Scheme I).

Scheme I



2

4 **3**

Normally, treatment of aromatic *N*-oxides with acid anhydrides results in deoxygenation, with con-

(1) Part XXIX: E. C. Taylor, K. L. Perlman, Y.-H. Kim, I. P. Sword, and P. A. Jacobi, *J. Amer. Chem. Soc.*, in press.
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(4) T. Fukushima and T. Shiota, *J. Biol. Chem.*, 247, 4549 (1972).
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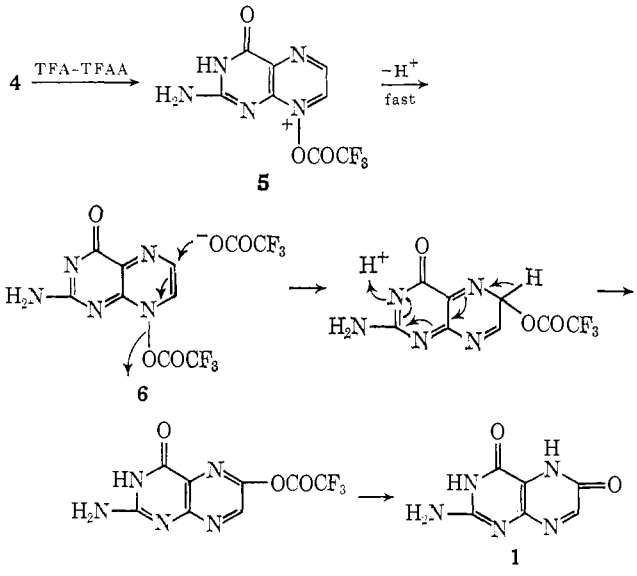
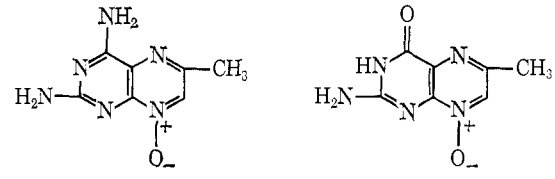
Scheme II



comitant introduction of oxygen (as an acyloxy grouping, subsequently hydrolyzed to a cyclic amide) α to the ring nitrogen.[11] However, in initial experiments with **4** we were unable to induce reaction either with neat acetic anhydride or with mixtures of acetic acid–acetic anhydride even on prolonged (48 hr) reflux. Additionally, no reaction could be detected with acetyl chloride, dichloroacetyl chloride, or benzoyl chloride in DMF or pyridine at temperatures ranging from ambient to 100°. Somewhat surprised at this apparent lack of reactivity of **4**, we turned our attention to the use of trifluoroacetic acid–trifluoroacetic anhydride (TFA–TFAA). This reagent mixture has been used in the past to effect rearrangement of relatively unreactive (nonbasic) *N*-oxides,[11] and in addition was expected to facilitate detection of any resultant molecular transformations by periodic nmr inspection of reaction mixture aliquots (**4** shows two well resolved doublets at δ 8.35 and 8.50 (J = 4.5 Hz) in TFA; any rearrangement product should exhibit only a single C–H proton absorption). Indeed, **4** dissolved almost immediately in 50:50 TFA–TFAA at 50° to give a bright yellow solution, an aliquot of which showed no trace of starting material, and a sharp singlet at δ 8.60. When **4** was dissolved in TFA–TFAA at room temperature, the initial nmr spectrum of the mixture showed the presence of starting material (**4**) (resolved doublets) as well as rearrangement product (sharp singlet). During the course of 3–4 hr, all absorptions due to **4** slowly disappeared with concurrent strengthening of the singlet at δ 8.60; the final spectrum was identical with that obtained from reaction at 50°. To our surprise, however, following the usual work-up (evaporation of solvents and basic hydrolysis), the only product isolated, with no detectable contaminants (tlc), was *xanthopterin* (**1**). Although *N*-oxide rearrangements to a position β to the ring nitrogen are occasionally observed in heterocyclic chemistry, mixtures of products are usually obtained. The above extremely facile rearrangement of pterin 8-oxide (**4**) to xanthopterin (**1**) (consistently in 95–100% yield) may well be unique in its homogeneity.

We suggest that this conversion probably proceeds as shown in Scheme II;[12] the usual α rearrangement is apparently blocked by very rapid deprotonation of the intermediate acyloxypteridinium salt **5**. 2,4-Diaminopteridine 8-oxide (**3**) could be rearranged analogously to 2,4-diamino-6(5*H*)-pteridinone but only under forcing conditions (refluxing TFA–TFAA, 5 hr).[13] Neither 2,4-diamino-6-methylpteridine 8-oxide (**7**) nor 6-methylpterin 8-oxide (**8**) (in which the position to which β rearrangement would occur is effectively blocked by methyl substitution) could be induced to rearrange under any conditions.



More detailed mechanistic studies of these transformations are in progress, and the inherent synthetic potentialities involved are currently under active exploration.[14]

(12) This pathway is analogous in principle to those proposed previously for β rearrangement reactions of aromatic *N*-oxides (see ref 11, pp 287–288).

(13) Alkaline hydrolysis of 2,4-diamino-6(5*H*)-pteridinone provided an alternate, although far less satisfactory, route to **1**.

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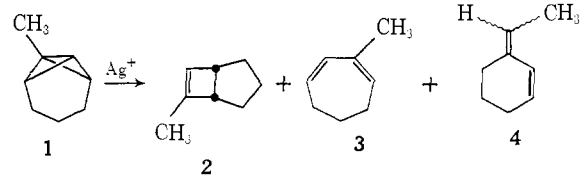
Stereospecificity, Regioselectivity, and Kinetic Deuterium Isotope Effects in the Silver(I)-Catalyzed Isomerizations of 1-Methyltricyclo[4.1.0.0^{2,7}]heptanes to Bicyclo[3.2.0]hept-6-enes[1]

Sir:

Wide variations in kinetic response and product distributions are now recognized to accompany minor substituent changes in bicyclo[1.1.0]butanes and tricyclo[4.1.0.0^{2,7}]heptanes when these are subjected to transition metal catalyzed rearrangement. An enduring significant problem concerns the detailed nature of the mechanistic changeover which operates under conditions of Ag^+ catalysis to divert, for example, the behavior of tricyclo[4.1.0.0^{2,7}]heptane which gives only 1,3-cycloheptadiene to that exhibited by **1** ($k_{Ag}^{40°}$ = 5.10 × 10^{-3} M^{-1} sec^{-1}) which affords chiefly **2** (44%) together with **3** (26%) and **4** (29%, syn:anti = 4:1)



under the identical conditions.[2] Although extensive

(1) Silver(I) Ion Catalyzed Rearrangements of Strained σ Bonds. XVIII. For part XVII, see L. A. Paquette, S. E. Wilson, G. Zon, and J. A. Schwartz, *J. Amer. Chem. Soc.*, **94**, 9222 (1972).

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