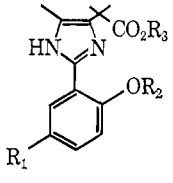
of the lactone linkage of I was accomplished through sodium borohydride (6 hydride equiv) reduction in DMF at ambient temperature for 2 days which provided IV, as white microneedles, in 60% yield (mp >340° dec; ir (KBr) 1640 (ImH^+) and 1035 cm^{-1} ($-SO_3^-$); nmr (D_2O–KOD) δ 1.33 (s, 6), 2.32 (s, 3), 3.65 (s, 2), 6.77 (d, 1, J = 8.5 Hz), 7.52 (q, 1, J = 8.5, J = 2.5 Hz), and 8.15 ppm (d, 1, J = 2.5 Hz); pK_a (H_2O, 1 M KCl) 5.8 (ImH^+) and 8.9 (PhOH). *Anal.* Calcd for $C_{14}H_{18}N_2O_5S$: C, 51.52; H, 5.56; N, 8.59; S, 9.83. Found: C, 51.45 H, 5.51; N, 8.61; S, 9.73).

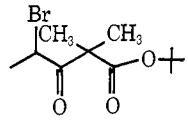
If I is dissolved in H_2O below pH 6, it rearranges quantitatively *via* a first-order process to III which is relatively stable. At higher pH's, I hydrolyzes to II *via* III following consecutive first-order kinetics. The rate constants for the two processes differ sufficiently at 3° and pH 12.4 so that it can be shown that most if not all of II arises from III and not directly from I. That III is in fact the acetyl ester was shown by comparison of uv repetitive scans recorded during alkaline hydrolysis (and the identity of the corresponding rates) with authentic III. The sample of authentic III was prepared from II employing a similar acetylation procedure as for I and a reaction time of 30 hr (mp >265° turns yellow, decomposing without melting; uv (H_2O at pH 5) 275 nm; ir (KBr) 1780 (COOPh), 1730 (CO_2H), 1645 (ImH^+), 1045 and 655 cm^{-1} (SO_3^-); nmr (DMSO-d_6) δ 1.65 (s, 6), 2.28 (s, 3), 2.38 (s, 3), and 7.2–8.1 ppm (m, 3). *Anal.* Calcd for $C_{16}H_{18}N_2O_7S$: C, 50.25; H, 4.74; S, 8.39. Found: C, 50.47; H, 4.60; S, 8.41).

The assignment of the tetrahedral structure to I rests upon five pieces of evidence. (1) I exhibits only one carbonyl peak at 1780 cm^{-1} which disallows the simultaneous presence of a carboxylic acid and an acetyl group as would be required of either a mixed anhydride or *N*-acetyl derivative of II. Seven derivatives (II, III, and V–IX) containing a free carboxyl group



V, R_1 = H; R_2 = H; R_3 = H
VI, R_1 = H; R_2 = CH_3; R_3 = H
VII, R_1 = H; R_2 = $COCH_3$; R_3 = H
II, R_1 = SO_3^-; R_2 = H; R_3 = H
VIII, R_1 = SO_3^-; R_2 = CH_3; R_3 = H
III, R_1 = SO_3^-; R_2 = $COCH_3$; R_3 = H
IX, R_1 = SO_3^-; R_2 = $COCH_2C(CH_3)$; R_3 = H
X, R_1 = H; R_2 = CH_3; R_3 = $C(CH_3)_3$

have been prepared and all exhibit a carbonyl band in the region 1710–1735 cm^{-1}. The absorption at 1780 cm^{-1} is, however, expected for a lactone carbonyl with electronegative substituents α to the ether oxygen. (2) The quantitative conversion in dilute aqueous solution of I → III *via* rate constants independent of $[I]_0$ requires an intramolecular "acetyl group" transfer. (3) The gem dimethyl groups of I exhibit magnetic nonequivalence in contrast to those in compounds II, III, V, VI, and X. This feature is invariant with solvent or the states of ionization. One possible explanation for this difference is the rigidity of the fused ring system. However, recent findings[7] concerning similarly disposed groups in another fused lactone system do not support this hypothesis. The source of nonequivalence in I is evidently the asymmetric nature of the tetrahedral carbon itself. Hence, in compound XI the α-dimethyl



XI

groups give rise to two resonances with $\Delta\delta$ = 9 Hz.[8] (4) The reducibility of the carboxyl carbonyl to an alcohol with sodium borohydride establishes that I does not possess a free carboxyl group. No reduction occurred with compounds I or III. (5) The unusually high magnetic field position of the methyl group added as acetyl chloride (1.82 ppm) indicates a unique environment. Molecular models of I show that one of two possible ring conformations forces this methyl group into the π-electronic region of the benzenoid ring. Thus, an anisotropic paramagnetic shielding of *ca.* 0.7 ppm is experienced by the methyl protons. No other structure can explain this observation.

Although the structure of I contains the "trialkyl lock" device of Cohen,[9] the ability to isolate I would appear to be a combination of insolubility and crystal lattice energy. Compound V (differing from II only by the sulfonic acid) has been repeatedly acetylated under the same reaction conditions as II with only the phenyl acetate isolated and no evidence for the formation of a tetrahedral intermediate. Further experiments are being conducted in order to deduce the mechanism of the tetrahedral to phenyl acetate rearrangement and the catalysis of this process by buffer species.

Acknowledgment. Supported by a grant from the National Institutes of Health.

(7) Personal communication from L. Cohen to J. M. Karle and I. L. Karle, *J. Amer. Chem. Soc.*, **94**, 9182 (1972).
(8) This study.
(9) S. Milstien and L. A. Cohen, *J. Amer. Chem. Soc.*, **94**, 9158 (1972); R. T. Borchardt and L. A. Cohen, *ibid.*, **94**, 9166, 9175 (1972).

Gary A. Rogers, Thomas C. Bruice*
Department of Chemistry, University of California
Santa Barbara, California 93106
Received March 17, 1973

Specific Ortho Substitution of Aromatic Heterocyclic Amines. Conversions of 2-Aminopyridines

Sir:

Methods for the selective alkylation of aromatic heterocyclic compounds are generally quite limited.[1] In view of the recent report from our laboratory on the specific ortho alkylation of anilines,[2] we felt that a method might be at hand for the facile, specific substitution of aromatic heterocyclic amines. In order to test the validity of this premise, we have investigated the use of our alkylation process with 2-aminopyridine.

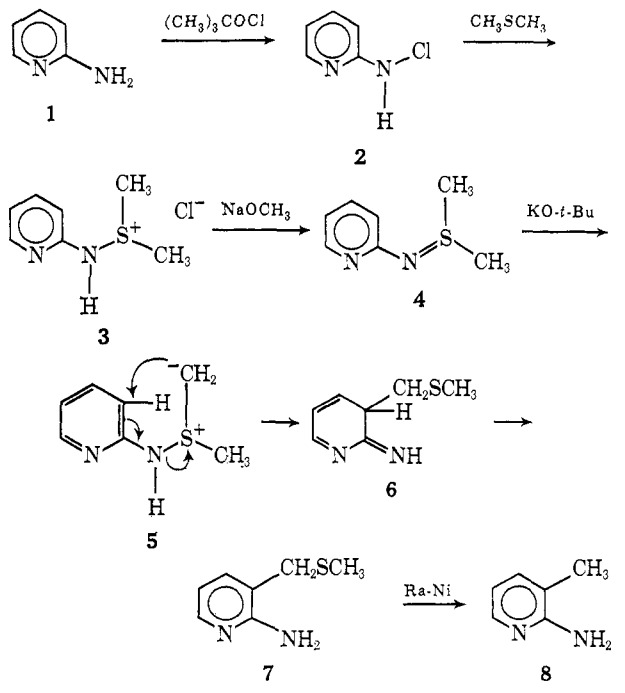
(1) For a leading reference to the known methods of alkylation of heterocyclics see E. C. Taylor and S. F. Martin, *J. Amer. Chem. Soc.*, **94**, 2874 (1972).
(2) P. G. Gassman and G. Gruetzmacher, *ibid.*, **95**, 588 (1973).

We now wish to report the details of this new method for the specific substitution of aromatic heterocyclics.

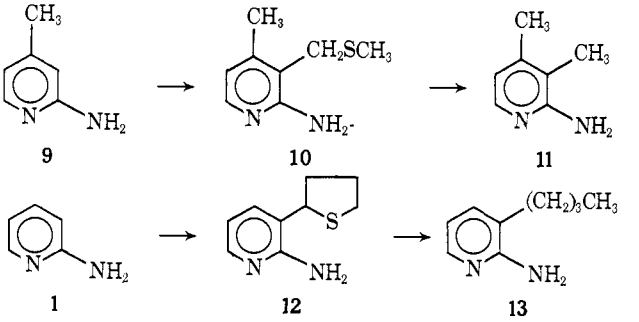
In a typical procedure, a solution of *tert*-butyl hypochlorite (0.085 mol) in 50 ml of methylene chloride was added to a solution of 2-aminopyridine (0.085 mol) in 100 ml of methylene chloride at −60° over a 20-min period. The reaction mixture was stirred for 20 min and dimethyl sulfide was added to give a light orange precipitate of azasulfonium salt. After stirring at −60° for 45 min, a solution of sodium methoxide (0.09 mol) in 30 ml of methanol was added at −60°. The reaction mixture was stirred for 1 hr, allowed to warm to room temperature, and diluted with water; the organic layer was separated and dried and the solvent was removed to give a quantitative yield of the crude, crystalline dimethylsulfilimine of 2-aminopyridine. Addition of the crude sulfilimine to a solution of potassium *tert*-butoxide (0.06 mol) in 330 ml of *tert*-butyl alcohol, followed by a 12-hr reflux, gave a 70% yield of purified 2-amino-3-methylthiomethylpyridine: nmr ($CDCl_3$, TMS), τ 8.05 (3 H, s), 6.40 (2 H, s), 4.85 (2 H, broad s), 3.38 (1 H, mult), 2.70 (1 H, mult), and 1.92 (1 H, mult). Raney nickel reduction of 2-amino-3-methylthiomethylpyridine gave a 71% yield of pure 2-amino-3-methylpyridine, mp 30.5–32° (lit.[3] mp 26.0–26.4°). Structure proof was established through spectral comparison with a commercial sample (liquid).

The procedure described above illustrates that our procedure can be used to alkylate certain aminoheterocyclics in high overall yield. Mechanistically, the process involves initial conversion of the 2-aminopyridine (**1**) (Scheme I) to its mono-*N*-chlorinated derivative,[4] **2**. Addition of the dimethyl sulfide then produces the azasulfonium salt, **3**. On short treatment at low temperature with base the sulfilimine, **4**, is formed. At higher temperatures, in the presence of strong base, the sulfilimine is equilibrated with the ylide, **5**, which rearranges to the imine, **6**. Hydrogen transfer and rearomatization then produces **7**. The overall 50% yield of **8** from **1** indicates an averaged yield of greater than 90% for each of the seven steps involved.

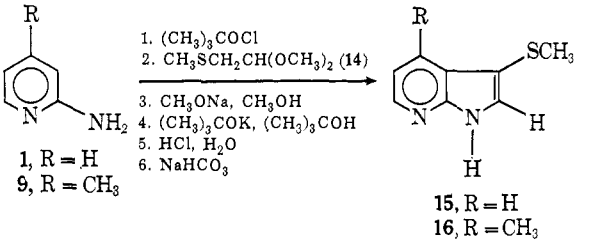
Scheme I



The alkylation reaction was not restricted to 2-aminopyridine or to dimethyl sulfide. Using the general procedure described above, 2-amino-4-methylpyridine (**9**) was readily converted into **10** (70% yield) which on Raney-nickel reduction gave **11** (70% yield), mp 81.5–82.0°;[5] nmr ($CDCl_3$, TMS) τ 8.03 (3 H, s), 7.94 (3 H, s), 5.14 (2 H, broad s), 3.58 (1 H, d, J = 5 Hz), and 2.54 (1 H, d, J = 5 Hz). In a related application of our general procedure, tetrahydrothiophene was used as the sulfide, to give a 59% yield of **12** from **1**. Raney-nickel reduction of **12** gave a 33% yield of 2-amino-3-*n*-butylpyridine (**13**).



The use of derivatives of β-carbonyl sulfides provided an important modification of our general procedure, which led to a simple process for the synthesis of certain azaindoles.[6] Treatment of 2-aminopyridine (**1**) with *tert*-butyl hypochlorite, followed by addition of the acetal, **14**, gave an azasulfonium salt which was dehydrohalogenated with sodium methoxide to produce a sulfilimine; this was equilibrated with the desired ylide in the presence of potassium *tert*-butoxide, as detailed in the general procedure described above. Rearrangement of the ylide gave the 3-substituted pyridine with the acetal function in the side chain. Acidification of a solution of this acetal with aqueous hydrochloric acid gave the corresponding aldehyde which spontaneously condensed with the 2-amino function to give, after neutralization, 3-thiomethyl-7-azaindole (**15**), mp 115.0–115.5°, in 45% overall yield from **1**. The structure was assigned on the basis of elemental analysis and spectral data: nmr ($CDCl_3$, TMS) τ 7.64 (3 H, s), 2.65 (1 H, d of d), 2.50 (1 H, s), 1.90 (1 H, d of d), 1.60 (1 H, d of d), and −2.72 (1 H, broad s).[7] The



(3) O. Seide, *Ber.*, **58**, 1733 (1925).

(4) Satisfactory elemental analyses have been obtained on all new compounds described in this communication except for **2**, **3**, **5**, and **6** which were not isolated.

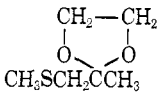
(5) This compound was previously described in the literature as a low melting solid (no melting point given): A. Albert and R. E. Willette, *J. Chem. Soc.*, 4063 (1964).

(6) For the use of β-keto sulfides in the synthesis of indoles from anilines, see P. G. Gassman and T. J. van Bergen, *J. Amer. Chem. Soc.*, **95**, 590, 591 (1973).

(7) For a discussion of the nmr spectral properties of 7-azaindoles see R. E. Willette, *Advan. Heterocycl. Chem.*, **9**, 99 (1968). Our spectra correlated very well with those of related compounds reported.

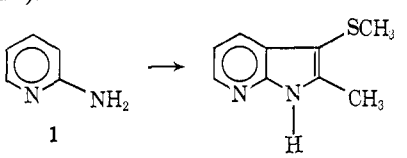
use of 2-amino-4-methylpyridine (**9**) in place of **1** led to **16** in 25% yield (46% based on unrecovered **9**): nmr ($CDCl_3$, TMS) τ 7.72 (3 H, s), 7.15 (3 H, s), 3.26 (1 H, d), 2.72 (1 H, s), 1.96 (1 H, d), and −2.34 (1 H, broad s).

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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Paul G. Gassman,* Chin Teh Huang
Department of Chemistry, The Ohio State University
Columbus, Ohio 43210
Received March 30, 1973

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

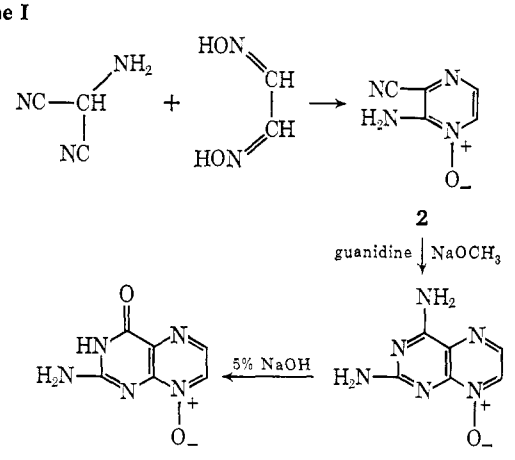
Sir:

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.
(2) R. Purrmann, *Justus Liebigs Ann. Chem.*, **546**, 98 (1940).
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(4) T. Fukushima and T. Shiota, *J. Biol. Chem.*, **247**, 4549 (1972).
(5) G. R. Pettit, L. E. Houghton, N. H. Rogers, R. M. Coomes, D. F. Berger, P. R. Reucroft, J. F. Day, J. L. Hartwell, and H. B. Wood, Abstracts, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, MEDI-37.
(6) (a) W. Koschara, *Z. Physiol. Chem.*, 277, 159 (1943); (b) J. R. Totter, *J. Biol. Chem.*, **154**, 105 (1944); (c) G. B. Elion, A. E. Light, and G. H. Hitchings, *J. Amer. Chem. Soc.*, 71, 741 (1949); (d) W. R. Boon and T. Leigh, *J. Chem. Soc.*, 1497 (1951); (e) A. Stuart and H. C. S. Wood, *ibid.*, 4186 (1963).
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(8) E. C. Taylor in "Chemistry and Biology of Pteridines," K. Iwai, M. Akino, M. Goto, and Y. Iwanami, Ed., International Academic Printing Co., Tokyo, 1970.
(9) E. C. Taylor, K. L. Perlman, I. P. Sword, M. Séquin-Frey, and P. A. Jacobi, *J. Amer. Chem. Soc.*, in press.
(10) E. C. Taylor and T. Kobayashi, *J. Org. Chem.*, in press.
(11) A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, New York, N. Y., 1971.