ethyl 2-pyridylacetate, 1.11 g of di-2-picolyl ketone, and 24 mg of 1-carboethoxy-2-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (**4**): mp 166–167°; nmr[12] ($CDCl_3$) δ 1.44 (t, J = 7 Hz, $-CH_2CH_3$), 4.47 (q, J = 7 Hz, $-CH_2CH_3$), 6.82 (ddd, J = 7.5, 6.5, 1.5 Hz, H_7), 7.22 (ddd, J = 7.5, 6.5, 1.2 Hz, H_5'), 7.37 (ddd, J = 9.2, 6.5, 1.4 Hz, H_8), 7.71 (ddd, J = 9.2, 1.5, 0.9 Hz, H_9), 7.92 (ddd, J = 8.6, 7.5, 1.9 Hz, H_4'), 8.29 (ddd, J = 5.3, 1.9, 1.0 Hz, H_6'), 9.11 (ddd, J = 7.5, 1.4, 0.9 Hz, H_6), 9.29 (ddd, J = 8.6, 1.2, 1.0 Hz, H_3'), and 19.75 (broad s, -OH); ir (Nujol) 1700 (ester), 1652, 1630, 1602, 1557, and 1231 cm^{-1}; mass spectrum m/e 310 (M^+), 309, 264 ($M^+ - C_2H_6O$), 237 ($M^+ - C_3H_5O_2$), 181, 146, 91, 78 (C_5H_4N).

Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.78; H, 4.55; N, 9.03. Found: C, 65.56; H, 4.46; N, 8.99.

Reaction of 2-Picolyllithium with Diethyl Carbonate. 1-Carboethoxy-2-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (**4**).—To a solution of phenyllithium (Alfa Chemical Co., 0.6 mol, 2.2 *M* in benzene–ether) in 500 ml of ether, 2-picoline (bp 128–129°, 56 g, 0.6 mol) was added over a 10-min period. The solution was refluxed for 30 min, and then diethyl carbonate (47 g, 0.4 mol) in 50 ml of ether was added rapidly. Reflux was maintained for an additional 30 min. The mixture was cooled, poured into ice water, adjusted with acid to pH ~8, and extracted with chloroform. After removal of the solvents, as well as unreacted 2-picoline, the residue was fractionally distilled, affording 2.0 g of ethyl 2-pyridylacetate, bp 110–113° (6 mm).

The distillation residue (11.7 g) was chromatographed, affording 917 mg of ethyl 2-pyridylacetate, 6.0 g (14%) of **4** (mp 166–167°), and 150 mg (1%) of 3-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (**3**): mp 175–177° (lit.[6] mp 181–182°); nmr ($CDCl_3$) δ 6.30 (d, J = 0.75 Hz, H_1), 6.73 (five lines), 7.21 (ddd, J = 6.0, 5.0, 1.0 Hz, H_5'), 7.21 (m, H_8 and H_9), 7.89 (ddd, J = 8.5, 6.0, 1.0 Hz, H_4'), 8.36 (ddd, J = 5.0, 1.9, 1.0 Hz, H_6'), 9.00 (broad d, H_6), 9.34 (ddd, J = 8.5, 1.0, 1.0 Hz, H_3'), and 18.3 (broad s, -OH); ir (Nujol) 3500–3100 (broad, OH), 1667, 1641, 1613, and 1589 cm^{-1}.

2-Hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (**3**).—The ester **4** (1.00 g, 3.22 mmol) suspended in 100 ml of a 5% sodium hydroxide solution was refluxed for 8 hr. After cooling to ambient temperature, the pH was adjusted to 7.5–8. The solution was extracted with chloroform, dried with anhydrous sodium sulfate, and concentrated *in vacuo*, affording 630 mg (82%) of 2-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one, mp 174.5–176°. Recrystallization from ethanol gave a sample of pure **3**, mp 176.5–178°.

Reaction of 2-Picoline with Diethyl Carbonate and Sodium Hydride.—Sodium hydride (50% dispersion, 2.15 g, 0.05 mol) in 1,2-dimethoxyethane (DME, 25 ml) was stirred under nitrogen with addition of a solution of 2-picoline (4.65 g, 0.05 mol), diethyl carbonate (11.8 g, 1.10 mol), and DME (20 ml). After the mixture was refluxed for 8 hr, it was poured into ice water. The pH of the aqueous layer was adjusted with dilute acid to 7.5–8 and the layer was extracted with chloroform. The extract was dried with sodium sulfate and concentrated *in vacuo*, removing all solvents and unreacted starting materials. Chromatography of the remaining yellow oil afforded 322 mg (2.7%) of diethyl 2-pyridylmalonate: bp 130–132° (1 mm); nmr ($CDCl_3$) δ 1.21 ($-CH_2CH_3$, t, J = 7 Hz), 4.22 ($-CH_2CH_3$, q, J = 7 Hz), 5.04 (CHCO, s), 7.05–7.88 (pyr H, m), and 8.44–8.65 (6-pyr H, m).

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.76; H, 6.38. Found: C, 61.06; H, 6.40.

Further elution afforded 1.099 g (13.3%) of ethyl 2-pyridylacetate [bp 110–117° (6 mm)], 131 mg (1.7%) of 1-carboethoxy-2-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (**4**, mp 166–168°), and only traces of **3**.

Registry No.—**2**, 39541-69-0; **3**, 39541-70-3; **4**, 39541-71-4; **5** dipicrate, 39541-72-5; 2-picolyllithium, 39541-73-6; diethyl carbonate, 105-58-8; 2-picoline, 109-06-8; sodium hydride, 7646-69-7.

(12) The nmr spectrum of **4** will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-2234.

Unambiguous Synthesis of a Monocyclic 5,6-Dihydro-1,2-oxazine[1]

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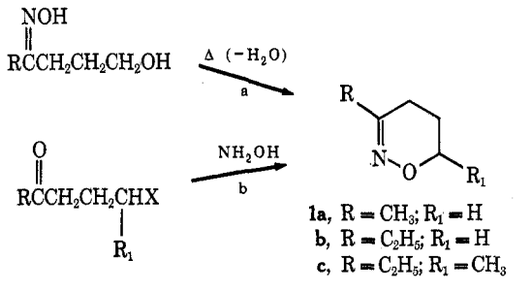
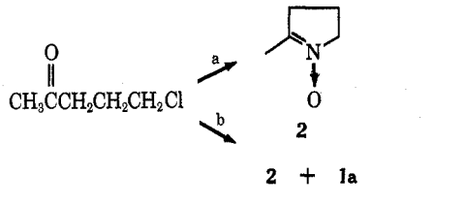
Recent review articles[2] to the contrary, considerable ambiguity exists regarding the published procedures[3,4] for the synthesis of monocyclic 4*H*-5,6-dihydro-1,2-oxazines. Neither Marshall and Perkin's cyclodehydration of a γ-hydroxy oxime (eq 1, path a) nor Wohlgemuth's oximation of a γ-halo ketone unequivocally produces the desired oxazine (eq 1, path b).[5,6]



(1)

Utilizing the procedure of Wohlgemuth,[4] 5-chloro-2-pentanone was treated with hydroxylamine hydrochloride–potassium carbonate in the molar ratio 1.0:1.1:0.5 (eq 2, path a). A compound, **2**, was obtained which analyzed for C_5H_9NO and which possessed all the physical properties previously described.[6] If this were 3-methyl-4*H*-5,6-dihydro-1,2-oxazine (**1a**), it would not be expected to show any significant uv absorption above 220 nm.[8] However, a maximum was observed at 227 nm (ϵ 8700). This, together with the ir data presented in Table I, led us to assign the structure 2-methylpyrroline 1-oxide (**2**) to this material.



(2)

(1) Work done at Seton Hall University, South Orange, N. J. 07079.

(2) (a) R. L. McKee in "Heterocyclic Compounds," Vol. 17, A. Weissberger, Ed., Interscience, New York, N. Y., 1962, p 329; (b) N. H. Cromwell in "Heterocyclic Compounds," Vol. 6, R. E. Elderfield, Ed., Wiley, New York, N. Y., 1957, p 559.

(3) J. R. Marshall and W. H. Perkin, *J. Chem. Soc.*, 861 (1891).

(4) H. Wohlgemuth, *Ann. Chim. (Paris)*, **2**, 403 (1914).

(5) Attempts to reproduce Marshall and Perkin's work have met with conflicting results.[7] Our own attempts to prepare **1a** by the author's procedure were unsuccessful.

(6) Wohlgemuth reported only that the compounds obtained were "water soluble, reduced ammoniacal silver nitrate in the cold and Fehling's solution when boiled."[4]

(7) (a) H. E. Glynn and W. H. Linnell, *Quart J. Pharmacol.*, **5**, 496 (1932); (b) M. Carmack, O. H. Bullitt, Jr., G. R. Handrick, L. W. Kissinger, and I. Von, *J. Amer. Chem. Soc.*, **68**, 1220 (1946).

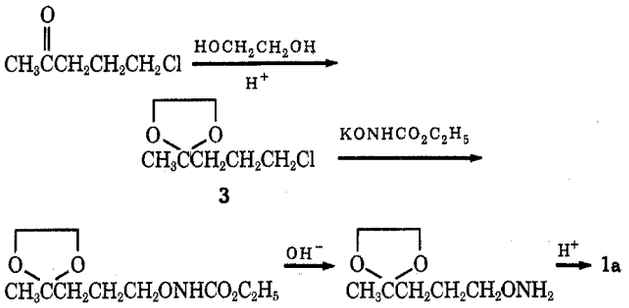
(8) C. N. R. Rao, "Ultraviolet and Visible Spectroscopy," Butterworths, London, 1961, pp 31–32.

TABLE I
UV AND IR SPECTRA OF PYRROLINE 1-OXIDES

Pyrroline 1-oxide	λ_{max}^{EtOH}, nm	ϵ_{max}	$\nu_{C=N}$, cm^{-1}	Ref
2,3,3-Trimethyl-	229	9000	1613 (s)	*a*
2,4,4-Trimethyl-	229	9120	1610 (s)	*b, c*
2	227	8700	1610 (s)	*d*

[a] R. Bonnett, S. C. Ho, and J. A. Raleigh, *Can. J. Chem.*, **43**, 2717 (1965). [b] R. Bonnett, R. F. C. Brown, U. M. Clark, and I. O. Sutherland, *J. Chem. Soc.*, 2094 (1959). [c] R. F. C. Brown, U. M. Clark, and A. Todd, *Proc. Chem. Soc.*, 97 (1957). [d] This work.

Repetition of the oximation with a molar ratio of ketone:hydroxylamine hydrochloride:potassium carbonate of 1.0:1.1:1.0 (eq 2, path b) gave a mixture of the previously obtained **2** together with a more volatile compound in a 1.0:1.4 ratio. This new (volatile) compound, although isomeric with **2**, exhibited no uv absorption above 220 nm. The ir spectrum displayed a medium-intensity band at 1620 cm^{-1} and a series of intense bands between 800 and 1010 cm^{-1}. The nmr consisted of a two-proton triplet at τ 6.11 and a three-proton singlet at τ 8.10 in the midst of a four-proton complex multiplet, τ 7.60–8.37. Based on this spectral data the structure **1a** was assigned to this compound. Further confirmation was obtained by a synthetic sequence which employed a preformed –NOC– linkage as outlined in eq 3.



(3)

The material obtained from this route was identical in every respect with the more volatile component from the oximation (eq 2, path b) of 5-chloro-2-pentanone. As far as we can ascertain from the literature, this represents the first unambiguous synthesis of a monocyclic 4*H*-5,6-dihydro-1,2-oxazine.

Experimental Section[9]

Oximation of 5-Chloro-2-pentanone (Eq 2, Path a).—Following the method of Wohlgemuth[4] a solution of 1.21 g (0.010 mol) of 5-chloro-2-pentanone, 0.77 g (0.011 mol) of hydroxylamine hydrochloride, 0.76 g (0.0055 mol) of potassium carbonate, 25 ml of 95% ethanol, and 25 ml of water was refluxed for 45 min. The reaction mixture (which had an approximate pH of 3, pHydrion paper) was cooled, concentrated under reduced pressure, saturated with sodium chloride, and extracted five times with 40-ml portions of methylene chloride. The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo* to leave 0.70 g of a clear liquid. Distillation through a short-path distillation apparatus gave 0.51 g of a colorless liquid (water soluble), bp 71–72° (0.4 mm), $n^{25}D$ 1.5129. On the basis of elemental analysis and ir, uv, and nmr spectral data this material was assigned the structure 2-methylpyrroline 1-oxide (**2**), rather than the expected, isomeric 3-methyl-4*H*-5,6-dihydro-1,2-oxazine (**1a**): ir (neat) 1610 (s), 1265 (s), 1228 cm^{-1} (vs); uv λ_{max}^{EtOH} 227 nm (ϵ 8700); nmr ($CDCl_3$) τ 5.98 (t, 2, J = 8.0 Hz, 5-CH_2), 7.18 (t, 2, J = 7.1 Hz, 3-CH_2), 7.97 (s, 3, 2-CH_3) in midst of complex multiplet, 7.60–8.02 (4-CH_2); mass spectrum (77.5 eV) *m/e* (rel intensity) 99 (58), 98 (16), 84 (3), 83 (2), 69 (6), 55 (10), 41 (100).

Anal. Calcd for C_5H_9NO: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.50; H, 9.30; N, 13.95.

The picrate was prepared in 95% ethanol and washed with several portions of ether, mp 73–74°.

Anal. Calcd for $C_{11}H_{12}N_4O_8$: C, 40.25; H, 3.68; N, 17.07. Found: C, 40.07; H, 3.39; N, 16.95.

Oximation of 5-Chloro-2-pentanone (Eq 2, Path b).—A solution of 1.54 g (0.22 mol) of hydroxylamine hydrochloride and 3.04 g (0.022 mol) of potassium carbonate in 25 ml of water was added to 2.42 g (0.020 mol) of 5-chloro-2-pentanone in 25 ml of 95% ethanol and the resulting mixture was refluxed for 3 hr. The solution was cooled and worked up as before to leave 2.33 g of a colorless liquid. The ir spectrum of this crude material exhibited bands at 1610 cm^{-1} (vs) and a series of five bands of medium intensity between 835 and 1050 cm^{-1}. Distillation through a short-path distillation apparatus yielded two products.

The more volatile component, bp 32–33° (0.4 mm), $n^{25}D$ 1.4607, weighed 0.45 g and was assigned the structure 3-methyl-4*H*-5,6-dihydro-1,2-oxazine (**1a**): ir (neat) 1620 (m), 1050 (s), 1010 (s), 950 (s), 900 (s), 840 (s), 655 cm^{-1} (s); uv featureless above 220 nm; nmr ($CDCl_3$) τ 6.11 (t, 2, J = 5.0 Hz, 6-CH_2), 8.10 (s, 3, 3-CH_3) in midst of complex multiplet, 7.60–8.37 (4, 4-CH_2, 5-CH_2); mass spectrum (77.5 eV) *m/e* (rel intensity) 99 (93), 98 (3), 85 (4), 84 (7), 73 (42), 71 (9), 69 (18), 68 (57), 56 (15), 55 (10), 54 (13), 43 (10), 42 (67), 41 (100).

Anal. Calcd for C_5H_9NO: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.43; H, 9.15; N, 14.25.

The hydrochloride prepared in ether had mp 130–131°.

Anal. Calcd for $C_5H_{10}ClNO$: C, 44.27; H, 7.44; Cl, 10.33. Found: C, 44.29; H, 7.44; Cl, 10.21.

The picrate was prepared in 95% ethanol, mp 108–109°.

Anal. Calcd for $C_{11}H_{12}N_4O_8$: C, 40.25; H, 3.68; N, 17.07. Found: C, 40.44; H, 3.87; N, 17.03.

The second component, 0.33 g of a colorless liquid, bp 72–73° (0.4 mm), was identical in all respects (refractive index and ir, uv, and nmr spectra) to the 2-methylpyrroline 1-oxide previously obtained by path a.

3-Methyl-4*H*-5,6-dihydro-1,2-oxazine (*via* Eq 3). 2-(3-Chloropropyl)-2-methyl-1,3-dioxolane (3).—A mixture of 23 ml of ethylene glycol, 24.2 g (0.2 mol) of 5-chloro-2-pentanone, 0.3 g of *p*-toluenesulfonic acid, and 500 ml of dry benzene was refluxed for 10 hr while the water produced was separated with a Dean–Stark trap. The benzene was removed *in vacuo* and the residue was taken up with chloroform and carefully basified with sodium methoxide. After washing one time with 5% sodium bicarbonate solution and one time with water, the organic layer was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to remove most of the solvent. Distillation through a 15-cm vacuum-jacketed Vigreux column gave 27.0 g (82.5%) of **3**, bp 111–113° (40 mm) [(lit.[10] bp 84–86° (14 mm)].

2-(3-Ethoxycarbonylaminooxypropyl)-2-methyl-1,3-dioxolane (4).—A mixture of 17.7 g (0.10 mol) of **3**, 10.7 g (0.12 mol) of hydroxyurethane,[11] 7.8 g (0.12 mol) of potassium hydroxide (85%), and 30 ml of absolute ethanol was refluxed with stirring for 6.5 hr. After cooling, the reaction mixture was washed onto a filter funnel with ether; the inorganic residue was washed six times with 50-ml portions of ether. The combined filtrates were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to leave 22.15 g of a viscous oil. Distillation through an 8-cm vacuum-jacketed Vigreux column gave 7.10 g of unreacted **3** and 7.70 g (58.3% based on consumed starting material) of **4**: bp 128–130° (0.4 mm); ir (neat) 3280 (m), 2980 (m), 1740 (s), 1480 (m), 1450 (m), 1380 (m), 1250 (s), 1120 (s), 1070 (s), 950 cm^{-1} (m).

Anal. Calcd for $C_{10}H_{19}NO_5$: C, 51.47; H, 8.20; N, 6.03. Found: C, 51.55; H, 8.15; N, 6.20.

(9) Boiling and melting points are uncorrected. Microanalyses were performed by Bernhardt Microanalytisches Laboratorium, Mulheim, Germany. Infrared spectra were recorded on a Beckman IR-10 spectrophotometer, nmr spectra on a Varian A-60A spectrometer, and uv spectra on a Beckman DB spectrophotometer. The mass spectra were recorded on a Consolidated Electrodynamics 21-130 mass spectrometer using a heated inlet system operating at 135°; the energy of the electron beam was 77.5 eV.

(10) C. A. Grob and R. Moesch, *Helv. Chim. Acta*, **42**, 728 (1959).

(11) R. T. Major, F. Dursch, and H. J. Hess, *J. Org. Chem.*, **24**, 431 (1959).

2-(3-Aminooxypropyl)-2-methyl-1,3-dioxolane (5).—A solution of 7.90 g (0.14 mol) of potassium hydroxide in 50 ml of water was added to 7.70 g (0.035 mol) of **4** and the solution was refluxed for 1 hr. After cooling, the reaction mixture was saturated with sodium chloride and extracted five times with 75-ml portions of ether. The combined organic extracts were dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure. Distillation of the residual liquid through an 8-cm vacuum-jacketed Vigreux column gave 3.58 g (74.3%) of **5**: bp 67–69° (0.5 mm); ir (neat) 3490 (w), 3320 (m), 3230 (w), 3160 (w), 1380 (s), 1255 (s), 1220 (s), 1065 cm^{-1} (vs); nmr ($CDCl_3$) τ 4.55 (br, 2, NH_2), 6.06 (s, 4, OCH_2CH_2O), 6.34 (t, 2, J = 6.0 Hz, CH_2ONH_2), 8.13–8.45 (m, 4, $CH_2CH_2CH_2ONH_2$), 8.70 (s, 3, CH_3).

Anal. Calcd for $C_7H_{15}NO_3$: C, 52.13; H, 9.37; N, 8.72. Found: C, 52.20; H, 9.35; N, 8.60.

Cyclization of Alkoxyamine 5 to 3-Methyl-4*H*-5,6-dihydro-1,2-oxazine (1a).—A solution of 3.50 g (0.23 mol) of **5** in 40 ml of ether was acidified with 10 ml of 3 *N* hydrochloric acid and stirred at room temperature for 30 min. Following removal of the ether under reduced pressure, the aqueous layer was basified with sodium bicarbonate and extracted three times with 75-ml portions of methylene chloride. The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo* to leave 2.43 g of a colorless liquid. Distillation through a short-path distillation apparatus gave 1.25 g (56.5%) of **1a**, bp 32–34° (0.4 mm). This material was identical in every respect with the lower boiling component isolated from the oximation of 5-chloro-2-pentanone with an excess amount of base (eq 2, path b).

The hydrochloride was prepared in ether, mp 130–131° (mixture melting point with the hydrochloride of the previously isolated 3-methyloxazine showed no depression, mp 130–131°).

Registry No.—**1a**, 39703-76-9; **1a** hydrochloride, 39703-77-0; **1a** picrate, 39703-78-1; **2**, 6931-10-8; **2** picrate, 13742-66-0; **3**, 5978-08-5; **4**, 39703-82-7; **5**, 39703-83-8; 5-chloro-2-pentanone, 5891-21-4; hydroxylamine hydrochloride, 5470-11-1; potassium carbonate, 584-08-7; hydroxyurethane, 589-41-3; potassium hydroxide, 1310-58-3.

Pteridines. XXVII. A New Synthetic Route to Pteridines and 7-Azapteridines[1a]

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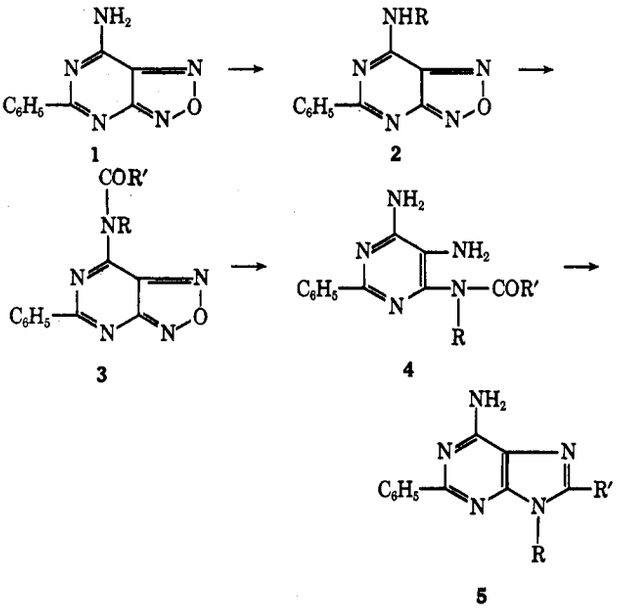
Received May 26, 1972

Recent investigations in this laboratory have shown that 7-aminofurazano[3,4-*d*]pyrimidines, prepared by lead tetraacetate oxidation of 4,6-diamino-5-nitrosopyrimidines, are useful, versatile intermediates for the unequivocal preparation of 2-, 8-, and 9-substituted adenines.[2] The sequence of reactions involved consists of introduction of the eventual adenine 9 and 8 substituents by reaction of the 7-aminofurazano[3,4-*d*]pyrimidine with an alkylamine, followed by acylation; reductive fission of the furazan ring then gives an intermediate 5-amino-6-acylaminopyrimidine which spontaneously cyclizes to the desired adenine. These reactions are summarized in Scheme I.

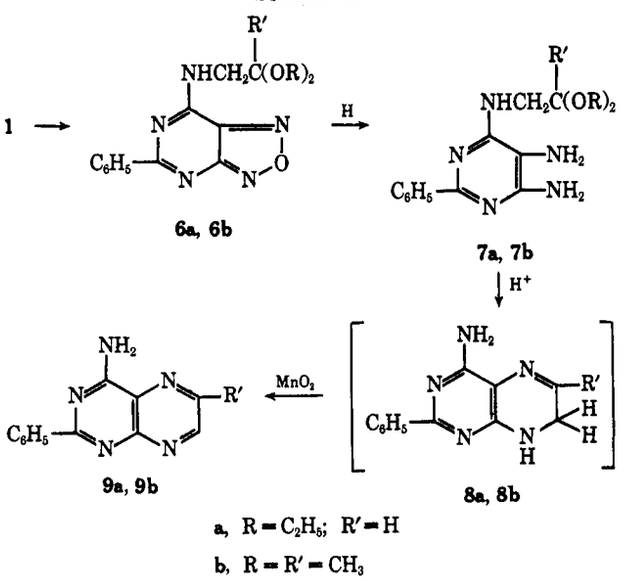
SCHEME I



It occurred to us that displacement of the 7-amino grouping by nucleophiles possessing a carbonyl functionality capable of cyclization with the 5-aminopyrimidine grouping released in the reductive fission of the furazan ring would allow the preparation of other fused pyrimidine systems, with the nature of the second fused ring dependent upon the structure of the initial nucleophile. This note describes the successful application of this concept to the preparation of pteridines and 7-azapteridines.

The conversion of 5-phenyl-7-aminofurazano[3,4-*d*]-pyrimidine (**1**) to pteridines was achieved as follows. The reaction of **1** with aminoacetaldehyde diethyl acetal took place readily at room temperature to give the 7-substituted aminofurazano[3,4-*d*]pyrimidine **6a** in 94% yield (see Scheme II). This latter compound was

SCHEME II



a, R = C_2H_5; R′ = H

b, R = R′ = CH_3

then subjected to catalytic reduction under neutral conditions to give the triaminopyrimidine **7a**. Treat-

(1) (a) For the previous paper in this series, see E. C. Taylor, M. J. Thompson, K. L. Perlman, R. Mengel, and W. Pfleiderer, *J. Org. Chem.*, **36**, 4012 (1971); (b) NIH Predoctoral Fellow, 1969–1972; (c) Gifu College of Pharmacy, Gifu, Japan; (d) NSF Predoctoral Fellow, 1968–1971.

(2) E. C. Taylor, G. P. Beardsley, and Y. Maki, *J. Org. Chem.*, **36**, 3211 (1971).