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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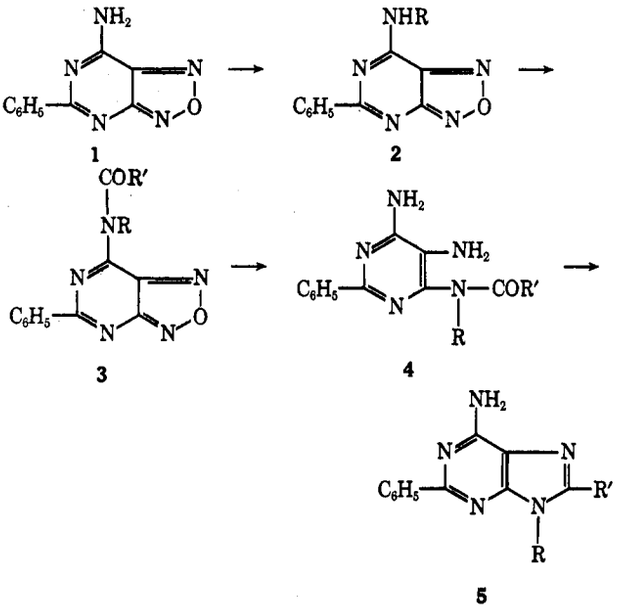
Recent investigations in this laboratory have shown that 7-aminofurazano[3,4-*d*]pyrimidines, prepared by lead tetraacetate oxidation of 4,6-diamino-5-nitrosopyrimidines, are useful, versatile intermediates for the unequivocal preparation of 2-, 8-, and 9-substituted adenines.[2] The sequence of reactions 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.

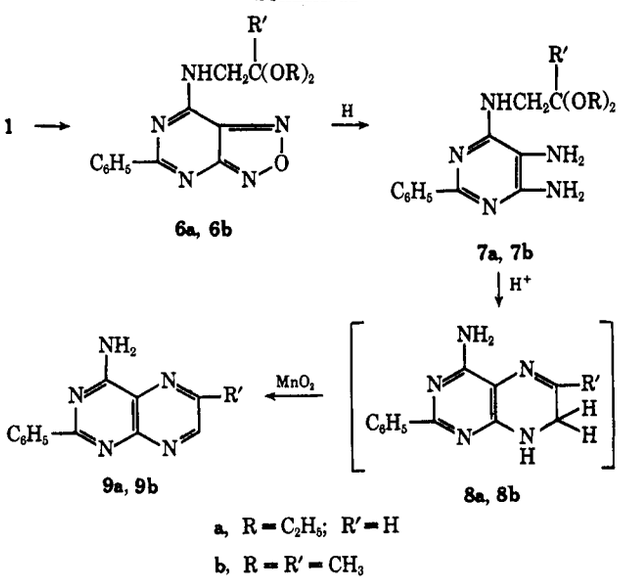
SCHEME I



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.

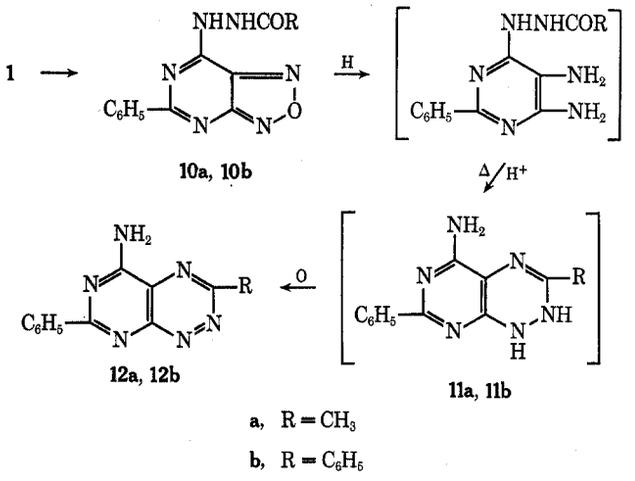
(2) E. C. Taylor, G. P. Beardsley, and Y. Maki, *J. Org. Chem.*, **36**, 3211 (1971).

ment of this latter intermediate with acid resulted in cleavage of the acetal protecting group; spontaneous cyclization then led to the dihydropteridine **8a**, which was not isolated but was oxidized *in situ* with manganese dioxide to give 2-phenyl-4-aminopteridine (**9a**). Obviously, the use of appropriately substituted α-aminocarbonyl components should lead through an analogous sequence of reactions to pteridines substituted selectively at position 6 or 7, or to 6,7-disubstituted derivatives carrying the same or different substituents. The deficiencies of classical pteridine syntheses for the unequivocal preparation of such compounds have been discussed previously.[1a,3]

To illustrate the potential utility of the furazanopyrimidine route to the preparation of 6-substituted pteridines, 2-phenyl-4-amino-6-methylpteridine (**9b**) was prepared by reaction of **1** with aminoacetone dimethyl acetal to give the intermediate 7-substituted aminofurazano[3,4-*d*]pyrimidine **6b**, which was reduced, and the resulting triaminopyrimidine was then treated with acid. Cyclization, followed by manganese dioxide oxidation as in the example described above, led to 2-phenyl-4-amino-6-methylpteridine (**9b**) in an overall yield of 60%. This new approach to the unequivocal synthesis of 6-substituted pteridines should be capable of considerable extension. It should be noted that intermediates analogous to **7** and **8** are also encountered in the classical pteridine synthesis which involves the reaction of a 5-nitro- or 5-arylazo-6-chloropyrimidine with an α-aminocarbonyl compound, followed by reductive cyclization to a 7,8-dihydropteridine and final oxidation.[4] The pteridine synthesis herein described provides an alternate route to the key intermediate **7** and may prove to be more flexible in view of the ready availability of the requisite furazano[3,4-*d*]pyrimidine precursors (**1**).[2]

7-Azapteridines were readily prepared from 5-phenyl-7-aminofurazano[3,4-*d*]pyrimidine (**1**) by utilization of acid hydrazides as the attacking nucleophile, followed by an analogous sequence of reduction and subsequent ring-closure reactions. For example, the reaction of **1** with acethydrazide at room temperature gave 5-phenyl-7-acetylhydrazinofurazano[3,4-*d*]-pyrimidine (**10a**) in 63% yield. Catalytic reduction followed by acid-catalyzed cyclization and final oxidation of the initially formed dihydro-7-azapteridine **11a** with isoamyl nitrite gave 5-amino-3-methyl-7-phenylpyrimido[5,4-*e*]-*as*-triazine (2-phenyl-4-amino-6-methyl-7-azapteridine) (**12a**) in 53% overall yield from **10a** without isolation of any intermediates. Similarly, acid-catalyzed reaction of **1** with benzhydrazide gave the intermediate benzoylhydrazinofurazano[3,4-*d*]pyrimidine **10b** which, when subjected to an analogous sequence of reactions, gave 5-amino-3,7-diphenylpyrimido[5,4-*e*]-*as*-triazine (**12b**) in 80% overall yield. Once again, it would appear that this latter sequence of reactions constitutes a general synthetic route to 6-substituted 7-azapteridines (Scheme III).

SCHEME III



Experimental Section

***N*-(5-Phenylfurazano[3,4-*d*]pyrimid-7-yl)aminoacetaldehyde Diethyl Acetal (6a).**—A mixture of 2.15 g of 5-phenyl-7-aminofurazano[3,4-*d*]pyrimidine (**1**) and 3 ml of aminoacetaldehyde diethyl acetal was stirred overnight at room temperature and then warmed to 70–80° for 1 hr. The oily mixture was dissolved in chloroform, and the solution was extracted several times with water and once with cold 0.1 *N* hydrochloric acid, dried over sodium sulfate, and filtered. The solution was evaporated to dryness, yielding an amber oil which solidified upon addition of a small amount of ether. Recrystallization from a mixture of ether and hexane afforded 3.1 g (94%) of pale yellow prisms, mp 88–90°.

Anal. Calcd for $C_{16}H_{19}N_5O_3$: C, 58.35; H, 5.82; N, 21.27. Found: C, 58.45; H, 5.75; N, 21.48.

***N*-(2-Phenyl-5,6-diaminopyrimid-4-yl)aminoacetaldehyde Diethyl Acetal (7a).**—A solution of 0.50 g of **6a** in 25 ml of ethanol was hydrogenated over 20 mg of 10% Pd/C at room temperature and 1 atm of hydrogen pressure until hydrogen uptake ceased. The solution was filtered and evaporated under reduced pressure to give a reddish oil which solidified upon scratching. Several recrystallizations from a mixture of ether and hexane afforded 0.30 g (62%) of faintly pink plates, mp 101–102°.

Anal. Calcd for $C_{16}H_{23}N_5O_2$: C, 60.55; H, 7.30; N, 22.07. Found: C, 60.61; H, 7.33; N, 22.44.

2-Phenyl-4-aminopteridine (9a).—The crude oil from the reduction of 1.0 g of **6a** was dissolved in 50 ml of 0.5 *N* hydrochloric acid. The solution was stirred at room temperature for 4 hr. The resulting suspension was adjusted to pH 7 by addition of saturated aqueous sodium bicarbonate, and the suspended solid was collected by filtration, washed with water, and dissolved in 100 ml of THF. To this solution was added several grams of anhydrous magnesium sulfate and 1 g of activated manganese dioxide.[5] The suspension was stirred at room temperature overnight, filtered, and evaporated to dryness under reduced pressure. The residue was dissolved in cold, dilute hydrochloric acid, the solution was treated with charcoal and filtered, and the product was precipitated by adjusting the filtrate to pH 7 by addition of aqueous ammonia. The solid was collected by filtration and recrystallized from methanol to give colorless plates, mp 241–243° (lit.[6,7] mp 240–241°, 239°). The ultraviolet spectrum of this material was also identical with that reported.[6]

***N*-(5-Phenylfurazano[3,4-*d*]pyrimid-7-yl)aminoacetone Dimethyl Acetal (6b).**—A mixture of 1.0 g of 5-phenyl-7-aminofurazano[3,4-*d*]pyrimidine (**1**) and 1.5 ml of aminoacetone dimethyl acetal was allowed to stand at room temperature overnight. The mixture was diluted with chloroform, washed with cold 1 *N* hydrochloric acid, dried, filtered, and evaporated to afford an amber oil which slowly solidified. Recrystallization

(3) E. C. Taylor in "Chemistry and Biology of Pteridines (Folic Acid Included)," K. Iwai, M. Akino, M. Goto, and Y. Iwanami, Ed., International Academic Printing Co., Tokyo, 1970, pp 79–93.

(4) See, for example, (a) W. R. Boon, W. G. M. Jones, and G. R. Ramage, *J. Chem. Soc.*, 96 (1951); (b) W. R. Boon and W. G. M. Jones, *ibid.*, 591 (1951); (d) W. R. Boon and T. Leigh, *ibid.*, 1497 (1951); (d) A. Stuart and H. C. S. Wood, *ibid.*, 4186 (1963); (e) K. J. M. Andrews, W. E. Barber, and B. P. Tong, *ibid.*, 928 (1969).

(5) L. A. Carpino, *J. Org. Chem.*, **35**, 3971 (1970).

(6) R. M. Evans, P. G. Jones, P. J. Palmer, and F. F. Stevens, *J. Chem. Soc.*, 4106 (1956).

(7) J. Weinstock, R. Y. Dunoff, J. E. Carevic, J. G. Williams, and A. J. Villani, *J. Med. Chem.*, **11**, 618 (1968).

from a mixture of isopropyl ether and hexane afforded 1.35 g (92%) of pale yellow needles, mp 139–141°.

Anal. Calcd for $C_{15}H_{17}N_5O_3$: C, 57.13; H, 5.43; N, 22.21. Found: C, 56.90; H, 5.42; N, 21.93.

2-Phenyl-4-amino-6-methylpteridine (9b).—A solution of 1.0 g of **6b** in 100 ml of ethanol was hydrogenated over 100 mg of 10% Pd/C at room temperature and 50 psi of hydrogen pressure until the uptake of hydrogen ceased. The catalyst was removed by filtration and the solution was evaporated under reduced pressure to afford a yellow oil. This was dissolved in 100 ml of water to which had been added several drops of concentrated hydrochloric acid. The solution was kept at room temperature under an atmosphere of nitrogen overnight. The solution was neutralized with aqueous sodium bicarbonate solution, and the yellow solid which formed was collected by filtration and treated with activated manganese dioxide in THF containing magnesium sulfate. After several hours, the solution was filtered and evaporated and the resulting dark oil was dissolved in cold dilute hydrochloric acid to give a homogeneous solution which was decolorized with charcoal and neutralized with aqueous sodium bicarbonate. The resulting precipitate was collected by filtration and recrystallized from methanol to afford 0.51 g (60%) of pale yellow plates, mp 242–244° (lit.[7] mp 240–241°). Its nmr spectrum was identical with the reported spectrum.[6]

5-Phenyl-7-acetylhydrazinofurazano[3,4-*d*]pyrimidine (10a).—A suspension of 2.00 g (9.38 mmol) of 5-phenyl-7-aminofurazano-[3,4-*d*]pyrimidine (**1**) and 3.44 g (46.8 mmol) of acethydrazide in 40 ml of 1 *N* ethanolic hydrogen chloride was stirred at room temperature for 24 hr and filtered, and the collected solid was recrystallized from ethanol to give 1.58 g (63%) of fine yellow needles, mp 266–267° dec.

Anal. Calcd for $C_{12}H_{10}N_6O_2$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.50; H, 3.83; N, 31.32.

5-Amino-3-methyl-7-phenylpyrimido[5,4-*e*]-*as*-triazine (12a).—A suspension of 0.30 g (1.11 mmol) of **10a** in 25 ml of ethanol containing 0.05 g of 10% Pd/C and 1.1 ml of 1 *N* ethanolic hydrogen chloride was shaken under 1 atm of hydrogen at room temperature until the hydrogen uptake ceased. The mixture was then refluxed for 2 hr and cooled, isoamyl nitrite (0.30 ml) was added, and stirring was continued for 16 hr at room temperature. Filtration through a Celite pad, evaporation of the filtrate under reduced pressure, and addition of water afforded an orange solid which was recrystallized from aqueous dimethylformamide to give 0.14 g (53%) of orange needles: mp 237° dec; uv $\lambda_{max}^{C_2H_5OH}$ 2.51 nm (log ϵ 3.73), 290 (3.93), 382 (2.96); nmr (DMSO-d_6) δ 3.08 (3 H, s), 7.6 (3 H, m), 8.5 (2 H, m), 9.0 (2 H, br, NH_2).

Anal. Calcd for $C_{12}H_{10}N_6$: C, 60.49; H, 4.23; N, 35.28. Found: C, 60.21; H, 4.08; N, 35.28.

5-Phenyl-7-benzoylhydrazinofurazano[3,4-*d*]pyrimidine (10b).—A suspension of 0.50 g (2.32 mmol) of **1** and 1.59 g (11.7 mmol) of benzhydrazide in 15 ml of 1 *N* ethanolic hydrogen chloride was stirred for 24 hr at room temperature and then filtered. The collected solid was recrystallized from ethanol to give 0.42 g (54%) of powdery flakes, mp 258–259° dec.

Anal. Calcd for $C_{17}H_{12}N_6O_2$: C, 61.44; H, 3.64; N, 25.29. Found: C, 61.64; H, 3.53; N, 25.02.

5-Amino-3,7-diphenylpyrimido[5,4-*e*]-*as*-triazine (12b).—A suspension of 0.25 g (0.75 mmol) of **10a** in 25 ml of ethanol containing 10% Pd/C was shaken under 1 atm of hydrogen at room temperature until hydrogen uptake ceased, 5 ml of 1 *N* ethanolic hydrogen chloride was added, the mixture was heated to boiling and filtered through Celite, and the filtrate then refluxed for 2 hr. Isoamyl nitrite (0.25 ml) was added, and the mixture was stirred for 24 hr at room temperature, neutralized with sodium bicarbonate, and concentrated to dryness under reduced pressure. The residue was triturated with water and then filtered. Recrystallization of the collected solid from aqueous dimethylformamide gave 0.18 g (80%) of fine yellow plates: mp >300°; uv $\lambda_{max}^{C_2H_5OH}$ 254 nm (log ϵ 3.70), 307 (4.22), 396 (3.34); nmr (DMSO-d_6) δ 7.68, 8.5–9.0 (12 H, m).

Anal. Calcd for $C_{17}H_{12}N_6$: C, 67.99; H, 4.03; N, 27.99. Found: C, 67.70; H, 4.15; N, 27.98.

Registry No.—**1**, 30720-36-6; **6a**, 39550-16-8; **6b**, 39550-17-9; **7a**, 39550-18-0; **9a**, 1084-59-9; **9b**, 19830-37-6; **10a**, 39550-21-5; **10b**, 39550-22-6; **12a**, 39550-23-7; **12b**, 39550-24-8; aminoacetaldehyde diethyl acetal, 645-36-3; aminoacetone diethyl acetal, 39550-25-9; acethydrazide, 1068-57-1.

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Reactions of Vinyl Acetate with Carbazole

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Organic transformations brought about by thallium(I) and thallium(III) compounds have received considerable attention.[1] Recently we have demonstrated the usefulness of thallium(I) ethoxide as a base for the alkylation, under mild conditions, of carbazole, phenothiazine, and to a lesser extent 5*H*-dibenz[*b*,*f*]-azepine.[2] A notable feature of this reaction is that alkylation employing thallium(I) ethoxide as the base, unlike those employing potassium metal or potassium amide, is subject to steric limitations, and can only be used for the introduction of primary alkyl groups.

We now wish to report a further instance of the differing behavior of carbazole in reactions induced by potassium hydroxide and thallium(I) ethoxide, respectively.

Lopatinski, *et al.*,[3] have shown that carbazole, vinyl acetate, and potassium hydroxide react in acetone at −10 to −20° to afford *N*-(α-acetoxyethyl)carbazole (**1a**). We have repeated this reaction and confirmed the identity of the product **1a**, although the reaction is best carried out below −30°. Upon treatment with methanol the ester **1a** is converted to *N*-(α-methoxyethyl)carbazole (**1b**), and this product was found to be identical with authentic material prepared from methanol and *N*-vinylcarbazole.[4]

In complete contrast, the reaction of vinyl acetate with carbazole and thallium(I) ethoxide at room temperature in DMF–ether afforded *N*-acetylcarbazole (57%) together with an insoluble, light-sensitive thallium compound. This material was tentatively identified as vinyloxythallium(I) (**3**); however, during subsequent manipulation of this unstable compound an insertion reaction[5] with atmospheric carbon dioxide occurred producing vinylcarbonatothallium (**4**). The infrared spectrum of **4** showed bands at 1550 (br) and 1020 and 920 cm^{-1}, appropriate to a carbonato[6] and vinyl group, respectively. No molecular ion could be detected in the mass spectrum; however, an ion at *m/e* 249 was identified as $^{205}TlCO_2$ by accurate mass measurement.

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