case, however, the *ortho* substituent makes a contribution to reactivity which is minor at most.

Thermodynamic Constants.—Activation energies and entropies have been calculated for those hydrolyses for which the appropriate data (Table I) are available. These are summarized in Table IV. In making comparisons of these thermodynamic constants the limits of error which are reported, and which in some instances are large, can be overlooked only at the risk of over-interpretation of the data. The E_a and ΔS^* values for the isomeric 1-carbophenoxyphenyl-1-phenylethyl chlorides are closely similar, a fact which is considered to support the conclusion that the $-COOC_6H_5$ group does not contribute extensively as a nucleophile to the reaction of the *ortho* isomer.

Benzhydryl bromides which bear nonparticipating *ortho* substituents (*e.g.*, $-OCOC_6H_5$)[1] have substantially higher E_a values for hydrolysis than do their *para* isomers. This difference is associated with hindrance by the *ortho* substituent to solvation in the transition state. The E_a values for *o*-carbophenoxybenzyhydryl bromide are generally less than those for the *para* isomer. The differential appears to be considerably smaller for reactions in 80% aqueous acetone than for reactions in media of lower water content, which are more conducive to *ortho*-substituent participation. The differential in E_a values for the carbophenoxybenzhydryl chlorides appears to be significantly larger than that for the bromides even if the limits of error are taken into account.

It is difficult to explain many of the observed differences in entropies of activation for the reactions of *ortho* and *para* isomers. Losses of entropy which result directly from involvement of the *ortho* substituent may be more than offset by reductions in entropy losses which, in the absence of participation, are associated with the solvation of the center of positive polarization in the transition state. The fact that the activation energy for hydrolysis of *o*-nitrobenzhydryl bromide is considerably larger than that for the *para* isomer can be offered as evidence that the *o*-NO_2 substituent does not make an important contribution to reactivity as a participating nucleophile. The relatively low value of $-\Delta S^*$ for the *ortho* isomer appears to counterbalance the high E_a value sufficiently so that the reactivities (Table I) of the *ortho* and *para* isomers are about the same.

Acknowledgment.—The authors are indebted to the National Science Foundation for a grant in support of this research.

Nucleophilic Displacement Reactions of 2-Amino-4-alkylthiopteridines[1-3]

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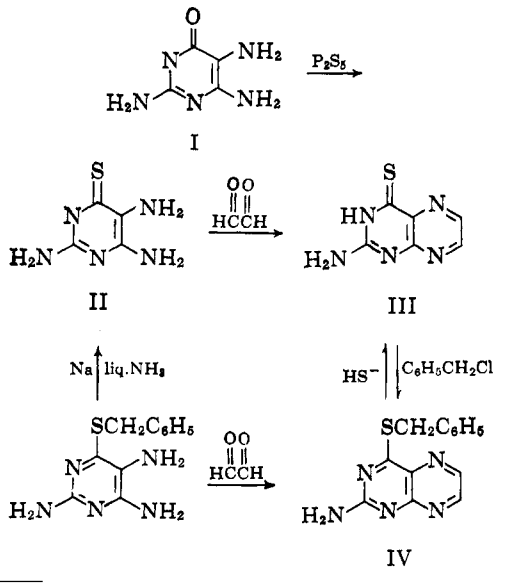
Received July 17, 1964

The synthesis of 2-amino-4-thiopteridine and of 2-amino-4-alkylthiopteridines is described. The latter compounds undergo nucleophilic attack in the 4-position by hydroxide, hydrosulfide, ammonia, hydrazine, and hydroxylamine under mild conditions. The differences in the susceptibility to nucleophilic displacement of 4-alkylthiopteridines and 6-alkylthiopurines are discussed.

The widespread clinical use, as antileukemic agents,[6] of folic acid analogs in which the hydroxy group in the 4-position of the pteridine ring was replaced by an amino group, raised interest in new approaches to the introduction of other substituents into the 4-position of pteridines. Nucleophilic displacement reactions with 2-amino-4-alkylthiopteridines appear to represent a convenient method for accomplishing this purpose.

While several groups of workers have described the synthesis of 6,7-disubstituted 2-amino-4-thiopteridines,[7-10] no 2-amino-4-thiopteridines or 2-amino-4-alkylthiopteridines unsubstituted in the pyrazine ring have been reported.

These compounds were obtained by the following synthetic sequence.



(1) This work was supported, in part, by grants from the U. S. Public Health Service (CA 3937) and the National Science Foundation (G 19329).

(2) Abstracted from a portion of a thesis submitted by J. J. McCormack to the faculty of the Graduate School of Yale University in partial fulfillment of the requirements for the Ph.D. degree.

(3) A preliminary account of this investigation was presented before the Medicinal Chemistry Section at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

(4) Predoctoral Fellow of Yale University, supported by a Research Training Grant (5-T1-6M-59-04) of the U. S. Public Health Service.

(5) To whom requests for reprints should be addressed.

(6) S. Farber, *et al.*, *New Engl. J. Med.*, **238**, 787 (1948).

(7) E. C. Taylor, R. B. Garland, and C. F. Howell, *J. Am. Chem. Soc.*, **78**, 210 (1956).

(8) M. J. Fahrenbach and K. H. Collins, U. S. Patent 2,756,230 (July 24, 1956).

(9) M. J. Fahrenbach and K. H. Collins, U. S. Patent 2,767,181 (Oct. 15, 1956).

(10) E. J. Modest, S. Chatterjee, S. A. Lemlein, and D. M. Brun, Abstracts, 138th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1960, p. 4-O.

Attempts to prepare 2-amino-4-thiopteridine by the direct thiation of 2-amino-4-hydroxypteridine with phosphorus pentasulfide were unsuccessful, even though direct thiation had been reported to be applicable to the synthesis of 4-thio-6,7-disubstituted pteridines from the corresponding oxo compounds.[10] The desired compound (III) could be obtained, however, by the condensation of glyoxal monohydrate with 2,5,6-triamino-4-thiopyrimidine (II).

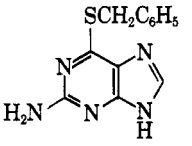
The thiopyrimidine (II) has been prepared by Elion, Lange, and Hitchings[11] using a reaction involving the coupling of 2,6-diamino-4-thiopyrimidine with *p*-chlorophenyldiazonium chloride, followed by reduction. Since the product of this reaction (II) is a useful intermediate in the synthesis of 6-thioguanine[11] as well as of 2-amino-4-thiopteridine,[12] it seemed desirable to investigate the preparation of this compound by the direct thiation of 2,5,6-triamino-4-hydroxypyrimidine (I), a comparatively inexpensive, commercially available compound.

While a large number of successful thiations of heterocyclic compounds has been described in which phosphorus pentasulfide in pyridine[13] was used, attempts to thiate I in this solvent were unsuccessful. The use of phosphorus pentasulfide in β-picoline, however, which had proved useful for the thiation of 5,6-diamino-4-hydroxypyrimidine,[14] resulted in the thiation of I to yield II. The latter compound could also be prepared by the debenzylation of 2,5,6-triamino-4-benzylthiopyrimidine with sodium in liquid ammonia.

2-Amino-4-benzylthiopteridine (IV) could be prepared either by the reaction of 2,5,6-triamino-4-benzylthiopyrimidine with glyoxal or by the reaction of III with benzyl chloride. Nucleophilic displacement occurred with the benzylthiopteridine (IV) under very mild conditions; thus, the addition of sodium hydrosulfide in refluxing ethanol yielded 2-amino-4-thiopteridine (III). Similarly, treatment with sodium hydroxide in ethanol yielded 2-amino-4-hydroxypteridine, shown to be identical with authentic material prepared by a modification of the method of Cain, Mallette, and Taylor.[15] The reaction of IV with hydrazine hydrate in refluxing methanol gave rise to the formation of 2-amino-4-hydrazinopteridine; this compound also was prepared by an alternative synthesis involving the reaction of 2,4-diaminopteridine with hydrazine hydrate. As in the previously described reaction of 2,4-diaminopteridine with alkylamines,[16] substitution took place only in the 4-position. The replacement of the benzylthio group of IV with ammonia or hydroxylamine resulted in the formation of 2,4-diaminopteridine and of 2-amino-4-hydroxylaminopteridine, respectively. The latter compound could be converted to the corresponding 2,4-diaminopteridine by reduction of the hydroxylamino group with sodium dithionate, a reaction that had been applied previously to both hydroxylaminopurines[17] and hydroxylaminopyrimidines.[18]

The high susceptibility to nucleophilic attack of 4-alkylthiopteridines,[19,20] 2-alkylthiopteridines,[20] and 4-alkoxypteridines[21,22] has been noted previously.

The relative ease of displacement of the benzylthio group of IV by various nucleophiles should be contrasted with the considerably more severe conditions required to effect nucleophilic displacements in the corresponding purine (V).

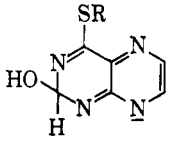


V

While 6-alkylthiopurines have been used as starting materials for the preparation of 6-alkylamino- and 6-arylaminopurines,[23] reactions with the various amines had to be carried out in sealed tubes at 110–180° over long periods of time. Treatment of 6-benzylthioguanine (V) with hydroxide or hydrosulfide in refluxing ethanol for 24 hr. resulted in recovery of the unchanged purine, while the corresponding pteridine (IV) underwent nucleophilic displacement under these conditions, in good yield, within 30 min. The great stability of several 6-alkylthiopurines to alkali under reflux conditions has been commented on previously.[24]

Differences in the chemical reactivities of purines and pteridines have been discussed by Taylor, *et al.*,[25] who observed that while 4-alkylthiopteridines undergo hydrolytic ring scission in sodium carbonate or sodium bicarbonate solution, the corresponding 6-alkylthiopurines are stable under these conditions. It is interesting to note that in aqueous or ethanolic sodium hydroxide, instead of the ring scission observed by Taylor and his co-workers,[25] nucleophilic displacement of the alkylthio group without damage to the pteridine ring occurs with 4-alkylthiopteridines as well as with 2-amino-4-alkylthiopteridines.

The relative lability of the pteridines in carbonate has been attributed[25] to resonance stabilization of the anionic reaction intermediate.



Similarly, it seems likely that the tetrahedral anionic reaction intermediates formed in nucleophilic displacement reactions of 4-alkoxy- or 4-alkylthiopteridines

(11) G. B. Elion, W. H. Lange, and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 2858 (1956).

(12) J. J. McCormack and H. G. Mautner, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, p. 16-O.

(13) For example, E. Klingsberg and D. Papa, *J. Am. Chem. Soc.*, **73**, 4988 (1951); E. A. Falco, E. Pappas, and G. H. Hitchings, *ibid.*, **78**, 1938 (1956); J. J. Fox, I. Wempen, A. Hampton, and I. L. Doerr, *ibid.*, **80**, 1669 (1958).

(14) A. G. Beaman and R. K. Robins, *ibid.*, **83**, 4038 (1961).

(15) C. K. Cain, M. F. Mallette, and E. C. Taylor, *ibid.*, **68**, 1998 (1946).

(16) E. C. Taylor and C. K. Cain, *ibid.*, **73**, 4384 (1951).

(17) A Giner-Sorolla and A. Bendich, *ibid.*, **80**, 3932 (1958).

(18) R. M. Cresswell and T. Strauss, *J. Org. Chem.*, **28**, 2563 (1963).

(19) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 3832 (1954).

(20) I. J. Pachter, P. E. Nemeth, and A. J. Villani, *J. Org. Chem.*, **28**, 1197 (1963).

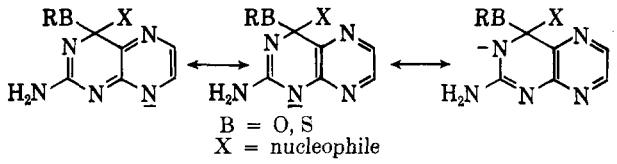
(21) B. Roth, J. M. Smith, and M. E. Hultquist, *J. Am. Chem. Soc.*, **73**, 2869 (1951).

(22) H. C. S. Wood in Ciba Foundation Symposium, Chemistry and Biology of Pteridines, Little, Brown and Co., Boston, Mass., 1954, p. 38.

(23) G. B. Elion, E. Burgi, and G. H. Hitchings, *J. Am. Chem. Soc.*, **74**, 411 (1952).

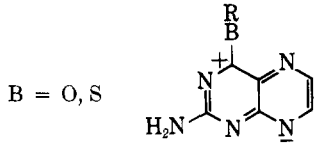
(24) T. F. Johnston, L. B. Holum, and J. A. Montgomery, *ibid.*, **80**, 6265 (1958).

(25) E. C. Taylor, R. J. Knopf, J. A. Cogliano, J. W. Barton, and W. Pfleiderer, *ibid.*, **82**, 6058 (1960).



should be resonance stabilized to a greater extent than the intermediate anions formed by nucleophilic attack on 6-substituted purines. In pteridines the negative charge of the anion can be localized on nitrogen atoms in the 1- and 3-positions of the pyrimidine ring and in the 8-position of the pyrazine ring. In corresponding purines only those tetrahedral anionic resonance forms in which the negative charge is carried on the ring nitrogens of the pyrimidine ring are likely to play an important role in the resonance stabilization of the anion, since in the imidazole ring a negative charge would have to be accommodated on the carbon in the 8-position rather than on a nitrogen atom. Since nitrogen is more electronegative than carbon this factor should reduce resonance stabilization of the purine anion relative to that of the pteridine anion.

The possibility also must be considered that the tendency for electrons to be drawn into the 8-position of the π-deficient[26] pyrazine ring might activate the 4-position of pteridines to nucleophilic attack as shown.



Similarly the relative lack of reactivity of 6-alkylthiopurines and 6-alkylthio-9-methylpurines might be attributable to the deactivating effect of the nitrogen in the π-excessive imidazole ring.[26]

An investigation of the comparative kinetics of the nucleophilic displacement reactions of purines, pteridines, and related ring systems is now in progress in this laboratory.

Experimental

2,5,6-Triamino-4-thiopyrimidine (II). A. Debenzylation Method.—To a stirred suspension of 2.0 g. of 2,5,6-triamino-4-benzylthiopyrimidine[27] in 50 ml. of liquid ammonia were added slivers of sodium metal at −40 to −50° until a blue color persisted for at least 5 min. Excess ammonia was permitted to evaporate at room temperature. The flask was immersed in a Dry Ice–acetone bath and the residue was treated with 50 ml. of ethanol. The mixture was filtered and the filtrate was brought to pH 1 with concentrated hydrochloric acid. The precipitate was collected, suspended in 40 ml. of water, stirred, and chilled overnight. The water-insoluble product was removed by filtration and purified by the method of Elion, Lange, and Hitchings.[11] A yield of 20% of the purified dihydrochloride was obtained; ultraviolet spectrum (0.1 *N* HCl): λ_{max} 310 mμ (ϵ_{max} 22,400), lit.[11] λ_{max} 310 mμ (ϵ_{max} 21,800).

For an analytical sample the residue obtained after the evaporation of excess ammonia was treated with 30 ml. of water. The mixture was chilled and filtered, and the filtrate was brought to pH 6 with sulfuric acid. The solution was swirled in a Dry Ice–acetone bath until the free base started to separate.

Anal.[28] Calcd. for $C_4H_7N_5S$: C, 30.56; H, 4.49; S, 20.40. Found: C, 30.79; H, 4.76; S, 20.15.

B. Thiation Method.—To 500 ml. of β-picoline, which had been heated to reflux in a 1000-ml. round-bottom flask equipped with a reflux condenser and a Hershberg stirrer, was added, in small portions, 50.0 g. of phosphorus pentasulfide, while the solution was stirred vigorously. With continued heating and stirring 20.0 g. of 2,5,6-triamino-4-hydroxypyrimidine sulfate was added over a period of 15 min. After 1 hr. of heating, 2.5 ml. of water was added dropwise through the reflux condenser. The mixture was stirred and heated to reflux for 11 hr. more and then refrigerated. The supernatant picoline was discarded and the residual, black, gummy oil was heated on a steam bath with a mixture of 500 ml. of water and 60 ml. of concentrated hydrochloric acid until a brown suspension was obtained. Filtration yielded a dark brown solid which was discarded. The filtrate was refrigerated overnight. Filtration gave rise to a yield of 6.0 g. of orange, impure II. Evaporation of the clear, orange filtrate at 60° resulted in the formation of a heavy, red oil, which was dissolved in 100 ml. of hot ethanol. Addition of 100 ml. of concentrated hydrochloric acid, followed by refrigeration, resulted in the separation of the hydrochloride of II. The product was isolated by centrifugation, and then centrifuged successively with ethanol, ether, and petroleum ether (b.p. 36.5–56.5°). A yield of 9.5 g. of light yellow product was obtained. This material could be used for synthetic work without further purification.

2-Amino-4-methylthiopteridine.—Into a stirred solution of 50 ml. of absolute ethanol were placed 1.7 g. of 2,5,6-triamino-4-methylthiopyrimidine and the mixture was heated slowly to boiling. After addition of 1.0 g. of solid glyoxal monohydrate, the solution was permitted to boil for 5 min. and then evaporated to dryness under reduced pressure. The residue was treated with 100 ml. of boiling water. The hot mixture was filtered and the filtrate was refrigerated, resulting in separation of the yellow product which was purified by recrystallization from boiling water. A yield of 30% of purified product melting at 215–218° dec.[29] was obtained; ultraviolet spectrum (95% ethanol): λ_{max} 211, 233, 269, 309, and 383 mμ (ϵ_{max} 15,600, 15,300, 13,500, 3400, and 7600).

Anal. Calcd. for $C_7H_7N_5S$: C, 43.55; H, 3.66; N, 36.25; S, 16.54. Found: C, 43.45; H, 3.45; N, 36.20; S, 16.39.

2-Amino-4-benzylthiopteridine (IV).—A stirred solution of 5.0 g. of 2,5,6-triamino-4-benzylthiopyrimidine in 100 ml. of absolute ethanol was heated to boiling and treated with 2.0 g. of solid glyoxal monohydrate. The mixture was permitted to boil for 2 min. On chilling, the yellow crystalline product separated. It was removed by filtration, washed once with ethanol and twice with water and purified by recrystallization from ethanol. A yield of 70% of the pteridine melting at 182–183° was obtained; ultraviolet spectrum (95% ethanol): λ_{max} 211, 232, 268, 310, and 383 mμ (ϵ_{max} 25,500, 19,000, 13,500, 3730, and 8580).

Anal. Calcd. for $C_{13}H_{11}N_5S$: C, 58.00; H, 4.10; N, 26.00, S, 11.90. Found: C, 58.04; H, 4.32; N, 25.90; S, 11.70.

2-Amino-4-thiopteridine (III). A. Hydrosulfide Addition Method.—A solution of 1.0 g. of 2-amino-4-benzylthiopteridine in 50 ml. of absolute ethanol was treated with 2.0 g. of sodium hydrosulfide and heated to reflux for 30 min. The hot reaction mixture was filtered rapidly and the residue was washed with 95% ethanol. The filtrate was diluted with 35 ml. of water and brought carefully to pH 2 with 6 *N* hydrochloric acid. After 5 min. the residue was removed by filtration and washed with ether. The product was recrystallized from hot water, washed subsequently with ether, 95% ethanol, and ether, and dried in an Abderhalden drying pistol at 120°. A yield of 50% was obtained; ultraviolet spectrum (0.1 *N* HCl): λ_{max} 207, 249, 283, and 372 mμ (ϵ_{max} 25,150 infl., 7440, 6080, and 9900).

Anal. Calcd. for $C_6H_5N_5S$: C, 40.20; H, 2.82; S, 17.85. Found: C, 40.05; H, 3.12; S, 17.60.

B. Glyoxal Cyclization Method.—A mixture of 2.0 g. of the dihydrochloride of II and 2.0 g. of glyoxal monohydrate was suspended with stirring in 10 ml. of water. The pH of the solution was adjusted *carefully* to 3 with 1.5 *M* ammonium hydroxide solution. On chilling, a yield of 0.6 g. of III was obtained. The product was removed by filtration and washed successively with ethanol, ether, and petroleum ether. Ultraviolet and infrared

(26) A. Albert, "Heterocyclic Chemistry," Athlone Press, London, 1959, p. 42.

(27) G. D. Daves, C. W. Noell, R. K. Robins, H. C. Koppel, and A. G. Beaman, *J. Am. Chem. Soc.*, **82**, 2633 (1960).

(28) Microanalyses were carried out at the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(29) All melting points are corrected.

spectra showed it to be identical with material prepared by the above method.

Benzylation of 2-Amino-4-thiopteridine.—Into 25 ml. of 28% aqueous ammonium hydroxide were placed 1.0 g. of 2-amino-4-thiopteridine. With vigorous stirring a solution of 0.7 ml. of benzyl chloride in 3 ml. of dioxane was added slowly. Stirring was continued for 1 hr. at room temperature. The precipitate was removed and triturated with 50 ml. of ethanol. The mixture was filtered and water was added to the filtrate until the solution became cloudy. On chilling, a 15% yield of yellow crystalline product with spectral characteristics and melting point identical with those of 2-amino-4-benzylthiopteridine prepared by glyoxal cyclization was obtained.

This product could be prepared conveniently in an over-all yield of 40% by the condensation of the dihydrochloride of II with glyoxal monohydrate, followed by benzylation, without isolation of the intermediate 2-amino-4-thiopteridine.

2-Amino-4-hydroxypteridine.—To a solution of 300 mg. of 2-amino-4-benzylthiopteridine in 25 ml. of absolute ethanol were added 1 g. of sodium hydroxide pellets. The mixture was heated to reflux for 30 min. The reaction mixture was chilled, acidified with 3 *N* hydrochloric acid, and refrigerated for 2 days. The solid product was obtained in 55% yield. Its identity with 2-amino-4-hydroxypteridine obtained by a modification of the method of Cain, Mallette, and Taylor,[15] using solid glyoxal monohydrate rather than glyoxal sodium bisulfite, was established by ultraviolet and infrared spectroscopy and paper chromatography.

4-Hydroxypteridine.—A mixture of 300 mg. of 4-methylthiopteridine and 1.0 g. of sodium hydroxide pellets in 25 ml. of absolute ethanol was heated with stirring to 70° for 30 min. and then evaporated to dryness. The residue was treated with 10 ml. of water and the pH of the mixture was adjusted to 3 with hydrochloric acid. On refrigeration, the product was obtained in 60% yield. Ultraviolet and infrared spectra were identical with those of 4-hydroxypteridine prepared by the method of Albert, *et al.*[30]

2-Amino-4-hydroxylaminopteridine.—A mixture of 4.0 g. of hydroxylamine hydrochloride and 2.0 g. of 2-amino-4-benzylthiopteridine in 100 ml. of ethanol was heated with stirring to reflux for 10 min. and then evaporated to dryness under vacuum. The residue was suspended in 500 ml. of water and the pH was adjusted to 5 with 1 *N* sodium hydroxide solution. On heating, a yellow solution was obtained which was filtered. The filtrate was refrigerated overnight. The yellow, analytically pure precipitate was removed by filtration, washed with water, and dried.

(30) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

The substance, which was obtained in 75% yield, gave a violet color with ferric chloride and could be converted to 2,4-diaminopteridine upon treatment with boiling aqueous sodium dithionate; ultraviolet spectrum (0.1 *N* HCl): λ_{max} 217 and 340 mμ (ϵ_{max} 23,000 and 9300).

Anal. Calcd. for $C_6H_6N_6O \cdot 3H_2O$: C, 31.00; H, 5.20; N, 36.20; H_2O, 23.34. Found: C, 31.13; H, 5.42; N, 35.90; H_2O, 23.42.

2-Amino-4-hydrazinopteridine. A. From 2-Amino-4-benzylthiopteridine.—A solution of 2.5 g. of 2-amino-4-benzylthiopteridine in 50 ml. of methanol was treated with 2.5 ml. of 85% hydrazine hydrate and heated to reflux for 15 min. with stirring. The solution was refrigerated overnight, the product was removed by filtration and washed with successive portions of water, ethanol, and ether. The residue was recrystallized from hot water and dried over phosphorus pentoxide. A yield of 40% was obtained; ultraviolet spectrum (0.1 *N* HCl): λ_{max} 236, 285, 318 infl., 334, and 347 infl. mμ (ϵ_{max} 12,120, 5000, 7900, 9800, and 8600).

Anal. Calcd. for $C_6H_7N_7 \cdot H_2O$: C, 37.00; H, 4.65; N, 50.25; H_2O, 9.21. Found: C, 37.50; H, 4.93; N, 50.62; H_2O, 8.93.

Reaction with *p*-nitrobenzaldehyde[31] yielded the yellow hydrazone, m.p. 311° dec., which was recrystallized from acetic acid.

Anal. Calcd. for $C_{13}H_{10}N_8O_2 \cdot H_2O$: C, 47.60; H, 3.67. Found: C, 47.48; H, 3.73.

B. From 2,4-Diaminopteridine.—A suspension of 350 mg. of 2,4-diaminopteridine in 25 ml. of 85% hydrazine hydrate was heated with stirring to 140° for 1 hr. On chilling, the product was obtained in 80% yield. Ultraviolet and infrared spectra showed it to be identical with material prepared from 2-amino-4-benzylthiopteridine.

2,4-Diaminopteridine.—A solution of 250 mg. of 2-amino-4-benzylthiopteridine in a mixture of 25 ml. of ethanol and 25 ml. of concentrated aqueous ammonium hydroxide was heated in a pressure bottle on a steam bath for 6 hr., cooled to room temperature, and evaporated to dryness under reduced pressure. The residue was recrystallized from 50 ml. of boiling water. A 50% yield of material with infrared and ultraviolet spectra identical with those of 2,4-diaminopteridine prepared by the method of Mallette, Cain, and Taylor[15] was obtained.

Acknowledgment.—We are indebted to Mrs. J. K. Krackov for determining the ultraviolet spectra reported.

(31) R. S. Shriner, R. L. Fuson, and D. Y. Austin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 219.

Photochemistry of Stilbenes. IV. The Preparation of Substituted Phenanthrenes[1a-c]

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Received July 6, 1964

The synthetic value of the photoconversion of stilbenes to phenanthrenes in solution in the presence of small amounts of iodine and dissolved oxygen is demonstrated by a variety of examples of the preparation of substituted phenanthrenes using this photoreaction.

A general discussion of the scope and mechanism of the photoconversion of stilbenes to phenanthrenes in solution in the presence of oxidants such as iodine and oxygen has been given in an earlier paper in this series.[1a] In the present paper the synthetic value of this photoreaction for the preparation of substituted phenanthrenes will be considered in more detail.

The most satisfactory conditions that have been developed for preparative-scale reactions involve the irradiation with an unfiltered mercury arc of a stirred solution of 0.01 mole of the stilbene derivative and 0.0005 mole of iodine dissolved in 1 l. of cyclohexane or benzene open to the air. The preparative-scale results using this mixture of two oxidants, iodine and dissolved oxygen, are far superior to those achieved using oxygen alone; under the latter conditions the required irradiation times are much longer and the products may be obtained in low yield and low purity.[2,3]

(1) (a) Part III: F. B. Mallory, C. S. Wood, and J. T. Gordon, *J. Am. Chem. Soc.*, **86**, 3094 (1964). (b) Taken in part from the Ph.D. Dissertation of C. S. Wood, Bryn Mawr College, 1963. (c) Presented in part before the Organic Division at the 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept., 1961. (d) John Simon Guggenheim Memorial Foundation Fellow, 1963–1964.

(2) F. B. Mallory, J. T. Gordon, and L. C. Lindquist, Abstracts, 3rd Delaware Valley Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb., 1960.

(3) P. Hugelshofer, J. Kalvoda, and K. Schaffner, *Helv. Chim. Acta*, **43**, 1322 (1960).