A New Unambiguous Synthesis of 6-Thiopteridines (1,2)

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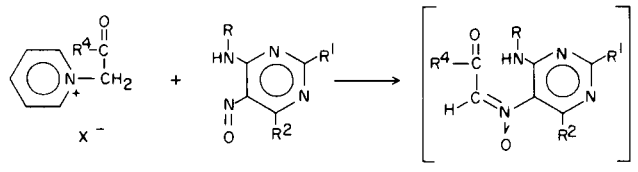
Sir:

Early attempts to prepare 6-thiosubstituted pteridines were uniformly unsuccessful (3,4) and examples of these compounds were not reported in the literature until 1964 when Clark reported the preparation of 6-benzylthiopteridine (5). Only a few examples of 6-thiopteridines have been reported since that time and these compounds have been prepared either by the nucleophilic displacement of 6-chloropteridines with thiols (6,7), or the nucleophilic addition of thiols to a localized 5,6-double bond of the pteridine nucleus (6,8,9). The unavailability of 6-halogenpteridines and the structural requirements imposed by localizing the 5,6-double bond make these routes unsatisfactory as general preparative methods for the synthesis of many 6-thiosubstituted pteridines.

We now wish to describe a new and direct one-step unambiguous synthesis which gives 6-alkylthio and 6-arylthiopteridines in good yields. The method involves the reaction of pyridinium-activated acetates (I, R^4 = alkoxyl), acetophenones (I, R^4 = phenyl or substituted phenyl), other methyl ketones (I, R^4 = alkyl), and acetonitriles (VI) with 4-amino-5-nitrosopyrimidines (II, R = H) or 4-acylamino-5-nitrosopyrimidines (II, R = acyl) to give 6-thio-substituted pteridines. It is presently believed that pyrimidine nitrones (III) are formed *in situ* by the reaction of nitrosopyrimidines (II) with the pyridinium-activated methylenes (I) or their corresponding ylids (10). Nucleophilic addition of the thiol (11) to III gives a hydroxylamine intermediate (IV) which subsequently loses water then cyclizes to give the 6-thiopteridine derivative (V). Pyridinium-activated acetonitriles (VI) give 7-amino-6-thiopteridines (VII) by a similar sequence (12).

This new method is quite general and permits a wide variety of substitution patterns on the pteridine nucleus. This method is also highly versatile in that the three starting materials (pyridinium salt, 4-amino-5-nitrosopyrimidine, and thiol) may all be independently varied. This feature allows a multitude of new pteridine derivatives to be produced from a few readily available starting materials (13).

The potassium acetate-catalyzed reaction of 4,6-diamino-5-nitroso-2-phenylpyrimidine (II, R = H, R^1 = C_6H_5, R^2 = NH_2) with 1-(cyanomethyl)pyridinium chloride (VI, X = Cl) and thiophenol in refluxing ethanol gives 4,7-diamino-2-phenyl-6-phenylthiopteridine (VII, R^1 = R^3 = C_6H_5, R^2 = NH_2, 66% yield). Acylated 2,4,6-triamino-5-nitrosopyrimidine derivatives (14) also give the expected 6-thiopteridine derivatives under mild conditions. Thus 2-amino-4,6-diacetamido-5-nitrosopyrimidine (II, R = $-COCH_3$, R^1 = NH_2, R^2 = $-NHCOCH_3$) with 1-(cyanomethyl)pyridium chloride (VI, X = Cl) and thiophenol in refluxing ethanol gives 4-acetamido-2,7-diamino-6-phenylthiopteridine (VIII, R = C_6H_5, 72% yield). This product is identical in all respects with an authentic sample prepared by another unambiguous synthetic route (15). Substitution of *n*-hexylmercaptan for thiophenol in this system



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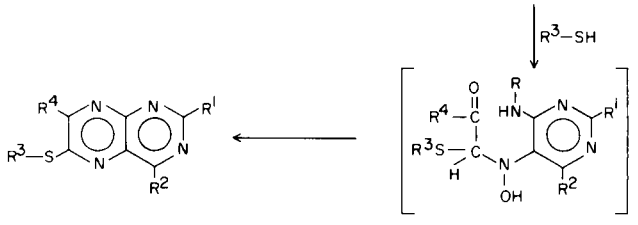

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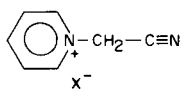

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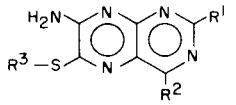

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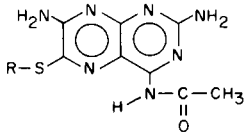

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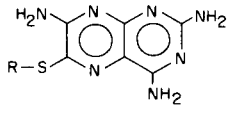

IX

gives 4-acetamido-2,7-diamino-6-(*n*-hexylthio)pteridine (VIII, R = C_6H_{13}, 73% yield). When 2,4,6-triacetamido-5-nitrosopyrimidine is used in similar reactions the corresponding 2,4-diacetamidopteridines are obtained.

Variations of the pyridinium salt in this reaction system give a variety of substituents in the seven position of the pteridine nucleus. For example, 2-amino-4,6-diacetamido-5-nitrosopyrimidine (II, R = $-COCH_3$, R^1 = NH_2, R^2 = $NHCOCH_3$), thiophenol and 1-(carbethoxymethyl)pyridinium chloride (I, R^4 = $-OC_2H_5$, X = Cl) react to give 4-acetamido-2-amino-6-phenylthio-7(8*H*)-pteridinone (V, R^1 = NH_2, R^2 = $NHCOCH_3$, R^3 = C_6H_5, R^4 = OH, 56% yield) (16). Similarly, acetonylpyridinium chloride (I, R^4 = CH_3, X = Cl), 1-(3,3-dimethyl-2-oxo-1-butyl)-pyridinium bromide (I, R^4 = *t*-Bu, X = Br), and phenacylpyridinium bromide (I, R^4 = C_6H_5, X = Br) give the analogous pteridines (V, R^1 = NH_2, R^2 = $NHCOCH_3$, R^3 = C_6H_5) with methyl- (R^4 = CH_3), *t*-butyl- (R^4 = *t*-Bu) and phenyl- (R^4 = C_6H_5) in the seven position, respectively.

Either acidic or basic hydrolysis of acylamino 6-thiopteridines produces the corresponding 2,4-diaminopteridines. These pteridines are sulfur containing analogs of the clinically useful 2,4-diamino-6-substituted pteridine antifolates (17). For example, hydrolysis of 4-acetamido-2,7-diamino-6-phenylthiopteridine (VIII, R = C_6H_5) with concentrated hydrochloric acid at room temperature followed by neutralization gives 2,4,7-triamino-6-phenylthiopteridine (IX, R = C_6H_5, 100% yield). Hydrolysis with aqueous sodium hydroxide or concentrated ammonium hydroxide also gives the same products in somewhat lower yields.

When aqueous alcoholic sodium hydroxide is used to catalyze reactions involving acylated 2,4,6-triamino-5-nitrosopyrimidines, 2,4-diaminopteridines are produced directly in a single reaction. For example, under these conditions, 2-amino-4,6-diacetamido-5-nitrosopyrimidine (II, R = $COCH_3$, R^1 = NH_2, R^2 = $NHCOCH_3$), 1-cyanomethylpyridium chloride (VI, X = Cl), and thiophenol gives 2,4,7-triamino-6-phenylthiopteridine (IX, R = C_6H_5, 71% yield) directly.

Thus, we now have available a simple unambiguous two-step sequence or if desired, a one-step reaction for producing a variety of 2,4-diaminopteridines of potential pharmacological interest. The extension of the new synthetic method to other types of nucleophiles and other heterocyclic systems is under current investigation.

REFERENCES

(1) This work was supported by a private grant to Brigham Young University from Mr. Paul J. Parish.

(2) Part of this work was reported at the 25th Annual Northwest Regional Meeting of the American Chemical Society held June 17-19, 1970 at Seattle, Washington.

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(8) A. Albert and J. H. McCormack, *J. Chem. Soc.*, 6930 (1965).

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(10) The reaction of aromatic nitroso compounds with pyridinium-activated methylene compounds is known to give nitrones as intermediates in the Krohnke synthesis of aldehydes as well as several other reactions. (a) F. Krohnke, *Angew. Chem.*, **65**, 605 (1953). (b) F. Krohnke and W. Zecher, *Angew. Chem. Int. Ed. Engl.*, **1**, 626 (1962). (c) F. Krohnke, *ibid.*, **2**, 225, 380 (1963).

(11) To our knowledge, the nucleophilic addition of thiols to nitrones has not yet been reported in the literature; however, a number of other nucleophiles including cyanide ion have been demonstrated to give 1,3-addition products with nitrones. (a) G. R. Delpierre and M. Lamchen, *Quant. Rev.* (London), 329 (1965). The addition of thiols or their corresponding anions to nitrones is, therefore, not completely unexpected considering the similarities (nucleophilicity, basicity, and polarizability) between thiols and cyanide. (b) R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.*, **98**, 1827 (1967).

(12) Satisfactory elemental analyses and spectral data (IR, UV, Fluorescence and NMR) were obtained for all new compounds reported. The analytical samples all moved as single spots on descending paper chromatography using several different solvent systems.

(13) A wide variety of 4-amino-5-nitrosopyrimidines and thiols are available from several commercial sources. The requisite pyridinium salts are easily prepared by allowing the corresponding commercially available bromo-, chloro-, iodo-, or sulfonate compounds to react with pyridine.

(14) I. J. Pachter, P. E. Nemeth, and A. J. Villani, *J. Org. Chem.*, **28**, 1197 (1963). Investigations carried out in this laboratory have demonstrated that the structures of the two acylated derivatives of 2,4,6-triamino-5-nitrosopyrimidine are 2-amino-4,6-diacetamido-5-nitrosopyrimidine and 2,4,6-triacetamido-5-nitrosopyrimidine for the diacylated and triacylated products, respectively. This work will be reported in a future publication.

(15) This route involves the Timmis condensation [G. M. Timmis, *Nature*, **164**, 139 (1949)] of phenylthioacetonitrile with 2-amino-4,6-diacetamido-5-nitrosopyrimidine in hot *N*,*N*-dimethylformamide in the presence of sodium acetate and will be described in a future publication.

(16) In those instances wherein the 7-substituent may be thought of as hydroxyl, it is expected that the compound actually exists as the keto-tautomer as implied by the pteridinone name.

(17a) I. Brodsky, S. Kahn, and J. H. Moyer, III, Eds., "Cancer Chemotherapy," Grune and Stratton, New York, 1967. (b) F. E. Knock, "Anticancer Agents," Charles C. Thomas, Publisher, Springfield, Illinois, 1967. (c) A. Albert, "Selective Toxicity," 4th ed., Methuen and Co. Ltd., London, 1968, pp. 216-218.