[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

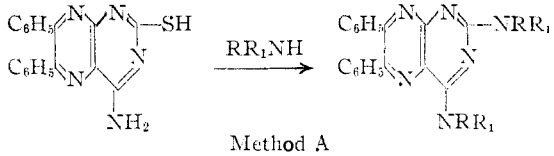
Pteridines. VIII. The Synthesis of 2,4-Bis-(alkylamino)-6,7-diphenylpteridines

BY E. C. TAYLOR, JR.[1]

Three general methods are described for the synthesis of 2,4-bis-(alkylamino)-6,7-diphenylpteridines (I), of interest because of their possible biological activity. Method A involves the reaction between an alkylamine and 4-amino-2-mercapto-6,7-diphenylpteridine (II); Method B, the reaction between an alkylamine and 2,4-dichloro-6,7-diphenylpteridine (III); and Method C, the reaction between an alkylamine and 2,4-diamino-6,7-diphenylpteridine (IV) in the presence of a trace of hydrochloric acid. A possible mechanism for this latter reaction is advanced.

As a continuation of previous work on the synthesis of potential pteroylglutamic acid (folic acid) antagonists,[2] a number of 2,4-bis-(alkylamino)-6,7-diphenylpteridines (I) have been prepared and are reported in the present paper.

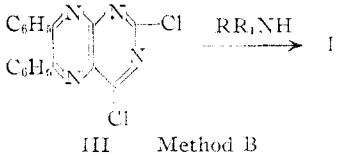
Three general methods for the synthesis of compounds of type I have been developed. Method A is an extension of a reaction previously reported[3] which involves the reaction of alkylamines with 4-amino-2-mercapto-6,7-diphenylpteridine (II).



II I

It was demonstrated previously that although low boiling, moderately basic amines (such as methylamine, dimethylamine, morpholine and piperidine) gave predominantly the corresponding 4-amino-2-alkylamino-6,7-diphenylpteridines, the use of high boiling, strongly basic amines (such as benzylamine and 2-hydroxyethylamine) led exclusively to the 2,4-bis-(alkylamino) derivatives. This reaction has now been utilized for the synthesis of a number of additional compounds of type I.

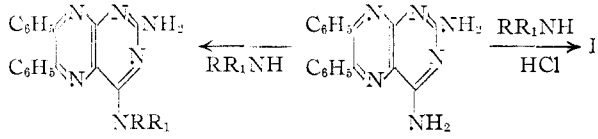
To confirm the structures assigned to the products of the above reaction, 2,4-dichloro-6,7-diphenylpteridine (III) was prepared by the action of phosphorus pentachloride and phosphorus oxychloride on 2,4-dihydroxy-6,7-diphenylpteridine and treated with the same amines (Method B). In every case, the product, a 2,4-bis-(alkylamino)-6,7-diphenylpteridine, was identical with the corresponding product obtained by Method A. Moreover, this method was utilized for the preparation



III Method B

of two compounds, 2,4-dimorpholino-6,7-diphenylpteridine and 2,4-dipiperidino-6,7-diphenylpteridine which could not be prepared by Method A (see Table I).

It was recently demonstrated that certain alkylamines react with 2,4-diamino-6,7-diphenylpteridine (IV) to give the corresponding 2-amino-4-alkylamino derivatives (V).[3] It has now been found that, in the presence of a trace of hydrochloric acid, the action of alkylamines on IV constitutes a general synthetic route to 2,4-bis-(alkylamino)-6,7-diphenylpteridines (I) (Method C). Thus, IV and benzylamine gave 2-amino-4-benzylamino-



V IV Method (C)

6,7-diphenylpteridine in 67% yield when heated together under reflux in the absence of a solvent, but addition of a small amount of hydrochloric acid to the reaction mixture led to the formation of 2,4-bis-(benzylamino)-6,7-diphenylpteridine in 91% yield. In a like manner, in the presence of a small amount of hydrochloric acid, IV reacted with hydrazine, 2-hydroxyethylamine, piperidine, morpholine, 3-dimethylaminopropylamine, 3-diethylaminopropylamine and 3-isopropylaminopropylamine to give the corresponding 2,4-bis-(alkylamino) derivatives. The reaction was useful even with those amines which failed to give 4-alkylamino derivatives (V) with 2,4-diamino-6,7-diphenylpteridine (IV) in the absence of acid. Thus, although no reaction took place when IV and piperidine were heated together in a sealed tube at 200° for 20 hours, addition of a few drops of concentrated hydrochloric acid resulted in the formation of 2,4-dipiperidino-6,7-diphenylpteridine in 40% yield. In the majority of those cases studied, this method gave I in higher yield than either Method A or Method B.

Table I lists the compounds of type I prepared, along with the yields obtained by each preparative method, the solvents employed for recrystallization, melting points, and microanalytical data.[4]

Although several mechanisms may be written for the conversion of IV to I by Method C, the one which is consistent with the mechanism proposed previously for the reaction of 4-amino- or 4-hydroxy-2-mercaptopteridines with amines[3] involves a nucleophilic attack of the amine at C_4, resulting in ring opening and the formation of a guanidinopyrazine intermediate VI. In the absence of acid, VI recyclizes either by loss of alkylamine to regenerate IV or by loss of ammonia to give V. In the case of the less basic amines piperidine and morpholine, the equilibrium IV⇆VI probably lies far to the left; the initial catalytic effect of acid in promoting the conversion of IV to I could be explained by assuming salt formation

(1) du Pont Postdoctoral Fellow in Chemistry, 1950-1951.

(2) For leading references, see E. C. Taylor, Jr., and C. K. Cain, THIS JOURNAL, **74**, 1644 (1952).

(3) E. C. Taylor, Jr., and C. K. Cain, *ibid.*, **73**, 4381 (1951).

(4) The biological activity of these compounds will be reported at a later date.

TABLE I: 2,4-BIS-(ALKYLAMINO)-6,7-DIPHENYLPTERIDINES

R	% Yield by method A	% Yield by method B	Temp., °C. Method C	Crystallized from	M.p., °C.[a]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
—NHCH$_2$C$_6$H$_5$	79	87	91	Reflux	Aq. ethanol	226–226.5	$C_{32}H_{26}N_6$	77.7	77.6	5.3	5.5	17.0	17.3
—NHNH$_2$	100[b,c]	91	66	Reflux	Aq. dimethylformamide	Dec. >230	$C_{18}H_{16}N_8$	62.8	63.1	4.7	4.6	32.5	32.4
—NHCH$_2$CH$_2$OH	100	87	100	Reflux	Aq. dimethylformamide	211–212	$C_{22}H_{22}N_6O_2$	65.7	66.1	5.5	5.5	20.9	20.9
—N⟨ ⟩CH$_2$	[d]	88	40[e]	200	Aq. dimethylformamide	180–181	$C_{28}N_{30}N_6$	74.6	74.6	6.7	6.6	18.7	18.7
—N⟨ ⟩O	[f]	91	65[e]	200	Methylene chloride–petroleum ether	200–201.5	$C_{26}H_{26}N_6O_2$	68.7	68.9	5.8	5.8	18.5	18.7
—NH(CH$_2$)$_3$N(CH$_3$)$_2$	84	92	86[e]	180	Aq. dimethylformamide	144.5–145.5	$C_{28}H_{36}N_8$	69.4	69.5	7.5	7.6	23.1	23.3
—NH(CH$_2$)$_3$N(C$_2$H$_5$)$_2$	90	78	95	Reflux	Methylene chloride–petroleum ether	137.3–138	$C_{32}H_{44}N_8$	71.1	71.1	8.2	8.3	20.7	20.5
—NH(CH$_2$)$_3$NHCH(CH$_3$)$_2$	82	81	92	Reflux	Methylene chloride–petroleum ether	141–142	$C_{30}H_{40}N_8$	70.3	70.4	7.9	8.0	21.9	22.0

[a] All melting points are corrected. [b] Forty milliliters of ethanol was added to the reaction mixture to increase the solubility of the 4-amino-2-mercapto-6,7-diphenylpteridine. [c] The product was obtained analytically pure without recrystallization. [d] 4-Amino-2-piperidino-6,7-diphenylpteridine was formed in 65% yield. [e] No reaction took place at the temperature of the boiling amine; the reaction was carried out by heating the reactants in a sealed tube at the indicated temperature for 20 hours and then working up the reaction mixture as usual. [f] 4-Amino-2-morpholino-6,7-diphenylpteridine was formed in 45.5% yield.

at the 4-imino group,[5] thus facilitating attack of the amine at C_4.

The catalytic effect of acid in changing the course of the reaction to give I rather than V is most readily understandable if one assumes that salt formation with the basic guanidino grouping facilitates a thermal elimination[7] of ammonia (or ammonium ion) to give the substituted cyanamide VIII. Such a dearrangement to cyanamide and ammonia has been demonstrated in the thermal decomposition of guanidine carbonate.[6] The cyanamide VIII would be expected to react readily with the amine under the reaction conditions[7] to give IX, which in turn would cyclize to I, the observed product of the reaction.

The supposition that the conversion of IV to I involves a thermal step (VII → VIII) which is catalyzed by acid is supported by observations on the reaction between IV and 3-dimethylamino-

(5) It has been suggested on the basis of hydrolysis and diazotization studies (E. C. Taylor, Jr., and C. K. Cain, THIS JOURNAL, **71**, 2538 (1949)) that the most probable structure for compounds of type IV is one which contains an amino group in the 2-position and an imino group in the 4-position.

For convenience in nomenclature, however, such compounds are customarily referred to as 2,4-diaminopteridines.

(6) T. L. Davis and H. W. Underwood, Jr., *ibid.*, **44**, 2595 (1922).

(7) V. Migrdichian, "The Chemistry of Organic Cyanogen Compounds," Reinhold Publishing Corp., New York, N. Y., 1947, p. 66.

propylamine. No reaction took place when the two components were heated together in the absence of acid at 102°, the temperature of the boiling amine. When the two components were heated in a sealed tube at 180°, again in the absence of acid, the only product isolated was 2-amino-4-(3-dimethylaminopropylamino)-6,7-diphenylpteridine. Addition of a small amount of hydrochloric acid to the reaction mixture heated at 102° resulted in the formation of an impure product consisting largely of 2,4-bis-(3-dimethylaminopropylamino)-6,7-diphenylpteridine but containing a small amount of the 2-amino-4-(3-dimethylaminopropylamino) derivative. Addition of hydrochloric acid to the reaction mixture heated at 180°, however, gave 2,4-bis-(3-dimethylaminopropylamino)-6,7-diphenylpteridine in 86% yield.

These results suggest that the 4-alkylamino-2-amino derivative V may be an intermediate between IV and I, at least in those cases where a primary amine is employed. This possibility is supported by the observation that 2-amino-4-benzylamino-6,7-diphenylpteridine was converted to 2,4-bis-(benzylamino)-6,7-diphenylpteridine by heating with benzylamine and a trace of hydrochloric acid.

The results discussed above serve to explain the observation of Roth, Smith and Hultquist[8] that 2-methylamino-4-chloro-6,7-diphenylpteridine[9] upon heating with ammonia gave principally 2,4-diamino-6,7-diphenylpteridine and not 4-amino-2-methylamino-6,7-diphenylpteridine. In view of the present work, the former compound would be the expected product of the reaction.

(8) B. Roth, J. M. Smith, Jr., and M. E. Hultquist, THIS JOURNAL, **73**, 2864 (1951).

(9) The yield of this compound obtained by the aforementioned authors corresponds to the formation of the hydrochloride of 2-methylamino-4-chloro-6,7-diphenylpteridine rather than the free base. Thus sufficient acid was undoubtedly present in the reaction mixture to effect the observed disproportionation. The chlorination of an analogous compound, 2-amino-4-hydroxy-6,7-diphenylpteridine, under similar conditions (C. K. Cain, E. C. Taylor, Jr., and L. J. Daniel, *ibid.*, **71**, 892 (1949)) gave the hydrochloride of the resulting chloropteridine. Although the amination of this latter compound with methylamine was reported to give only 2-amino-4-methylamino-6,7-diphenylpteridine, a reinvestigation of the reaction product revealed the probable presence of a small amount of the bis-(methylamino) derivative.

Experimental[10]

The following are typical experimental procedures for the methods indicated.

Method A.—A mixture of 4.0 g. of 4-amino-2-mercapto-6,7-diphenylpteridine (II)[2] and 40 ml. of the amine was heated under reflux until the evolution of hydrogen sulfide had ceased (usually about ten hours). The excess amine was removed by evaporation[11] under reduced pressure and the residue triturated with water until it had solidified. It was then separated by filtration, washed thoroughly with water and recrystallized from the appropriate solvent.

Method B.—To 20 ml. of the amine in a 50-ml. round-bottomed flask was added slowly 4.0 g. of 2,4-dichloro-6,7-diphenylpteridine (III).[3] When the initial vigorous exothermic reaction had subsided, the reaction mixture was heated under reflux for one hour and then worked up as described above.

Method C.—A mixture of 4.0 g. of 2,4-diamino-6,7-diphenylpteridine (IV) in 30 ml. of the amine containing two drops of concentrated hydrochloric acid was heated under the conditions indicated in Table I, the excess amine removed by evaporation under reduced pressure and the residue worked up as indicated above.

The products from Methods A, B and C were identical as shown by mixed melting point determinations and by a comparison of their infrared absorption spectra.[12]

2-Amino-4-(3-dimethylaminopropylamino)-6,7-diphenylpteridine.—A mixture of 2.5 g. of 2,4-diamino-6,7-diphenylpteridine (IV) and 30 ml. of 3-dimethylaminopropylamine was sealed in a glass bomb tube and heated at 180° for 20 hours. The excess amine was removed by distillation under reduced pressure and the residue recrystallized from aqueous dimethylformamide; yield 2.9 g. (91%); m.p. 218.5–219.5° (cor.).

Anal. Calcd. for $C_{23}H_{25}N_7$: C, 69.2; H, 6.3; N, 24.5. Found: C, 69.4; H, 6.4; N, 24.3.

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(10) Microanalyses were made by Miss Emily Davis, Mrs. Jean Fortney and Miss Katherine Pih.

(11) With 2-hydroxyethylamine, water was added directly to the reaction mixture. The product crystallized on cooling. With benzylamine, 50 ml. of ethanol was added first, followed by sufficient hot water to induce crystallization.

(12) The author is indebted to Miss Elizabeth M. Petersen for the determination of the infrared absorption spectra.