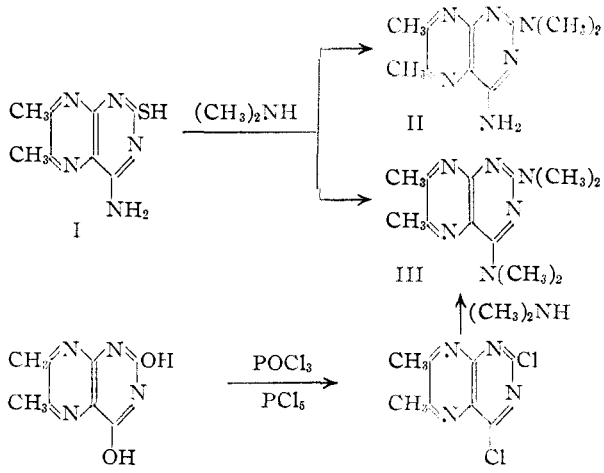
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE BAKER LABORATORY OF CHEMISTRY, CORNELL UNIVERSITY]

Pteridines. VI. Replacement Reactions of Amino, Hydroxyl and Mercapto Groups in the Pteridine Series[1,2]

BY E. C. TAYLOR, JR.,[3] AND C. K. CAIN[3]

The reaction between methylamine or dimethylamine and a 4-amino-2-mercaptopteridine (IVa) at elevated temperatures and pressures has been shown previously to lead to 4-amino-2-alkylaminopteridine derivatives (X). It is now found that under more strenuous conditions some 2,4-bis-(alkylamino)-pteridine derivative (XI) is also formed. When high boiling, strongly basic amines (ethanolamine, benzylamine, etc.) are employed, XI is formed exclusively in excellent yield. The reaction of 4-hydroxy-2-mercaptopteridines (IVb) with amines leads even more readily to XI. The structure of XI is established by comparison with an authentic sample prepared by the action of the amine on the appropriate 2,4-dichloropteridine. The reaction between these amines and a 2,4-diamino- or 2-amino-4-hydroxypteridine leads in good yield to the corresponding 2-amino-4-alkylaminopteridine (XII) and constitutes a direct synthetic approach to those compounds from readily available starting materials. The mechanism of these reactions is discussed.

A previous report[4] has described the synthesis of several 4-amino-2-alkylaminopteridine derivatives by the reaction between alkylamines and a 4-amino-2-mercapto-(or methylmercapto)-pteridine in absolute ethanol at 180°. It was observed in the course of this work that the action of dimethylamine on 4-amino-2-mercapto-6,7-dimethylpteridine (I) gave, in addition to the reported 4-amino-2-dimethylamino-6,7-dimethylpteridine (II), a small amount of an acetone-soluble material. Upon careful purification, this material has been found to give microanalytical values corresponding to a bis-(dimethylamino) derivative. The substance has now been shown to be 2,4-bis-(dimethylamino)-6,7-dimethylpteridine (III) by comparison with an authentic sample prepared by the action of dimethylamine on 2,4-dichloro-6,7-dimethylpteridine.



Subsequent experiments have revealed several additional anomalies in the reaction between a 4-amino-2-mercaptopteridine and an alkylamine. Treatment of 4-amino-2-mercapto-6,7-diphenylpteridine with ethanolamine either in alcoholic solution at elevated temperatures and pressures or in the absence of a solvent under reflux gives a quantitative yield of 2,4-bis-(ethanolamino)-6,7-diphenylpteridine. All attempts to modify the reaction so as to produce 4-amino-2-ethanolamino-6,7-diphenylpteridine have failed, only the bis-(ethanolamino) derivative being formed in each case. Likewise, treatment of 4-amino-2-mercapto-6,7-diphenylpteridine with benzylamine gives 2,4-bis-(benzylamino)-6,7-diphenylpteridine, none of the 4-amino-2-benzylamino-6,7-diphenylpteridine being isolated. The product was shown conclusively to have the structure assigned by comparison with an authentic sample prepared by the action of benzylamine on 2,4-dichloro-6,7-diphenylpteridine. Finally, treatment of 4-hydroxy-2-mercapto-6,7-dimethylpteridine with methylamine gives good yields of 2,4-bis-(methylamino)-6,7-dimethylpteridine.

In view of these observations, the following mechanism is proposed for the reaction between a 4-amino-(or hydroxy)-2-mercaptopteridine and a primary or secondary alkylamine.

The reaction is initiated by a nucleophilic attack of the alkylamine at carbon atom 4 (IV → V) accompanied by proton loss. The resulting electronic shifts followed by ring opening and addition of a proton give VII, which would be expected to be the first stable intermediate. The acyclic thiourea derivative VII would react readily with the alkylamine under the conditions employed to give VIII. Elimination of the alkylamine either directly from VIII or through the cyclic intermediate IX formed from VIII by ring closure through internal addition would give the normal product X, while elimination of ammonia (or water) would give the 2,4-bis-(alkylamino) derivative XI.[5]

The following observations are in support of such a mechanism: (1) The simultaneous formation of 4-amino-2-dimethylamino-6,7-dimethylpteridine (II) (corresponding to X) and 2,4-bis-(dimethylamino)-6,7-dimethylpteridine (III) (corresponding to XI) from the reaction between 4-amino-2-mercapto-6,7-dimethylpteridine (I) and dimethylamine. This is most satisfactorily explained through the postulation of a common intermediate system such as represented by VIII ⇄ IX. (2) The ready formation of the 2,4-bis-(alkylamino) derivatives (XI) when ethanolamine or benzylamine is used as the amine reactant. The use of a

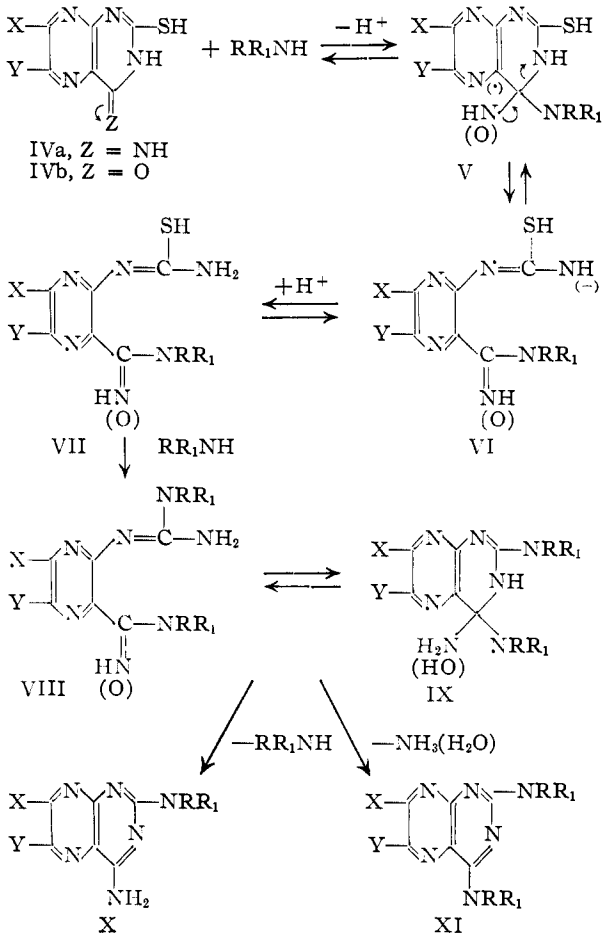
(1) For the preceding paper in this series, see E. C. Taylor, Jr., and C. K. Cain, THIS JOURNAL, 71, 2538 (1949).

(2) Presented before the Organic Division at the 119th Meeting of the American Chemical Society, Cleveland, Ohio, April, 1951.

(3) du Pont Postdoctoral Fellow in Chemistry, University of Illinois.

(4) C. K. Cain and E. C. Taylor, Jr., Abstracts of Papers, 116th of the American Chemical Society, Atlantic City, N. J., September, 1949, p. 25M.

(5) Although there is no evidence for the actual existence of an intermediate corresponding to IX, an intermediate similar to VIII has been isolated from a related reaction and will be reported along with further evidence for ring opening in a forthcoming communication.



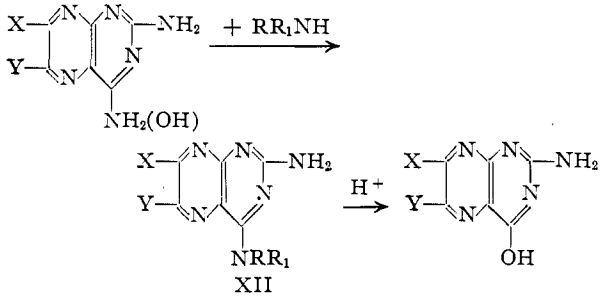
high boiling, strongly basic amine coupled with high reaction temperatures would be expected to favor the elimination of ammonia (or water) from the system VIII ⇄ IX. Water should be more readily eliminated from such a system than ammonia, and this is in line with the observation that the action of methylamine on 4-hydroxy-2-mercapto-6,7-dimethylpteridine leads to the bis-(alkylamino) derivative XI whereas with 4-amino-2-mercapto-6,7-dimethylpteridine under comparable conditions only the 4-amino-2-alkylamino derivative X is formed.[4] (3) The ready formation of 2,4-diamino-6,7-diphenylpteridine from 4-amino-2-methylmercapto-6,7-diphenylpteridine and ammonia in absolute ethanol.[4] In view of the usual inertness of 2-methylmercaptopyrimidines toward alcoholic ammonia[6] and of the smooth conversion of thiourea derivatives to guanidines by the action of ammonia or amines,[7] it seems attractive to postulate that replacement of the methylmercapto group in this reaction and of the mercapto group in the previous reactions takes place predominately as suggested.[8]

(6) T. B. Johnson and C. O. Johns, *Am. Chem. J.*, **34**, 175 (1905).

(7) N. V. Sidgwick, "The Organic Chemistry of Nitrogen," New Edition, Revised by T. W. J. Taylor and W. Baker, Oxford University Press, 1937, p. 298.

(8) Replacement of a 2-mercapto group by an alkylamino group takes place in similar heterocylic systems where there is little likelihood of such a mechanism being possible, *e.g.*, with 2-mercapto-4,5,6-triaminopyrimidine, but the ease of replacement of -SH by -NRR$_1$, as measured qualitatively by the ease of hydrogen sulfide evolution, is much greater with the pteridines than with the simple pyrimidines and is comparable with the ease of replacement with thiourea itself. These observations would seem to indicate that although the 2-mercapto group may be replaced either in the cyclic or in the acyclic form, the latter is the preferred mechanism in those cases where the ring can be opened to give intermediates of reasonable stability.

If the proposed reaction mechanism is correct and the 2-mercapto group is replaced in the acyclic form, then the initiating step of nucleophilic attack by the amine followed by ring opening, as well as the elimination step, should be independent of the initial presence of the 2-mercapto group and should take place with any 2-substituted-4-amino-(or hydroxy)-pteridine. The reaction between such a pteridine and a suitable alkylamine, *e.g.*, one which had yielded a 2,4-bis-(alkylamino) derivative XI in the previous reaction, should yield the corresponding 4-alkylamino derivative. This prediction has been experimentally verified. Ethanolamine reacts with 2,4-diamino-6,7-dimethylpteridine to give 2-amino-4-ethanolamino-6,7-dimethylpteridine and with 2,4-diamino-6,7-diphenylpteridine to give 2-amino-4-ethanolamino-6,7-diphenylpteridine. Likewise, benzylamine reacts with 2,4-diamino-6,7-diphenylpteridine to give 2-amino-4-benzylamino-6,7-diphenylpteridine. The same products are obtained when the corresponding 2-amino-4-hydroxypteridine derivatives are employed. The structure of these compounds has been established by ready acid hydrolysis to the corresponding 2-amino-4-hydroxypteridines. This method represents a smooth and direct synthetic



approach to 2-amino-4-alkylaminopteridines (XII) from the readily available 2,4-diamino-[9] or 2-amino-4-hydroxy[10] derivatives.

The preceding work suggests that replacement reactions should be observed in reactions between a 4-alkylaminopteridine and a second alkylamine in those cases where the attacking amine would be expected to displace the initial amine from the intermediate system corresponding to VIII ⇄ IX. This prediction has been verified. Ethanolamine reacts smoothly with 2,4-bis-(methylamino)-6,7-dimethylpteridine (XIII) to give 4-ethanolamino-2-methylamino-6,7-dimethylpteridine (XIV) and methylamine.

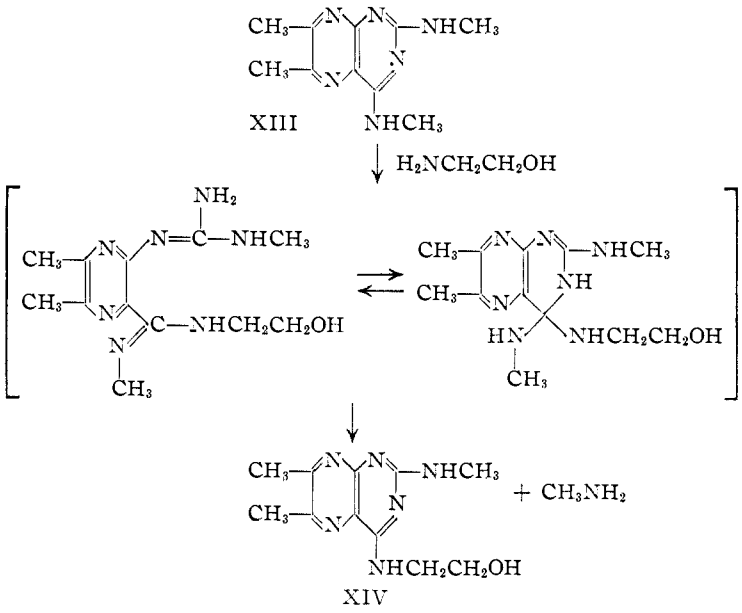
Experimental[11]

2,4-Bis-(dimethylamino)-6,7-dimethylpteridine (III). **A. From 4-Amino-2-mercapto-6,7-dimethylpteridine** (I).—A mixture of 6.0 g. of 4-amino-2-mercapto-6,7-dimethylpteridine, 10 g. of absolute dimethylamine and 100 ml. of abso-

(9) M. F. Mallette, E. C. Taylor, Jr., and C. K. Cain, THIS JOURNAL, **69**, 1814 (1947).

(10) C. K. Cain, M. F. Mallette and E. C. Taylor, Jr., *ibid.*, **68**, 1996 (1946).

(11) Microanalyses by Miss Emily Davis, Mrs. Jean Fortney and the Clark Microanalytical Laboratory. All melting points are uncorrected.



XIII XIV

lute ethanol was sealed in a glass bomb and heated at 180° for 12 hours and then at 210–220° for four hours. Evaporation of the ethanol and excess dimethylamine under reduced pressure left a brownish residue which was extracted with 50 ml. of boiling acetone. The acetone-insoluble material (4 g.) was shown to be 4-amino-2-dimethylamino-6,7-dimethylpteridine (II) by its ultraviolet absorption spectrum.[4] The acetone-soluble material (2 g.) was dissolved in benzene and extracted with four 25-ml. portions of 15% acetic acid. Neutralization of the acetic acid solution with concentrated ammonium hydroxide gave a yellow solid which was taken up in benzene. Evaporation of the benzene left a yellow solid which was purified by recrystallization from acetone followed by crystallization from benzene to yield 1.5 g. (21%) of yellow crystalline product; m.p. 165–166°.

Anal. Calcd. for $C_{12}H_{18}N_6$: C, 58.5; H, 7.4; N, 34.1. Found: C, 58.5; H, 7.1; N, 34.0.

B. From 2,4-Dichloro-6,7-dimethylpteridine.—A mixture of 3 g. of 2,4-dihydroxy-6,7-dimethylpteridine, 50 ml. of phosphorus oxychloride and 4 g. of phosphorus pentachloride was heated under reflux for four hours. The dark reaction mixture was filtered through a fritted glass funnel to remove a considerable amount of insoluble material and the excess phosphorus oxychloride removed by evaporation under reduced pressure. The residue was treated with ice and the dark red solid filtered off, washed thoroughly with ice-cold water and dried overnight in a vacuum desiccator; yield 1.9 g. The solid was extracted with 50 ml. of hot methylene chloride, the extract treated with Norit and the filtrate evaporated to dryness. The dark red residue was placed in a glass bomb with 50 ml. of absolute ethanol and 5 g. of anhydrous dimethylamine, the bomb sealed and heated at 110° for eight hours. Evaporation of the excess dimethylamine and ethanol yielded an orange residue which was dissolved in 100 ml. of 15% acetic acid, treated with Norit, and the filtrate neutralized with concentrated ammonium hydroxide. The yellow solid which separated was purified as described under A above; m.p. 165–166°. A mixed melting point with the product from A showed no depression and the ultraviolet absorption spectra of both compounds were identical.

2,4-Bis-(ethanolamino)-6,7-diphenylpteridine.—A mixture of 1.0 g. of 4-amino-2-mercapto-6,7-diphenylpteridine and 10 ml. of freshly distilled ethanolamine was heated under reflux for four hours. After cooling, 50 ml. of water was added to the reaction mixture and the precipitated solid collected by filtration and washed well with water; yield 1.2 g. (quantitative). Recrystallization from 50% ethanol gave light yellow crystals melting at 209–210°.

Anal. Calcd. for $C_{22}H_{22}N_6O_2$: C, 65.7; H, 5.5; N, 20.9. Found: C, 66.1; H, 5.5; N, 20.9.

2,4-Dichloro-6,7-diphenylpteridine.—Three grams of 2,4-dihydroxy-6,7-diphenylpteridine (dried in a vacuum desiccator over calcium chloride overnight) was added to 40 ml. of phosphorus oxychloride and the mixture warmed to 50°. To the clear yellow solution thus formed was added a solution of 6 g. of phosphorus pentachloride in 30 ml. of phosphorus oxychloride, and the resulting solution heated under reflux for 2.5 hours. The heavy tan-colored precipitate which first formed rapidly dissolved to give a deep cherry-red solution, the color of which darkened slightly on continued refluxing. The phosphorus oxychloride was removed by distillation under reduced pressure and the residue treated with 50 g. of ice. The yellow solid which precipitated was collected by filtration, washed thoroughly with ice-cold water and dried immediately in a vacuum desiccator. It is important to avoid letting the reaction mixture stand before this point or it will turn dark; yield 3.2 g. The yellow solid was dissolved in 50 ml. of methylene chloride, the solution treated with Norit and the filtrate evaporated to 10 ml. The product crystallized as a microcrystalline yellow solid upon addition of low boiling petroleum ether; yield 3.09 g. (92%); m.p. 189–192° (dec.).

2,4-Bis-(benzylamino)-6,7-diphenylpteridine. A. From 4-Amino-2-mercapto-6,7-diphenylpteridine.—A mixture of 0.50 g. of 4-amino-2-mercapto-6,7-diphenylpteridine and 3 ml. of freshly distilled benzylamine was heated under reflux for four hours. The condenser was then removed and the mixture heated at 150° for one-half hour until the evolution of hydrogen sulfide had completely ceased. Twenty milliliters of ethanol was added to the cooled reaction mixture, the solution heated to boiling and hot water added until crystallization commenced. Cooling gave 0.59 g. (79%) of yellow needles. The product was recrystallized first from 75% ethanol and then from 40% aqueous dimethylformamide; m.p. 220–221°.

Anal. Calcd. for $C_{32}H_{26}N_6$: C, 77.7; H, 5.3; N, 17.0. Found: C, 77.6; H, 5.5; N, 17.3.

B. From 2,4-Dichloro-6,7-diphenylpteridine.—Five hundred milligrams of 2,4-dichloro-6,7-diphenylpteridine was added slowly to 5 ml. of freshly distilled benzylamine. A vigorous exothermic reaction took place to give a clear, deep red solution. After heating under reflux for three hours, 20 ml. of ethanol was added, the solution treated three times with Norit and the filtrate treated with hot water until crystallization commenced; yield 0.61 g. (87%). The product was purified as described in A above. Mixed melting points of the products from A and B showed no depression and infrared spectra were identical.

2,4-Bis-(methylamino)-6,7-dimethylpteridine (XIII).—A mixture of 4.5 g. of 4-hydroxy-2-mercapto-6,7-dimethylpteridine,[12] 6 g. of anhydrous methylamine and 100 ml. of absolute ethanol was sealed in a glass bomb and heated at 180–190° for 18 hours. Evaporation of the ethanol and excess methylamine left a yellow solid which was purified by suspending in hot water, adding concentrated hydrochloric acid until all the material was in solution, neutralizing with 10% sodium hydroxide and cooling; yield 4 g. (85%). The compound was recrystallized from methanol for analysis; m.p. 255–256°.

Anal. Calcd. for $C_{10}H_{14}N_6$: C, 55.0; H, 6.4; N, 38.5. Found: C, 54.8; H, 6.3; N, 38.7.

2-Amino-4-ethanolamino-6,7-dimethylpteridine.—A mixture of 0.50 g. of 2,4-diamino-6,7-dimethylpteridine and 15 ml. of freshly distilled ethanolamine was heated together under reflux for eight hours. The reaction mixture was cooled, 25 ml. of water added and the precipitated solid collected by filtration and washed well with water; yield 0.61 g. (quantitative). The product was obtained in the form of long, silky yellow needles upon recrystallization from water; m.p. 245–245.5°.

Anal. Calcd. for $C_{10}H_{14}N_6O$: C, 51.3; H, 6.0; N, 35.9. Found: C, 51.5; H, 6.0; N, 36.2.

2-Amino-4-ethanolamino-6,7-diphenylpteridine.—A mixture of 0.50 g. of 2,4-diamino-6,7-diphenylpteridine and 10 ml. of freshly distilled ethanolamine was heated under re-

(12) E. M. Gal, THIS JOURNAL, **72**, 3532 (1950).

flux for eight hours. After cooling, 30 ml. of water was added and the precipitated solid collected by filtration, washed thoroughly with water and dried; yield 0.57 g. (quantitative). Recrystallization first from 95% ethanol and then from 75% aqueous dimethylformamide gave long yellow needles, m.p. 258–259° (dec.).

Anal. Calcd. for $C_{20}H_{18}N_6O$: C, 67.0; H, 5.1; N, 23.4. Found: C, 67.3; H, 5.3; N, 23.2.

2-Amino-4-benzylamino-6,7-diphenylpteridine.—A mixture of 0.50 g. of 2,4-diamino-6,7-diphenylpteridine and 10 ml. of freshly distilled benzylamine was heated under reflux for eight hours. Addition of 50 ml. of 50% ethanol and cooling gave 0.44 g. (68%) of yellow crystals which were recrystallized from 40% aqueous dimethylformamide; m.p. 237–238°.

Anal. Calcd. for $C_{25}H_{20}N_6$: C, 74.2; H, 5.0; N, 20.8. Found: C, 74.5; H, 5.3; N, 21.1.

Acid Hydrolysis of 2-Amino-4-alkylaminopteridines.—A solution of 0.10 g. of the 2-amino-4-alkylaminopteridine in 4 ml. of 6 *N* hydrochloric acid was heated under reflux for one-half hour. The reaction mixture was evaporated to dryness, the residue dissolved in 10 ml. of 2 *N* sodium hydroxide and poured into 10 ml. of 3 *N* acetic acid. The product was identified as the corresponding 2-amino-4-hydroxypteridine by melting point and ultraviolet absorption spectrum.[2,10]

4-Ethanolamino-2-methylamino-6,7-dimethylpteridine (XIV).—A mixture of 0.30 g. of 2,4-bis-(methylamino)-6,7-dimethylpteridine and 10 ml. of freshly distilled ethanolamine was heated under reflux for 36 hours, at the end of which time the slow evolution of methylamine had ceased. Water was added to the cooled reaction mixture and the aqueous solution subjected to continuous ether extraction for four hours. Evaporation of the ether extract gave a yellow solid which was dissolved in methanol, treated with Norit and filtered. The product crystallized out in yellow needles upon the addition of an equal volume of benzene; yield 0.218 g. (64%). The compound was recrystallized from acetone for analysis; m.p. 214–215°.

Anal. Calcd. for $C_{11}H_{16}N_6O$: C, 53.2; H, 6.5; N, 33.9. Found: C, 53.5; H, 6.6; N, 33.9.

URBANA, ILLINOIS RECEIVED APRIL 9, 1951

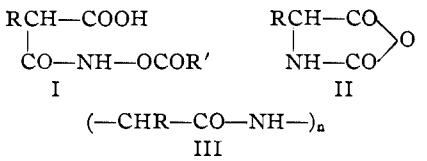
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Polypeptides Formed by the Lossen Rearrangement

BY CHARLES D. HURD AND LUDWIG BAUER

Two alkylcarboxyacetohydroxamic acids, HOOC–CHR–CONHOH, have been synthesized and studied to determine their behavior in the Lossen rearrangement. The radical R represents benzyl and ethyl. Polypeptides related to phenylalanine and α-aminobutyric acid were obtained. These polypeptides were insoluble in water but solubility was found in some organic solvents. All of the polypeptide fractions were hydrolyzable to the amino acids if sufficiently forced.

This work extends the findings of Hurd and Buess[1] on the rearrangement of α-carboxy hydroxamic acid derivatives into glycine and norleucine type polypeptides. An azasuccinic anhydride (II) was regarded as an intermediate between the hydroxamic derivative (I) and the polypeptide (III).



The present study takes up polypeptides, similarly prepared, which are composed of phenylalanine and α-aminobutyric acid units (R in III representing benzyl and ethyl, respectively).

A recent article by Hanby, Waley and Watson[2] mentions an attempt to synthesize 3-benzylazasuccinic anhydride by the Lossen rearrangement of α - carboxy - β - phenylpropiono - (benzoylhydroxamic) acid (I, R = benzyl). They gave no indication of their reaction conditions, but their article created the impression that the Lossen rearrangement failed to proceed. Since we have been studying this compound among others and have found that it does rearrange smoothly, we submit this report at the present time.

Tracey's summary[3] presents concisely the chemical and physical aspects of the Leuchs polymerization of azasuccinic anhydrides into polypeptides. Studies appearing since this summary are those of Hanby,[2] Coleman,[4] and by Wessely, Riedl and Tuppy.[5] That azasuccinic anhydrides were isolable on rearranging 2-carboxyalkanoyl azides in ether was demonstrated by Curtius and Sieber.[6] These anhydrides could be polymerized to polypeptides by conventional procedures. In contrast to this formation of polypeptides by both the Curtius and Lossen rearrangements, it is of interest to note that they are not formed by the Hofmann rearrangement. Instead, malonamic acids[7] give rise to amino acids. Similarly the Schmidt reaction on malonic acid[8] and on benzylmalonic acid gives glycine (29%) and DL-phenylalanine (16%) directly.

Preparation of the benzoylated α-carboxy hydroxamic acids followed the general procedure of Hurd and Buess.[1] Rearrangement of the sodium salts of these acids proceeds smoothly either in water solution or benzene suspension. With either approach polypeptide formation was observed accompanied by evolution of carbon dioxide and formation of sodium benzoate. The polypeptides did not melt sharply and were remarkably insoluble in water or boiling hydrochloric acid. They gave the ninhydrin test by adsorption.

Poly-DL-phenylalanine prepared in water was totally soluble in hot anhydrous formic acid, pyridine, formodimethylamide, *m*-cresol, and could be precipitated on adding water to the cold solution. If, however, this polymer was prepared in benzene, it was totally soluble only in *m*-cresol or pyridine. Whether or not this difference in solubility in formic acid and cresol gives an indication of the

(1) Hurd and Buess, THIS JOURNAL, **73**, 2409 (1951).
(2) Hanby, Waley and Watson, *J. Chem Soc.*, 3010 (1950).
(3) Tracey, *Annual Reports of the Chemical Society*, **46**, 225 (1949).
(4) Coleman, *J. Chem. Soc.*, 3222 (1950), and preceding papers.
(5) Wessely, Riedl and Tuppy, *Monatsh.*, **81**, 861 (1950).
(6) Curtius and Sieber, *Ber.*, **55**, 1543 (1922).
(7) Huang, Lin and Li, *J. Chinese Chem. Soc.*, **15**, 31 (1947), and preceding papers.
(8) Adamson, *J. Chem. Soc.*, 1564 (1939); Briggs, *et al.*, *ibid.*, 61 (1942).