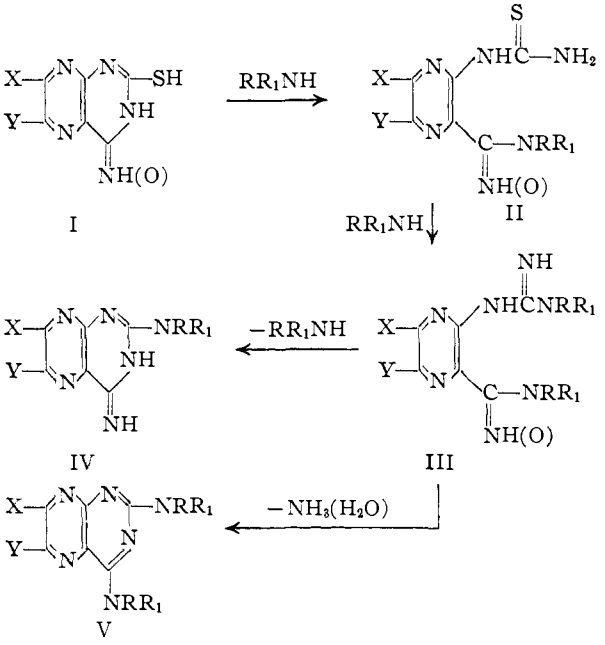
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Studies on the Aminolysis of Heterocyclic Amides. I. The Aminolysis of 6,7-Diphenyllumazine

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

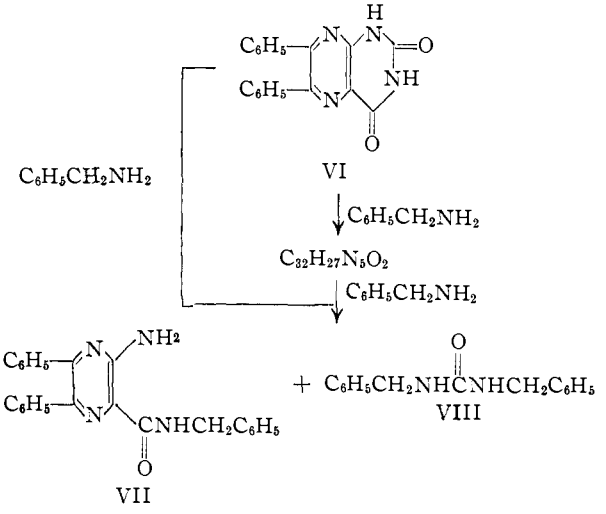
The action of an alkylamine on 6,7-diphenyllumazine has been shown to give first an N-substituted amide of a 3-(3-alkylureido)-5,6-diphenylpyrazinoic acid, which may then be converted to an N-substituted amide of 3-amino-5,6-diphenylpyrazinoic acid by further reaction with the amine. The mechanism of these transformations has been discussed and the results have been interpreted as a substantiation for the ring cleavages previously postulated in the reaction of 4-amino- and 4-hydroxy-2-mercaptopteridines with alkylamines.

The action of alkylamines on 4-amino-2-mercapto- and 4-hydroxy-2-mercaptopteridines (I) has been shown previously[2a,b] to lead either to 4-amino-2-alkylaminopteridines (IV) or to 2,4-bis-(alkylamino)-pteridines (V) or in some cases to mixtures of the two products, depending upon the reaction conditions and the nature of the amines employed. The mechanism which is proposed for these transformations[2a] involves preliminary nucleophilic attack of the alkylamine at C_4 followed by ring opening to give a thioureidopyrazine intermediate (II). Replacement of the mercapto group is then postulated to take place, with subsequent ring closure of III to give either IV or V or both.

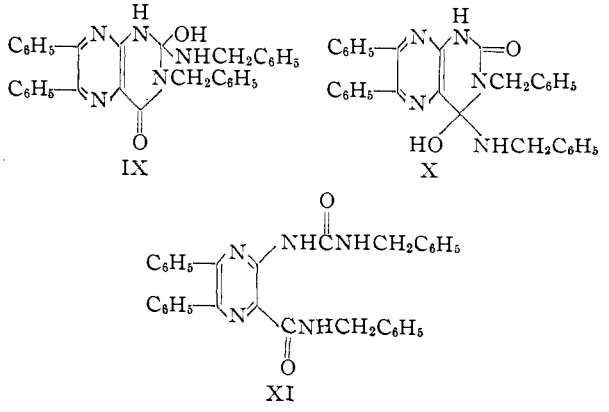


Although this mechanism is in excellent agreement with the experimental results and satisfactorily explains all observed products, no direct experimental verification for the existence of the postulated acyclic intermediates was presented.[2a] The present paper describes some experiments on the aminolysis of 6,7-diphenyllumazine (6,7-diphenyl-2,4(1H,3H)-pteridinedione) (VI) with alkylamines and presents evidence for the formation in these reactions of intermediates corresponding to II and III.

The reaction between 6,7-diphenyllumazine (VI) and alkylamines was shown to take place in two steps. For example, when VI and benzylamine were heated together for 15 minutes at the boiling point of the amine in the absence of a solvent, the only product isolated was a colorless crystalline solid having the composition $C_{32}H_{27}N_5O_2$. Further heating of this compound with benzylamine resulted in the formation of 3-amino-N-benzyl-5,6-diphenylpyrazinamide (VII) and N,N'-dibenzylurea (VIII). These compounds were also formed directly from VI by allowing the reaction with benzylamine to proceed for eight hours without isolation of the intermediate.



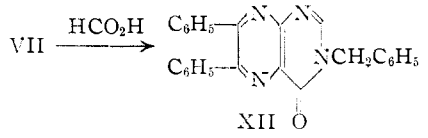
The three most probable structures for the compound of composition $C_{32}H_{27}N_5O_2$ are IX, X and XI. The infrared absorption spectrum in chloroform solution showed a strong carbonyl absorption band at 1660 cm.$^{-1}$ and a medium carbonyl absorption band at 1690 cm.$^{-1}$, in support of struc-



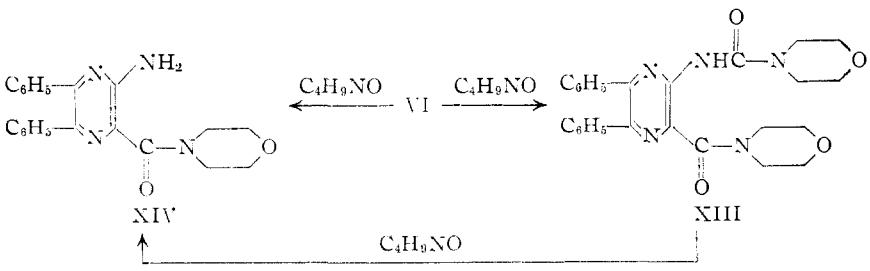
(1) du Pont Postdoctoral Fellow in Chemistry, 1950–1951.

(2) (a) E. C. Taylor, Jr., and C. K. Cain, THIS JOURNAL, **73**, 4384 (1951); (b) E. C. Taylor, Jr., and C. K. Cain, *ibid.*, **74**, 1644 (1952).

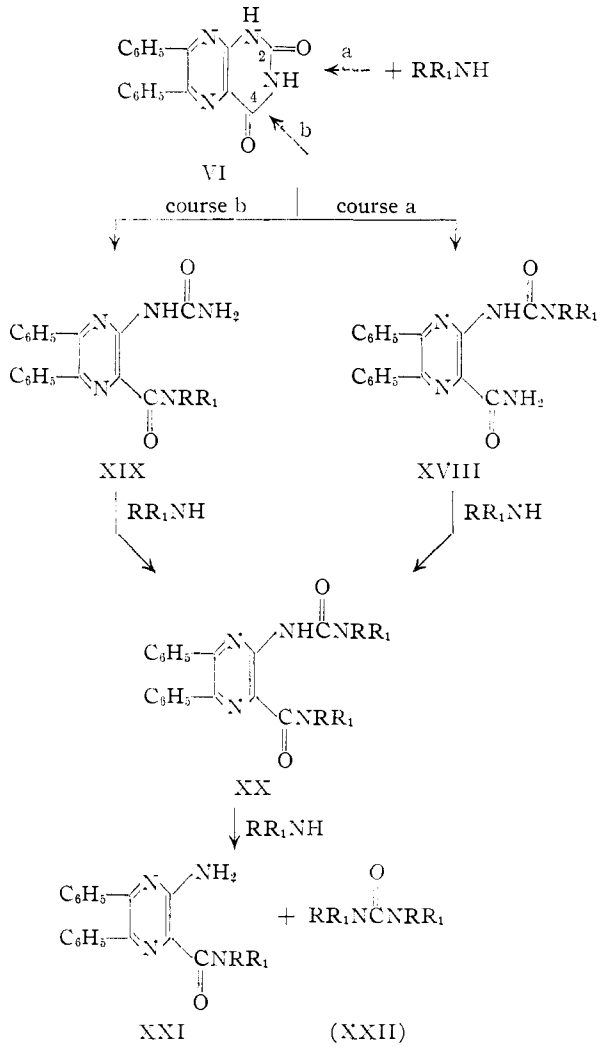
ture XI.[3] The compound was recovered unchanged after heating under reflux with acetic anhydride and fused sodium acetate for several hours, thus excluding structures IX and X. VII was shown to have the structure assigned by comparison with an authentic sample of 3-amino-N-benzyl-5,6-diphenylpyrazinamide prepared from the known 3-amino-5,6-diphenylpyrazinoic acid by esterification followed by reaction of the methyl ester with benzylamine. Finally, formic acid and acetic anhydride converted VII into 3-benzyl-6,7-diphenyl-4-(3H)-pteridinone (XII).[4]



The reaction between 6,7-diphenyllumazine (VI) and morpholine was shown to take a similar course. The first product isolated was 3-(morpholinocarbonylamino)-5,6-diphenylpyrazinoic acid morpholide (XIII), corresponding in structure to XI. Under the usual conditions of heating under reflux in the absence of a solvent, morpholine failed even after 48 hours to react further with this compound. However, when the dimorpholide XIII and morpholine were heated in a sealed tube at 140° for 12 hours and then at 190° for six hours, cleavage of the morpholinocarbonylamino grouping took place to give 3-amino-5,6-diphenylpyrazinoic acid morpholide (XIV). No attempt was made to isolate 4,4′-carbonyldimorpholine corresponding to the N,N′-dibenzylurea isolated from the previous reaction. Again, XIV was formed directly from the lumazine without the isolation of the dimorpholide XIII by heating with morpholine in a sealed tube at 190° for 12 hours. The failure of morpholine to cleave XIII under atmospheric pressure is consistent with the observation[5] that morpholine and urea give only N-carbamylmorpholine and no 4,4′-carbonyldimorpholine under similar conditions. Similarly, 6,7-diphenyllumazine (VI) and piperidine, heated together under reflux in the absence of a solvent, gave 3-(piperidinocarbonylamino)-5,6-diphenylpyrazinoic acid piperidide (XV), corresponding in structure to XI and XIII.



When either VI or XV and piperidine were heated together in a sealed tube at 200°, 3-amino-5,6-diphenylpyrazinoic acid piperidide (XVI) was formed.



When 6,7-diphenyllumazine (VI) was heated under reflux with an excess of β-hydroxyethylamine, 3-amino-N-(β-hydroxyethyl)-5,6-diphenylpyrazinamide (XVII) was obtained. No attempt was made in this case to isolate the ureido intermediate corresponding to XI, XIII and XV. It would thus appear that the action of primary and secondary amines on 6,7-diphenyllumazine (VI) constitutes a general synthetic procedure for the preparation of N-substituted amides of 3-amino-5,6-diphenylpyrazinoic acid; presumably the same reaction course would be followed with other 2,4-dihydroxypteridines (lumazines).

The initial attack of an alkylamine on 6,7-diphenyllumazine (VI) could occur either at C_2 (course a) or at C_4 (course b). In the former case, the pyrazinamide formed (XVIII) could undergo direct aminolysis to XX, the first isolated product, while in the latter case, XX could be formed by degradation of the ureido grouping of XIX through

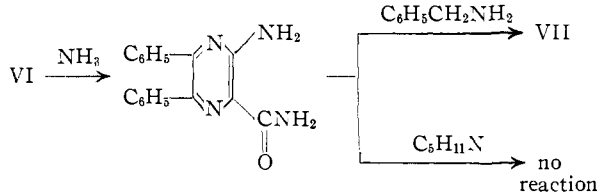
(3) The author is indebted to Miss Elizabeth M. Petersen for the determination of the infrared absorption spectrum.

(4) The conversion of N-substituted amides of 3-amino-2-pyrazinoic acids to 3-substituted 4-(3H)-pteridinones is currently being investigated and will be reported in a future communication from this Laboratory.

(5) C. A. Weisel, H. S. Mosher and F. C. Whitmore, THIS JOURNAL, **67**, 1055 (1945).

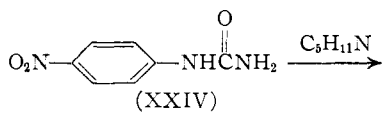
a thermal "urea dearrangement"[6] to an isocyanate, followed by addition of the alkylamine.

The exclusion of course a and the establishment of course b as the probable mechanism for this transformation is a result of the following observations. An intermediate similar to the unsubstituted amide XVIII was prepared from 6,7-diphenyllumazine (VI) by cleavage with ammonia under conditions of high temperature and pressure. The product of this reaction, 3-amino-5,6-diphenylpyrazinamide (XXIII), reacted with benzylamine

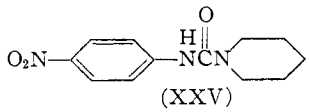


XXIII

under the conditions employed for the conversion of VI to XI to give a product identical with VII. However, the pyrazinamide XXIII failed to react with piperidine under conditions which successfully converted VI into 3-(piperidinocarbonylamino)-5,6-diphenylpyrazinoic acid piperidide (XV). Hence, a compound containing the free amide grouping $-CONH_2$ cannot be an intermediate in the conversion of VI to XX, and course a is excluded as a general mechanism for this transformation. Although attempts to synthesize an intermediate corresponding to the ureidopyrazine XIX have to date been unsuccessful, indirect support for the supposition that course b represents the probable mechanism was derived from the observation that *p*-nitrophenylurea (XXIV) could be converted to 1-(*p*-nitrophenyl)-3-(piperidino)-urea (XXV) by heating with piperidine under conditions which realized the conversion of VI to XV. Recent work in this Laboratory has demon-



(XXIV)



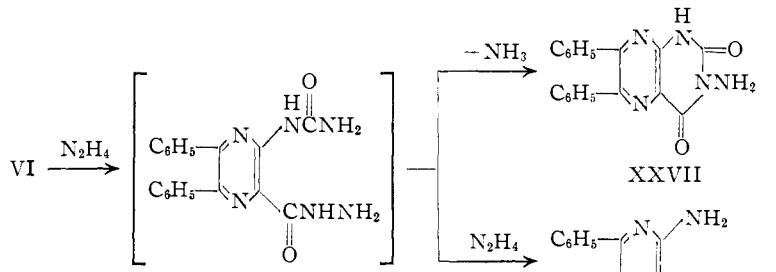
(XXV)

strated a striking parallelism between the reactivity of a 4(3H)-pteridinone and 6-nitro-4(3H)-quinazolone,[7] thus providing strong justification for any analogy drawn between the reactivity of a ureidopyrazine (XIX) and *p*-nitrophenylurea (XXIV). The reaction between urea and primary and secondary amines to form monosubstituted and *sym*-disubstituted ureas is well-known.[6] Thus the initial reaction between 6,7-diphenyllumazine (VI) and alkylamines would appear to be a nucleophilic attack of the amine at C_4 resulting in cleavage of the pyrimidine ring as indicated by course b above.

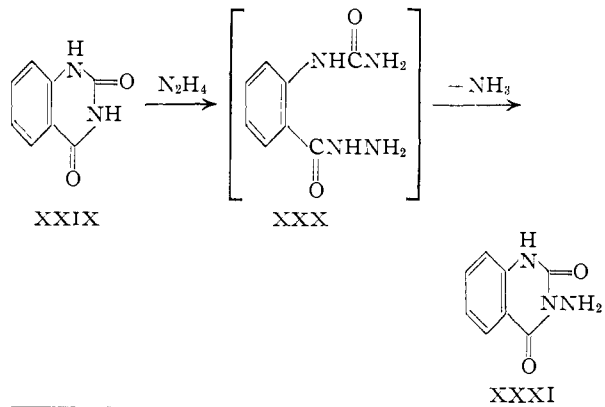
(6) T. L. Davis and H. W. Underwood, Jr., *ibid.*, **44**, 2595 (1922).
(7) This work will be the subject of a forthcoming publication.

The mechanism for the conversion of XX to XXI and XXII is not certain. With a primary amine, either a second "urea dearrangement" may take place giving rise to the pyrazinamide XXI and an alkyl isocyanate, which then reacts with excess amine to give the N,N'-disubstituted urea XXII, or straightforward aminolysis of the amide grouping occurs to give the two products directly. With a secondary amine, a "urea dearrangement" cannot occur, since the only isocyanate which could be formed would recombine with the amine to regenerate XX. It thus seems more attractive to postulate that the cleavage of XX is a result of a direct aminolysis of an amide by an amine.[8]

Additional evidence for the correctness of the postulate that the attack of an amine on 6,7-diphenyllumazine (VI) occurs *via* course b was found in the reaction of VI with hydrazine. The main product of the reaction was 3-amino-5,6-diphenylpyrazinoic acid hydrazide (XXVI), but a small amount of 3-amino-6,7-diphenyl-2,4(1H,3H)-



pteridinedione (XXVII) was also formed. The formation of the latter compound is of particular significance, since it establishes the existence of the acyclic ureido intermediate XXVIII, corresponding in structure to XIX. An intermediate similar to XXVIII is probably formed in the analogous conversion of 2,4(1H,3H)-quinazolinedione (XXIX) to 3-amino-2,4(1H,3H)-quinazolinedione (XXXI) by the action of hydrazine.[9,10] The formation of such acyclic ureido intermediates (XIX, XXVIII, XXX) is consistent with the



(8) M. E. Smith and H. Adkins, THIS JOURNAL, **60**, 657 (1937).
(9) F. Kunckell, *Ber.*, **43**, 1234 (1910).
(10) A. Drapsky and B. Gaudian, *J. prakt. Chem.*, **147**, 43 (1936).

mechanism proposed by Leonard and Curtin[11] for the reaction between 4(3H)-quinazolone and alkylamines.

Thus the mechanism previously postulated for the reaction between a 4-amino- or 4-hydroxy-2-mercaptopteridine and alkylamines involving ring opening at C_3–C_4 to give a ureidopyrazine intermediate (II, III)[2a] has received support from the present work in which the actual isolation and characterization of several such intermediates in related reactions has been achieved.

Experimental[12]

N-Benzyl-3-(3-benzylureido)-5,6-diphenylpyrazinamide (XI).—A mixture of 3.0 g. of 6,7-diphenyllumazine (VI)[13] in 20 ml. of freshly distilled benzylamine was heated under reflux for 15 minutes. Addition of 50 ml. of absolute ethanol to the clear yellow solution and scratching caused the immediate separation of long, colorless needles; yield 2.18 g. (41.5%). The product was obtained as a complex containing one molecule of ethanol of crystallization after recrystallization from absolute ethanol; m.p. 88–93°.

Anal. Calcd. for $C_{32}H_{27}N_5O_2 \cdot C_2H_5OH$: C, 73.0; H, 5.9; N, 12.5. Found: C, 72.9; H, 5.7; N, 12.7.

Recrystallization from methylene chloride–petroleum ether gave colorless prisms free from solvent of crystallization; m.p. 150–151°.

Anal. Calcd. for $C_{32}H_{27}N_5O_2$: C, 74.8; H, 5.3; N, 13.6. Found: C, 74.9; H, 5.4; N, 13.8.

Attempted Reaction of XI with Acetic Anhydride.—A mixture of 0.60 g. of XI, 10 ml. of acetic anhydride and 3 g. of freshly fused sodium acetate was heated under reflux for two hours. The reaction mixture was then cooled, poured into ice and the resulting mixture allowed to stand overnight. The solidified oil was broken up, collected by filtration and recrystallized first from 50% aqueous ethanol and then from methylene chloride–petroleum ether. The product melts at 150–151°; a mixed melting point with a sample of XI showed no depression.

3-Amino-N-benzyl-5,6-diphenylpyrazinamide (VII) (Method A).—A solution of 0.50 g. of N-benzyl-3-(3-benzylureido)-5,6-diphenylpyrazinamide (XI) in 10 ml. of freshly distilled benzylamine was heated under reflux for eight hours. The cooled mixture was diluted with 20 ml. of ethanol, heated to boiling and sufficient hot water added to induce precipitation. On cooling, a heavy yellow crystalline mass separated; yield 0.348 g. (94%). The product was obtained in the form of long, yellow needles after recrystallization from absolute ethanol; m.p. 188.5–189°.

Anal. Calcd. for $C_{24}H_{20}N_4O$: C, 75.8; H, 5.3; N, 14.7. Found: C, 75.6; H, 5.5; N, 14.8.

N,N'-Dibenzylurea (VIII).—The ethanol filtrates from the recrystallizations of VII above were evaporated to 20 ml. and 20 ml. of hot water added. The solid which separated was recrystallized three times from ether; m.p. 168°. The reported melting point for N,N'-dibenzylurea is 167°.[14]

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 75.0; H, 6.7; N, 11.7. Found: C, 76.0; H, 6.8; N, 11.7.

The same products (VII and VIII) were obtained without isolation of the intermediate XI by heating 6,7-diphenyllumazine (VI) under reflux with benzylamine for eight hours and working up the reaction mixture as described above.

3-Amino-5,6-diphenylpyrazinoic Acid, Methyl Ester.—Two milliliters of concentrated sulfuric acid was added slowly with stirring to a solution of 1.0 g. of 3-amino-5,6-diphenylpyrazinoic acid[13] in 15 ml. of absolute methanol cooled to 10°. The resulting clear yellow solution was allowed to stand at room temperature for 24 hours and then poured into 75 ml. of water. The precipitated solid was collected by filtration, suspended in 100 ml. of 5% sodium bicarbonate solution, refiltered, washed with water and dried; yield 0.91 g. (86%). Recrystallization from aqueous methanol gave long yellow needles melting at 204–206°.

Anal. Calcd. for $C_{18}H_{15}N_3O_2$: C, 70.8; H, 5.0; N, 13.8. Found: C, 70.9; H, 5.1; N, 13.6.

3-Amino-N-benzyl-5,6-diphenylpyrazinamide (VII) (Method B).—A mixture of 165 mg. of the methyl ester of 3-amino-5,6-diphenylpyrazinoic acid and 2 ml. of benzylamine was heated under reflux for ten minutes. Addition of 15 ml. of 50% aqueous ethanol and cooling caused the separation of light yellow needles; yield 190 mg. (92.5%); m.p. 188.5–189°. A mixed melting point with a sample of VII prepared by the action of benzylamine on 6,7-diphenyllumazine showed no depression, and infrared spectra of the two samples were identical.

3-Benzyl-6,7-diphenyl-4(3H)-pteridinone (XII).—A solution of 1.0 g. of 3-amino-N-benzyl-5,6-diphenylpyrazinamide (VII) in 20 ml. of 85% formic acid and 20 ml. of acetic anhydride containing 1.0 g. of freshly fused sodium acetate was heated under reflux for five hours. The clear yellow reaction solution was evaporated to dryness under reduced pressure, and then evaporated repeatedly to dryness with 50-ml. portions of ethanol. Recrystallization of the residue from aqueous ethanol gave 0.42 g. (41%) of colorless plates; m.p. 248°.

Anal. Calcd. for $C_{25}H_{18}N_4O$: C, 76.9; H, 4.6; N, 14.4. Found: C, 77.1; H, 4.5; N, 14.6.

3-(Morpholinocarbonylamino)-5,6-diphenylpyrazinoic Acid Morpholide (XIII).—A solution of 0.50 g. of VI in 15 ml. of morpholine was heated under reflux for 14 hours. The excess morpholine was removed by distillation under reduced pressure and the residue triturated with hot water. On cooling, light yellow crystals separated which were collected by filtration, washed thoroughly with water and dried. Recrystallization from methylene chloride–petroleum ether gave 0.53 g. (71%) of colorless silky needles; m.p. 262–264°.

Anal. Calcd. for $C_{26}H_{27}N_5O_4$: C, 65.9; H, 5.8; N, 14.8. Found: C, 65.7; H, 5.8; N, 14.8.

3-Amino-5,6-diphenylpyrazinoic Acid Morpholide (XIV).—A solution of 1.0 g. of XIII in 20 ml. of morpholine was sealed in a glass bomb tube and heated at 140° for 12 hours and then at 190° for six hours. After removal of the excess morpholine under reduced pressure, the residue was recrystallized from absolute ethanol and the resulting yellow crystals washed thoroughly with absolute ethanol and dried. A further recrystallization from methylene chloride–petroleum ether gave 0.64 g. (84%) of yellow needles; m.p. 190.5–191°.

Anal. Calcd. for $C_{21}H_{20}N_4O_2$: C, 70.0; H, 5.6; N, 15.6. Found: C, 69.8; H, 5.6; N, 15.6.

XIV was formed in 91% yield from VI by heating with morpholine in a sealed tube at 190° for 12 hours and working up the reaction mixture as indicated above.

3-(Piperidinocarbonylamino)-5,6-diphenylpyrazinoic Acid Piperidide (XV).—A mixture of 3.0 g. of VI, 30 ml. of piperidine and 10 ml. of dimethylformamide was heated under reflux for 16 hours, filtered hot from unreacted VI (1.8 g.) and the hot filtrate treated with boiling water to incipient crystallization. Upon cooling, the solution deposited 1.76 g. (39.5%) of white platelets which were recrystallized from aqueous dimethylformamide; m.p. 215–217°.

Anal. Calcd. for $C_{25}H_{31}N_5O_2$: C, 71.6; H, 6.7; N, 14.9. Found: C, 71.9; H, 6.8; N, 14.9.

3-Amino-5,6-diphenylpyrazinoic Acid Piperidide (XVI).—A suspension of 5.0 g. of VI in 50 ml. of piperidine was sealed in a glass bomb tube and heated at 200° for 20 hours. The excess piperidine was removed by evaporation under reduced pressure, the residue triturated with water, filtered and washed thoroughly with water. Recrystallization from aqueous acetone gave 3.8 g. (67%) of the desired product in the form of long yellow needles; m.p. 156°.

Anal. Calcd. for $C_{22}H_{22}N_4O$: C, 73.7; H, 6.2; N, 15.6. Found: C, 73.6; H, 6.1; N, 15.7.

3-Amino-N-(β-hydroxyethyl)-5,6-diphenylpyrazinamide (XVII).—A solution of 0.50 g. of VI in 15 ml. of freshly distilled β hydroxyethylamine was heated under reflux for 12 hours, cooled and diluted with water. The solid which separated was collected by filtration and recrystallized from 50% aqueous ethanol to give 0.453 g. (84%) of feathery yellow needles; m.p. 186.5–187°.

(11) N. J. Leonard and D. Y. Curtin, *J. Org. Chem.*, **11**, 341 (1946).

(12) Microanalyses were made by Miss Emily Davis, Mrs. Jean Fortuey and Mrs. Katherine Pih. All melting points are corrected.

(13) J. Weijlard, M. Tishler and A. E. Erickson, THIS JOURNAL, **67**, 802 (1945).

(14) T. L. Davis and K. C. Blanchard, *ibid.*, **45**, 1816 (1923).

Anal. Calcd. for $C_{19}H_{18}N_4O_2$: C, 68.3; H, 5.4; N, 16.8. Found: C, 68.2; H, 5.2; N, 16.2.

3-Amino-5,6-diphenylpyrazinamide (XXIII).—A mixture of 2.0 g. of VI and 40 ml. of concentrated ammonium hydroxide was sealed in a glass bomb tube and heated at 185° for 16 hours. After cooling, the excess ammonium hydroxide was removed by evaporation under diminished pressure and the crystalline residue recrystallized from aqueous ethanol; yield 1.67 g. (94%). The product was obtained in the form of pale yellow needles after repeated recrystallizations from aqueous ethanol; m.p. 203.5–205°.

Anal. Calcd. for $C_{17}H_{14}N_4O$: C, 70.3; H, 4.9; N, 19.3. Found: C, 70.6; H, 4.9; N, 19.3.

Reaction of XXIII with Benzylamine.—A mixture of 0.3 g. of XXIII in 1 ml. of benzylamine was heated under reflux for 15 minutes, diluted with 10 ml. of ethanol and hot water added to incipient crystallization. Scratching caused the separation of 0.31 g. (76%) of light yellow needles which were recrystallized from absolute ethanol; m.p. 188.5–189°. A mixed melting point with an authentic sample of 3-amino-N-benzyl-5,6-diphenylpyrazinamide (VII) showed no depression.

Attempted Reaction of XXIII with Piperidine.—A mixture of 0.06 g. of XXIII, 5 ml. of piperidine and 2 ml. of dimethylformamide was heated under reflux for 16 hours. Removal of the piperidine and dimethylformamide under reduced pressure and crystallization of the residue from aqueous acetone gave 0.053 g. of yellow needles; m.p. 203.5–205°. A mixed melting point determination with a sample of XXIII showed no depression.

1-(*p*-Nitrophenyl)-3-(piperidino)-urea (XXV).—A mixture of 2.0 g. of *p*-nitrophenylurea[15] and 20 ml. of piperidine was heated under reflux for eight hours, the excess piperidine removed by evaporation under reduced pressure and the crystalline residue recrystallized from aqueous ethanol. The product was obtained as well-formed, light yellow needles, m.p. 165–166°, and showed no depression in melting point when mixed with an authentic sample of XXV prepared by the action of piperidine on *p*-nitrophenyl isocyanate; yield 2.43 g. (88%).

3-Amino-5,6-diphenylpyrazinoic Acid Hydrazide (XXVI).—A mixture of 1.0 g. of VI and 10 ml. of 85% hydrazine hydrate was heated under reflux for six hours. The reaction mixture was allowed to stand at 0° for three hours; the orange crystalline solid which had separated was filtered and washed thoroughly with ice-cold water. Recrystallization from absolute methanol gave 0.705 g. (73%) of long orange needles; m.p. 250–251°.

Anal. Calcd. for $C_{17}H_{15}N_5O$: C, 66.9; H, 4.9; N, 22.9. Found: C, 67.0; H, 4.8; N, 23.1.

The 3-Amino-6,7-diphenyl-2,4(1H,3H)-pteridinedione (XXVII).—The mother liquor from the reaction mixture above was evaporated to dryness, the residue washed well with water and dried. It was then extracted with 50 ml. of hot methylene chloride. Addition of 50 ml. of low-boiling petroleum ether caused the separation of a small amount of a colorless solid which was collected by filtration and recrystallized from methylene chloride–petroleum ether; m.p. (dec.) 259–260°.

Anal. Calcd. for $C_{18}H_{13}N_5O_2$: C, 65.2; H, 4.0; N, 21.1. Found: C, 65.0; H, 4.1; N, 21.1.

Evaporation of the methylene chloride–petroleum ether filtrates yielded an additional amount (*ca.* 0.015 g.) of 3-amino-5,6-diphenylpyrazinoic acid hydrazide (XXVI).

URBANA, ILLINOIS RECEIVED AUGUST 23, 1951

(15) J. F. L. Reudler, *Rec. trav. chim.*, **33**, 35 (1914).

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY,[1] PHILADELPHIA]

Chemistry of Epoxy Compounds. XIII.[2] Urea Complex Formation in Determining the Configurations of the 9,10-Dihydroxystearic Acids

BY DANIEL SWERN, LEE P. WITNAUER AND H. B. KNIGHT

In describing the stereochemical relationships in the conversion of oleic and elaidic acids to 9,10-dihydroxystearic acids by way of the intermediate oxirane and chlorohydroxy compounds, it has been necessary to make certain assumptions because at some of the reaction stages the configurations of the long-chain compounds are not known. Based upon the ability of low-melting 9,10-dihydroxystearic acid, m.p. 95° (prepared from elaidic acid by hydroxylation with potassium permanganate), to form a crystalline complex readily with urea in quantitative yield, and the reluctance of high-melting 9,10-dihydroxystearic acid, m.p. 131° (prepared from oleic acid by hydroxylation with potassium permanganate), to form a complex, it has been shown unambiguously that the hydroxyl groups in the high-melting isomer are on opposite sides of the chain whereas in the low-melting isomer they are substantially on the same side. Study of urea complexes prepared from the methyl esters of these hydroxy acids supports this conclusion. This information confirms the fact that hydroxylation with potassium permanganate proceeds by *cis* or normal addition, and that opening of the oxirane ring of the isomeric 9,10-epoxystearic acids involves an inversion.

Recently,[3] we described the stereochemical relationships in the conversion of oleic and elaidic acids to 9,10-dihydroxystearic acids by way of the intermediate oxirane and chlorohydroxy compounds. This scheme was self-consistent and in harmony with accepted theories of the Walden inversion and double bond addition reactions, but differed in some important respects from schemes proposed earlier by Atherton and Hilditch[4] and also by King.[5] Subsequently, King[6] modified his original scheme, and it is now fairly certain that our original formulation[3] is correct.

In devising reaction schemes for these higher molecular weight compounds, much of the reasoning is based upon similar reactions which have been carried out with simple related compounds of known configurations, because at some of the reaction stages the configurations of the long-chain compounds are not known. Of the various compounds investigated in the stereochemical studies just discussed, the configurations of oleic (*cis*-9-octadecenoic) and elaidic (*trans*-9-octadecenoic) acids,[7,8] and *cis*-9,10-epoxystearic acid, m.p. 59.5°, and *trans*-9,10-epoxystearic acid, m.p. 55.5°,[9] are known with certainty. It would be of great value for these

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) This paper was presented at the Spring Meeting of the American Chemical Society, Buffalo, N. Y., March, 1952. For paper XII, see THIS JOURNAL, **72**, 4315 (1950).

(3) Swern, *ibid.*, **70**, 1235 (1948).

(4) Atherton and Hilditch, *J. Chem. Soc.*, 204 (1943).

(5) King, *ibid.*, 387 (1942).

(6) King, *ibid.*, 1817 (1949).

(7) Rao and Daubert, THIS JOURNAL, **70**, 1102 (1948).

(8) Shreve, Heether, Knight and Swern, *Anal. Chem.*, **22**, 1261 (1950).

(9) Witnauer and Swern, THIS JOURNAL, **72**, 3364 (1950).