[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

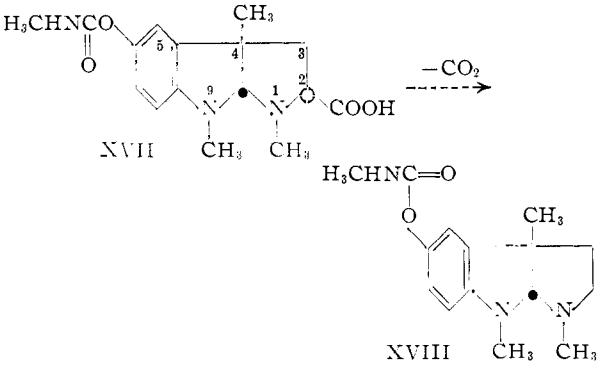
The Synthesis of 2-Carboxydeoxyeserolines *via* β-Methyl-ψ-tryptophan[1]

BY BERNHARD WITKOP WITH RICHARD K. HILL[2]

RECEIVED MAY 19, 1955

On refluxing in glacial acetic acid 4-acetamino-4,4-dicarbethoxy-2-methylbutyraldehyde phenylhydrazone (I) underwent both Fischer and internal cyclization to yield, *via* a derivative of β-methyl-ψ-tryptophan (II), a deoxyeseroline derivative III. 2-Carboxybisnordeoxyeseroline (IX) was obtained, *via* IV, V, VI, VII and VIII, by controlled saponification and decarboxylation reactions. The stereochemical and phylogenetic implications are discussed.

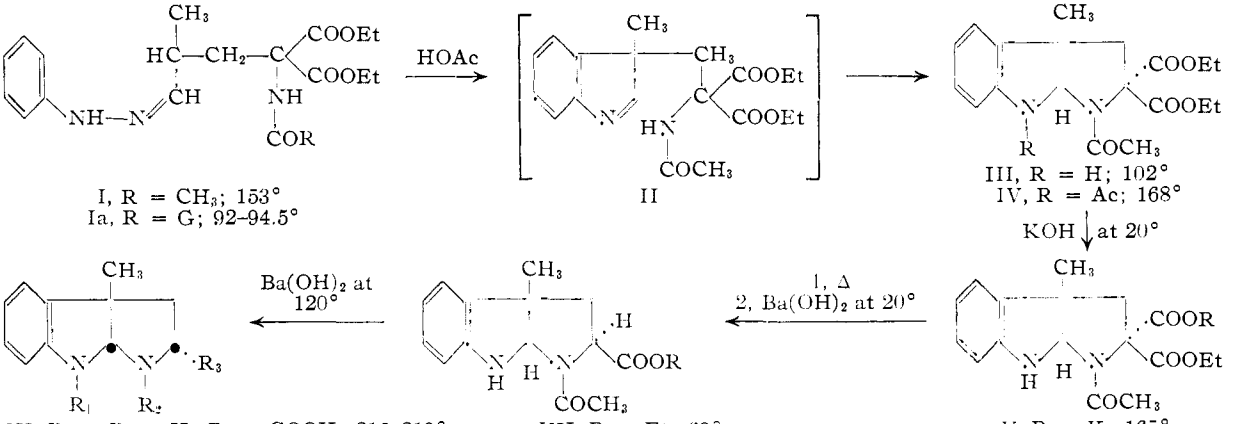
The fact that in animal metabolism[3] tryptophan is oxidized to 5-hydroxytryptophan[4,5] which then undergoes decarboxylation to 5-hydroxytryptamine (serotonin) raises the question whether a similar sequence of reactions may not be operative in the plant for the synthesis of 5-hydroxyindole alkaloids. The recent isolation of 5-hydroxytryptophan from the culture medium of *Chromobacterium violaceum*[6] points to the possibility of such a pathway in plants. To put this view to a test, *e.g.*, in the eserine series, it would be necessary to have at hand 2-carboxyeserine (XVII), formed *via* 5-hydroxytryptophan, as a substrate for a decarboxylase possibly occurring in plant tissue or extracts of *Physostigma venenosum* leading to eserine (XVIII). This paper describes an approach to 2-carboxydeoxyeserolines (Chart I).



4-Acetamino-4,4-dicarbethoxy-2-methylbutyraldehyde phenylhydrazone (I)[7] on refluxing with glacial acetic acid would be expected to give the indolenine II, *i.e.*, a derivative of an acetylated β-methyl-ψ-tryptophan. The acetyl group at N^b was expected to prevent internal addition of $-HN^b-$ to the reactive indolenine double bond.[8] The reaction product, however, had a dihydroindole spectrum (λ_{max} (log ϵ): 300 (3.42), 244 (3.85)) and was the cyclized deoxyeseroline III, which could be acetylated further to IV.

In order to simplify the subsequent hydrolysis and removal of carbethoxy and acetyl groups Kissman explored the addition of dibenzyl carbobenzyloxyaminomalonate and formaminomalonate[9] to α-methylacrolein. Compared with the facile addition of the anion of diethyl acetaminomalonate to α-methylacrolein the reactions with the less reactive or sterically more hindered benzyl esters were difficult and either led to self-condensation of the aldehyde or to low yields. The formyl analog of I, *i.e.*, Ia, was prepared.

The action of hot alcoholic or aqueous acid or base on the diester III led to darkening and decomposition. After storage in the cold with 20% ethanolic aqueous alkali the potassium salt of the acid ester V was obtained,[10] which could be converted di-



(1) Presented in part at the Fourth National Medicinal Chemistry Symposium of the American Chemical Society at Syracuse, N. Y., June 17–19, 1954; *cf.* Abstracts, p. 77.

(2) Department of Chemistry, Princeton University.

(3) *Cf.* V. Erspamer, *Rend. sci. farmitalia*, **1**, 5 (1954).

(4) A. Ek and B. Witkop, THIS JOURNAL, **76**, 5579 (1954).

(5) S. Udenfriend, C. T. Clark and E. Titus, *ibid.*, **75**, 501 (1953).

(6) C. Mitoma, H. Weissbach and S. Udenfriend, *Nature*, **175**, 994 (1955).

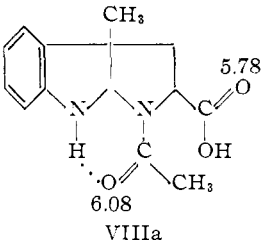
(7) D. T. Warner and O. A. Moe, THIS JOURNAL, **71**, 2587 (1949).

(8) *Cf.* A. Ek, H. M. Kissman, J. B. Patrick and B. Witkop, *Experientia*, **8**, 36 (1952).

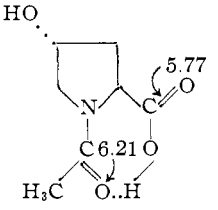
(9) H. Kissman and B. Witkop, THIS JOURNAL, **76**, 5379 (1954).

(10) A similar stepwise hydrolysis has been described in the meantime by L. Berlinguet, *Can. J. Chem.*, **32**, 31 (1954).

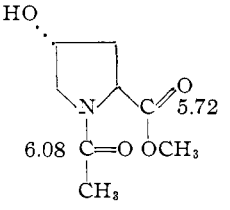
rectly to the ester VII by dry distillation or *via* the free ester acid VI by heating with soda lime. Methanolic barium hydroxide in the cold saponified the ester VII to the acetamino acid VIII, in which hydrogen bonding of the amide carbonyl with NH (VIIIa) appears not to be possible from a study of Briegleb models. A nearly planar 7-membered hydrogen-bonded ring resulting from the same type of interaction of the carboxyl group with the N-acetyl as in N-acetylhydroxyproline (XII, *cf.* ester XIII),[11] can be constructed conveniently only if the carboxyl were *trans* to the quaternary C-methyl group. The fact that the infrared spectrum of VIII gives no indication of internal hydrogen bonding lends support to the assumption that the carboxyl



VIIIa



XII



XIII

group is *cis* to the quaternary methyl. Much stronger alkaline hydrolysis, namely, refluxing in saturated aqueous barium hydroxide for 17 hours, was required to deacetylate VIII to the amino acid IX.

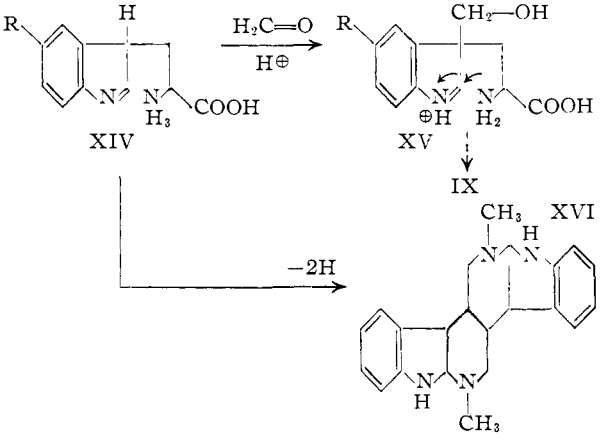
The thermal decarboxylation of IX, to the known X → XI,[12] though of no preparative value, met with the same difficulties as the decarboxylation of the homologous tetrahydroharmane-3-carboxylic acid.[13]

The stereochemistry of the amino acid as tentatively represented in IX is based on three assumptions: (i) the smooth internal cyclization of II should lead to the more stable *cis* arrangement of the two five-membered rings; (ii) the partial hydrolysis of the diester III is probably selective involving saponification of the less hindered carbethoxy group; (iii) regardless of the position of the carboxy function in VII or VIII the action of strong base in the final deacetylation will lead to epimerization at C(2) to give the most stable arrangement, presumably COOH *trans* to the quaternary C-methyl.

One of the many precedents for this epimerization is the conversion of hydroxy-L-proline to allohydroxy-D-proline by the action of hot concentrated baryta.[14]

In the hope to obtain the acetamino acid isomeric with VIII, the amino acid IX was treated with (excess) acetic anhydride in pyridine. The crystalline compound, m.p. 255–256°, obtained by this procedure was the product of a more complicated reaction than mere acetylation (*cf.* Experimental).

The introduction of a quaternary C-methyl group into (5-hydroxy)-tryptophan has its analogies, *e.g.*, in the C-methylation of (dihydro)-berberine which



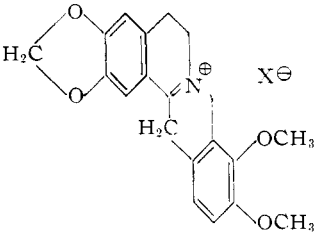
occurs readily with formaldehyde.[15] The reaction corresponds to the well-known C-methylation of an enamine[16] (indole) giving rise to the labile β-hydroxymethylindolenine (XV), which undergoes reduction and internal cyclization to an eserine. Related examples of the β-reactivity of β-substituted indoles are the postulated oxidative dimerization of N-methyltryptamine leading to calycanthine (XVI),[17] and the closure of the spiropyrrolidine ring in the synthesis of strychnine.[18]

Experimental[19]

4-Acetamino-4,4-dicarbethoxy-2-methylbutyraldehyde

(14) H. Leuchs and K. Bormann, *Ber.*, **52**, 2086 (1919); D. S. Robinson and J. P. Greenstein, *J. Biol. Chem.*, **195**, 383 (1952). The equilibration in this instance leads to the *cis*-arrangement of hydroxyl and carboxyl on the same side of the five-membered ring, an indication that polar rather than steric effects control the course of epimerization.

(15) H. W. Bersch, *Arch. Pharm.*, **283**, 192 (1950). The structure of the dihydroberberine cation which combines with formaldehyde in acidic solution has in the meantime been proven to have the immonium structure [B. Witkop, THIS JOURNAL, in preparation].



(16) Again one of the oldest and best known examples is the reaction of methyl iodide with dihydroberberine which leads to C-methyl derivatives. See also R. Robinson, *J. Chem. Soc.*, **109**, 1038, 1029 (1916); G. Stork, R. Terrell and J. Szmuszkovicz, THIS JOURNAL, **76**, 2029 (1954).

(17) After the completion of his ingenious synthesis of calycanine from isoindigo in 1950 (R. B. Woodward and V. M. Clark, 1950, unpublished), Dr. Woodward favored XVI as a possible expression for calycanthine [personal communication and various seminars at Harvard University in 1950; *cf.* R. Robinson and H. J. Teuber, *Chemistry and Industry*, 783 (1954)].

(18) R. B. Woodward, *et al.*, THIS JOURNAL, **76**, 4749 (1954).

(19) All melting points are corrected, all boiling points uncorrected. The analyses were performed by Dr. W. C. Alford and associates of the Institutes' Analytical Service Laboratory.

(11) *Cf.* S. Mizushima, *Adv. Protein Chem.*, **9**, 308 (1954).

(12) T. Hoshino and K. Tamura, *Ann.*, **400**, 42 (1933).

(13) *Cf.* D. G. Harvey and W. Robson, *J. Chem. Soc.*, 97 (1938). The peroxide-catalyzed decarboxylation in boiling tetralin, *J. Pharm. Soc. Jap.*, **67**, 218, 243 (1947); *C. A.*, **45**, 9508 (1951), has not been tried yet in these cases and might be superior to the purely thermal one.

Phenylhydrazone (I).—The sodium ethoxide-catalyzed addition of diethyl acetaminomalonate to α-methylacrolein in benzene solution following the directions of Warner and Moe[20] gave, after addition of phenylhydrazine and recrystallization from methanol, the colorless crystalline phenylhydrazone of the addition compound, m.p. 152.5–153.5° (reported 147°[7]) in 72% yield.

Anal. Calcd. for $C_{19}H_{27}N_3O_5$: C, 60.46; H, 7.21; N, 11.14. Found: C, 60.39; H, 7.33; N, 11.33.

Infrared spectrum (chloroform): 2.93 (NH), 5.75vs (ester CO), 5.96s (amide CO), 6.23s (phenyl), 6.68s, 7.31s.

4-Formamino-4,4-dicarbethoxy-2-methylbutyraldehyde Phenylhydrazone (Ia).—To a solution of 1.1 g. of diethyl formaminomalonate in 35 ml. of absolute ethanol was added a solution of 0.01 g. of sodium in 15 ml. of ethanol. The stirred mixture was then placed in an ice-bath and a solution of 0.35 g. of freshly distilled methylacrolein in 7 ml. of ethanol was added dropwise over a period of 75 minutes. Stirring was continued for an additional hour at room temperature. The solution was acidified with 0.5 ml. of glacial acetic acid and to this mixture was added 0.5 ml. of phenylhydrazine. After refluxing for 4 hours, the solution was freed from solvent *in vacuo* and the reddish residue was dissolved in 50 ml. of ether. The solution was extracted first with 5 ml. of 1 *N* hydrochloric acid and then with an equal volume of water. Drying over magnesium sulfate and evaporation of the solvent left an orange oil which was redissolved in benzene–cyclohexane and chromatographed on alumina. Elution with benzene yielded a reddish oil which could not be made to solidify. A second fraction on elution with chloroform–benzene (1:4) solidified on treatment with hexane. The substance was recrystallized several times from hexane. There was obtained a colorless compound, m.p. 92–94.5° (174 mg.), which turned somewhat yellow on standing in the light.

Anal. Calcd. for $C_{18}H_{25}N_3O_5$: C, 59.48; H, 6.94; N, 11.56. Found: C, 59.40; H, 6.82; N, 11.10.

Elution with pure chloroform and finally with methanol yielded other oily fractions which could not be crystallized.

1-Acetyl-2,2-dicarbethoxybisnordeoxyeseroline (III).—The cyclization of the phenylhydrazone was effected by refluxing in ten times its weight of glacial acetic acid for three hours. The reaction mixture was diluted with water and made alkaline. The resinous precipitate was extracted with ether. The basic material was extracted from the ether solution by 2 *N* hydrochloric acid. Basification and renewed extraction with ether gave, after recrystallization from methanol–water, colorless prisms, m.p. 102°, in yields up to 40%.

Anal. Calcd. for $C_{19}H_{24}N_2O_5$: C, 63.32; H, 6.71; N, 7.94. Found: C, 63.07; H, 6.82; N, 7.81.

The ultraviolet spectrum in ethanol showed $\lambda_{max.}$ (log ε): 300 (3.42), 244 (3.85). The infrared spectrum in chloroform showed the following major bands: 2.93 (NH), 5.75 vs. (ester CO), 6.10s (amide CO), 6.74m, 6.81m, 6.90m.

1,9-Diacetyl-2,2-dicarbethoxybisnorseroline (IV).—The monoacetyl compound (III, 50 mg.) was refluxed with acetic anhydride for 30 minutes. Water was added and the solution warmed until all the acetic anhydride was hydrolyzed. The neutral product was extracted with ether and the ether extract washed with dilute base. After drying (sodium sulfate) and evaporation of the ether extract the diacetyl compound, after recrystallization from methanol, was obtained as colorless prisms (35 mg.), m.p. 150–168° (yield 60%).

Anal. Calcd. for $C_{21}H_{26}N_2O_6$: C, 62.67; H, 6.51; N, 6.96. Found: C, 62.72; H, 6.39; N, 7.09.

The infrared spectrum (chloroform) shows no bands in the OH or NH region, CO of ester at 5.69 and one very strong amide CO at 5.95 μ.

1-Acetyl-2-carboxy-2-carbethoxybisnordeoxyseroline (VI).—Since treatment of the diester III with dilute aqueous acid or base at elevated temperature led to colored non-crystalline products, the following procedure was adopted: The acetyl diester (III, 5 g.) was dissolved in 15 ml. of warm ethyl alcohol (95%) and to this solution was added 50 ml. of 20% aqueous potassium hydroxide. The mixture was shaken and left at room temperature for 18 hours. After cooling in ice for one hour the crystalline precipitate (4.2 g.) was collected, washed with a little ice-water and dried, m.p. 161–165°. The potassium salt is easily soluble in water. The analysis of this crude, very hygroscopic potassium salt (C, 50.40; H, 5.83; N, 7.47; values corrected for residue of potassium carbonate) would indicate a dihydrate of the potassium salt of the half-ester V; however, combustion using vanadium pentoxide would be needed to confirm this assumption (residue in this case potassium vanadate). When 3.9 g. of this salt was dissolved in 20 ml. of warm water and brought to *p*H 4 by the addition of 2 N sulfuric acid, some effervescence was observed. The colorless solid was filtered, washed with water and dried. On recrystallization from ethanol–ether colorless plates (2.6 g.) were obtained, m.p. 110–111°.

Anal. Calcd. for $C_{17}H_{20}N_2O_5 \cdot H_2O$: C, 58.29; H, 6.35; N, 8.00. Found: C, 58.21; H, 6.34; N, 8.04.

Infrared spectrum (Nujol): 2.92, 3.02, 3.08, 3.17, 5.83vs, 6.08sh, 6.15s, 6.24m, 6.84s, 6.90s, 7.11s, 7.42m.

A solution of the acid ester in methanol on addition of a methanolic solution of copper acetate deposited on standing at room temperature light-green needles of a copper salt, m.p. < 360°.

1-Acetyl-2-carbethoxy-bisnordeoxyeseroline (VII). A. By Decarboxylation with Soda Lime.—When an intimate mixture of finely powdered acid ester VI with one-fourth of its weight of soda lime was heated in an oil-bath to 100–110° smooth decarboxylation was observed close to or slightly below the melting point. After the end of effervescence the residue distilled *in vacuo* as a colorless viscous oil at 140° (bath) at 0.1 mm. By slow evaporation of a solution of the oil in carbon tetrachloride crystals were obtained which were used to seed solutions of the ester base in pentane. By this procedure glistening colorless scales were obtained from pentane, m.p. 67–69°.

Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; N, 9.72. Found: C, 66.32; H, 6.75; N, 9.94.

Infrared spectrum (chloroform): 2.95 (strong and sharp HN), 5.74s (ester carbonyl), 6.08vs (amide carbonyl).

The picrate crystallized from ether, recrystallizable from methanol, m.p. 130–132°.

Anal. Calcd. for $C_{16}H_{20}N_2O_3 \cdot C_6H_3N_3O_7$: C, 51.06; H, 4.48; N, 13.53. Found: C, 50.79; H, 4.64; N, 13.5.

B. By Dry Distillation of Potassium Salt V.—When the dry potassium salt (V, m.p. 165°) was heated in an oil-bath foaming started at 140°. When foaming stopped vacuum was applied and the product distilled at 140–170° (0.1 mm.). The residue was potassium carbonate (soluble in water with basic reaction, yielding CO_2 on acidification). The distillate, a viscous glass, easily soluble in hot pentane, ether and benzene, gave a picrate with ethereal picric acid, appearing first oily, crystallizing on scratching. On slow and careful crystallization from equal parts of methanol–ether yellow thin rectangular prisms were obtained, m.p. 144–146°. By mixed melting point and infrared comparison this picrate was identical with, but somewhat purer than, the picrate, m.p. 130–132°, obtained by procedure A.

Anal. Calcd. for $C_{16}H_{20}N_2O_3 \cdot C_6H_3N_3O_7$: C, 51.06; H, 4.48; N, 13.54. Found: C, 50.96; H, 4.65; N, 13.41.

1-Acetyl-2-carboxy-bisnordeoxyeseroline (VIII).—Preliminary experiments showed that the ester base VII could be saponified by the action of 2 *N* methanolic alkali in the cold. In order not to have alkali ions present with the expected amino acid the following procedure was chosen: about 2 mmoles (560 mg.) of glassy VII, as directly obtained from thermal decarboxylation of 700 mg. of potassium salt, V, was dissolved in the minimum amount of methanol and 320 mg. of barium hydroxide octahydrate (~2 mmoles) added in methanol. The reaction mixture was allowed to evaporate slowly at room temperature. After 30 hours the crystalline residue was washed with ether to remove some sticky unhydrolyzed or contaminating material (~65 mg.). The remaining crystalline solid was easily soluble in methanol and cold aqueous acid or base. The picrate was water-soluble and remained as a lacquer on evaporation. The free acetamino acid appeared from hot water on slow cooling in tufts of shiny colorless flakes (first crop 195 mg., second crop 170 mg.), m.p. 106–108° (bubbly colorless melt, distinct evolution of gas does not start until 260°).

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.28; H, 6.29; N, 10.66.

(20) D. T. Warner and O. A. Moe, THIS JOURNAL, **70**, 2763 (1948).

Infrared spectrum (chloroform): 2.95, 5.78m, 6.08vs, 6.20m.

2-Carboxybisnordeoxyseroline (IX).—Preliminary experiments showed that the prolonged action of hot 2 *N* hydrochloric acid on the acetamino acid VIII led to dark red solutions. Deacetylation was, therefore, effected by the action of base. To a solution of 170 mg. of VIII in 3 ml. of hot water was added a large excess (950 mg.) of barium hydroxide octahydrate. The mixture was kept refluxing for 17 hours using an oil-bath (temperature 140°). (It had been noticed before that three hours on the steam-bath failed to effect deacetylation.) After this time the barium ions were removed with about 6 ml. of 1 *N* sulfuric acid. The filtrate of the barium sulfate on slow evaporation left 115 mg. of slightly yellow crystals. Recrystallized from 5 ml. of hot water the amino acid appeared as fans of flat needles which were still slightly yellow and became colorless on crushing, m.p. 206–209°. On recrystallization from methanol there was obtained colorless glistening needles, m.p. 216–219° (yellow melt, vigorous bubbling). The amino acid is hardly soluble in chloroform. The ninhydrin reaction is yellow (*cf.* hydroxyproline) producing a precipitate.

Anal. Calcd. for $C_{12}H_{14}N_2O_2 \cdot {}^3/_4H_2O$: C, 62.06; H, 6.74; N, 11.72. Found: C, 62.48; H, 6.53; N, 11.74.

The sample, m.p. 206–209°, recrystallized from water gave an analysis (C, 61.53; H, 6.47) in fair agreement with the monohydrate. Drying for 5 hours at 60° led to a weight loss of only 1.69%.

Infrared spectrum (Nujol): 2.87, 2.99 (both sharp distinct bands), 3.90 (fairly broad ammonium band), 6.08s (carboxylate ion), 6.24s (phenyl), 6.73s, 6.85s, 7.25s. By comparison proline shows a weak band at 3.0 (fairly broad), ammonium at 4.20, carboxyl at 6.15 (Nujol). Allohydroxyproline shows carboxyl at 6.11 (Nujol).

ULTRAVIOLET SPECTRUM

In methanol	λmax I	log ε	λmax II	log ε
*p*H 7	292	3.40	238	3.88
*p*H 1	292	3.30	238	3.87
*p*H 11	297	3.44	245	3.88

Attempted Decarboxylation.—After heating 20 mg. of the amino acid IX to 210° until there was no more bubbling, the residue proved to be insoluble in ether as well as in 0.1 *N* hydrochloric acid.

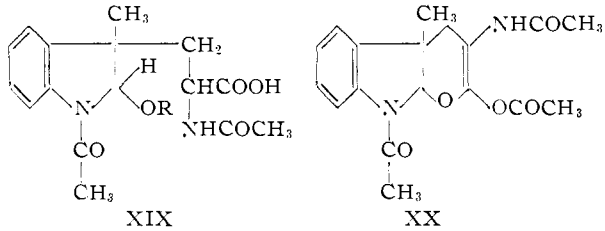
Reaction with Acetic Anhydride.—The amino acid IX (50 mg.) in 1 ml. of pyridine was treated with four drops of acetic anhydride. After standing for one day at room temperature the solution was evaporated to dryness in the desiccator. The residue was washed with ether and taken up in chloroform. On slow evaporation fine needles appeared which became colorless on washing with chloroform, m.p. 256–257° (dec., sublimation proceeds). The crystalline compound was almost insoluble in cold chloroform.

Anal. Calcd. for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.15; OAc, 12.5; OAc + 2NAc, 37.5. Found: C, 62.46; H, 5.81; N, 7.66; OAc, 13.6; OAc + 2NAc, 39.8.

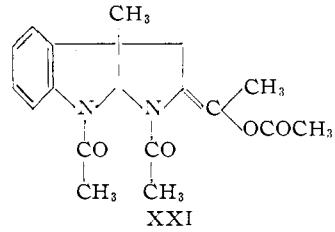
The "neutralization equivalent" determination which would not differentiate between a free carboxyl and a suitable enol acetate was 316; calcd. for $C_{18}H_{20}N_2O_5$, 344.

Infrared spectrum (Nujol): no bands in the NH, OH region 5.82m (CO of carboxyl); 6.00vs (CO of amide); 6.18s (phenyl?); 6.30s; 6.93s.

The absence of a secondary amide band in the infrared as well as the ultraviolet spectrum [λ_{max} (log ϵ): 286 (3.24), 275 (3.31), 245 (4.10) (taken in ethanol, essentially unchanged on addition of ethanolic HCl or KOH)] are difficult to reconcile with Bamberger cleavage of the eserine system, yielding a compound XIX (H = Ac or H) which could be visualized to lose water giving XX. Structure XXI is also a possibility although incorporation of one mole of water would be required to approximate the analytical figures.



XIX XX



XXI

BETHESDA 14, MD.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

Transannular Reactions of Peptides. The Peptide Nitrogen in a 10-Membered Ring[1,2]

BY LOUIS A. COHEN AND BERNHARD WITKOP

RECEIVED JULY 18, 1955

In the ten-membered lactam VIII prepared by spontaneous rearrangement of the hydroperoxide VII of $\Delta^{1(9)}$-octahydroquinoline (IV) the nitrogen atom is sufficiently close to the ketone carbonyl to permit formation of a carbinolamine IX as the only stable modification. The structure of IX has been proved by exhaustive reduction with lithium aluminum hydride to the known base 1-azabicyclo[5.3.0]decane (XIII). Upon catalytic reduction, IX loses its carbinol function to yield the bicyclic amide XIV. Both IX and XIV form stable hydrochlorides. Thus, two reductive methods have been found capable of demonstrating the existence of transannular adducts of the peptide nitrogen.

The properties of amide bonds are of particular relevance in elucidating the structure of natural polypeptides and proteins. Recent investigations[3] have suggested that, given the proper steric conditions, amide bonds can exhibit a chemical reactivity greater than is usually attributed to them. The present study describes the interaction of an amide nitrogen with a ketone across a ten-membered ring.[4]

The cyclic keto-amide VIII was prepared from $\Delta^{1(9)}$-octahydroquinoline (IV) as outlined in Chart I. The well-known β-carbon alkylation of an enamine[5] recently applied to the preparative

(1) Presented in part at the XIVth International Congress of Pure and Applied Chemistry, Zurich, July 21–27, 1955, Abstracts p. 206.

(2) Oxidation Mechanisms XVI; previous paper, *J. Org. Chem.*, **19**, 1824 (1954).

(3) (a) A. Stoll, A. Huffmann and Th. Petrzilka, *Helv. Chim. Acta*, **34**, 1544 (1951); (b) W. Hausmann, J. R. Weisiger and L. C. Craig, THIS JOURNAL, **77**, 731 (1955); (c) A. T. James and R. L. M. Synge, *Biochem. J.*, **50**, 109 (1951).

(4) K. Wiesner, *et al.*, THIS JOURNAL, **77**, 679 (1955), have suggested similar transannular adducts as intermediates in the oxidation of dimethylapoerysopine derivatives.

(5) R. Robinson, *et al.*, *J. Chem. Soc.*, **109**, 1029, 1038 (1916); 976 (1952).