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.

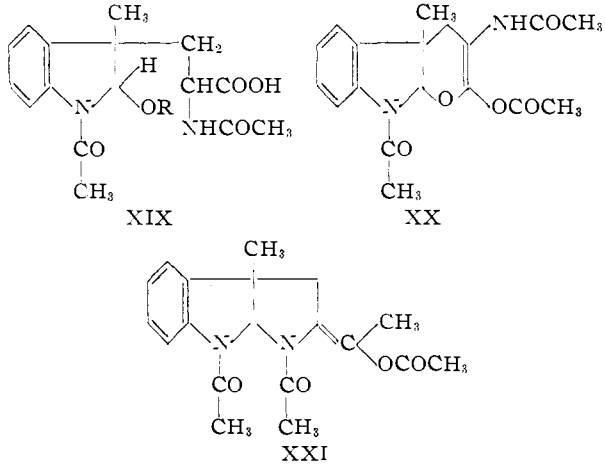
Reaction with Acetic Anhydride.—The amino acid IX (50 mg.) in 1 ml. of pyridine was treated with four drops of acetic anhydride. After standing for one day at room temperature the solution was evaporated to dryness in the desiccator. The residue was washed with ether and taken up in chloroform. On slow 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.

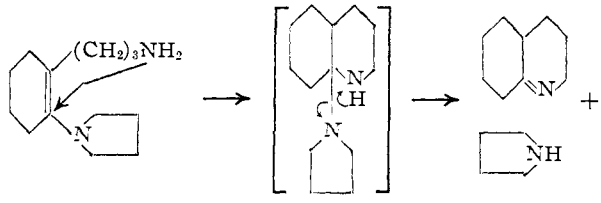
(2) Oxidation Mechanisms XVI; previous paper, *J. Org. Chem.*, **19**, 1824 (1954).

(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).

alkylation of ketones *via* the enamines[6] was utilized to prepare 2-(2-cyanoethyl)-cyclohexanone (V). In initial preparations, the ethylene ketal blocking group VI was used to protect the ketone from lithium aluminum hydride reduction. However, direct reduction of the enamine II was found superior with respect to both time and yield. The displacement of the pyrrolidine enamine by the internal base was readily effected by a catalytic



amount of water or by pyrolysis. However, the use of a large amount of water shortened the hydrolysis time considerably.

The unsaturated base, $\Delta^{1(9)}$-octahydroquinoline (IV), as expected,[7] was very sensitive to oxidation. A molar equivalent of oxygen was absorbed in several hours without the aid of a catalyst. When oxygenation was conducted in ethyl acetate, the hydroperoxide VII crystallized out of solution during the course of the reaction. In the solid state it had retained its peroxidic nature even after several months; in solution the hydroperoxide underwent rapidly the type of rearrangement previously observed with hydroperoxides of Schiff bases,[8] enamines[9] and comparable unsaturated nitrogen compounds.[10] Figure 1 shows the course of the rearrangement with time. As VII rearranges, the ketone band at 5.85 μ and the amide band at 6.12 μ appear. However, the ketonic absorption soon begins to disappear and, after 18 hours, has only slight intensity. Figure 2 shows the influence of acid upon the rate of formation of the ketolactam as measured by infrared absorption at 5.85 μ. The increase in rate of disappearance of the ketone with stronger acid suggests that the second reaction, *i.e.*, the transannular addition of –NH to the ketone, is also acid-catalyzed. The transannular addition in VIII of the amide nitrogen to the ketone to yield IX is a spontaneous process. Purified IX shows only amide absorption; the residual bands at 5.85 and 5.99 μ in the 18-hour spectrum are due to side reactions. In solvents such as chloroform and methylene chloride the hydroperoxide reacts with the solvent to form 10-hydroxy-$\Delta^{1(9)}$-octahydroquinoline (X), which has been isolated as a significant by-product of the rearrangement in these solvents. The residual absorption at 5.85 μ is apparently due to a volatile oxidation product of the solvent since it disappears when the dried residue of the solution of the rearrangement product is again examined in the infrared. It was subsequently found that rearrangement of the hydroperoxide in water or water–dioxane mixtures at 25° led to the formation of VIII → IX exclusively. The transannular adduct is devoid of activity toward ketone reagents and appears to react exclusively as a carbinolamine.

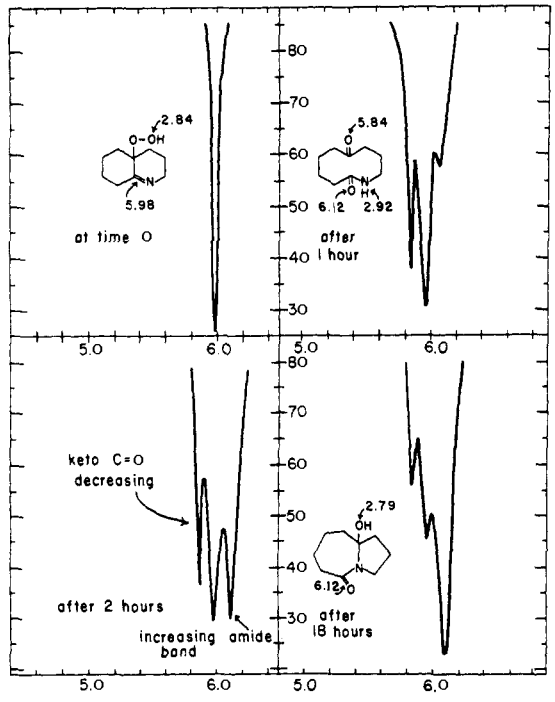


Fig. 1.—Rearrangement of hydroperoxide in CH_2Cl_2.

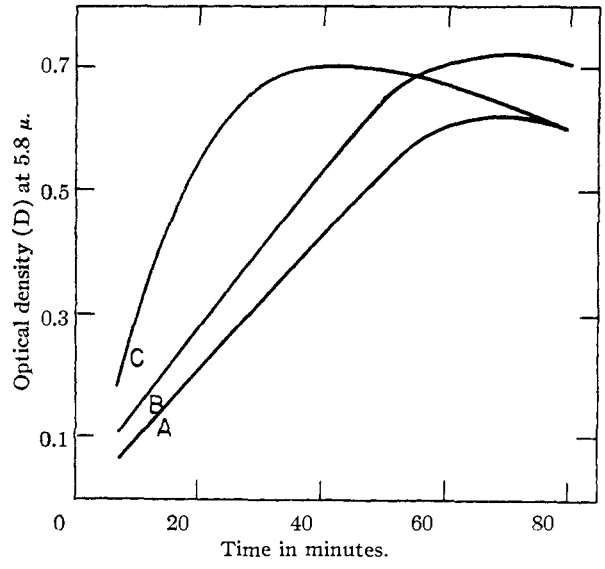


Fig. 2.—The influence of acid upon the rate of ketone formation in the rearrangement of hydroperoxide VII in chloroform: A, neutral: *B*, 0.001 *N* *p*-TsOH; C, 0.01 *N* *p*-TsOH.

Two chemical methods demonstrated the stability of the adduct. Upon hydrogenation with platinum and mineral acid, IX lost its hydroxylic

(6) G. Stork, R. Terrell and J. Szmuszkovicz, THIS JOURNAL, **76**, 2029 (1954). We are greatly indebted to Prof. Stork for details on the addition of cyclohexenylpyrrolidine to acrylonitrile prior to complete publication.

(7) *Cf.* B. Witkop, J. B. Patrick and M. Rosenblum, *ibid.*, **73**, 2641 (1951).

(8) B. Witkop and J. B. Patrick, *ibid.*, **73**, 2196 (1951).

(9) B. Witkop, *Bull. soc. chim.*, 423 (1954).

(10) B. Witkop and H. M. Kissman, THIS JOURNAL, **75**, 1975 (1953).

function, forming XIV. Additional proof that a C–N bond has been formed was provided by the reduction of XIV with lithium aluminum hydride to 1-azabicyclo[5.3.0]decane (XIII).[11] The oxygen-free base XIII was also formed when IX was reduced directly with lithium aluminum hydride. In neither case was there obtained any reduction product of the open ketolactam. The removal of the hydroxyl function by both acidic and basic reducing agents is consistent with formulating IX as a true carbinolamine.[12]

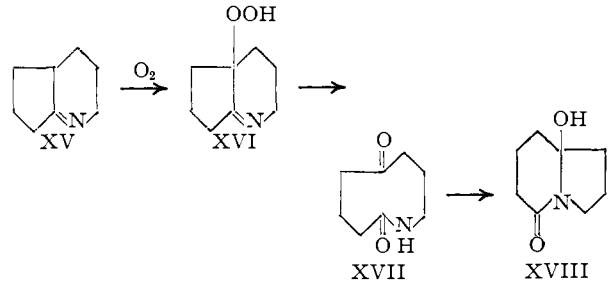
Reaction of IX with methoxide ion in dioxane led to the formation of two new products, m.p. 180 and 149°, presumed to result from reopening of IX to VIII and a consequent aldol-type condensation.[13]

The higher-melting material is isomeric with IX, shows no ultraviolet absorption and an infrared band at 6.02 μ, probably due to the amide. The analysis of the lower-melting material suggests the loss of one molecule of water. The ultraviolet spectrum exhibits a peak at 225 mμ (log ϵ 4.0) which is unaffected by acid but shifted by base to the region below 220 mμ. The infrared spectrum contains bands of equal intensity at 6.05 and at 6.18 μ. A possible course of the reaction is outlined in formulas XXI and XXII (Chart I). The tentative nature of these assignments must be emphasized since conclusive chemical evidence has not yet been obtained.

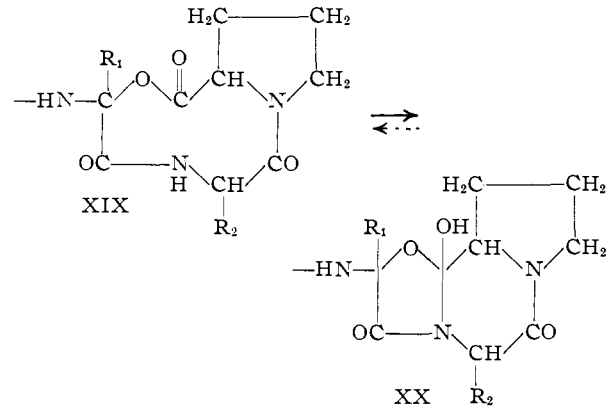
Comparison of the infrared spectra of the unpurified products formed in the rearrangement of the hydroperoxide VII in chloroform with the two neutral fractions obtained in the treatment of *trans*-decahydroquinoline with molecular oxygen at 80–100°[14] showed close similarity, suggesting that the course of oxidation of decahydroquinoline is at least a twofold one: (i) initial abstraction of 2 hydrogen atoms from nitrogen and C(9) leading to the hydroperoxide VII and from there to the lactam (VIII → IX) or (ii) further or independent dehydrogenation of the heterocyclic ring[15] with the formation of a 3-hydroxyl group prior or subsequent to the abstraction of hydrogen.

Catalytic reduction of the hydroperoxide VII led first to the formation of 10-hydroxy-$\Delta^{1(9)}$-octahydroquinoline (X) and, after uptake of a further mole of hydrogen, to 10-hydroxydecahydroquinoline (XI). The rate of the two reduction steps is sufficiently different to permit the isolation of X. Reduction of X to XI also occurred with lithium aluminum hydride. The rings of XI are presumed to have a *trans* fusion.

An analogous series of reactions, XVI – XVIII, was realized with the lower homolog $\Delta^{1(8)}$-hexahydro-1-pyrindene (XV) and will be the subject of a subsequent report. The transannular interaction across a 9-membered ring calls to mind the



amide–lactone interaction observed in the peptide portion of the ergot alkaloids[16] where subdivision of a nine-membered ring into five- and six-membered rings is effected by addition of the amide –NH to a lactone carbonyl (XIX → XX). The



study of transannular phenomena is being extended to model systems containing lactone–amide and amide–amide functions.

Experimental[17]

1-(1-Cyclohexenyl)-pyrrolidine (I).[6]—A solution of 294 g. (3 moles) of cyclohexanone and 284 g. (4 moles) of pyrrolidine in 150 ml. of benzene was refluxed using a water separator. Removal of water was complete after 4.5 hours. Excess pyrrolidine and benzene were removed *in vacuo* and the product was used without further purification.

1-[2-(2-Cyanoethyl)-1-cyclohexenyl]-pyrrolidine (II).—To the crude cyclohexenylpyrrolidine in 200 ml. of dioxane was added 175 g. (3.3 moles) of freshly distilled acrylonitrile. The mixture was refluxed for 1.5 hours and the solvent removed *in vacuo*, leaving a dark red oil. The material was distilled at 10 mm. and the fraction boiling at 150–172° was collected as a crude product, 530 g. (87% yield). Since the compound darkens on storage, it was distilled just before use, collecting the fraction boiling at 170–172° (10 mm.). The compound should be stored at 0° to prevent extensive decomposition.

1-(2-[3-Aminopropyl]-1-cyclohexenyl)-pyrrolidine (III).—To 500 ml. of absolute ether was added 7.6 g. (0.2 mole) of powdered lithium aluminum hydride. A solution of 40.8 g. (0.2 mole) of II in 100 ml. of ether was added over 1 hour with mechanical stirring. After an additional 30 minutes of stirring, the flask was chilled in ice while the excess was decomposed with ethyl acetate and water. The ether solution was decanted, the residue was extracted with 2 × 200 ml. of ether and the combined extracts (without drying) were concentrated to a pale yellow oil.

$\Delta^{1(9)}$-Octahydroquinoline (IV).—The product (III) was dissolved in 15 ml. of water containing 1 ml. of 2 *N* sodium hydroxide. The solution was heated on a steam-cone for 1 hour under nitrogen. After a few minutes the solution

(11) N. J. Leonard and W. C. Wildman, THIS JOURNAL, **71**, 3089 (1949).

(12) For examples and literature on transannular interactions of secondary and tertiary aminoketones see N. J. Leonard, R. C. Fox and M. Ōki, *ibid.*, **76**, 5708 (1954).

(13) *Cf.* B. Witkop and S. Goodwin, *ibid.*, **75**, 3371 (1953).

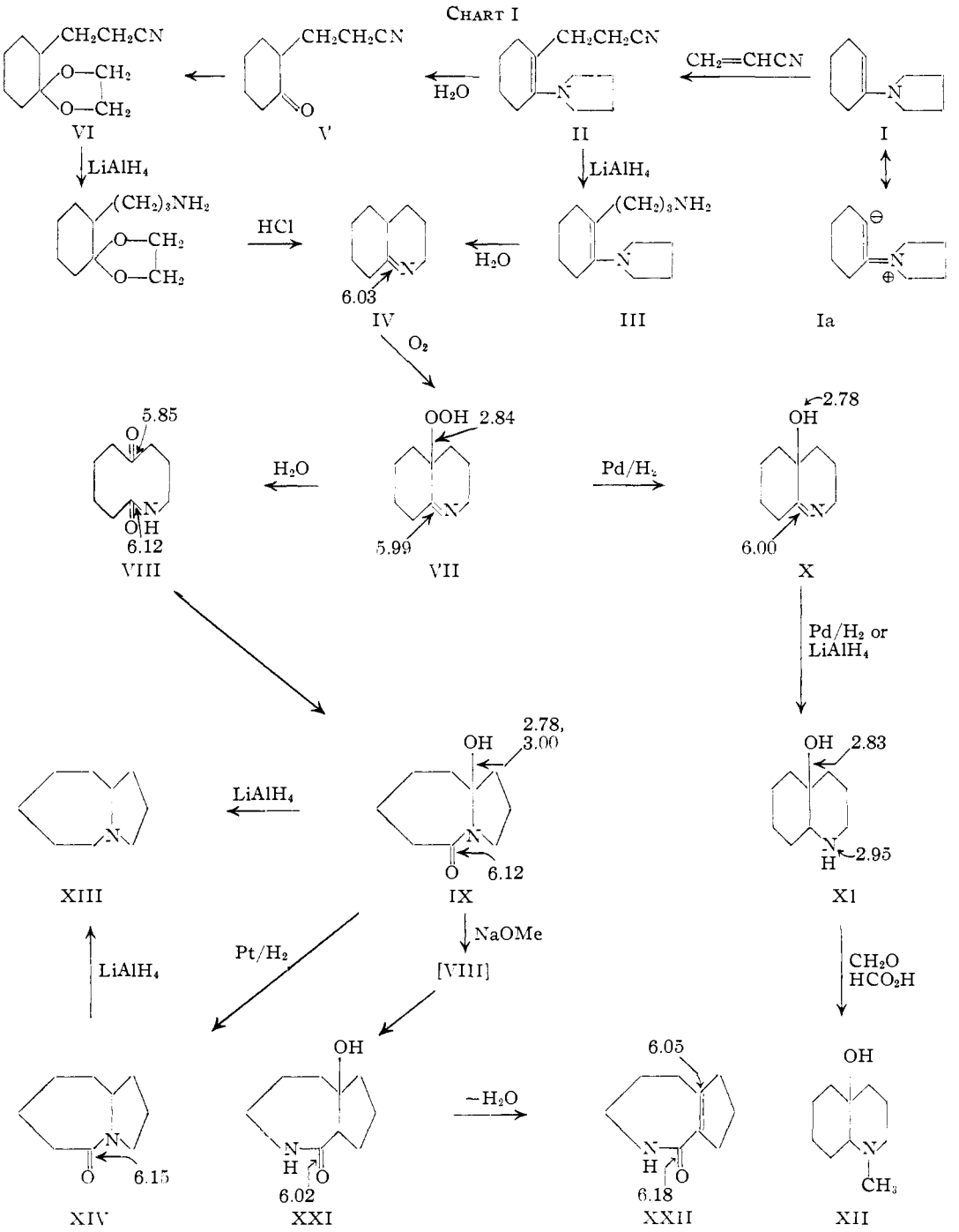
(14) B. Witkop, *Experientia*, **10**, 419 (1954).

(15) It has been observed in the past that the catalytic oxygenation of tetrahydrocarbazole (*cf.* ref. 8) can sometimes lead exclusively to carbazole instead of 11-hydroperoxytetrahydrocarbazolenine.

(16) A. Stoll, "Fortschritte der Chemie Organischer Naturstoffe," Springer Verlag, Wien, 1952, p. 134.

(17) All melting points were taken on a Kofler block and are corrected. All boiling points are uncorrected.

CHART I



began to separate into two layers. Distillation at 13 mm. gave 13.5 g. of IV, b.p. 89–91° (50% yield based on II). The pale yellow oil was redistilled at 10 mm. and the fraction boiling at 77–79° was collected. The compound is very sensitive to oxygen and should be stored under nitrogen at or below 0°.[17a]

The picrate was obtained as yellow needles from water and recrystallized from methanol–water, m.p. 136.5–137.0°.

Anal. Calcd. for $C_{15}H_{18}N_4O_7$: C, 49.18; H, 4.95; N, 15.30. Found: C, 48.98; H, 5.06; N, 15.24.

The methiodide was prepared in benzene at 5° and was obtained as needles, m.p. 118–122°. The compound is sensitive to air and darkens readily.

(17a) Although oxidation is rapid at room temperature, it is very slow at 0°.

Anal. Calcd. for $C_{10}H_{18}NI$: C, 43.02; H, 6.50; I, 45.46. Found: C, 42.76; H, 6.56; I, 45.73.

The hydrochloride was prepared with ethereal hydrogen chloride and recrystallized from methylene chloride–ethyl acetate as small cubes, m.p. 245–247°.

Anal. Calcd. for $C_9H_{16}NCl$: Cl, 20.42. Found: Cl, 20.79.

2-Cyanoethylcyclohexanone (V).[6]—Compound II was prepared, as previously described, on a one-mole scale. Without removal of the dioxane solvent, 50 ml. of water was added and the mixture heated for three hours on a steam-cone. The red solution was concentrated *in vacuo*, the residue distilled and the fraction boiling at 110–160° (14 mm.) was collected. It was redistilled to give 92 g. (61%) of V, **b.p.** 141–145° (10 mm.).

Ethylene Ketal of 2-Cyanoethylcyclohexanone (VI).—To a solution of 53 g. (0.35 mole) of V in 200 ml. of benzene were added 25 g. of ethylene glycol and 0.5 g. of *p*-toluene sulfonic acid and the mixture refluxed using a water separator. At 12-hour intervals were added 0.5-g. portions of *p*-toluenesulfonic acid. After 2 days, the theoretical amount of water had separated. The solvent was removed *in vacuo* and the residue extracted with ether. The ether extract was concentrated and the residual sirup distilled at 10 mm. to give 54 g. (80%) of the ketal, b.p. 157–159°.

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.32; H, 8.73; N, 7.14.

$\Delta^{1(9)}$-Octahydroquinoline (IV).—A solution of 54 g. (0.28 mole) of VI in 300 ml. of ether was reduced with 11.1 g. (0.28 mole) of powdered lithium aluminum hydride in three separate runs. The hydride was added over 1 hour to the stirred ether solution and the suspension was refluxed for an additional four hours. The excess hydride was decomposed with ethyl acetate and water, the ether decanted and the residue extracted with 3 75-ml. portions of ether. All three runs were worked up in a similar manner. The ether extracts were combined, dried and concentrated to a pale yellow oil. It was dissolved in a mixture of 100 ml. of concentrated hydrochloric acid and 300 ml. of water, and refluxed for 1 hour under nitrogen. The solvent was removed *in vacuo* and the residue, a brown oil, was chilled in ice, diluted with 50 ml. of 6 *N* potassium hydroxide and extracted with 6 150-ml. portions of ether. The dried extract was concentrated to a yellow oil which was distilled at 0.2 mm. to yield 12 g. (31%) of IV, b.p. 35–40°.

Attempts were made to reduce V catalytically to the aminoketone with palladium and mineral acid. Although traces of IV were obtained, most of the nitrile was hydrolyzed, as evidenced by the precipitation of ammonium chloride.

10-Hydroperoxy-$\Delta^{1(9)}$-octahydroquinoline (VII).—A solution of 2.8 g. (0.02 mole) of IV in 20 ml. of ethyl acetate was magnetically stirred in a closed system containing oxygen. In 3.5 hours absorption had stopped with the uptake of 0.9 molar equivalent. When 50% had been absorbed, the hydroperoxide began to crystallize.[18] The flask was chilled in ice, the product filtered and washed with 25 ml. of cold ethyl acetate. The dry solid weighed 2.65 g. (87%) (small needles) m.p. 99–100°. In the solid state the hydroperoxide is fairly stable. Samples kept at −5° for two months still gave strong positive tests with starch–iodide paper.

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.78; H, 8.89; N, 8.05.

7-Hydroxy-2-keto-1-azabicyclo[5.3.0]decane (IX).—A suspension of 3.0 g. of the hydroperoxide VII in 50 ml. of water–dioxane (1:1) was shaken overnight at 25°. Solution was complete and a starch–iodide test was negative. The solvent was removed *in vacuo* below 35° and the product obtained as a colorless crystalline solid, plates, m.p. 104–106°. It was recrystallized from ethyl acetate and from ligroin (65–67°), m.p. 107–109°. A sample purified by chromatography on alumina melted at 109–109.5°.

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 64.04; H, 8.76; N, 8.36.

Rearrangement of the hydroperoxide in other solvents, including chloroform, methylene chloride and acetone, led to the formation of 10-hydroxy-$\Delta^{1(9)}$-octahydroquinoline (X) as a by-product *via* interaction with the solvent, and was further complicated by the presence of colored impurities. Water–dioxane was found to give a colorless product free of X. The presence of X can be detected by the formation of a precipitate with picric acid in ether, since IX does not form a picrate.

The hydrochloride was prepared with ether–HCl and was obtained as clusters of fine needles. It begins to sublime at 70° and melts at 79–80°.

Anal. Calcd. for $C_9H_{16}NO_2Cl$: C, 52.55; H, 7.84. Found: C, 52.18; H, 7.52.

Reaction of IX with Alkali.—A solution of 1 g. of IX in 20 ml. of dioxane containing 1 ml. of 2 *N* sodium methoxide[19] was heated on a steam-cone for one hour. The solvent was removed *in vacuo* and the residue extracted with chloroform. Evaporation of the chloroform left a solid brown residue. It was submitted to continuous extraction with cyclohexane, 100-ml. extracts being collected separately at one hour intervals. Slow evaporation of the solvent and repeated crystallizations from ethyl acetate–cyclohexane led to the separation of two products. The first was obtained as cubes or platelets, m.p. 179–180°.

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.60; H, 8.71; N, 8.49.

The second compound separated as needles, m.p. 147–149°.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 70.88; H, 8.84; N, 9.12.

Neither basic nor ketonic properties were shown by either compound. The high-melting compound was recovered unchanged when refluxed with iodine–xylene.

10-Hydroxy-$\Delta^{1(9)}$-octahydroquinoline (X).—A solution of 0.41 g. (0.003 mole) of octahydroquinoline in 10 ml. of ethyl acetate was converted to the crystalline hydroperoxide as described above. Without isolation of the hydroperoxide, 0.5 g. of 10% palladium-on-charcoal was added together with 10 ml. of ethyl acetate. The hydroperoxide redissolved as hydrogenation proceeded; the reaction was stopped after absorption of one molar equivalent of hydrogen. The filtered solution was concentrated and the residual oil triturated with petroleum ether (30–40°). The crystalline product was washed twice with petroleum ether and once with ether; m.p. 108–110°. It was recrystallized from ligroin (65–67°), separating as cubes, m.p. 115–115.5°. The same melting point is obtained when the compound is purified by sublimation.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.43; H, 10.01; N, 9.04.

The picrate was prepared in ether and separated as a yellow powder, m.p. 117°, darkening at 175–180°.

Anal. Calcd. for $C_{15}H_{18}N_4O_8$: C, 47.12; H, 4.75; N, 14.66. Found: C, 47.71; H, 5.13; N, 14.04.

The hydrochloride separated as needles from ether, and was recrystallized from ethanol–ether; m.p. 186–187°. The compound is fairly hygroscopic.

Anal. Calcd. for $C_9H_{16}NOCl$: C, 56.99; H, 8.50; N, 7.39; Cl, 18.69. Calcd. for $C_9H_{16}NOCl \cdot {}^1/_2H_2O$: C, 54.41; H, 8.56; N, 7.05; Cl, 18.00. Found: C, 54.72; H, 8.68; N, 7.09; Cl, 18.85.

10-Hydroxydecahydroquinoline (XI).—A solution of 1 g. of $\Delta^{1(9)}$-octahydroquinoline in 10 ml. of ethyl acetate was oxygenated to the crystalline hydroperoxide. An additional 15 ml. of ethyl acetate and 0.1 g. of 5% palladium-on-charcoal were added. The first molar equivalent of hydrogen was absorbed in one hour and 70% of the second in five hours. An additional 0.1 g. of catalyst was added and rapid hydrogenation ensued until a total of two molar equivalents had been absorbed. The solution was filtered and concentrated to a gray solid. The compound crystallized from benzene–petroleum ether (30–40°) or from hot ligroin (65–67°) as thin hexagonal plates, m.p. 120–130°. It was recrystallized from hot ligroin; m.p. 150–151°. For melting points taken on a hot-stage it is necessary to use a large sample, since most of the material is lost by sublimation before the melting point is reached.

Reduction of X to XI could be effected also by lithium aluminum hydride in dioxane.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.62; H, 10.89; N, 9.18.

The picrate separated slowly from water as yellow, rectangular plates, m.p. 194–195°. It was recrystallized from ethyl acetate as large cubes, m.p. 195–195.5°.

Anal. Calcd. for $C_{15}H_{20}N_4O_8$: C, 46.87; H, 5.25; N, 14.58. Found: C, 46.83; H, 5.23; N, 14.36.

The hydrochloride was prepared with ether–HCl and separated as small cubes, m.p. 221–225°. It was recrystallized from methylene chloride–petroleum ether, m.p. 227.5°.

Anal. Calcd. for $C_9H_{18}NOCl$: C, 56.39; H, 9.46; N, 7.31. Found: C, 55.83; H, 9.11; N, 7.41.

(18) To obtain a crystalline hydroperoxide, it is essential that the octahydroquinoline be of high purity. The rate of oxidation is also highly sensitive to the purity of the base, freshly distilled samples absorbing 200–300 ml. of oxygen within ten minutes.

(19) Sodium hydroxide was without effect on IX under similar conditions.

The N-acetyl compound was prepared with acetic anhydride at 25°. It was crystallized from benzene–petroleum ether as hard granules, m.p. 99°.

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.56; H, 9.56; N, 7.14.

N-Methyl-10-hydroxydecahydroquinoline (XII).—To a mixture of 5 ml. of 98% formic acid and 5 ml. of 40% formalin was added 0.2 g. of XI and the solution heated for two hours on a steam cone. The solvents were removed *in vacuo*, the residue made strongly alkaline and extracted with 2 25-ml. portions of ether. Concentration of the dried extract gave 170 mg. of oil which was converted to the hydrochloride with ethereal HCl and separated as cubes, m.p. 187–193°.

The picrate was obtained from an aqueous solution of the hydrochloride; it separated as tufts of fine yellow needles, liquefied at 153–154° and cleared at 157°.

Anal. Calcd. for $C_{16}H_{22}N_4O_8$: C, 48.24; H, 5.57; N, 14.07. Found: C, 48.04; H, 5.74; N, 13.74.

The methiodide was prepared in benzene. It was crystallized from methanol–ether as colorless granules, m.p. 236–237° with slight decomposition.

Anal. Calcd. for $C_{11}H_{22}INO$: C, 42.45; H, 7.13; N, 4.50. Found: C, 41.77; H, 6.86; N, 4.33.

2-Keto-1-azabicyclo[5.3.0]decane (XIV).—To a solution of 0.34 g. of ketolactam IX in 10 ml. of methanol were added 50 mg. of PtO_2, 3 drops of acetic acid and 1 drop of water. After four hours of hydrogenation the only uptake observed was that corresponding to reduction of the catalyst. After addition of 1 ml. of concd. hydrochloric acid hydrogenation was rapid and ceased after 1 hour with the absorption of one molar equivalent. The solution was filtered and concentrated to a colorless crystalline residue. The compound was recrystallized by slow evaporation from methylene chloride; it separated as clusters of needles which began to sublime at 95° and melted at 103–105°.

Anal. Calcd. for $C_9H_{16}NOCl$: C, 56.99; H, 8.50; N, 7.39; Cl, 18.69. Found: C, 57.27; H, 8.69; N, 7.37; Cl, 18.61.

The free lactam was obtained by saturating an alkaline solution of the hydrochloride with sodium sulfate and extracting with ether. The compound is a colorless oil which crystallized below 0°. It did not form a picrate in ether.

1-Azabicyclo[5.3.0]decane (XIII). A. By Reduction of the Ketolactam (IX).—To a solution of 0.8 g. of ketolactam IX in 10 ml. of dioxane was added 1 g. of powdered lithium aluminum hydride, and the mixture refluxed for 48 hours. Excess hydride was decomposed with ethyl acetate and water and the suspension was concentrated to dryness *in vacuo*. The residue was extracted with 3 25-ml. portions of hot petroleum ether (65–67°) and the combined extracts concentrated to a colorless oil (0.36 g.) with strong amine odor. The oil was dissolved in 10 ml. of ether and converted to the picrate. The crystalline precipitate was washed with cold water and recrystallized twice from methanol by slow evaporation. It separated as clusters of large needles, m.p. 215–216°, undepressed on admixture with the picrate of XIII (m.p. 214–215°) prepared by Clemmensen reduction of 1-ketoquinolizidine.[20] The infrared spectra were identical.

Anal. Calcd. for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47; N, 15.21. Found: C, 49.09; H, 5.18; N, 14.94.

B. By Reduction of Lactam (XIV).—To a suspension of 50 mg. of lactam hydrochloride XIV in 10 ml. of dioxane was added 0.2 g. of powdered lithium aluminum hydride and the mixture refluxed for 24 hours. After addition of water and concentration to dryness, the residue was extracted with 2 × 20 ml. of ether and the base precipitated as the picrate. The yellow precipitate of long plates was recrystallized twice from methanol; it separated as large needles, m.p. 214–215°. A mixed m.p. with authentic picrate[20] gave no depression.

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(20) *Cf.* ref. 11. This sample was kindly supplied by Dr. Nelson J. Leonard.

BETHESDA 14, MARYLAND

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY AND THE NEW YORK STATE PSYCHIATRIC INSTITUTE]

Thioesters of Glutamic Acid[1]

BY HOWARD SACHS AND HEINRICH WAELSCH

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The syntheses of S-α- and γ-glutamylglutathione *via* the corresponding thiophenyl esters of carbobenzyloxyglutamic acid are reported. The protecting group was removed by treatment with a mixture of glacial acetic acid, hydrobromic acid and phenol. The homogeneity and structures of the compounds were confirmed in a number of ways. When the corresponding carbobenzyloxythioglutamic acids were used as the starting material, mixtures of α- and γ-isomers were obtained indicating rearrangement during the synthetic procedure.

Recently, a study of the non-enzymatic and enzymatic hydrolysis and transfer reactions of S-acetyl GSH[2] has been reported.[3] The possibility that thioesters of amino acids may be intermediates in the synthesis of amide bonds has been discussed. It was hoped that some information on the role of thioesters of amino acids in biosynthetic processes might be obtained by the use of model substrates and in particular of thioesters of glutamic acid.

In this paper the syntheses of S-α- and S-γ-glutamyl GSH (I, II) are presented.[4]

In the syntheses of glutamyl thioesters the α- or γ-derivative has to be prepared with the exclusion of the other isomer. Also, despite the confirmed homogeneity of the starting material it is necessary to prove unequivocally the structure of the final product in order to exclude rearrangement during the synthetic procedure. This stringent requirement for the glutamyl compounds is a consequence

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(2) The following abbreviations and symbols are used (*cf.* ref. 5a): GSH, glutathione; Z, carbobenzyloxy, $C_6H_5CH_2OCO$; Bz, $C_6H_5CH_2$; Et, C_2H_5; Glu-, $NHCH(CH_2CH_2COOH)CO$, $C_5H_7O_3N$; when the γ-carboxyl group of glutamic acid is substituted, the substituent in the γ-position is indicated below the line: $\underline{\text{Glu}}$; otherwise, a free γ-COOH group is implied. Configuration follows compound in parentheses and refers to the glutamic acid moiety since only thiophenol or natural GSH served as the mercaptan, *e.g.*, N-carbobenzyloxy-L-glutamic acid α-thiophenyl ester, Z.Glu.S.C_6H_5(L); N-carbobenzyloxy S-γ-L-glutamylglutathione, Z.$\underline{\text{Glu}}$.OH(L); S-α-L-glutamylglutathione, H.Glu.$\underline{\text{SG}}$(L).

(3) H. Strecker, P. Mela and H. Waelsch, *J. Biol. Chem.*, **212**, 223 (1955).

(4) A preliminary report has been given, *cf.* H. Sachs, *Federation Proc.*, **13**, 951 (1954); H. Sachs, H. J. Strecker and H. Waelsch, *Science*, **120**, 791 (1954).