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

Addition and Condensation Reactions of 2-Pyridone

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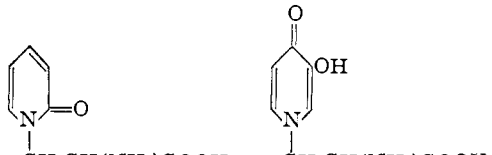
2-Pyridone was used as a model compound for the study of reactions leading to structure I, which is analogous to the proposed structure for leucenol (II). Taking advantage of the ease with which 2-pyridone adds to acrylonitrile,[2] the reaction between 2-pyridone and α-acetamidoacrylic acid was studied. The adduct was obtained and by



hydrolysis the desired product (I) resulted. By substitution of 3-methoxy-4-pyridone for 2-pyridone and using a similar series of reactions, the successful synthesis of leucenol was attained.[3]

Many reactions of 2-pyridone which might lead to structure I were explored, before a satisfactory method was discovered. Some new chemistry of 2-pyridone was uncovered which is described in this communication.

2-Pyridone and acrylonitrile react readily to form β-(N-2-pyridone)-propionitrile[2] and by hydrolysis β-(N-2-pyridone)-propionic acid results. In an attempt to prepare the corresponding α-bromo compound from which the amino compound I could be made by the action of ammonia, β-(N-2-pyridone)-propionic acid was treated with bromine and red phosphorus. The isolated product contained two unreactive atoms of bromine from which it was deduced that two bromine atoms had probably been substituted in the 3,5-positions of the pyridone ring. 2-Pyridone has been shown by Koenigs and Geigy[4] to react very readily with bromine with formation of 3,5-dibromo-2-pyridone.

2-Pyridone and chloroacetaldehyde condense to the hydrochloride of N-2-pyridone acetaldehyde. The free base could not be obtained crystalline but a crystalline oxime and semicarbazone were prepared. The methods ordinarily successful for converting an aldehyde into the corresponding amino acid, which would permit the synthesis of I, failed.

2-Pyridone and bromopyruvic acid gave a product which appeared to be the 2-pyridonium salt of N-2-pyridone pyruvic acid hydrobromide since 2-pyridone was readily removed in the cold by means of picric acid and an immediate precipitate of silver bromide with silver nitrate suggested a hydrobromide. Since the reduction of the pyridone ring in the conversion of the keto to the primary amino group seemed likely from other experiments, this possible route to I was abandoned.

2-Pyridone adds to butadienesulfone with potassium hydroxide as catalyst to give the one-to-one addition product. It does not add under similar conditions to mesityl oxide.

The reaction of sodium 2-pyridone with α,β-dibromopropionic acid in an attempt to prepare α-bromo-β-(N-2-pyridone)-propionic acid was unsuccessful. Instead, a water soluble product ($C_8H_8NO_3Br$) resulted, the constitution of which was thoroughly investigated. Its aqueous solution was acid to congo red and gave an immediate precipitate of silver bromide with aqueous silver nitrate. The same product resulted from sodium 2-pyridone and ethyl α,β-dibromopropionate, followed by hydrolysis. After some knowledge of the structure was obtained, it was discovered that it could be more conveniently prepared from 2-pyridone and α-bromoacrylic acid. α-Bromoacrylic acid was probably an intermediate in the formation of the compound when α,β-dibromopropionic acid was used as a starting material. Ethyl α-bromoacrylate also reacted with 2-pyridone and the product upon heating in aqueous solution on the steam-bath gave the 2-pyridone α-bromoacrylic acid compound.

The structure of this adduct was determined through a study of its reactions. By treatment with ammonia the halogen atom was replaced by an amino group and the product was an amino acid which was isomeric but different from I and gave no color with ninhydrin. It was, therefore, assumed to be α-(N-2-pyridone)-β-aminopropionic acid (III). Upon treatment with dry hydrogen bromide, water was eliminated and the hydrobromide of a β-lactam (IV) was formed which by means of aqueous ammonia reverted to the amino acid. The amino acid upon treatment with dilute alkali was transformed with loss of ammonia to the corresponding hydroxy acid (V), which could be obtained directly from the 2-pyridone α-bromoacrylic acid adduct by the action of dilute aqueous alkali. It was also synthesized from 2-pyridone and glycidic acid. By the action of acetic anhydride, merely acetylation of the hydroxyl group took place, and no dehydration to the corresponding acrylic acid could be detected. The hydroxy acid was stable to and unchanged by boiling with 48% hydrobromic acid.

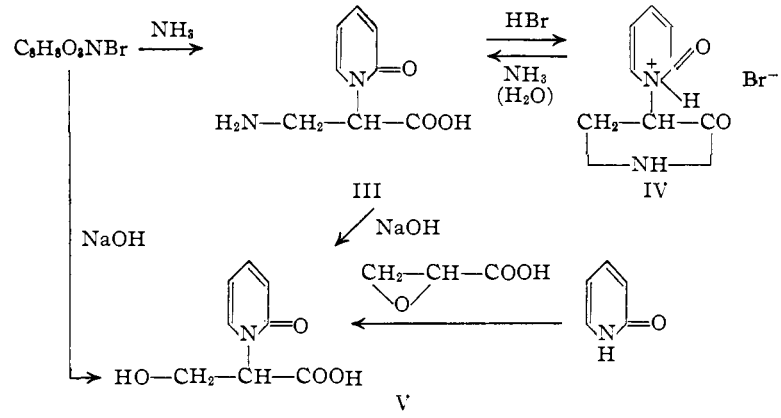
Electrometric titration of the 2-pyridone α-

(1) From a thesis presented by Viron V. Jones to the Graduate College of the University of Illinois, May, 1949, in partial fulfillment of the requirements for the degree of Doctor of Philosophy. He held the Cincinnati Chemical Works Fellowship, 1946-1949.

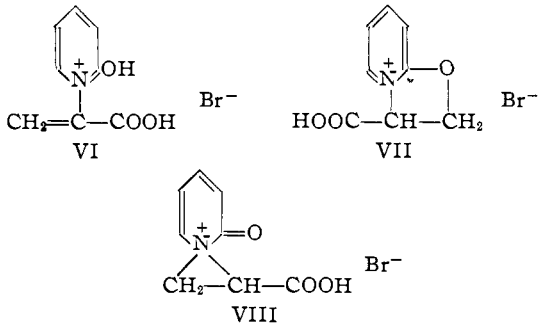
(2) Adams and Jones, THIS JOURNAL, **69**, 1803 (1947).

(3) Adams and Johnson, *ibid.*, **71**, 705 (1949).

(4) Koenigs and Geigy, *Ber.*, **17**, 591 (1884).



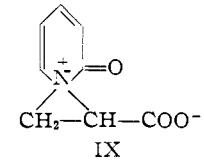
bromoacrylic acid adduct with sodium hydroxide exhibited a curve having but one end-point and typical for that of a strong monobasic acid. The strength of the acid and high activity of the halogen is comparable to that of a betaine hydrobromide $(R_3NCH_2COOH)^+(Br)^-$. Three possible structures, (VI, VII, VIII), which will serve to explain the electrometric titration, water solubility and the ionizable bromine, can be postulated for the adduct.



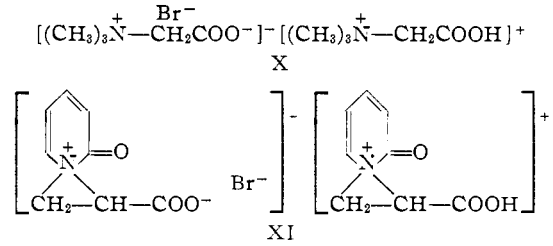
The infrared absorption showed two bands in the carbonyl region, one at 1760 cm.$^{-1}$, attributed to a carboxyl, and one at 1649 cm.$^{-1}$, to a pyridone carbonyl (Fig. 1). The absorption coincides well with that of β-(N-2-pyridone)-propionic acid. These data are presented as evidence against formula VI and VII. Moreover, 2-propoxypyridine has no absorption in the carbonyl region, while N-*n*-propylpyridone has a strong band at 1660 cm.$^{-1}$ (Fig. 1).

Formula VIII is in accord with the structure of similar compounds proposed by Cromwell[5] as intermediates in the reaction of amines with α-bromo-α,β-unsaturated ketones. The formation of a β-amino or β-hydroxy acid by the action of ammonia or aqueous alkali on the 2-pyridone α-bromoacrylic acid adduct may be explained on the basis of this formula by assuming cleavage in the β-position to the carboxyl group, thus leaving the pyridone residue in the α-position.

When VIII reacted in the cold with silver oxide or sodium bicarbonate, a halogen-free product resulted, insoluble in non-polar solvents, soluble in water and lower alcohols. A molecular weight determined by the freezing point depression of water showed it to be monomeric. Infrared data indicated a free carboxyl ion which must exist as an internal salt. A comparison of the infrared spectrum of a betaine hydrobromide with that of the corresponding betaine was made. A carbonyl band at 1740 cm.$^{-1}$ in the former and a carbonyl band at 1625 cm.$^{-1}$ in the latter was found, a difference of 115 cm.$^{-1}$. The absorption of the 2-pyridone α-bromoacrylic acid adduct shows a carbonyl band at 1760 cm.$^{-1}$ and that of the hydrobromide free product, a carbonyl band at 1630 cm.$^{-1}$, a difference of 130 cm.$^{-1}$. It has been shown that the carboxyl group in compounds containing zwitterions absorbs at a lower wave number than compounds containing normal carboxyl groups.[6] These results support the postulation that the hydrobromide-free product has structure IX. Another similarity to the betaines is found in the formation of a hemihydrobromide.



Stoltzenberg[7] prepared a hemihydrochloride and hemihydrobromide of the betaine of N-trimethylglycine. The 2-pyridone α-bromoacrylic acid adduct reacts with one-half mole of silver oxide to give a compound containing one atom of bromine for two pyridone residues. The same product resulted from mixing equimolar quantities of the 2-pyridone α-bromoacrylic acid adduct and the hydrohalide-free product. Structures for such hemihalides can be formulated on the basis of the assumption that a proton from the carboxyl of the betaine hydrobromide is accepted by a molecule of the betaine base with a crystalline salt resulting (X and XI).



(5) Cromwell and Cram, THIS JOURNAL, **65**, 301 (1943); Cromwell and Witt, *ibid.*, **65**, 308 (1943).

(6) Wright, *J. Biol. Chem.*, **127**, 137 (1939).

(7) Stoltzenberg, *Z. physiol. Chem.*, **92**, 470 (1914).

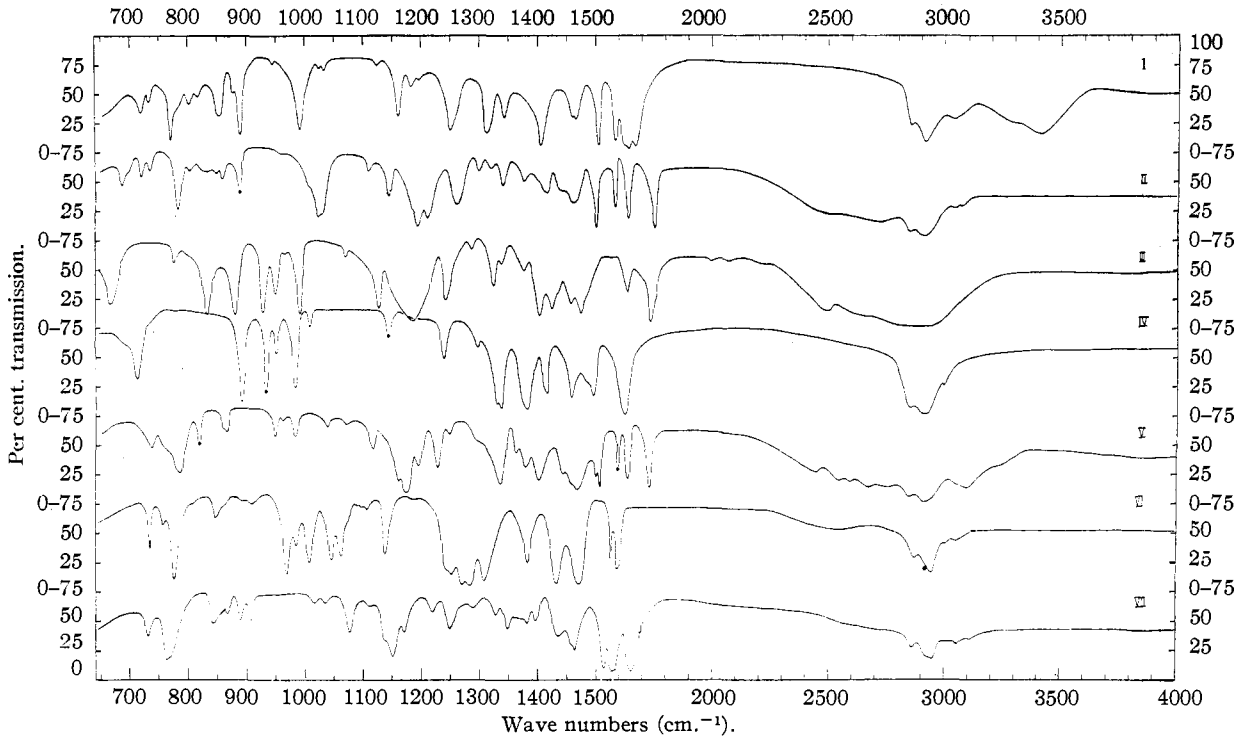
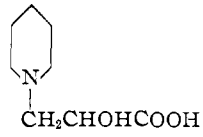


Fig. 1.—I, Hydrobromide-free 2-pyridone α-bromoacrylic acid product; II, 2-pyridone α-bromoacrylic acid adduct; III, betaine hydrobromide; IV, betaine; V, N-2-pyridonepropionic acid hydrobromide; VI, 2-propoxypyridine; VII, N-*n*-propyl-2-pyridone. Compounds I–V (inc.) were run as nujol mulls; compounds V and VI, which were liquids, were run in a 0.025 mm. cell.

The reduction products of the 2-pyridone α-bromoacrylic acid adduct were also investigated. With palladium on charcoal as catalyst, two moles of hydrogen were absorbed and a sirup resulted which would not crystallize. It contained an ionizable bromine since a copious precipitate of silver bromide formed upon treatment with silver nitrate. By the action of ammonia, an amino acid resulted, identical with the hydrogenation product of α-(N-2-pyridone)-β-aminopropionic acid (III) in which the pyridone residue had been reduced to piperidone. The intermediate sirup is probably the piperidone analog of VIII.

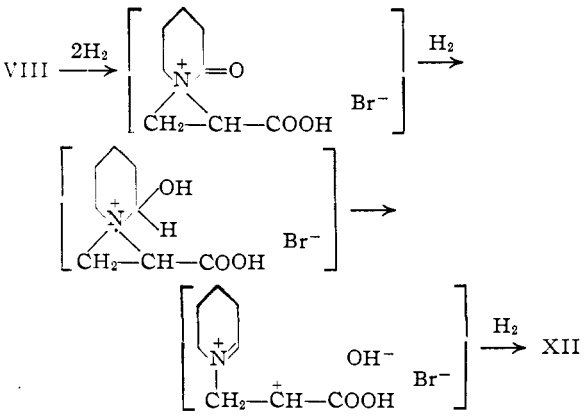
On the other hand, when platinum oxide was used as a catalyst, four moles of hydrogen were absorbed and a crystalline compound, $C_8H_{15}NO_3$·HBr, was obtained. A free base resulted upon treatment with silver oxide. Esterification to a methyl ester hydrobromide occurred when boiled in methanol but not by treatment with diazomethane. The free base was not identical with β-(N-2-piperidone)-propionic acid or α-(N-2-piperidone)-propionic acid formed by the reduction with hydrogen and platinum oxide of the corresponding pyridones. Moreover, the corresponding hydrobromide of β-(N-2-pyridone)-propionic acid absorbed only two moles of hydrogen.

A clue to the structure of this reduction product was obtained by its pyrolysis at 185° (1 mm.) in a sublimation apparatus. Piperidine hydrobromide was obtained, indicating that the oxygen in the pyridone ring in the starting compound had migrated to the propionic acid residue. The infrared spectrum of the reduction product showed no carbonyl group other than the carboxyl and a band at 3400 cm.$^{-1}$ indicative of a hydroxyl. The product proved to be α-hydroxy-β-piperidinopropionic acid (XII). It was synthesized from α-hydroxy-β-chloropropionic acid and piperidine or from piperidino-acetaldehyde hydrochloride by treatment with sodium cyanide followed by hydrolysis.



XII

The mechanism of the formation of XII probably involves first reduction of the pyridone nucleus to the piperidone since by hydrogenation of the 2-pyridone α-bromoacrylic acid adduct with palladium on charcoal as catalyst, followed by treatment with ammonia, a piperidone derivative resulted. If the piperidone carbonyl is next reduced, a pseudo base will be formed which may rearrange to a carbonium hydroxide. The latter upon reduction could yield the hydrobromide of the hydroxy acid (XII).



Ethyl α-bromo-β-ethoxypropionate and sodium 2-pyridone yielded a compound with the composition $C_{15}H_{16}O_4N_2$. The product was assumed to be ethyl α,β-di-(N-2-pyridone)-propionate. Both the ethoxy group and bromine atom appear to have been replaced by pyridone residues.

Experimental

α-Acetamido-β-(N-2-pyridone)-propionic Acid.—A mixture of 0.5 g. of α-acetamidoacrylic acid[8] and 0.5 g. of 2-pyridone[2] was heated on a metal-bath at 140° for one hour. The thick sirup which formed was dissolved in 5 ml. of chloroform and allowed to evaporate overnight. A small amount of solid separated in the sirup. This product was stirred with 5 ml. of acetone and left in the refrigerator for one day. A small amount of colorless granules was obtained. After recrystallization from methanol, the product melted at 199° (cor.) with decomposition.

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.56; H, 5.40. Found: C, 53.20; H, 5.50.

α-Amino-β-(N-2-pyridone)-propionic Acid.—A mixture of 0.3 g. of α-acetamido-β-(N-2-pyridone)-propionic acid and 5 ml. of 48% hydrobromic acid was refluxed for six hours. The excess acid was removed by distillation on the steam-cone under reduced pressure. The sirup which remained was made just basic to litmus paper with concentrated ammonia, and evaporated to dryness. The residue was crystallized from the minimum amount of water. The yield was 0.17 g. (72%) of a product melting at 236° (cor.) with decomposition. It gave a blue color with ninhydrin solution.

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.75; H, 5.53. Found: C, 52.75; H, 5.79.

Bromination of β-(N-2-Pyridone)-propionic Acid; β-(3,5-Dibromo-N-2-pyridone)-propionic Acid.—A mixture of 15 g. of β-(N-2-pyridone)-propionic acid,[2] 3.6 g. of red phosphorus and 30 ml. of carbon tetrachloride contained in a three-necked round-bottom flask was cooled in an ice-bath and equipped with dropping funnel, stirrer and reflux condenser. To this was added dropwise with stirring 60 g. of bromine. After completion of the addition, the mixture was gradually heated until nearly all the hydrogen bromide had been removed. The carbon tetrachloride was distilled on the steam-cone leaving a dark semi-solid material which was then boiled with a little water and diluted to 400 ml. with water. After cooling in an ice-bath, fine white granules precipitated. The yield was 10 g. (32%). The product was recrystallized from 50% ethanol and melted at 182° (cor.). It gave a negative test with boiling silver nitrate solution.

Anal. Calcd. for $C_8H_7NO_3Br_2$: C, 29.44; H, 2.22; N, 4.31. Found: C, 29.63; H, 2.23; N, 4.40.

(8) Bergmann and Grafe, *Z. physiol. Chem.*, **187**, 187 (1930).

N-2-Pyridone Acetaldehyde Hydrochloride.—A mixture of 20 g. of methyl chloroacetal and 10 g. of water containing ten drops of concentrated hydrochloric acid was refluxed until the two phases disappeared. To this hot solution was added 10 g. of 2-pyridone and the refluxing continued for one hour. All the volatile materials were distilled on a steam-cone at 20 mm. After addition of 50 ml. of acetone to the resulting sirup, it was placed in a refrigerator overnight. A solid crystalline mass resulted which upon filtration gave 12 g. (66%) of product. After recrystallization from absolute ethanol, the melting point was 139–140° (cor.).

This product upon treatment with aqueous sodium bicarbonate or sodium hydroxide yielded a sirup which would not crystallize. The sirup was soluble in ethanol and ether, but insoluble in water. It gave a positive reaction to Tollens reagent.

Anal. Calcd. for $C_7H_8NO_2Cl$: C, 48.48; H, 4.62; N, 8.17; Cl, 20.42. Found: C, 48.53; H, 4.58; N, 7.97; Cl, 20.25.

After neutralization of the hydrochloride with solid sodium bicarbonate and extraction with ether, the N-2-pyridone acetaldehyde was treated with pyridine and hydrogen cyanide and a trace of solid potassium hydroxide. After standing and subsequent treatment with ammonia, followed by hydrobromic acid hydrolysis, no amino acid could be isolated.

Similarly, ammonium carbonate and sodium cyanide did not give the desired condensation product.

N-2-Pyridone Acetaldoxime.—A solution of 20 ml. of 95% ethanol containing 1.0 g. of 2-pyridone acetaldehyde hydrochloride and 1.0 g. of hydroxylamine hydrochloride was made just basic to moist litmus paper with 10% aqueous sodium hydroxide, and evaporated to dryness on a steam-cone. The residue was extracted with 20 ml. of ether and yielded 0.75 g. (85%) of a light yellow solid upon evaporation. Recrystallization from carbon tetrachloride resulted in a product melting at 78–79° (cor.).

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.25; H, 5.33; N, 18.41. Found: C, 55.41; H, 5.14; N, 18.32.

N-2-Pyridone Acetaldehyde Semicarbazone.—A mixture of 1.0 g. of 2-pyridone acetaldehyde hydrochloride, 1.5 g. of semicarbazide hydrochloride and 1.5 g. of sodium acetate was dissolved in 20 ml. of water and heated on a steam-cone for five minutes. A white precipitate formed after cooling in an ice-bath. The yield of product was 1.1 g. (100%). After crystallization from methanol, the product melted at 155–156° (cor.).

Anal. Calcd. for $C_8H_{10}O_2N_4$: C, 49.49; H, 5.16; N, 28.87. Found: C, 49.46; H, 5.14; N, 28.80.

Reaction of 2-Pyridone and Bromopyruvic Acid.—To 75 ml. of chloroform containing 3.4 g. of bromopyruvic acid,[9] 4 g. of 2-pyridone was added and the mixture held at 55° for ten hours. After evaporation to a thick sirup, 50 ml. of acetone was added and then five drops of 48% hydrobromic acid. Upon standing in a refrigerator for twenty-four hours, a granular solid formed weighing 5.8 g. (78%). After recrystallization from 95% ethanol, the melting point was 143–145° (cor.) with decomposition.

Anal. Calcd. for $C_{13}H_{13}O_5N_2Br$: C, 43.72; H, 3.67. Found: C, 43.65; H, 3.49.

This product gave a 2-pyridone picrate from ethanol and a positive test with Tollens reagent.

Reaction of 2-Pyridone and Butadiene Sulfone.—A mixture of 5.0 g. of 2-pyridone and 7.0 g. of butadiene sulfone was refluxed for two hours in 50 ml. of absolute ethanol containing two pellets of potassium hydroxide. The ethanol was distilled off on a steam-cone using vacuum toward the end. The resulting thick sirup was stirred up with 25 ml. of acetone and placed in a refrigerator overnight. A mass of fine white crystals formed. The filtrate yielded upon evaporation a second crop of crystals, making the total yield of 8.2 g. (73%). The product was purified by recrystallization from acetone, m. p. 136–137°.

(9) Sprinson and Chargaff, *J. Biol. Chem.*, **164**, 411 (1946).

Anal. Calcd. for $C_9H_{11}NO_3S$: C, 50.70; H, 5.17; N, 6.57. Found: C, 51.00; H, 5.08; N, 6.64.

Under analogous conditions, no condensation product of 2-pyridone and mesityl oxide resulted.

Reaction of α,β-Dibromopropionic Acid and the Sodium Salt of 2-Pyridone.—A mixture of 20 g. of the dihydrate of the sodium salt of 2-pyridone and 30 g. of α,β-dibromopropionic[10] acid in 50 ml. of acetone was heated on a steam-cone until bumping became too severe. The solvent was then allowed to evaporate aided by a stream of air. The resulting thick pasty mass was extracted once with 50 ml. of hot nitromethane and filtered from the sodium bromide. Ether was added to the filtrate until faint cloudiness appeared and then placed in a refrigerator overnight. The yield of almost white granular material was 22 g. (64%). After recrystallization once from 95% ethanol and once from water, the melting point was 122–123° (cor.).

The product was soluble in water forming a solution acid to congo red paper. The very pure material was insoluble in all organic solvents, but when crude was soluble in ethanol. The aqueous solution formed instantly a voluminous precipitate with aqueous silver nitrate solution.

Anal. Calcd. for $C_8H_8O_3NBr \cdot H_2O$: C, 36.41; H, 3.79; N, 5.30. Found: C, 36.76; H, 3.81; N, 5.19.

The sample was dried in an Abderhalden at 100° and 1 mm. to constant weight.

Anal. Calcd. for $C_8H_8O_3NBr$: C, 39.04; H, 3.27; N, 5.69. Found: C, 39.18; H, 3.01; N, 5.64.

Electrometric Titration.—A solution of 0.242 g. of the adduct hydrate in 25 ml. of water was titrated electrometrically with 0.0895 *N* sodium hydroxide. The initial *p*H was 2.0 and readings were taken at regular intervals to the phenolphthalein end-point. The resulting curve was typical of that for strong acids such as hydrobromic acid, and there was but one end-point. Calcd. for $C_8H_{10}NO_4Br$: mol. wt., 264. Found: mol. wt., 267.

Reaction of Sodium 2-Pyridone and Ethyl α,β-Dibromopropionate.—To a mixture of 12 g. of anhydrous sodium 2-pyridone in 100 ml. of absolute ethanol was added 28 g. of ethyl α,β-dibromopropionate.[10] A reaction occurred with the evolution of heat. The mixture was refluxed until bumping became severe (about fifteen minutes), and filtered from an inorganic residue. The filtrate was evaporated to a sirup and after taking up in 50 ml. of isopropyl alcohol was filtered from more of the inorganic material. The isopropyl alcohol was evaporated leaving a sirup which was soluble in water and ethanol but insoluble in ether and benzene. The aqueous solution was acid to congo red paper and yielded instantly a heavy precipitate of silver bromide with cold silver nitrate solution. The sirup did not crystallize after standing in a warm place for one week, but after mixing with acetone and allowing to stand in the refrigerator for two days, 6 g. of a crystalline product, m. p. 122°, was isolated. The melting point of this mixed with a 2-pyridone bromoacrylic acid adduct showed no depression.

Reaction of 2-Pyridone and α-Bromoacrylic Acid.—A mixture of 10 g. of 2-pyridone and 16 g. of α-bromoacrylic acid[10] and 0.2 g. of water containing 0.5 g. of *t*-butylcatechol was heated on the steam-cone with occasional stirring for one hour. The resulting thick sirup was dissolved in 50 ml. of boiling isoamyl alcohol and allowed to stand at room temperature for twenty-four hours then transferred to a refrigerator overnight. The fine white crystalline solid weighed 19 g. (70%). After recrystallization from a small volume of water it melted at 122–123° (cor.). This is the preferred method of synthesis.

Reaction of 2-Pyridone and Ethyl α-Bromoacrylate.—A mixture consisting of 9.5 g. of 2-pyridone and 18 g. of ethyl α-bromoacrylate[10] was heated for four hours on the steam-cone. A thick sirup resulted which was acid to moist congo red paper, and which yielded instantly a heavy precipitate of silver bromide with silver nitrate solution. The sirup was soluble in water and ethanol, but insoluble in ether and benzene. No crystallization occurred after standing in a warm place for three days, but when stirred with 25 ml. of acetone and allowed to stand in the refrigerator twenty-four hours, a granular precipitate formed. The yield was 4.5 g. and after recrystallization from ethanol melted at 120°.

Reaction of the 2-Pyridone Bromoacrylic Adduct with Ammonia; α-(N-2-Pyridone)-β-aminopropionic Acid.—A mixture of 2.0 g. of the adduct hydrate and 20 ml. of concentrated aqueous ammonia was refluxed for one hour. The resulting solution was evaporated to a solid and a sirup on the steam-cone aided by a stream of air. It was then dissolved in 25 ml. of methanol and allowed to stand twenty-four hours in the refrigerator, after which the granular crystals were filtered. An additional amount of material was obtained by evaporating the filtrate to dryness and recrystallizing from the minimum amount of boiling methanol. The total yield was 1.0 g. (71%) and after recrystallization from 50% methanol it melted at 213–215° (cor.) with decomposition. The pure product was soluble in water, insoluble in ethanol and non-polar solvents, and gave a negative test with ninhydrin and with Nessler reagent.

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.54; N, 15.40. Found: C, 52.89; H, 5.41; N, 15.33.

Reaction of α-(N-2-Pyridone)-β-aminopropionic Acid and Hydrobromic Acid; α-(N-2-Pyridone)-β-aminopropiolactam Hydrobromide.—Dry hydrogen bromide was passed into a suspension of 0.35 g. of the amino acid in 2 ml. of absolute ethanol until a clear solution resulted. This solution, after standing in a refrigerator overnight, yielded 0.45 g. (89%) of fine colorless crystals. After recrystallization from 95% ethanol the product melted at 298–299° (cor.) with decomposition.

Anal. Calcd. for $C_8H_9N_2O_2Br$: C, 39.20; H, 3.72; N, 11.43; Br, 32.60. Found: C, 39.36; H, 3.75; N, 11.63; Br, 32.72.

A little of this material was dissolved in 0.5 ml. of water and made basic to litmus with aqueous ammonia. After evaporating to dryness, the residue was dissolved in the minimum amount of methanol and set in an ice-bath. The white granular crystals melted at 211–213° (cor.) with decomposition and the melting point of a mixture with α-(N-2-pyridone)-β-aminopropionic acid showed no depression.

Reaction of α-(N-2-Pyridone)-β-aminopropionic Acid and Sodium Hydroxide; α-(N-2-Pyridone)-β-hydroxypropionic Acid.—A solution of 0.5 g. of sodium hydroxide in 5 ml. of water and 0.8 g. of the amino acid was refluxed for one-half hour. Ammonia was liberated. The resulting solution was made acid to congo red paper with concentrated hydrochloric acid and allowed to remain in the refrigerator overnight. The granular crystals weighed 0.42 g. (52%) and melted at 168–172°. This proved to be identical with the hydroxy acid prepared by treating the 2-pyridone-α-bromoacrylic acid adduct with alkali.

Reaction of the 2-Pyridone Bromoacrylic Adduct with Sodium Hydroxide; α-(N-2-Pyridone)-β-hydroxypropionic Acid.—A solution of 6.8 g. of the adduct hydrate and 2.0 g. of sodium hydroxide in 25 ml. of water was refluxed for one hour. After cooling somewhat, 2.5 g. of concentrated sulfuric acid was added carefully and the mixture allowed to remain in the refrigerator overnight. The yield of fine granular crystals was 3.8 g. (79%). After recrystallization from methanol, the melting point was 173–175° (cor.).

Anal. Calcd. for $C_8H_9NO_4$: C, 52.45; H, 4.97. Found: C, 52.72; H, 5.18.

A mixture of 1.5 g. of the hydroxy acid and 10 ml. of 48% hydrobromic acid was refluxed for four hours. The excess acid was distilled *in vacuo* and the semicrystalline residue was taken up in 5 ml. of water. After neutralizing with sodium carbonate to congo red, a crystalline precipitate formed which was unchanged hydroxy acid.

α-(N-2-Pyridone)-β-acetoxypropionic Acid.—Upon refluxing 1 g. of this compound with 5 ml. of acetic an-

(10) Marvel, Cook and Cowan, THIS JOURNAL, **62**, 3495 (1940).

hydride for fifteen minutes and distilling the excess anhydride *in vacuo*, a thick sirup was obtained which solidified on standing. It was washed with acetone and recrystallized from methanol. The yield of colorless flakes was 0.47 g. (39%). The pure product melts at 224–225° (cor.).

Anal. Calcd. for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.93; N, 6.23. Found: C, 53.11; H, 4.99; N, 6.07.

Reaction of 2-Pyridone and Glycidic Acid; α-(N-2-Pyridone)-β-hydroxypropionic Acid.—A mixture of 1.3 g. of the potassium salt of glycidic acid[11] and 0.95 g. of 2-pyridone in 2 ml. of ethanol was heated on the steam-cone for one hour. The sirup was taken up in 10 ml. of absolute ethanol and made just acid to congo red paper with hydrochloric acid and evaporated to dryness. The residue was extracted with 1.0 ml. of glacial acetic acid to remove the inorganic residue. The acetic acid was distilled on the steam-cone using vacuum. The sirup was transferred to a vacuum desiccator containing moist sodium hydroxide and allowed to stand overnight. The material solidified and after recrystallizing from 10 ml. of absolute ethanol yielded 1.0 g. (55%) of a tan-colored solid. After recrystallizing from methanol, the product melted at 173° (cor.) and the melting point of this mixed with the product obtained from the alkali treatment of the 2-pyridone α-bromoacrylic acid adduct showed no depression.

Reaction of the 2-Pyridone α-Bromoacrylic Acid Adduct and One Mole of Silver oxide.—A solution of 2.6 g. of the very pure adduct hydrate in 20 ml. of methanol was poured into a mortar and macerated for two minutes with the silver oxide prepared from 1.7 g. of silver nitrate. The silver bromide was removed by filtration and the filtrate evaporated at room temperature aided by a stream of filtered air. The crystalline residue was stirred with 10 ml. of *n*-propyl alcohol and filtered. The yield was 1.0 g. (56%). The melting point was elevated to 105–107° (cor.) by dissolving in the minimum amount of cold methanol and repeating the evaporation and *n*-propyl alcohol treatment. The product which is merely the adduct with a molecule of hydrogen bromide eliminated was insoluble in acetone, ether and benzene. It was soluble in hot *n*-propyl alcohol but no crystalline product could be obtained by cooling.

Anal. Calcd. for $C_8H_7NO_3.H_2O$: C, 52.45; H, 4.97. Found: C, 52.98; H, 5.13.

Upon drying in an Abderhalden, the melting point was 159–165° (cor.).

Anal. Calcd. for $C_8H_7NO_3$: C, 58.17; H, 4.28. Found: C, 58.45; H, 4.41.

Upon dissolving the product in concentrated hydrobromic acid and evaporating, a sirup resulted which on standing crystallized. It proved to be the 2-pyridone α-bromoacrylic acid adduct.

Reaction of the 2-Pyridone α-Bromoacrylic Acid Adduct and One-Half Mole of Silver Oxide.—A solution of 0.2 g. of the adduct hydrate in 25 ml. of methanol was macerated in a mortar for several minutes with the silver oxide prepared from 0.67 g. of silver nitrate. After removing the silver bromide by filtration, the filtrate was evaporated at room temperature to a crystalline residue aided by a stream of air. The solid was dissolved in the minimum amount of boiling absolute ethanol and allowed to stand for forty-eight hours in a refrigerator. The yield of granular crystals was 0.8 g. (50%). Recrystallization from methanol yielded a product melting at 156° (cor.) with decomposition. This product is a hemihydrobromide. An aqueous solution gave a heavy precipitate of silver bromide with silver nitrate solution.

Anal. Calcd. for $C_{18}H_{15}N_2O_6Br$: C, 46.72; H, 3.69. Found: C, 46.49; H, 3.54.

This product was also prepared by mixing 0.45 g. of the 2-pyridone α-bromoacrylic acid adduct hydrate and 0.25 g. of the hydrobromide-free compound in 2 ml. of 50% methanol and evaporating to dryness. The residue upon recrystallizing from ethanol yielded 0.37 g. of crystals melting at 156° (cor.) with decomposition. No depression in melting point was observed when mixed with the hemihydrobromide prepared by the silver oxide method.

Hydrogenation of the 2-Pyridone α-Bromoacrylic Acid Adduct with Palladium on Charcoal and Treatment of the Product with Ammonia; α-(N-2-Piperidone)-β-aminopropionic Acid.—A solution of 2 g. of the adduct hydrate in 100 ml. of hot 95% ethanol was hydrogenated at 50° and 50 lb. hydrogen pressure using 1.0 g. of palladium–charcoal catalyst. Two moles of hydrogen were absorbed. The solution was filtered and evaporated to a sirup. A solution of 50 ml. of methanol saturated with ammonia was added to the sirup and allowed to evaporate in a warm place. The resulting sirup was placed in a vacuum desiccator for two days. A small amount of granular material formed. This was washed with acetone and recrystallized from methanol. The yield of product was 0.5 g. melting at 177–179° (cor.) with decomposition.

Anal. Calcd. for $C_8H_{14}N_2O_3 \cdot H_2O$: C, 47.04; H, 7.93; N, 13.73. Found: C, 47.10; H, 7.63; N, 13.38.

α-(N-2-Pyridone)-β-aminopropionic Acid.—A solution of 1 g. of the amino acid in 50 ml. of 50% ethanol was hydrogenated at 50-lb. pressure and at 50° using 50 mg. of platinum oxide catalyst. Twelve hours was required for complete hydrogenation during which two moles of hydrogen was absorbed. The solution was filtered to remove the catalyst and evaporated at room temperature to a thick sirup. After drying in a vacuum desiccator for one day, a hard glass formed which from isoamyl alcohol yielded 0.65 g. (59%) of a white powder. Purification was effected by recrystallization from methanol, m. p. 177–179° (cor.) with decomposition. A melting point of a mixture with the product prepared in the previous experiment showed no depression.

Hydrogenation of the 2-Pyridone α-Bromoacrylic Acid Adduct with Platinum Oxide Catalyst.—A solution of 100 ml. of 95% ethanol containing 4.0 g. of the adduct hydrate and 50 mg. of platinum oxide was hydrogenated at 50° and 50 lb. pressure. In three hours four moles of hydrogen had been taken up and no further absorption occurred. The platinum was filtered off and the filtrate evaporated at room temperature aided by a stream of air. The crystalline solid which remained was washed with acetone. The yield was 3.2 g. (83%). The melting point of the sample purified by recrystallizing from nitromethane was 173–174° (cor.).

Anal. Calcd. for $C_8H_{18}NO_3Br$: C, 37.80; H, 6.36; N, 5.52. Found: C, 38.10; H, 6.36; N, 5.45.

Maceration in a mortar of 0.9 g. of the product in 10 ml. of methanol with silver oxide prepared from 0.61 g. of silver nitrate, was continued until the brown color disappeared. The filtrate from this slurry was evaporated at room temperature aided by a stream of air. The residual solid was crystallized from methanol and weighed 0.5 g. (82%). After further purification, the product melted at 219–220° (cor.) with decomposition.

This product was soluble in water and methanol, insoluble in the higher alcohols and all non-polar solvents. When refluxed with 48% hydrobromic acid for four hours, the original hydrobromide was obtained in 86% yields.

Anal. Calcd. for $C_8H_{15}NO_3$: C, 55.46; H, 8.75; N, 8.09. Found: C, 55.33; H, 8.83; N, 8.07.

Esterification of the Hydrogenated 2-Pyridone α-Bromoacrylic Acid Adduct.—A solution of 5 g. of the hydrogenated adduct in 50 ml. of methanol and 1 ml. of 48% hydrobromic acid was refluxed for twelve hours. The volatile materials were removed by distillation on a steam-cone using vacuum toward the end. A thick sirup remained which solidified upon cooling. The yield of material, after recrystallization from isopropyl alcohol, was 4.5 g. (86%). The melting point after further recrystallization from the same solvent was 141° (cor.).

Anal. Calcd. for $C_9H_{18}NO_3Br$: C, 40.31; H, 6.79. Found: C, 40.14; H, 6.78.

(11) Freudenberg, *Ber.*, **47**, 2027, 2034 (1914).

Attempts to obtain the free ester by treatment with silver oxide and methanol resulted in hydrolysis and only the free acid could be isolated. Diazomethane in methanol failed to methylate the free acid.

Pyrolysis of the Platinum Oxide Hydrogenated 2-Pyridone α-Bromoacrylic Acid Adduct.—The pyrolysis was conducted by heating 0.62 g. of the four mole hydrogenated 2-pyridone α-bromoacrylic acid adduct in a sublimation apparatus at 175–185° (1 mm.). At first considerable bubbling occurred, but after about one hour the mass became solid, and the temperature was elevated to 205–210°. A white product sublimed onto the cold finger weighing 0.35 g. (88%). After recrystallization from nitromethane, the product melted at 236° which was identified as piperidine hydrobromide.

The same product was obtained by allowing the pyrolysis temperature to remain at 185°, and the solid mass taken up in nitromethane. Upon cooling and adding an equal volume of dioxane, the piperidine hydrobromide separated.

Reaction of Piperidine and α-Hydroxy-β-chloropropionic Acid.—A mixture of 2.0 g. of α-hydroxy-β-chloropropionic acid and 4.0 g. of piperidine was heated on a steam-cone for one hour. Upon cooling, a solid and a sirup remained. This was stirred with 15 ml. of dioxane and chilled in an ice-bath. The piperidine hydrochloride which separated was removed by filtration, and the filtrate allowed to evaporate. The resulting sirup was left in a vacuum desiccator overnight. A crystalline product was obtained after allowing to stand under 25 ml. of ether in a warm place and replacing the colored ether with fresh ether every two hours over a period of one day. The solid was washed with dioxane and weighed 1.6 g. (55%). The product was purified by recrystallizing from methanol, m. p. 219° (cor.) with decomposition. The melting point when mixed with the four mole hydrogenated 2-pyridone α-bromoacrylic acid adduct base showed no depression.

Piperidinoacetaldehyde Hydrochloride.—A mixture of 22 g. of piperidinoacetaldehyde methyl acetal[12] and 20 ml. of concentrated hydrochloric acid was refluxed for one hour. The aqueous acid was distilled on a steam-cone *in vacuo* leaving a thick sirup. After standing in a vacuum desiccator containing sodium hydroxide for twenty-four hours, the sirup became hard without crystallizing. The sirup was dissolved in 25 ml. of nitromethane and allowed to evaporate aided by a stream of air. A crystalline solid and sirup remained. About 50 ml. of acetone was stirred into the mixture and a flocculent precipitate formed. After filtering from the solution, the gummy solid was dissolved in 15 ml. of nitromethane and allowed to remain in the refrigerator overnight. The solid mass was washed with ice-cold nitromethane leaving 5 g. of an almost white material melting at 106–107°. This product checks with that prepared by Stoermer who reported a melting point of 106°. Upon evaporation, the filtrate yielded a gummy sirup which could not be induced to crystallize.

α-Hydroxy-β-piperidinopropionitrile.—A solution of 5 g. of the aldehyde hydrochloride prepared in the previous experiment in 15 ml. of water was added slowly to an ice-cold solution consisting of 1.5 g. of sodium cyanide in 25 ml. of water. A solid product precipitated immediately weighing 4.5 g. (95%). After recrystallizing from benzene, the product melted at 97–98° (cor.).

Anal. Calcd. for $C_8H_{14}N_2O$: C, 62.35; H, 9.09. Found: C, 62.50; H, 9.28.

This product could be advantageously prepared in 73% yield directly from the crude piperidinoacetaldehyde hydrochloride sirup.

α-Hydroxy-β-N-piperidinopropionic Acid.—The hydrolysis was carried out by refluxing 2.4 g. of the nitrile for four hours with 10 ml. of concentrated hydrobromic acid. The excess acid was removed by distillation at atmospheric pressure until a solid separated, then further concentration was accomplished by evaporation on the steam-cone aided by a stream of air. The solid which remained was extracted with four 15-ml. portions of boiling *n*-propyl alcohol. This solution was evaporated to a solid and recrystallized from the minimum amount of boiling-hot isopropyl alcohol. The yield was 3.7 g. (92%) and after recrystallizing melted at 173–175° (cor.) with decomposition. The melting point when mixed with the four mole hydrogenated 2-pyridone α-bromoacrylic acid adduct showed no depression.

β-(N-2-Piperidone)-propionic Acid.—A solution of 2 g. of β-(N-2-pyridone)-propionic acid in 100 ml. of 95% ethanol was hydrogenated at 40 lb. pressure and room temperature using 1.0 g. of palladium on charcoal catalyst. After eighteen hours, two moles of hydrogen were absorbed. The catalyst was filtered from the solution which was then evaporated to dryness at room temperature aided by a stream of air. The white crystalline solid was recrystallized from acetone, yielding 1.4 g. (70%) of fine white flakes. After recrystallization the melting point was 148° (cor.).

Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.13; H, 7.68; N, 8.18. Found: C, 56.48; H, 7.80; N, 8.28.

An excess of dry hydrogen bromide was passed into a solution of 0.47 g. of this product contained in 10 ml. of chloroform. Upon cooling in an ice-bath, a white crystalline product separated. The yield of hydrobromide was 0.6 g. (95%). The sample was purified by recrystallizing from nitromethane, m. p. 179° (cor.), with decomposition.

Anal. Calcd. for $C_8H_{14}NO_3Br$: C, 38.11; H, 5.60; N, 5.56. Found: C, 38.25; H, 5.37; N, 5.42.

Reaction of Methyl α-Bromopropionate and the Sodium Salt of 2-Pyridone; α-(N-2-Pyridone)-propionic Acid.—A mixture of 5.8 g. of the anhydrous sodium salt of 2-pyridone, and 8.8 g. of methyl α-bromopropionate in 25 ml. of absolute ethanol was refluxed for one hour and filtered hot. The solution was distilled on the steam-cone using vacuum toward the end. The sirup remaining was soluble in water and chloroform but insoluble in ether. No crystalline product could be obtained from the sirup so it was saponified by heating for an hour on the steam-cone with a solution of 4.0 g. of sodium hydroxide in 10 ml. of water. This solution was then made acid with 25 ml. of ethanol containing 2.5 g. of concentrated sulfuric acid. An inorganic precipitate was filtered off and the filtrate evaporated to dryness. The residue was washed with 50 ml. of hot chloroform. The granular crystals remaining weighed 7.0 g. (84%). After recrystallizing from absolute ethanol, the melting point was 215–217° (cor.) with decomposition.

Anal. Calcd. for $C_8H_9NO_3$: C, 57.52; H, 5.43; N, 8.38. Found: C, 57.39; H, 5.18; N, 8.51.

α-(N-2-Piperidone)-propionic Acid.—A suspension of 2.0 g. of α-(N-2-pyridone)-propionic acid and 50 mg. of platinum oxide in 50 ml. of absolute ethanol was hydrogenated at 50-lb. pressure and 50°. Two moles of hydrogen were absorbed in two hours. After filtering from the catalyst, the filtrate was evaporated at room temperature aided by a stream of air. The crystalline solid which remained was recrystallized from benzene. The yield was 1.9 g. (93%). The melting point was elevated to 144° (cor.) after further recrystallization from the same solvent.

Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.13; H, 7.67; N, 8.18. Found: C, 56.27; H, 7.41; N, 8.25.

Reaction of Sodium 2-Pyridone and Ethyl α-Bromo-β-ethoxypropionate; α,β-Di-(N-2-pyridone)-propionic Acid.—A solution of 5.0 g. of the anhydrous sodium salt of 2-pyridone and 8.0 g. of ethyl α-bromo-β-ethoxypropionate[13] in 25 ml. of absolute ethanol was refluxed for four hours. The solvent was evaporated on the steam-cone aided by a stream of air until only a sirup and a solid remained. The sirup was extracted with 25 ml. of chloroform and the solvent distilled on the steam-cone using vacuum to remove the last trace of solvent. The sirup was allowed

(12) Stoermer, *Ber.*, **31**, 2542 (1898).

(13) Wood and DuVigneaud, *J. Biol. Chem.*, **134**, 413 (1940).

to remain in a vacuum desiccator overnight then extracted with 25 ml. of boiling xylene. The resulting solution was set in a warm place and evaporated. A crystalline residue resulted weighing 1.5 g. (12%). It melted at 151° (cor.) after recrystallization from xylene. No other crystalline product could be isolated.

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.50; H, 5.56. Found: C, 62.29; H, 5.32.

Summary

1. The reactions of 2-pyridone were studied with the objective of finding the best route to α-amino-β-(N-2-pyridone)-propionic acid, an analog of leucenol. The addition of 2-pyridone to α-acetamidoacrylic acid, followed by hydrolysis of the adduct, resulted in the product desired and provided the procedure for the successful synthesis of leucenol.

2. Other reactions of 2-pyridone which were explored during this investigation were numerous. β-(N-2-Pyridone)-propionic acid upon treatment with bromine and phosphorus gave β-(3,5-dibromo-N-2-pyridone)-propionic acid. 2-Pyridone gave the expected N-substituted products upon condensation with chloroacetaldehyde and bromopyruvic acid. It added to butadiene sulfone.

3. An extensive study was made of the condensation product of sodium 2-pyridone with α,β-dibromopropionic acid. The product was water soluble and contained ionizable bromine. It could be made more advantageously from 2-pyridone and α-bromoacrylic acid.

4. The 2-pyridone α-bromoacrylic acid adduct reacted with ammonia to give α-(N-2-pyridone)-β-aminopropionic acid or with aqueous alkali to give the corresponding β-hydroxy compound. Upon reduction with hydrogen and palladium–charcoal catalyst two moles of hydrogen were absorbed and the piperidone analog resulted as shown by treatment with ammonia to give α-(N-2-piperidone)-β-aminopropionic acid which was also made by the reduction of the α-(N-2-pyridone)-β-aminopropionic acid. When the adduct was reduced with hydrogen and platinum oxide as a catalyst, four moles of hydrogen were absorbed and α-hydroxy-β-piperidinopropionic acid was the product as shown by synthesis from piperidine and α-hydroxy-β-chloropropionic acid or from piperidinoacetaldehyde through the cyanohydrin. The mechanism of these transformations is discussed.

5. The 2-pyridone α-bromoacrylic acid adduct was titrated as a monobasic acid. With one molecule of silver oxide it yielded a betaine and with one-half mole of silver oxide a betaine hemihydrobromide. The infrared spectra of betaine hydrobromide and betaine compared closely with those of the 2-pyridone α-bromoacrylic acid adduct and the hydrobromide-free analog, thus showing similar groupings. The structure of the adduct is postulated as an ethylene-immonium bromide which permits a satisfactory explanation of all the experimental facts.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

An Improved Apparatus for the Study of Reactions in Liquid Ammonia[1,2]

BY GEORGE W. WATT AND C. W. KEENAN[3]

Apparatus of the type described by Johnson and Fernelius[4] and modified extensively by Watt and Moore[5] for the conduct of reactions in liquid ammonia at its boiling point involves two serious shortcomings. Neither the original nor the modified apparatus provides for (a) the possibility of conducting titrations in a closed system (a procedure frequently advantageous in establishing the stoichiometry of reactions of liquid ammonia solutions of alkali and alkaline earth metals), or (b) the substantially quantitative removal of solid reaction products following *in situ* filtration and washing, without exposure of these products to the atmosphere. Both of these objectives are realized through use of the apparatus described in the present paper.

Two relatively simple reactions were chosen to demonstrate the operability of the equipment, *i. e.*, the reduction of ammonium bromide and silver(I) bromide with liquid ammonia solutions of potassium.[6] These cases show that the equipment described below permits one to exercise close analytical control over all reactants and products, including gaseous products; the importance of so-doing has been emphasized elsewhere.[7]

Experimental

Apparatus.—The apparatus designed to meet the needs indicated above is shown in Fig. 1. In general, this equipment is similar to that described by Watt and Moore[5]; consequently only the improvements will be pointed out here.

(1) The major part of this work was done under the sponsorship of the Office of Naval Research, Contract N6onr-26610.

(2) The liquid ammonia employed in these studies was generously supplied by E. I. du Pont de Nemours and Company.

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(4) Johnson and Fernelius, *J. Chem. Education*, **7**, 981 (1930).

(5) Watt and Moore, THIS JOURNAL, **70**, 1197 (1948).

(6) Several investigators have shown that silver(I) salts other than the bromide are reduced to elemental silver by the action of liquid ammonia solutions of alkali and alkaline earth metals [*cf.*, Kraus and Kurtz, THIS JOURNAL, **47**, 43 (1925); Burgess and Smoker, *ibid.*, **52**, 3573 (1930); *Chem. Revs.*, **8**, 265 (1931); Zintl, Goubeau and Dullenkopf, *Z. physik. Chem.*, **A154**, 1 (1931); Burgess and Smoker, THIS JOURNAL, **59**, 459, 462 (1937)].

(7) Fernelius and Watt, *Chem. Revs.*, **20**, 202, 216 (1937).