TABLE I

Compound	Isomer	% yield	Mp, °C	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
8a hydrochloride	B	50	230–232[a]	69.49	69.22	8.61	8.59	7.72	7.63
8b	A	74	135–138	80.55	80.41	8.51	8.54	6.96	6.96
8c	A	98	123.5–126.5	68.63	68.52	8.51	8.48	6.96	7.19
8d fumarate	A	87	193–195[b]	60.58	60.50	8.14	8.09	7.07	6.96

[a] From methanol–ether. [b] From isopropyl alcohol–ether.

(0.088 mole) of 2-(1-pyrrolidinyl)-9-azabicyclo[3.3.2]decan-10-one (isomer A) and 112.4 g (0.35 mole) of mercuric acetate in 400 ml of 5% aqueous acetic acid was heated for 1 hr on the steam bath. The resulting suspension was cooled and filtered. The clear filtrate was saturated with hydrogen sulfide and the precipitate was removed by filtration. Methylene chloride extraction of the filtrate yielded 9.1 g of a brown solid. Sublimation of the product yielded 6.5 g (0.04 mole, 45%) of a white solid, mp 200–207° (softening at 190°).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.67; H, 7.90; N, 8.40.

Isomer B (3.0 g) was oxidized under the same conditions, giving a 4% yield of sublimed product, mp 196–206° (softening at 190°). Mixture melting point with the keto lactam obtained from isomer A was 195–206°. The infrared spectra in potassium bromide pellets and nmr spectra in deuteriochloroform of the two products were superimposable.

5-Amino-4-oxocyclooctanecarboxylic Acid Hydrochloride (4).—A solution of 0.3 g (0.0018 mole) of 9-azabicyclo[3.3.2]decane-2,10-dione in 10 ml of 6 *N* hydrochloric acid was heated under reflux for 3 hr and then kept overnight at room temperature. The hydrochloric acid was removed at the water pump, leaving a yellowish solid, mp 205–210° dec. Recrystallization from methanol–ether gave 0.15 g (0.00067 mole, 37%) of a white solid, mp 213° dec.

Anal. Calcd for $C_9H_{15}NO_3 \cdot HCl$: C, 48.79; H, 7.27; Cl, 15.99; N, 6.32. Found: C, 48.26; H, 7.30; Cl, 15.95; N, 6.16.

2-(1-Pyrrolidinyl)-9-azabicyclo[3.3.2]decane Dihydrochloride (6). Isomer A.—2-(1-Pyrrolidinyl)-9-azabicyclo[3.3.2]decan-10-one (isomer A) (17.5 g, 0.078 mole) was dissolved in 50 ml of dry tetrahydrofuran and added to a suspension of 5.0 g of lithium aluminum hydride in 350 ml of the same solvent over a period of 15 min. The suspension was heated under reflux for 8 hr and then kept at room temperature for 16 hr.

The reaction mixture was cooled in an ice bath and 12 ml of water was added over a period of 20 min. The suspension was stirred for 1 hr and filtered. The inorganic residue was washed thoroughly with ether. The combined filtrates were evaporated, leaving 15 g (0.072 mole, 92%) of a colorless oil, bp 102–103° (0.4 mm). The product was characterized as its dihydrochloride, mp 191–194° (from methanol–ether). Consistent carbon and hydrogen analyses of the hydrochloride could not be obtained.

Anal. Calcd for $C_{13}H_{24}N_2 \cdot 2HCl$: N, 9.96. Found: N, 9.97.

Isomer B (1.0 g) was reduced under analogous conditions, giving a 96% yield of a colorless oil, bp 97° (0.3 mm), $n^{23}D$ 1.15291.

Anal. Calcd for $C_{13}H_{24}N_2$: C, 74.97; H, 11.61; N, 13.45. Found: C, 74.44; H, 11.65; N, 13.48.

5-Amino-4-(1-pyrrolidinyl)cyclooctanecarboxylic Acid Dihydrochloride (7).—A solution of 5.0 g (0.022 mole) of 2-(1-pyrrolidinyl)-9-azabicyclo[3.3.2]decan-10-one (isomer A) in 20 ml of 7.7 *N* hydrochloric acid was heated overnight under reflux. The water was removed under aspirator pressure, the last traces being removed by azeotropic distillation with toluene. The resulting brown oil was crystallized from isopropyl alcohol: yield, 3.3 g of a white dihydrochloride; mp 212–213° dec. The mother liquors were evaporated and the residue was resubmitted to the above acid hydrolysis: total yield, 4.4 g (0.014 mole, 64%). Recrystallization from methanol–ether raised the melting point to 215–216° dec.

Anal. Calcd for $C_{13}H_{24}N_2O_2 \cdot 2HCl$: C, 49.84; H, 8.37; N, 8.94. Found: C, 49.50; H, 8.36; N, 8.86.

1-(10-Oxo-9-azabicyclo[3.3.2]decan-2-yl)-1-methylpyrrolidinium Iodide.—A solution of 8.0 g (0.036 mole) of 2-(1-pyrrolidinyl)-9-azabicyclo[3.3.2]decan-10-one (isomer A) and 30 ml of methyl iodide in 150 ml of dry acetone was stirred at room temperature for 3 days. The resulting suspension was filtered, yielding 13.0 g of a white solid. Recrystallization from absolute ethanol gave 12.2 g (0.034 mole, 94%), mp 241–243° dec, of a white solid.

Anal. Calcd for $C_{14}H_{25}IN_2O$: C, 46.15; H, 6.91; N, 7.69. Found: C, 45.84; H, 7.20; N, 7.52.

Acylation of 2-(1-Pyrrolidinyl)-9-azabicyclo[3.3.2]decanes.—For the preparation of acyl derivatives, 2-(1-pyrrolidinyl)-9-azabicyclo[3.3.2]decane (either isomer) was dissolved in dry acetone containing anhydrous potassium carbonate in suspension. An equimolar amount of the desired acid chloride was slowly added, the stirred reaction mixture being cooled in an ice bath. The reaction mixture was stirred at room temperature for 16 hr. The solvent was removed and the residue was dissolved in 1 *N* hydrochloric acid. The solution was washed with ether, made basic with 5% sodium hydroxide, and extracted with methylene chloride. The methylene chloride solution was dried over anhydrous magnesium sulfate and evaporated. The residue was crystallized from ethyl acetate. The results are summarized in Table I.

Acknowledgment.—The author is indebted to Dr. G. I. Poos for many valuable discussions, and to Dr. Harold R. Almond and Mrs. M. C. Christie for analytical work.

3-Hydroxypicolinic Acid and Some of Its Derivatives

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The growing number of antibiotics[1] in which 3-hydroxypicolinic acid has been found has increased the desirability of a practical preparation of this acid and, even more so, of an intermediate that could be adapted for synthetic work.[2] There are known methods for the synthesis of 3-hydroxypicolinic acid, but one[3] of these leads to isomers; others[4] require many steps or proceed in low yield.[5]

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The present investigation shows that with 2-hydroxymethyl-3-hydroxypyridine as starting material it is possible first to protect the phenolic hydroxyl by benzylation and then to oxidize[6] the carbinol group and obtain 3-benzyloxypicolinic acid in a good over-all yield. This compound can be readily converted by hydrogenolysis[7] into 3-hydroxypicolinic acid. The 3-benzyloxypicolinic acid can also be used like a protected amino acid to form a mixed anhydride, *e.g.*, with pivaloyl chloride,[8] which then can couple to an amino acid or peptide. It is also possible, with the phenolic group blocked, to esterify the free carboxyl group with *p*-nitrophenol and obtain *p*-nitrophenyl 3-benzyloxypicolinate, a protected and activated form of 3-hydroxypicolinic acid. This active ester, under the conditions employed in the nitrophenyl ester method[9] of peptide synthesis, can react with the free amino group of an amino acid or peptide to introduce 3-benzyloxypicolinic acid into a peptide chain. The benzyl group can subsequently easily be removed by hydrogenolysis and the 3-hydroxypicolinic acid containing peptide can be obtained.[10]

Experimental Section[11]

2-Hydroxymethyl-3-benzyloxypyridine.—To a solution of 32 g (0.2 mole) of 2-hydroxymethyl-3-hydroxypyridine hydrochloride[12] in 100 ml of water, a solution of 26 g (0.45 mole) of potassium hydroxide in 100 ml of water containing 0.5 g of potassium iodide was added. The temperature was kept below 30° by external cooling and by controlling the rate of addition. To this solution, a solution of 30 ml (0.24 moles) of benzyl chloride in 300 ml of methanol was added and the entire mixture was stirred at room temperature in a closed vessel for 72 hr. After this period, the insoluble salt formed was filtered off, washed with methanol, and discarded. The combined filtrate and washings were concentrated *in vacuo* at a bath temperature of 30–35°. As all of the methanol was removed, the product separated and was filtered off. On standing, some additional product separated. The crude product weighed about 25 g (60% yield), mp 73–75°. It was purified by dissolving in about 200 ml of 1 *N* hydrochloric acid; after the acid solution had been extracted three times with 50 ml of chloroform, the aqueous solution was, while cooling, made alkaline with 20% potassium hydroxide solution. The crystalline product was filtered and washed with water; 20 g (45%) was obtained in this way, mp 80–81°.

If additional purification is required, the product can be either distilled under good vacuum or crystallized from hexane or water. The product obtained by any of these methods is a white, crystalline material, mp 81–82°, R_f 0.81, $\lambda_{max}^{95\%\ EtOH}$ 278 mμ (ε 7060) and 218 mμ (ε 19,520). The infrared spectrum shows a substituted phenyl band at 13.6 and 13.25 μ.

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.59; H, 6.12; N, 6.49.

3-Benzyloxypicolinic Acid Hydrochloride Sesquihydrate.—To a stirred suspension of 14.5 g (0.067 mole) of 2-hydroxymethyl-3-benzyloxypyridine, 7.7 g (0.049 mole) of potassium permanganate was added, and the mixture was heated to about 80° for 1 hr. After this period, a second portion of 7.7 g of potassium permanganate and 150 ml of water was added, and the heating and stirring were continued for 2 hr at 75–85°. The reaction mixture was allowed to cool slightly, and the manganese dioxide was filtered off and washed with 200 ml of hot water. The filtrate and washing were combined and extracted three times with 100-ml portion of chloroform and the extracts were discarded. The aqueous liquor was acidified with 200 ml of concentrated hydrochloric acid and allowed to stand overnight in the cold (5°). The product which separated was filtered and sucked dry. After drying in air, it weighed 15.5 g (80%) and is practically pure.

The product was purified by dissolving in 100 ml of methanol containing 5 ml of normal alcoholic hydrogen chloride. On dilution with 200 ml of ethyl acetate, the product separated in beautiful crystals, which were filtered and washed with ethyl acetate and allowed to dry in air. The yield of product was 11 g (55%). A second crop could be obtained by working up the mother liquor. The product melts at 108–112°, resolidifies at 130–135°, decomposes at 195–200°, and has $\lambda_{max}^{95\%\ EtOH}$ 288 mμ (ε 4097) and 217 mμ (ε 12,560); in the infrared spectrum a carbonyl band is found at 5.85 μ and monosubsituted benzene bands at 13 and 13.5 μ. After chromatography, the compound shows under ultraviolet light a spot (R_f 0.86) which can also be revealed with bromophenol spray.

Anal. Calcd for $C_{13}H_{11}NO_3 \cdot HCl \cdot 1.5H_2O$: C, 53.34; H, 5.17; Cl, 12.11; N, 4.79. Found: C, 53.20; H, 5.32; Cl, 12.27; N, 4.77.

3-Hydroxypicolinic Acid Hydrochloride.—A solution of 6.0 g (0.02 mole) of 3-benzyloxypicolinic acid hydrochloride sesquihydrate in 200 ml of 50% ethanol was hydrogenated at room temperature at 1 atm in the presence of 0.5 g of 5% palladium on charcoal for 5 hr, during which time the calculated amount of hydrogen was consumed. The catalyst was removed by filtration and washed with a little water, and the original filtrate and washing were combined and evaporated *in vacuo* at about 30°. The residue (3.2 g) was taken up in 100 ml of methanol and filtered. To the filtrate, 1 ml of 5 *N* alcoholic hydrogen chloride and 200 ml of ethyl acetate were added, and the mixture was allowed to stand overnight in the cold (5°). The product which separated was filtered and dried in air. It weighed 2.8 g (77%), mp 220–222° dec, $\lambda_{max}^{95\%\ EtOH}$ 304 mμ (ε 7760) and 224 mμ (ε 7320); the infrared spectrum reveals a carbonyl band at 5.85 μ and no benzene bands. Chromatography shows a strong fluorescent spot seen in ultraviolet light (R_f 0.47). This spot turns brownish when sprayed with ferric chloride solution.

Anal. Calcd for $C_6H_5NO_3 \cdot HCl$: C, 41.04; H, 3.45; Cl, 20.20; N, 7.98. Found: C, 41.29; H, 3.59; Cl, 20.23; N, 7.94.

***p*-Nitrophenyl 3-Benzyloxypicolinate.**—3-Benzyloxypicolinic acid hydrochloride sesquihydrate (22.0 g, 75 mmoles) was suspended in a mixture of ethyl acetate (320 ml) and triethylamine (11.2 ml) and stirred for 1 hr at room temperature. The crystalline triethylamine hydrochloride was filtered off and was washed with ethyl acetate (two 30-ml portions). *p*-Nitrophenol (11.12 g) and dicyclohexylcarbodiimide (16.48 g) were added to the filtrate, and the mixture was stirred for 2 hr at room temperature and 0.5 hr in an ice bath. The precipitate of dicyclohexylurea (9.6 g, 53%) was filtered off, and the filtrate was concentrated to dryness *in vacuo*. The crystalline residue was suspended in ether, filtered, and washed with ether, giving 14.38 g (51%), mp 120–121° dec, $\lambda_{max}^{95\%\ EtOH}$ 287 mμ (ε 11,980); the infrared spectrum has the characteristic band of nitrophenyl esters at 5.65 μ.

Anal. Calcd for $C_{19}H_{14}N_2O_5$: C, 65.14; H, 4.03; N, 8.00. Found: C, 65.24; H, 4.06; N, 8.14.

3-Benzyloxypicolinylglycine Ethyl Ester.—A suspension of 1.5 g (5 mmoles) of 3-benzyloxypicolinic acid hydrochloride sesquihydrate[13] in 6.0 ml of dry chloroform was cooled to −10° while stirring, and 0.7 ml of triethylamine was added when solution occurred. The solution was cooled to −20° and 1.1 ml of triethylamine and 0.7 ml of pivaloyl chloride were added. The temperature was allowed to rise to 0° over a period of 15 min and then brought back to −20° when in succession 0.7 g of glycine ethyl ester hydrochloride, 0.7 ml of triethylamine, and 4.0 ml of dry chloroform were added and the reaction mixture was allowed to come to room temperature and stirred for 3 hr. The mixture was diluted with 10 ml of chloroform and extracted successively with two 10-ml portions of water, three 10-ml portions of 0.5 *N* potassium bicarbonate, five 10-ml portions of water, and finally dried over anhydrous magnesium sulfate.

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(11) Melting points were capillary and uncorrected; ultraviolet spectra were determined on a Cary Model 15, infrared spectra on a Perkin-Elmer Model 21 in a mineral oil mull, and paper chromatography on Whatman No. 1 paper with butanol–acetic acid–water (4:1:5).

(12) Obtained from Nepera Chemical Co. Inc., Harriman, N. Y.

(13) The use of the anhydrous salt here might improve the yield.

After removal of the solvent, the residue rystallized. The crude product was dissolved in 8 ml of ethyl acetate and filtered, and the filtrate was diluted with 10 ml of hexane. On standing, 0.8 g of product separated: mp 85°, R_f 0.88.

Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.77; N, 8.91. Found: C, 65.12; H, 5.93; N, 8.98.

A sample of this compound was hydrolyzed in 6 *N* hydrochloric acid by heating for 16 hr at 110°, and the hydrolysate was chromatographed. Only two spots (R_f 0.13 and 0.45), corresponding to those for glycine and 3-hydroxypicolinic acid, respectively, could be detected.

3-Hydroxypicolinylglycine Ethyl Ester.—Hydrogen gas was bubbled through a solution of 314 mg (1 mmole) of 3-benzyloxypicolinylglycine ethyl ester dissolved in 10 ml of 50% ethanol containing 100 mg of 5% palladium on charcoal for 4 hr while stirring at room temperature. The catalyst was removed by filtration and washed with ethanol. The filtrate and washing were combined and concentrated under vacuum; the residue obtained crystallized. It was dissolved in 2 ml of ethyl acetate and a small amount of insoluble material was removed by centrifugation, after which the solution was diluted with 20 ml of hexane. A yield of 120 mg of a pure product melting at 90–91° was obtained.

Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39. Found: C, 53.82; H, 5.60.

A sample of this product, when chromatographed, showed a single spot strongly fluorescent under ultraviolet light that gives a positive reaction with ferric chloride solution. It had a R_f 0.9.

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A Simple Synthesis of Cyclopropene[1]

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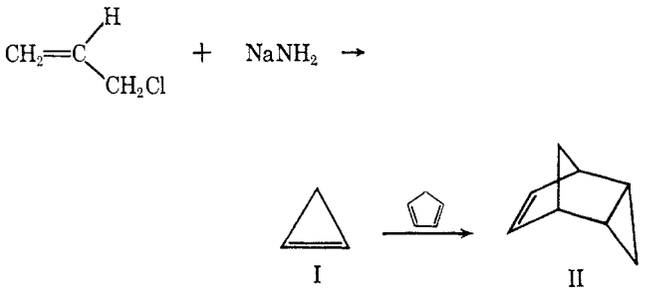
Recently in our laboratory the need arose to prepare a sample of cyclopropene (I). Since the known synthesis of this hydrocarbon is extremely laborious,[3] we were tempted to extend the method of Fisher and Applequist,[4] who recently prepared 1-methylcyclopropene from methallyl chloride and sodium amide in tetrahydrofuran.

It was found that I is indeed obtained when allyl chloride is added dropwise to a suspension of sodium amide under conditions where the unstable hydrocarbon can readily escape the reaction mixture. Cyclopropene was identified by its nmr spectrum[5] and its Diels–Alder reaction with cyclopentadiene at 0°, resulting in the formation of the tricyclic hydrocarbon II.[6] Although the yield of I did not exceed 10% under a variety of reaction conditions tried, the simplicity of the procedure and the ready availability of the starting materials make this reaction a practical synthesis, superior to the older method. No detailed study of the other reaction products has been made, but it appears that the main product is allylamine.

As has been pointed out before,[4] the mechanism of the reaction is probably closely related to that of several previously described reactions in which vinylcarbenes were shown to cyclize to cyclopropene derivatives.[7]



I II

Experimental Section

A three-neck flask (100–150 ml) was equipped with magnetic stirrer, addition funnel, nitrogen inlet capillary, and a jacketed column (condenser, ~20 in.) filled with glass helixes. The column was cooled with circulating ice–water. Connected to the column was a small gas wash flask filled with 2 *N* sulfuric acid. The wash flask was connected with a trap held at liquid nitrogen temperature. Because of the instability of cyclopropene it was found advantageous to keep the dead volume of the system to a minimum, allowing the product to reach the trap in a minimum time.

The flask was charged with commercial sodium amide (Fisher, 12 g, 0.3 mole) and mineral oil (20 ml) and was heated to 80°. To the stirred suspension was added dropwise allyl chloride (23 g, 0.3 mole) diluted with mineral oil (15 ml). A steady stream of gas evolved from the reaction mixture. After addition was complete (2–4 hr) and the gas evolution became slower, a slow rate of nitrogen was passed through the system to sweep the product into the trap. Heating was continued for another 2 hr. The cyclopropene collected in the trap was contaminated with allyl chloride (this contamination increases when nitrogen is passed too fast through the system). Purification of the product can be accomplished by vapor phase chromatography as described previously.[6] The use of other solvents, such as tetrahydrofuran or dimethoxydiethylene glycol, did not improve the yield and the product was found to be less pure.

In another experiment the sulfuric acid washing flask was eliminated and the gas stream was directly led into a solution of cyclopentadiene (6.6 g, 0.1 mole) in *n*-pentane (40 ml) held at 0°. After completion of the reaction the solvent was removed and distillation of the remainder afforded pure tricyclooctene (II) (3.2 g, 10%), mp 30–31° (lit.[6] mp 30–32°). The nmr spectrum of II was identical with that reported.[6]

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(1) Supported by National Science Foundation Grant GP-4214.
(2) A. P. Sloan Foundation Fellow, 1962–1966.
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