50 ml. of ether were placed in a hydrogenation bomb and saturated with ammonia. One gram of 5% palladium on charcoal catalyst was added and the hydrogenation was carried out at 1400 lb. pressure and at 125° for ten hours. The solvent was stripped and the residue was worked up to yield 0.6 g. (0.004 mole, 8%) of product, m.p. and mixed m.p. 120–121°.

Addition of Formic Acid.—Ethyl γ,γ,γ-trifluorocrotonate (10 g., 0.06 mole), 20 g. of 100% formic acid and 0.5 g. of toluenesulfonic acid were refluxed for 12 hours. The formic acid was removed *in vacuo* and the residue refluxed for four hours with a solution of 9 g. of sodium hydroxide dissolved in a mixture of 30 ml. of water and 10 ml. of alcohol. The solution was acidified and extracted with ether to yield 1 g. (0.007 mole, 12%) of β-hydroxy-γ,γ,γ-trifluorobutyric acid,[12] m.p. and mixed m.p. 74–76°.

Addition of Hydrogen Bromide to γ,γ,γ-Trifluorocrotonic Acid.—The acid (6 g., 0.043 mole) dissolved in 20 ml. of ethyl bromide was saturated with hydrogen bromide and heated in a sealed tube for five hours at 100°. After removal of solvent *in vacuo* and recrystallizing the residue from ether–petroleum ether (30–40°) there was obtained 8.9 g. (0.040 mole, 93%) of β-bromo-γ,γ,γ-trifluorocrotonic acid, m.p. 39–41°.

Anal. Calcd. for $C_4H_4O_2BrF_3$: C, 21.40; H, 1.80. Found: C, 21.71; H, 2.00.

Reaction of Ethyl β-Bromo-γ,γ,γ-trifluorobutyrate with: A. Ammonia.—The bromo ester (5 g., 0.02 mole) was shaken for 48 hours with 25 ml. of concd. ammonium hydroxide. Evaporation to dryness gave 1 g. (0.006 mole, 30%) of β-amino-γ,γ,γ-trifluorobutyramide, m.p. 120–121°.

B. Sodium Acetate.—The bromo ester (2 g., 0.009 mole) was in a solution of one gram of sodium acetate, 10 ml. of water and 20 ml. of ethyl alcohol. This was refluxed for six hours, diluted with 100 ml. of water and extracted with pentane. The solvent was evaporated and the residue distilled to yield 0.6 g. (0.004 mole, 60%) of ethyl γ,γ,γ-trifluorocrotonate, b.p. 114–115°, $n^{24}D$ 1.3605.

Reaction of Ethyl β-*p*-Bromobenzenesulfoxy-γ,γ,γ-trifluorobutyrate with: A. Ammonia.—The ester (2 g., 0.005 mole) and 3 ml. of liquid ammonia were heated in a sealed tube at 40° for 10 hours. The tube was opened and the ammonia was allowed to evaporate. The residue was recrystallized from acetonitrile to yield 0.5 g. (0.003 mole, 60%) of β-amino-γ,γ,γ-trifluorobutyramide, m.p. 120–121°.

The yield using aqueous ammonium hydroxide was 50%.

B. Sodium Acetate.—The *p*-bromobenzenesulfoxy ester (2 g., 0.005 mole) was refluxed for six hours in a solution of 1 g. of sodium acetate dissolved in 25 ml. of water and 14 ml. of alcohol. The mixture was diluted with 200 ml. of water and extracted with pentane. The pentane extract yielded 0.03 g. (0.002 mole, 40%) of ethyl γ,γ,γ-trifluorocrotonate, b.p. 114–115°, $n^{25.5}D$ 1.3582.

TALLAHASSEE, FLORIDA

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

Quinolizidine Derivatives. A Study of the Reductive Cyclization of Some γ-(2-Pyridyl)-butyronitriles

BY V. BOEKELHEIDE, W. J. LINN,[1] P. O'GRADY AND M. LAMBORG

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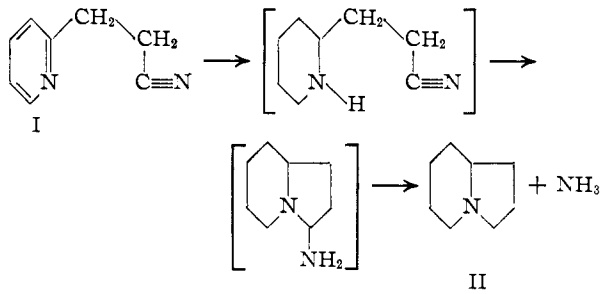
It is shown that γ-(2-pyridyl)-butyronitriles, on mild hydrogenation over platinum in the presence of acid, undergo cyclization to yield quinolizidine derivatives. Since the requisite γ-(2-pyridyl)-butyronitriles can be conveniently prepared in good yield from either 2-vinylpyridine or ethyl 2-pyridylacetate, this two-step procedure is particularly useful for preparing 1- and 3-substituted quinolizidines, compounds which are of interest because of their relationship to the lupin alkaloids.

In a previous communication,[2] we described a method for preparing quinolizidine derivatives. The essential steps of this method were (1) the addition of an active methylene compound to 2-vinylpyridine in a Michael condensation,[2,3] and (2) the reductive cyclization of the resulting pyridyl ketone or ester over platinum. One of the possible applications of this method lies in the synthesis of members of the lupin alkaloids, and for this purpose a modification of the method was desired which would permit the synthesis of quinolizidine derivatives that were unsubstituted at the 4-position. In the present paper it is shown that the reductive cyclization of pyridyl nitriles is a general reaction and a convenient method for preparing quinolizidine and indolizidine derivatives of the desired type.

The expectation that pyridyl nitriles would undergo reductive cyclization was based on the following reasoning. If conditions could be found under which the rate of reduction of the pyridine ring would be considerably faster than the rate of reduction of the nitrile group, the resulting piperidyl nitrile, if properly chosen, would undergo intramolecularly the type of reductive alkylation commonly encountered in reductions of nitriles. The proposed reaction scheme is illustrated below for the case of β-(2-pyridyl)-propionitrile.



When β-(2-pyridyl)-propionitrile (I), prepared by the method of Frank and Mirza,[4] was subjected to hydrogenation over platinum in an acidic medium, it was converted to indolizidine (octahydropyrrocoline, II) in 43% yield. Having thus obtained experimental evidence supporting the proposed reaction scheme, we investigated the generality of the reaction.

By a modification of previous procedures,[2,3] it was found possible to effect addition of ethyl cyanoacetate and phenylacetonitrile to 2-vinyl-

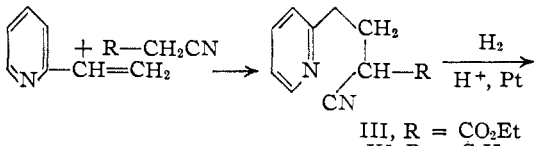
(1) du Pont Company Postgraduate Fellow, 1952–1953.

(2) V. Boekelheide and S. Rothchild, THIS JOURNAL, **71**, 879 (1949).

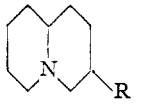
(3) W. von E. Doering and R. A. N. Weil, *ibid.*, **69**, 2461 (1947).

(4) We are indebted to Dr. R. L. Frank for this procedure, which is described in detail in the Ph.D. Thesis of John Mirza, University of Illinois, 1949.

pyridine in good yield. The resulting γ-(2-pyridyl)-butyronitriles, III and IV, underwent reductive cyclization in a comparable manner to the previous cyclization to give 3-carbethoxyquinolizidine (V) and 3-phenylquinolizidine (VI), respectively. As would be expected, both of these quinolizidine derivatives were obtained as mixtures of the two possible diastereoisomeric racemates. This was demonstrated by the isolation of picrates corresponding to each of the expected racemates.

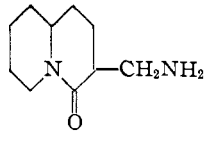


III, R = CO_2Et
IV, R = C_6H_5

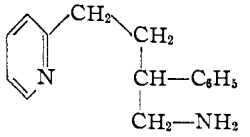


V, R = CO_2Et
VI, R = $-C_6H_5$
X, R = $-CH_2OH$

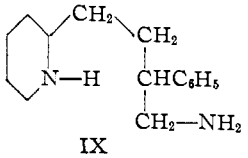
As a side-product, the reductive cyclization of α-carbethoxy-γ-(2-pyridyl)-butyronitrile (III) gave 3-aminomethyl-4-quinolizidone (VII). Similarly, the reduction of IV gave an appreciable quantity of the corresponding diamine (VIII). The formation of these side-products would indicate that reduction of the nitrile group can occur prior to reduction of the pyridine ring and, when it does, cyclization does not take place with the primary amine so formed. This idea, which is in accord with the proposed reaction scheme, was tested more rigorously by preparing a sample of VIII by the lithium aluminum hydride reduction of α-phenyl-γ-(2-pyridyl)-butyronitrile (IV) and subjecting this aminopyridine derivative to the conditions used in the reductive cyclization. The only product obtained in this case was the diamine (IX) resulting from a simple hydrogenation of the pyridine ring.



VII



VIII



IX

Additional support for the proposed reaction scheme was obtained when the reductive cyclization of α-phenyl-γ-(2-pyridyl)-butyronitrile (IV) was investigated using Raney nickel as catalyst instead of platinum. At 175°, the reduction of IV over Raney nickel gave the diamine (IX) as the major product with no indication of the formation of any cyclized material. Again, it would appear that cyclization was prevented by prior reduction of the nitrile group. When the reduction of IV over Raney nickel was investigated at still higher temperatures (200°), it was found that 3-phenylquinolizidine (VI) was formed in poor yield. Quite probably, the formation of 3-phenylquinolizidine in this case results from cyclization of the diamine (IX) in a manner analogous to the cyclization of carbinol amines over Raney nickel, as studied previously.[5] The possibility of preparing other quinolizidine derivatives by the Raney nickel procedure has not been investigated.

Since 3-carbethoxyquinolizidine was available from the reductive cyclization experiments, its conversion to 3-hydroxymethylquinolizidine, an isomer of lupinine, was studied. It was found that, on reduction with lithium hydride, 3-carbethoxyquinolizidine was converted to the corresponding 3-hydroxymethylquinolizidine in 54% yield. The product, so obtained, was a mixture of the two diastereoisomeric racemates and, through recrystallization of the corresponding picrolonate derivative followed by regeneration of the base, it was possible to obtain a sample of one of the racemates in a pure form. Recently, Winterfeld and Heinen have reported the preparation of 3-hydroxymethylquinolizidine (3-lupinine) by cyclization of 2-hydroxymethyl-4-(2′-pyridyl)-1-butanol.[6] The German authors reported partial separation of the two racemates by distillation. However, the lack of correspondence between the physical properties of their preparation and our own would suggest that either they have isolated a different racemate than we have or our own sample is of higher purity.

In our previous publication,[2] we reported that an attempt to prepare 3-hydroxymethylquinolizidine by the lithium aluminum hydride reduction of 3-carbethoxy-4-quinolizidone had given 4-quinolizidone as the product. Having been informed by Dr. Marion that 3-carbethoxy-4-quinolizidone could be successfully converted to 3-hydroxymethylquinolizidine with lithium aluminum hydride under the proper conditions, we have repeated our earlier experiments and indeed found that 3-hydroxymethylquinolizidine can be prepared in this way. Although this product, likewise, appeared to be a mixture of the two possible racemates, it was possible to isolate the same picrolonate derivative from this mixture as was isolated from the 3-hydroxymethylquinolizidine mixture obtained above by means of the reductive cyclization procedure. We are unable to advance any good explanation to account for the difference in behavior observed in our earlier experiments when 4-quinolizidone was isolated.[7]

In an extension of the general method of reductive cyclization, the synthesis of 1-hydroxymethylquinolizidine (XIV) was also investigated. The initial step in this preparation was the Michael condensation of ethyl 2-pyridylacetate with acrylonitrile. When the condensation was carried out according to the procedure of Rogers,[8] the desired γ-carbethoxy-γ-(2-pyridyl)-butyronitrile (XI) was obtained in 72% yield. This, on reductive cyclization over platinum, gave 1-carbethoxyquinolizidine

(5) V. Boekelheide and S. Rothchild, THIS JOURNAL, **70**, 864 (1948).

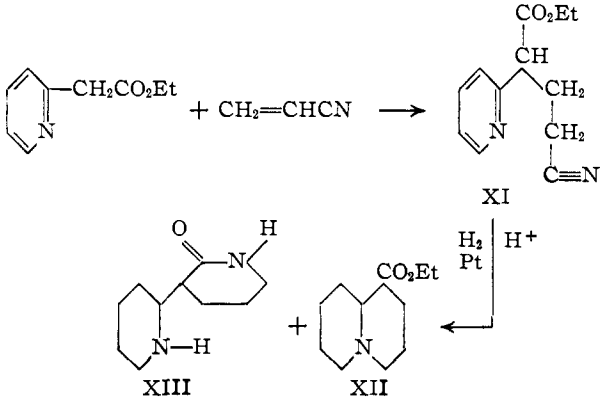
(6) K. Winterfeld and C. Heinen, *Ann.*, **573**, 85 (1951); *ibid.*, **578**, 171 (1952).

(7) We are indebted to Dr. Marion for calling our attention to this reaction. A detailed account of the lithium aluminum hydride reduction of 3-carbethoxy-4-quinolizidone will be published elsewhere by Dr. Marion.

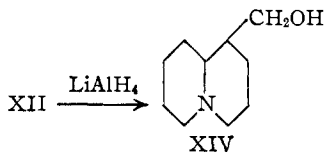
(8) A. O. Rogers, U. S. Patent 2,460,536 (1949); see *C. A.*, **43**, 3446 (1949).

(XII) in 29% yield. As illustrated below, the reduction of XI also gave 3-(2′-piperidyl)-2-piperidone (XIII) whose structure was established by its reduction with lithium aluminum hydride to the known 2,3′-bipiperidyl.[9]

The fact that 1-carbethoxyquinolizidine is formed in about the same yield as is 3-(2′-piperidyl)-2-piperidone would indicate that the rate of reduction of the pyridine ring in this case must be of the same order of magnitude as the rate of reduction of the nitrile group. This is based on the assumption that prior reduction of the pyridine ring leads exclusively to 1-carbethoxyquinolizidine whereas prior reduction of the nitrile group leads only to 3-(2′-piperidyl)-2-piperidone.



When 1-carbethoxyquinolizidine was reduced with lithium aluminum hydride, it was readily converted to a mixture of the two possible racemates of 1-hydroxymethylquinolizidine, XIV (*d,l*-lupinine and *d,l*-epilupinine). In view of the difficulties encountered by others in their attempts to separate or isomerize mixtures of lupinine and epilupinine,[10] we have not attempted to separate either *d,l*-lupinine or *d,l*-epilupinine in a pure state. Although this three-step procedure is an attractive one for preparing a mixture of the racemates of 1-hydroxymethylquinolizidine, an alternate approach utilizing ethyl acrylate instead of acrylonitrile is probably better suited for a large scale preparation of these derivatives. This alternate method is described in the experimental section.



Despite the fact that the yields so far encountered in the reductive cyclization of pyridyl nitriles have only been fair, the reaction is a versatile one and appears to be of general utility for synthesizing quinolizidine and indolizidine derivatives. As was shown in the case of the 1- and 3-hydroxymethylquinolizidines, it is possible by this method to prepare in relatively few steps compounds which would otherwise be accessible only by fairly lengthy reaction schemes. Possible applications of this method for the synthesis of other members of the lupin alkaloids are being investigated.

(9) F. Blau, *Monatsh.*, **13**, 330 (1892).

(10) G. R. Clemo and J. Rudinger, *J. Chem. Soc.*, 2714 (1951).

Experimental[11]

β-(2-Pyridyl)-propionitrile (I).—Although the preparation of β-(2-pyridyl)-propionitrile has been described by Doering and Weil,[3] the following procedure adapted from that of Frank and Mirza[4] was far more convenient and gave much higher yields. To a solution of 105 g. (1 mole) of freshly distilled 2-vinylpyridine and 204 g. (2 moles) of acetic anhydride there was added dropwise with stirring a solution of 130 g. (2 moles) of potassium cyanide in 250 ml. of water. The rate of addition of the aqueous cyanide solution was controlled to maintain gentle boiling of the mixture. After the addition of the cyanide was complete, the mixture was heated on a steam-bath with stirring for 16 hours. The mixture was then cooled and sufficient aqueous sodium carbonate was added to bring the solution to a *p*H of 8. It was then extracted several times with chloroform and the combined chloroform extracts were dried over magnesium sulfate. After removal of the chloroform *in vacuo*, the residual oil was distilled to give 88 g. (67%) of a colorless oil; b.p. 97–99° at 2 mm., $n^{20}D$ 1.5175. A picrate, prepared from this oil, melted at 140–142° dec. (lit.[3] m.p. 140–142° dec.).

Reductive Cyclization of β-(2-Pyridyl)-propionitrile.—A solution containing 13.2 g. of β-(2-pyridyl)-propionitrile, 100 mg. of Adams catalyst, 50 ml. of water, 16.2 ml. of 12 *N* hydrochloric acid and 50 ml. of ethanol was subjected to hydrogenation at room temperature and 3 atm. pressure of hydrogen. Hydrogen uptake was complete in 8 hours. After removal of the catalyst, the solution was concentrated to one-half volume under reduced pressure. While the resulting solution was maintained in an ice-bath, it was made basic by addition of a 10% aqueous sodium hydroxide solution and then was extracted three times with ether. The combined ether extracts were dried over potassium carbonate and then concentrated under reduced pressure. Distillation of the residual oil gave 5.4 g. (43%) of a colorless oil; b.p. 50–51° at 20 mm., $n^{20}D$ 1.4700. A picrate, prepared from this oil, was obtained, after crystallization from ethanol, as yellow crystals, m.p. 228.5–230°. A mixed melting point determination with an authentic sample of the picrate of indolizidine (m.p. 228–229°)[5] showed no depression of melting point.

α-Carbethoxy-γ-(2-pyridyl)-butyronitrile (III).—To a mixture of 500 g. of ethyl cyanoacetate containing 3 g. of sodium and maintained at 100°, there was added dropwise with stirring 90.0 g. of freshly distilled 2-vinylpyridine. After the addition was complete (1 hr.), the solution was maintained at 100–110° with stirring for an additional 5 hours. The solution was then cooled to room temperature and allowed to stand overnight. The reaction mixture was then added to an equal volume of cold 3 *N* hydrochloric acid. The organic layer containing recovered ethyl cyanoacetate was separated and the aqueous solution was extracted once with ether. The aqueous solution was then cooled strongly and made basic by addition of an aqueous potassium carbonate paste. The oil, which separated, was extracted thoroughly with ether, the combined ether extracts were dried over sodium sulfate, and then the ethereal solution was concentrated. Distillation of the residual oil gave 90.5 g. (48%) of a light yellow oil; b.p. 136–138° at 0.3 mm., $n^{20}D$ 1.5010.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46. Found: C, 65.94; H, 6.57.

The **picrate** of α-carbethoxy-γ-(2-pyridyl)-butyronitrile was obtained after crystallization from ethanol as yellow crystals, m.p. 102–103°.

Anal. Calcd. for $C_{18}H_{17}N_5O_9$: C, 48.32; H, 3.83. Found: C, 48.21; H, 3.73.

α-Phenyl-γ-(2-pyridyl)-butyronitrile (IV).—A solution of 180 g. of phenylacetonitrile containing 1.0 g. of sodium was maintained at 150–160° while 30.0 g. of freshly distilled 2-vinylpyridine was added dropwise with stirring. After the addition was complete, the reaction mixture was stirred at 160–170° for 5 hours. The reaction mixture was then cooled and added to an equal volume of cold 3 *N* hydrochloric acid. After separation of the recovered phenyl-

(11) Analyses by Mrs. G. L. Sauvage, Miss Claire King and Miss Viola Williams.

acetonitrile, the aqueous layer was extracted once with ether. The aqueous layer was then cooled in an ice-bath and made basic by addition of an aqueous paste of potassium carbonate. The oil, which separated, was extracted with ether and the combined extracts were dried over sodium sulfate. After concentration of the ethereal solution, the residual oil was distilled to give 48.8 g. (77%) of a light yellow oil; b.p. 149–151° at 0.5 mm., $n^{20}D$ 1.5633.

Anal. Calcd. for $C_{15}H_{14}N_2$: C, 81.04; H, 6.34. Found: C, 80.67; H, 6.12.

The **picrate** of α-phenyl-γ-(2-pyridyl)-butyronitrile was obtained after crystallization from ethanol as yellow crystals, m.p. 135–136°.

Anal. Calcd. for $C_{21}H_{17}N_5O_7$: C, 55.87; H, 3.77. Found: C, 55.54; H, 3.70.

Reductive Cyclization of α-Carbethoxy-γ-(2-pyridyl)-butyronitrile (III).—A mixture containing 25 g. of α-carbethoxy-γ-(2-pyridyl)-butyronitrile, 100 mg. of Adams catalyst, 25 ml. of 12 *N* hydrochloric acid, 100 ml. of ethanol and 100 ml. of water was subjected to hydrogenation at room temperature under 3 atm. pressure of hydrogen. Hydrogen uptake was rapid and corresponded to 5 molar equivalents of hydrogen at the end of 4 hours. After removal of the catalyst, the solution was concentrated to about one-half volume under reduced pressure and then was made basic by addition of an aqueous paste of potassium carbonate with continuous stirring and cooling (evolution of ammonia). The organic layer was extracted with benzene, the combined benzene extracts were concentrated, and the residual oil was distilled. This gave two main fractions: fraction I, b.p. 70–80° at 0.3 mm., and fraction II, b.p. 80–105° at 0.3 mm.

Redistillation of fraction I gave 6.2 g. of a colorless oil, b.p. 73–75° at 0.3 mm., $n^{20}D$ 1.4760. This fraction contains the mixture of racemates corresponding to 3-carbethoxyquinolizidine (V).

Anal. Calcd. for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02. Found: C, 68.39; H, 9.91.

When 900 mg. of oil from fraction I was treated with ethanolic picric acid, it yielded 1.25 g. of yellow crystals, m.p. 155–158°. After a further recrystallization from ethanol, there was obtained a sample of crystals melting at 158–159°. This corresponds to the picrate of one of the racemates of 3-carbethoxyquinolizidine.

Anal. Calcd. for $C_{18}H_{24}N_4O_9$: C, 49.09; H, 5.45. Found: C, 48.92; H, 5.42.

Concentration of the mother liquor from picrate preparation above caused the separation of an additional 200 mg. of a yellow solid. This, on recrystallization from ethanol, gave yellow crystals, m.p. 144–146°. This corresponds to the picrate of the second racemate of 3-carbethoxyquinolizidine.

Anal. Calcd. for $C_{18}H_{24}N_4O_9$: C, 49.09; H, 5.45. Found: C, 49.09; H, 5.51.

Redistillation of fraction II gave 5.5 g. of a colorless oil; b.p. 120–123° at 2 mm., $n^{20}D$ 1.5070. This corresponds to 3-aminomethyl-4-quinolizidone (VII).

Anal. Calcd. for $C_{10}H_{18}N_2O$: C, 65.38; H, 9.89. Found: C, 65.20; H, 9.59.

The **picrate** of 3-aminomethyl-4-quinolizidone was obtained after recrystallization from ethanol, as yellow crystals, m.p. 188–190°.

Anal. Calcd. for $C_{16}H_{21}N_5O_8$: C, 46.72; H, 5.11. Found: C, 47.03; H, 5.30.

The relative amounts of fractions I and II varied in different runs and were remarkably dependent on small changes in the reaction conditions. The total amount of the fractions I and II was fairly constant. The experiment cited above is intended to be typical of the results obtained and does not represent an optimum run for the preparation of 3-carbethoxyquinolizidine.

Reductive Cyclization of α-Phenyl-γ-(2-pyridyl)-butyronitrile (IV).—A mixture containing 27.0 g. of α-phenyl-γ-(2-pyridyl)-butyronitrile, 100 mg. of Adams catalyst, 25 ml. of 12 *N* hydrochloric acid, 100 ml. of ethanol and 100 ml. of water was subjected to hydrogenation at room temperature under 3 atm. pressure of hydrogen. When the hydrogen uptake was complete (36 hr.), the catalyst was removed and the solution was concentrated to one-half volume under reduced pressure. The cooled solution was then made strongly alkaline (evolution of ammonia) by addition of an aqueous paste of potassium carbonate. The aqueous solution was then extracted three times with chloroform and the combined chloroform extracts were dried over sodium sulfate. After removal of the chloroform, the residual oil was distilled to give three fractions: fraction I, b.p. 122–130° at 1.5 mm., weighed 6.0 g.; fraction II, b.p. 130–145° at 1.5 mm., weighed 2.4 g.; and fraction III, b.p. 153–157° at 1.5 mm., weighed 7.5 g.

Fractions I and II represent the two racemates corresponding to 3-phenylquinolizidine (VI). A mixture of the two fractions was redistilled for analysis.

Anal. Calcd. for $C_{15}H_{21}N$: C, 83.66; H, 9.83. Found: C, 83.33; H, 9.96.

The **picrate** from fraction I was obtained, after several recrystallizations from ethanol, as yellow crystals, m.p. 152–153°. This corresponds to the picrate of one of the racemates of 3-phenylquinolizidine.

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.77; H, 5.44. Found: C, 56.75; H, 5.36.

The **picrate** from fraction II was obtained, after several recrystallizations from ethanol, as yellow crystals, m.p. 171–172°. This corresponds to the picrate of the second racemate of 3-phenylquinolizidine.

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.77; H, 5.44. Found: C, 56.74; H, 5.38.

The **picrate** from fraction III was obtained, after recrystallization from ethanol, as yellow crystals, m.p. 202–203°. These were shown by a mixed melting point determination to be identical with the dipicrate of 2-phenyl-4-(2′-pyridyl)-*n*-butylamine (see below).

Anal. Calcd. for $C_{27}H_{24}N_8O_{14}$: C, 47.36; H, 3.53. Found: C, 47.17; H, 3.86.

2-Phenyl-4-(2′-pyridyl)-*n*-butylamine (VIII).—To a cold solution of 128 ml. of a 0.7 *M* ethereal solution of lithium aluminum hydride, there was added dropwise with stirring a solution of 20.0 g. of α-phenyl-γ-(2-pyridyl)-butyronitrile in 20 ml. of dry ether. After the addition was complete, the mixture was allowed to warm to room temperature and was allowed to stand with stirring for one hour. The reaction mixture was decomposed by the successive addition of 3 ml. of water, 3 ml. of a 20% aqueous sodium hydroxide solution and finally 15 ml. more of water. The ethereal solution was removed by decantation and the precipitated hydroxides were washed twice with 50-ml. portions of warm ether. After the combined ether solutions had been dried over sodium sulfate, the ether was removed and the residual oil was distilled, yielding 13.2 g. (65%) of a light yellow oil; b.p. 153–154° at 1.0 mm., $n^{20}D$ 1.5741.

Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.25; H, 8.42. Found: C, 79.50; H, 8.56.

The **dipicrate** of 2-phenyl-4-(2′-pyridyl)-*n*-butylamine readily formed in ethanol and, after recrystallization from a large volume of ethanol, was obtained as yellow crystals, m.p. 203–204°.

Anal. Calcd. for $C_{27}H_{24}N_8O_{14}$: C, 47.37; H, 3.53. Found: C, 47.70; H, 3.86.

2-Phenyl-4-(2′-piperidyl)-*n*-butylamine (IX).—A mixture containing 5.5 g. of 2-phenyl-4-(2′-pyridyl)-*n*-butylamine, 50 mg. of Adams catalyst, 6.5 ml. of 12 *N* hydrochloric acid, 25 ml. of ethanol and 25 ml. of water was subjected to hydrogenation at room temperature and under 3 atm. pressure of hydrogen. When hydrogenation was complete, the reaction mixture was worked up in the same manner described previously for the reductive cyclizations. There was obtained 3.6 g. (50%) of a colorless oil; b.p. 138–140° at 1.0 mm., $n^{20}D$ 1.5373.

Anal. Calcd. for $C_{15}H_{24}N_2$: C, 77.53; H, 10.41; N, 12.06. Found: C, 77.48; H, 10.90; N, 12.02.

3-Hydroxymethylquinolizidine (X).—To 40 ml. of a 0.7 *M* ethereal solution of lithium aluminum hydride there was added dropwise with stirring 4.7 g. of 3-carbethoxyquinolizidine. After the mixture had been boiled under reflux for two hours, it was decomposed by addition of moist ether followed by an excess of dilute hydrochloric acid. The aqueous layer was then removed and added to a well-cooled, concentrated solution of potassium hydroxide containing tartrate ion. The resulting solution was extracted several times with ether and the combined ether extracts were dried over sodium sulfate. After removal of the ether, the re-

sidual oil was distilled, yielding 2.0 g. (54%) of a viscous colorless oil, b.p. 101–109° at 2 mm. Upon standing overnight the oil solidified giving white crystals, m.p. 44–53°. This corresponds to a mixture of the two racemates of 3-hydroxymethylquinolizidine (3-lupinine).[6]

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31. Found: C, 70.86; H, 11.48.

When this solid was treated with an excess of phenyl isocyanate, it gave a phenylurethan which, after several recrystallizations from a benzene–hexane mixture, was obtained as white crystals m.p. 114–115° (Winterfeld and Heinen[6] reported a phenylurethan of 3-lupinine melting at 92–95°).

Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39. Found: C, 70.98; H, 8.53.

A **picrolonate** of 3-hydroxymethylquinolizidine was obtained, after two recrystallizations from ethanol, as golden crystals, m.p. 226–227° dec.

Anal. Calcd. for $C_{20}H_{27}N_5O_6$: C, 55.41; H, 6.28. Found: C, 55.53; H, 6.49.

When a sample of the picrolonate of 3-hydroxymethylquinolizidine was suspended in 20 ml. of chloroform and treated with three 10-ml. portions of a 4% lithium hydroxide solution, the free base was regenerated in the chloroform layer. After the chloroform layer had been separated, it was washed with water, dried and concentrated. The resulting solid, after two sublimations under reduced pressure, gave white crystals, m.p. 61–62°. This corresponds to one of the racemates of 3-hydroxymethylquinolizidine (Winterfeld and Heinen[6] reported that their preparation of 3-lupinine melted at 53–57°).

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31. Found: C, 71.52; H, 11.45.

Reduction of α-Phenyl-γ-(2-pyridyl)-butyronitrile (IV) over Raney Nickel. (a) 2-Phenyl-4-(2′-piperidyl)-*n*-butylamine (IX).—A mixture containing 6.1 g. of α-phenyl-γ-(2-pyridyl)-butyronitrile, 1 g. of Raney nickel catalyst and 18 ml. of ethanol was subjected to hydrogenation at 175° and under 100 atm. pressure of hydrogen for one hour. After removal of the catalyst and solvent the residual oil was distilled yielding 3.9 g. (46%) of a colorless oil, b.p. 141–143° at 1.0 mm.

Anal. Calcd. for $C_{15}H_{24}N_2$: C, 77.53; H, 10.41. Found: C, 78.06; H, 10.09.

The **diphenylthiourea** of 2-phenyl-4-(2′-piperidyl)-*n*-butylamine was prepared for purposes of characterization and was obtained from a benzene–hexane mixture as white crystals, m.p. 80–81°. This was shown by a mixed melting point determination to be identical with a sample of the diphenylthiourea (m.p. 80–81°) prepared from the 2-phenyl-4-(2′-piperidyl)-*n*-butylamine obtained previously from the platinum reduction (see above).

Anal. Calcd. for $C_{29}H_{34}N_4S_2$: C, 69.32; H, 6.82. Found: C, 69.89; H, 7.02.

(b) **3-Phenylquinolizidine (VI).**—A solution of 9.3 g. of α-phenyl-γ-(2-pyridyl)-butyronitrile in 25 ml. of ethanol was subjected to hydrogenation at 200° in the presence of Raney nickel catalyst and under 150 atm. pressure of hydrogen. When hydrogen was no longer absorbed, the catalyst and solvent were removed and the residual oil was distilled to yield 1.4 g. of a colorless oil, b.p. 115–120° at 0.4 mm. This, on conversion to the corresponding picrate, gave yellow crystals, m.p. 150–151°, which were shown to be identical by a mixed melting point determination with the corresponding picrate of 3-phenylquinolizidine previously obtained.

γ-Carbethoxy-γ-(2-pyridyl)-butyronitrile (XI).—The procedure employed is essentially that described by Rogers[8] for obtaining mono-addition of acrylonitrile to active methylene compounds. To a mixture of 40.0 g. of ethyl 2-pyridylacetate[12] and 0.2 g. of sodium maintained at 175–180°, there was added dropwise with stirring 6.4 g. of acrylonitrile. After addition was complete, the solution was maintained at 175–180° with stirring for 1.5 hours longer. The mixture was then cooled, diluted with ethylene chloride, and washed three times with a saturated aqueous solution of ammonium chloride. The ethylene chloride layer was separated, dried and concentrated. Distillation of the residual oil gave 14.8 g. of recovered ethyl 2-pyridylacetate and 19.8 g. (72%) of a light yellow oil, b.p. 137–140° at 0.7 mm., $n^{20}D$ 1.5030.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46; N, 12.84. Found: C, 66.06; H, 6.06; N, 13.30.

The **picrate** of γ-carbethoxy-γ-(2-pyridyl)-butyronitrile was obtained, after recrystallization from ethanol, as yellow crystals, m.p. 82–83°.

Anal. Calcd. for $C_{18}H_{17}N_5O_9$: C, 48.33; H, 3.80. Found: C, 48.47; H, 3.60.

Reductive Cyclization of γ-Carbethoxy-γ-(2-pyridyl)-butyronitrile.—A mixture containing 5.0 g. of γ-carbethoxy-γ-(2-pyridyl)-butyronitrile, 50 mg. of Adams catalyst, 5.6 ml. of 12 *N* hydrochloric acid, 20 ml. of ethanol and 20 ml. of water was subjected to hydrogenation at room temperature and under 3 atm. pressure of hydrogen. When five molar equivalents of hydrogen had been absorbed, the hydrogenation was stopped and the catalyst was removed. The solution was concentrated to one-half volume under reduced pressure and was then made basic by addition of an aqueous paste of potassium carbonate. The resulting solution was extracted carefully with chloroform and the combined chloroform extracts were dried and then concentrated. Distillation of the residual oil gave two fractions. The lower-boiling fraction consisted of 1.4 g. (29%) of a colorless oil, b.p. 95–100° at 1.0 mm. This corresponds to 1-carbethoxyquinolizidine (XII).

Anal. Calcd. for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02. Found: C, 68.53; H, 10.32.

A **picrate** of this oil formed slowly and, after recrystallization from ethanol, was obtained as yellow crystals, m.p. 137.5–138°. This corresponds to the picrate of one of the possible racemates of 1-carbethoxyquinolizidine. A picrate corresponding to the other racemate could not be isolated.

Anal. Calcd. for $C_{18}H_{24}N_4O_9$: C, 49.09; H, 5.49. Found: C, 49.13; H, 5.76.

The higher-boiling fraction from the reductive cyclization crystallized on the condenser and consisted of 1.5 g. of a white solid. A sample of this material, after recrystallization from an ethanol–ethyl acetate mixture, melted at 170–171°. This corresponds to 3-(2′-piperidyl)-2-piperidone (XIII).

Anal. Calcd. for $C_{10}H_{18}N_2O \cdot H_2O$: C, 59.98; H, 10.06. Found: C, 59.98; H, 9.80.

To prove the identity of the 2-(2′-piperidyl)-2-piperidone it was reduced to the known 2,3′-bipiperidyl. This reduction was carried out with lithium aluminum hydride following the same procedure described previously for the lithium aluminum hydride reduction of α-phenyl-γ-(2-pyridyl)-butyronitrile except that the reaction time was lengthened to 12 hours. From 1.3 g. of the 3-(2′-piperidyl)-2-piperidone there was obtained 0.5 g. of a white solid, m.p. 67–68° (lit.[9] gives a m.p. of 68° for 2,3′-bipiperidyl). The picrate of this solid was obtained, after crystallization from ethanol, as yellow crystals, m.p. 215–216° (lit.[9] gives 215° as the m.p. for 2,3′-bipiperidyl picrate).

1-Hydroxymethylquinolizidine (XIV).—A solution of 1.19 g. of 1-carbethoxyquinolizidine in 5 ml. of dry ether was added dropwise with stirring to 15 ml. of a 0.5 *M* ethereal solution of lithium aluminum hydride. After the addition was complete, the mixture was boiled under reflux for 4 hours. The mixture was then decomposed by addition of moist ether and the precipitated hydroxides were removed by decantation. The hydroxides were then digested with chloroform and the combined ether and chloroform extracts were dried over sodium sulfate. After removal of the solvent *in vacuo*, the residual oil was distilled yielding 0.5 g. of a colorless oil, b.p. 85–90° at 0.7 mm.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31. Found: C, 71.21; H, 11.56.

A **methiodide** formed readily when this oil was treated with methyl iodide; after crystallization from methanol, the methiodide was obtained as white crystals, m.p. 287–288° dec. Since the methiodides of *d,l*-lupinine and *d,l*-epilupinine have previously been reported to melt at 303° (dec.) and 248°, respectively,[13] the methiodide obtained in our preparation corresponds to that of *d,l*-lupinine.

(12) R. B. Woodward and E. C. Kornfeld, *Org. Syntheses*, **29**, 44 (1949).

(13) G. R. Clemo, W. M. G. Morgan and R. Raper, *J. Chem. Soc.*, 965 (1937).

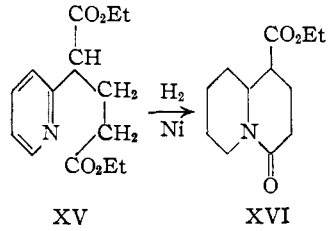
Anal. Calcd. for $C_{11}H_{22}NOI$: C, 42.45; H, 7.13. Found: C, 42.63; H, 7.26.

Diethyl α-(2-Pyridyl)-glutarate (XV).—This was prepared by the addition of ethyl acrylate to ethyl 2-pyridylacetate[12] according to the general procedure of Rogers.[8] To a solution of 0.2 g. of sodium in 50.0 g. of ethyl pyridylacetate maintained at 130–140°, there was added dropwise with stirring 10.0 g. of ethyl acrylate. After the mixture had been heated at 130–140° for two hours, it was cooled and diluted with benzene. The benzene solution was washed with water and then concentrated. Distillation of the residual oil gave 29.5 g. of recovered ethyl 2-pyridylacetate and 20.4 g. (82%) of a colorless oil, b.p. 140–146° at 1 mm., $n^{20}D$ 1.4964.

Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.21. Found: C, 63.73; H, 6.99.

1-Carbethoxy-4-quinolizidone (XVI).—The conversion of diethyl α-(2-pyridyl)-glutarate to 1-carbethoxy-4-quinolizidone (XVI) was accomplished by hydrogenation over Raney nickel catalyst as illustrated below. A mixture containing 17.0 g. of diethyl α-(2-pyridyl)-glutarate, 2 g. of Raney nickel catalyst and 15 ml. of ethanol was subjected to hydrogenation at 175° and under 100 atm. pressure of hydrogen. When hydrogen was no longer absorbed, the reaction mixture was cooled and the catalyst and solvent were removed. Distillation of the residual oil gave 11.6 g. (80%) of a colorless oil; b.p. 155–158° at 2 mm., $n^{20}D$ 1.4949.

Anal. Calcd. for $C_{12}H_{19}NO_3$: C, 64.00; H, 8.44. Found: C, 64.04; H, 8.43.



XV XVI

Although 1-carbethoxy-4-quinolizidone was not actually converted to 1-hydroxymethylquinolizidine, such a conversion has previously been reported for 1-carbomethoxy-4-quinolizidone.[14]

In view of the high yields encountered in the preparation of XV and XVI, this would appear to be the best approach for a large scale preparation of *d,l*-lupinine or *d,l*-epilupinine.

(14) V. Boekelheide and J. P. Lodge, Jr., THIS JOURNAL, **73**, 3681 (1951).

ROCHESTER, NEW YORK

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

The Veratrine Alkaloids. XXXV. Veracevine, the Alkanolamine of Cevadine and Veratridine[1]

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The gentle saponification of cevadine and so-called veratrine yields a new alkanolamine, veracevine. Further treatment with alkali progressively isomerizes veracevine to cevagenine and finally cevine. The mild saponification conditions used for its formation and a study of its ultraviolet and infrared spectra, demonstrate that *veracevine and not cevine or cevagenine* is the genuine alkanolamine present in ester form in the principal constituents of veratrine. Veracevine, like cevine, contains one double bond and eight hydroxyl groups. Germine has been similarly isomerized to an unsaturated base analogous to cevine, and given the trivial name pseudogermine.

In a previous paper Jaffe and Jacobs[2] presented data on the isomerism observed with the highly hydroxylated veratrine bases cevine, germine and protoverine. Under the influence of alkali these singly unsaturated bases, in which the double bond was assumed to be in the neighborhood of a hydroxyl bearing carbon atom, were observed to change from a normal form designated as the α-base to a β-base owing to a double bond shift with development of a characteristic absorption in the ultraviolet. This isomerization was followed in turn by a change to the carbonyl-containing iso bases. More recent studies have shown that other changes occur under the influence of alkali. This has been presented in part in two recent articles of Stoll and Seebeck[3] who correctly concluded that cevine which was previously assumed to be the parent base occurring in the natural ester alkaloids is itself a product of alkali isomerization. Under gentler conditions a ketonic base, cevagenine, was isolated which they concluded to be the original base occurring in the natural alkaloids. However, our more recent data have led us to a different conclusion.

We have found that crystalline cevadine, which was separated over alumina from commercial veratrine (E. Merck and Co.), when carefully saponified at 0° yields up to 90% of a new base which crystallized as needles from ether and which has been given the trivial name veracevine (m.p. 181–183°, $[\alpha]D$ −24° in abs. EtOH). A similar result was obtained with veratrine itself which is said to be principally a mixture of cevadine and veratridine, thus demonstrating that veratridine is also a veracevine ester. Analytical data were in accord with the formulation $C_{27}H_{43}NO_8$. In the ultraviolet it showed essentially uneventful end absorption as in the case of α-cevine. Although its infrared spectrum (Fig. 1) differed from that of α-cevine, it showed a weak band at 1635 cm.$^{-1}$ approximating the α-cevine band at 1625 cm.$^{-1}$ and both suggesting ethylenic absorption. Like cevine it showed no carbonyl absorption in the ultraviolet or infrared. When the saponification of cevadine was effected at a higher temperature (40°) some cevagenine was also isolated. It was subsequently found that veracevine itself was isomerized to cevagenine under the conditions of Stoll and Seebeck. The yield of cevagenine depends upon the temperature as well as the time and

(1) The essential data obtained by us concerning the isolation and characterization of veracevine as a precursor of cevagenine and cevine was contained in a manuscript received by THIS JOURNAL Oct. 22, 1952.

(2) H. Jaffe and W. A. Jacobs, *J. Biol. Chem.*, **193**, 325 (1951).

(3) A. Stoll and E. Seebeck, *Helv. Chim. Acta*, **35**, 1270, 1942 (1952).