[Contribution from the Warner Institute for Therapeutic Research]

ATTEMPTED SYNTHESES OF PELLETIERINE[1]

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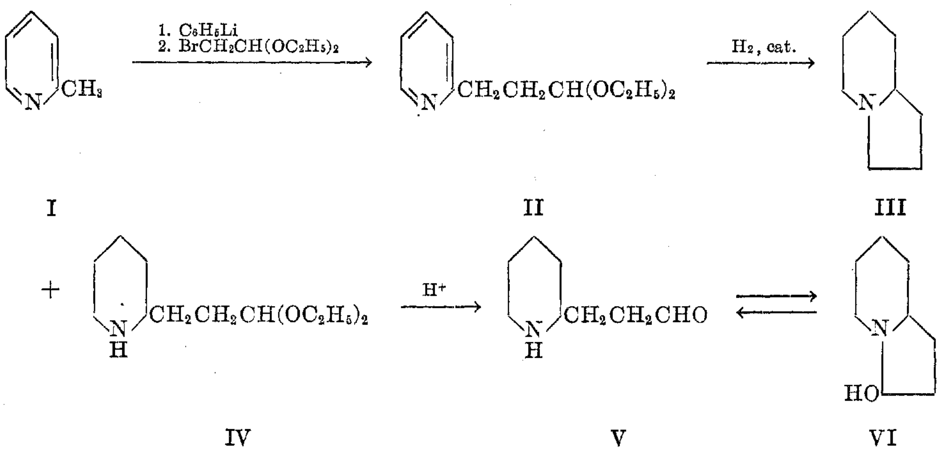
Although the structure of the anthelmintic alkaloid pelletierine as β-(2-piperidyl)propionaldehyde (V) was established over thirty years ago by Hess and Eichel (1), this relatively simple molecule has thus far resisted all synthetic attempts upon it.

Wibaut and Beets (2) experienced little difficulty in converting α-picoline (I) to β-(2-pyridyl)propionaldehyde diethyl acetal (II) which they subsequently (3) could hydrogenate to δ-coniceine (octahydropyrrocoline) (III) (4) or β-(2-piperidyl)propionaldehyde diethyl acetal (pelletierine acetal, IV) or mixtures of both depending upon the concentration of II in the hydrogenation solvent. All attempts to hydrolyze pelletierine acetal to the free aldehyde (V) yielded only unstable viscous oils which rapidly resinified and the Dutch workers were unable to obtain even a functional derivative of the elusive aldehyde. Beets (5) later found that hydrogenation of a dilute hydrochloric acid solution of IV, after the solution had been heated, proceeded with uptake of four moles of hydrogen to give exclusively III, isolated in 89% yield as its picrate. This, together with other considerations, led Beets to suggest that pelletierine could and probably did exist in some sort of bicyclic structure such as VI.



Independently and simultaneously Spielman, Swadesh, and Mortenson (6) were attempting the same synthesis by essentially the same route. They were able to convert II to IV in 82% yield and they then could prepare, from IV, several pelletierine derivatives which corresponded in properties to those described by Hess as obtained from natural pelletierine; these included N-benzoyl-

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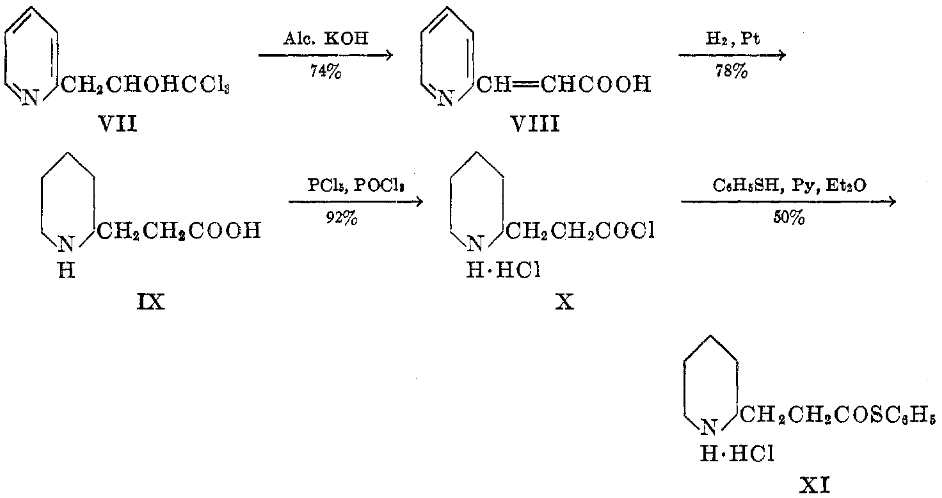
pelletierine (7), N-acetylpelletierine (7), and pelletierine ethyl urethane (8). But, just as the Dutch workers, they were unable to prepare free pelletierine from any of the derivatives they had and, likewise, suggested that the marked instability of pelletierine could possibly be due to its partial existence in the carbinol amine configuration VI.

Because both Wibaut and Beets and Spielman and co-workers had been unable to prepare pelletierine by acidic treatment of one of its most logical chemical precursors, there was devised a reaction scheme which had as its ultimate step a reaction carried out under essentially neutral conditions, namely, the Raney nickel desulfurization of a thiol ester group to an aldehyde group (9–12). To this end, the following sequence of reactions was carried out:



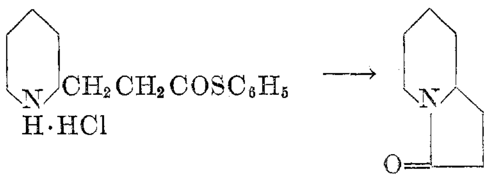
1,1,1,-Trichloro-2-hydroxy-3-(2-pyridyl)propane (VII) was prepared by the condensation of chloral with α-picoline according to the procedure of Tullock and McElvain (13). In the hydrolysis and dehydration of the trichlorocarbinol VII to β-(2-pyridyl)-acrylic acid (VIII) a variety of conditions was tried in addition to those reported by Einhorn and Liebrecht (14). Slow addition of VII to alcoholic caustic proved most desirable, since the reverse addition resulted in little product and much tar. The method used by Rabe and Kindler (15) for the 4-pyridyl isomer, which consisted of mixing alcoholic solutions of caustic and of VII and permitting the hydrolysis to proceed spontaneously was no better. A decided improvement, however, consisted of baking the dry hydrolysis mixture in a vacuum-oven overnight, indicating that the intermediate hydroxy acid does not dehydrate well in alcoholic solution.

The over-all one-step reduction by catalytic means of β-(2-pyridyl)acrylic acid (VIII) to β-(2-piperidyl)propionic acid (IX) is not reported in the chemical literature. Loeffler and Kaim (4) carried out the complete reduction with sodium and alcohol and Winterfeld and Holschneider (16) described the catalytic reduction of β-(2-pyridyl)propionic acid to IX but did not say how they obtained this propionic acid from VIII. We were able to obtain a satisfactory conversion of VIII to IX in one step with hydrogen and platinum oxide.

The hydrochloride of the amino acid (IX) was converted to the corresponding acid chloride (X) by Winterfeld and Holschneider (16) with thionyl chloride. We found that the reaction is greatly improved through the use of phosphorus pentachloride in phosphorus oxychloride as the solvent.

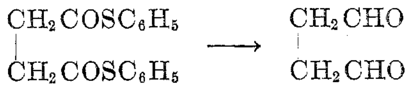
Several unsuccessful methods were attempted for the conversion of the acid chloride (X) to phenyl β-(2-piperidyl) thiolpropionate hydrochloride (XI): portionwise addition of X to an aqueous solution of the sodium salt of thiophenol (17); stirring a suspension of X and the lead salt of thiophenol in ether (18); and addition of X to an ethereal solution of thiophenol followed by the addition of tri-*n*-butylamine (19). The desired product was ultimately prepared, in satisfactory yield, merely by shaking a suspension of X in an ethereal solution of pyridine and thiophenol (20).

The conversion of the thiol ester (XI) to the aldehyde (V) was attempted using freshly prepared ordinary Raney nickel (21), as well as the more active W-4 catalyst of Pavlic and Adkins (22, 23), both with and without preliminary acetone deactivation as recommended by Spero, McIntosh, and Levin (10). In each case the only identifiable product obtained from the reaction was a neutral liquid subsequently identified as 3-ketoöctahydropyrrocoline (XII) (4). Our failure to obtain the desired aldehyde led us to suspect that the salt-forming hydrochloric acid in the amino ester molecule was reacting with the nickel catalyst to produce the free amino ester corresponding to XI, and that this free amino ester was spontaneously eliminating a molecule of thiophenol to produce XII; this suspicion was verified by treatment of XI with exactly one equivalent of sodium bicarbonate in alcohol to give a neutral liquid [β-(2-piperidyl)propionic acid melts at 147–148° (4)] which on hydrolysis and esterification gave ethyl β-(2-piperidyl)propionate; only structure XII satisfies these requirements.



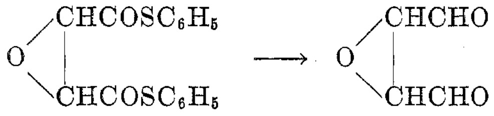
XI XII

The activity of our catalyst was demonstrated by the desulfurization of diphenyl dithiolsuccinate (XIII) to succindialdehyde (XIV) identified as its bis-2,4-dinitrophenylhydrazone, although no epoxysuccindialdehyde (XVI) was obtained from the corresponding diphenyl dithiolepoxysuccinate (XV).



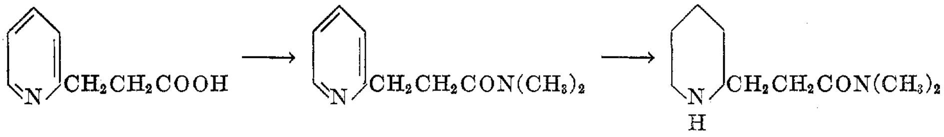
$$\begin{array}{l} CH_2COSC_6H_5 \\ | \\ CH_2COSC_6H_5 \end{array} \longrightarrow \begin{array}{l} CH_2CHO \\ | \\ CH_2CHO \end{array}$$

XIII XIV



XV XVI

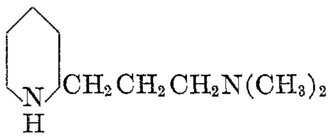
Our signal lack of success in the attempted conversion of the thiol ester to pelletierine forced us to seek some other mild reaction which avoided strongly acidic conditions for the transformation of a pelletierine precursor to the aldehyde. Such a reaction appeared to be the lithium aluminum hydride reduction of an amide. Although it has been amply demonstrated (24–31) that uncontrolled reduction of amides by this reagent leads to amines, Friedman (32) recently reported that excellent yields of aldehydes could be obtained by the low-temperature reduction of amides, preferably N,N-disubstituted, by suitable control of the amount of lithium aluminum hydride used. For this purpose N,N-dimethyl



XVII XVIII XIX

β-(2-piperidyl)propionamide (XIX) was prepared *via* the sequence XVII–XIX.

Reduction of this material under the conditions described by Friedman, however, gave as the only identifiable product the completely reduced substance γ-(2-piperidyl)propyldimethylamine (XX) in 20% yield.



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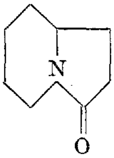
In view of Friedman's statement that amides containing an active hydrogen are less suitable for reduction to aldehydes than those lacking such a hydrogen, the reduction was tried on 3-ketoöctahydropyrrocoline (XII). Under the recommended low-temperature conditions a 63% recovery of unchanged lactam was obtained, plus a 21% yield of a higher-boiling, rapidly resinifying fraction that was immediately converted to an amorphous hydrobromide, which gave an approximately correct analysis for pelletierine hydrobromide; this, however, despite its fairly close agreement with the reported melting point of pelletierine hydrobromide, must be considered as polymeric because of its physical properties. When the reduction was carried out in refluxing ether for five hours followed by standing at room temperature for 15 hours there was still obtained a 58% recovery of starting material, but this time there was also isolated a 17% yield of the completely reduced substance octahydropyrrocoline (III).

Inspection of published reports of the complete reduction of lactams by lithium aluminum hydride reveals considerable variation in their ease of reduction: 60 hours in refluxing ether were used for the conversion of strychnine to strychnidine in 91% yield (33) and 72 hours at room temperature reduced (−)oxysparteine to (−)sparteine in 35% yield (34); a short while at room temperature is reported to reduce pyrrolidones (35) and N-alkyloxindoles (36), while several hours refluxing in tetrahydrofuran (37) or dioxane (38) was used to reduce a lactamic group in a tetrahydronaphthocarboline. These substances, including XII, fall roughly into two groups: those in which the lactamic nitrogen is at a bridgehead are reduced with difficulty while others are readily reduced indicating a probable steric factor to be operating.

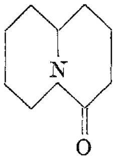
Repetition of the reduction at low temperature, followed by a shorter refluxing period, again gave some of the higher-boiling fraction. This material had an equivalent weight (by acid titration) of 139, gave an immediate precipitate with Tollen's reagent, and yielded a benzoyl derivative that melted in the same range as N-benzoylpelletierine; its boiling point, however, excluded structure V. With the thought that perhaps Hess' ability to distill pelletierine without its polymerization was due to the presence of traces of natural antioxidants carried along with it during its isolation, another reduction was carried out and there was added to the reaction mixture, immediately after decomposition of unreacted lithium aluminum hydride, a mixture of α-tocopherol and hydroquinone; further, the entire distillation apparatus was rinsed, prior to use, with an ethereal solution of these two antioxidants. A portion (one-fourth) of the ethereal reaction mixture was shaken out with 5% hydrobromic acid and yielded as a crystalline salt only the hydrobromide of 3-ketoöctahydropyrrocoline; the aqueous extract showed no reducing properties. The rest of the ethereal reaction mixture was fractionally distilled in the apparatus which had been rinsed with antioxidants and gave octahydropyrrocoline (11%), the unchanged lactam (72%), and the higher-boiling material (16%) showing reducing properties.

Because the reaction mixture prior to distillation showed no reducing properties and the higher-boiling material behaving as a polymeric pelletierine is only obtained by essentially pyrolysis (bath temperature 300°, vapor temperature 150–160° at less than 1 mm.) we believe that the monomeric pelletierine formed in the reduction undergoes aldol condensation polymerization as it is formed in the reaction mixture; these macromolecules are pyrolyzed to dimers or trimers on distillation, and then more slowly repolymerize again after distillation.

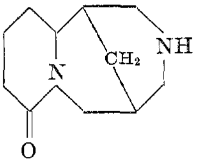
The above-mentioned formation of the hydrobromide of 3-ketoöctahydropyrrocoline (XII) seemed rather unusual in that amides are not usually thought of as substances which form isolable salts in aqueous solution. In looking for



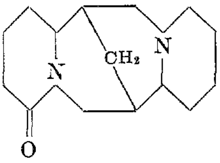
XII



XXI



XXII



XXIII

other examples of this phenomenon in addition to the hydrochloride formation of XII, reported by Loeffler and Kaim (4), we found that 4-ketoquinolizidine (XXI) forms a hydrochloride (39, 40); no attempt at salt formation was reported on 3-ketopyrrolizidine (41), and 5-ketoöctahydropyrrocoline is not described in the literature. More complex examples of nitrogen-bridgehead lactams that have salt-forming properties are cytisine (XXII) which forms a dihydrochloride (42) [as also does oxycytisine (43)] and lupanine, XXIII, which likewise forms a dihydrochloride (44). We hope to later present a satisfactory explanation of this phenomenon.

After this paper was written we learned that Galinovsky (45) has similarly carried out the lithium aluminum hydride reduction of 3-ketoöctahydropyrrocoline and obtained a material which, from his description of its properties, and in the absence of experimental details, we conclude to be identical with that obtained by us.

EXPERIMENTAL

β-(2-Pyridyl)acrylic acid (VIII). To a solution of 85% potassium hydroxide pellets (204 g., 3.1 moles) in alcohol (1300 cc.) there was added during a period of five hours a solution of 1,1,1-trichloro-2-hydroxy-3-(2-pyridyl)propane (13) (170 g., 0.71 mole) in alcohol (550 cc.) while the temperature of the mixture was maintained at 60–65°. Most of the salt was removed and the filtrate was taken to dryness under a vacuum. The residue was dissolved in one liter of water and the solution was boiled with charcoal (30 g.) for one hour, then filtered, and the filtrate brought to *p*H 4 with acetic acid. The precipitated solid weighed 20.0 g. and melted at 194–197° (dec.). To the filtrate were added more potassium hydroxide pellets (204 g., 3.1 moles), the alkaline solution was taken to dryness under a vacuum, and then baked in a vacuum-oven at 80° and 20 mm. overnight. The dry residue was taken up in 500 cc. of water and was adjusted to *p*H 4 with acetic acid and the second crop of product, 57.8 g., m.p. 202–204° [reported (46), 202–203°], was removed. The total yield was 77.8 g. (74%). Material which melts as low as 185° is suitable for the next step.

β-(2-Piperidyl)propionic acid hydrochloride (IX). A solution of β-(2-pyridyl)acrylic acid (14.9 g., 0.10 mole) in acetic acid (150 cc.) to which was added 0.25 g. of Adams' platinum oxide was shaken with hydrogen at room temperature under about three atmospheres pressure. The hydrogen consumption was 91% of the theoretical at the end of ten hours, when the hydrogenation was stopped. The solution, from which the catalyst had been removed, was stirred with 2 g. charcoal for one hour, filtered again, and to this filtrate there was added 10 cc. concentrated hydrochloric acid. Removal of all solvent under a vacuum left a crystalline residue which on recrystallization from alcohol (150 cc.) gave 11.8 g. of product in the first crop; on dilution of the mother liquor with ether there was obtained a second crop of 3.4 g. of equally good material. Total yield, 15.2 g. (78.5%), m.p. 183° [reported (4) for purified material, m.p. 188°].

β-(2-Piperidyl)propionyl chloride hydrochloride (X). β-(2-Piperidyl)propionic acid hydrochloride (39 g., 0.20 mole) was suspended in phosphorus oxychloride (200 cc.). To this mixture there was added, in one portion and with rapid stirring, finely ground phosphorus pentachloride (45.7 g., 0.22 mole). The temperature of the mixture rose spontaneously to 50° and was maintained there for one-half hour with a water-bath. The phosphorus oxychloride was removed by vacuum-distillation from the water-bath *at 50°*. The residue was washed five times with *pure dry* acetone and was then stored in a vacuum-desiccator. The product weighed 39.3 g. (92% yield) and melted at 116–118° [reported (16), 118–120°]. Since the material cannot be recrystallized without decomposition, and the less pure it is the higher its melting point lies (due to the contamination by the high-melting amino acid hydrochloride), the material was analyzed.

Anal. Calc'd for $C_8H_{14}ClNO \cdot HCl$: Cl, 33.49. Found: Cl, 32.87.

Phenyl β-(2-piperidyl)thiolpropionate (XI). A mixture of β-(2-piperidyl)propionyl chloride hydrochloride (39 g., 0.183 mole), thiophenol (40.3 g., 0.366 mole), pyridine (28.9 g., 0.366 mole), and dry ether (400 cc.) was placed in a tightly stoppered flask and shaken overnight. The solid was removed and crystallized from isopropyl alcohol (400 cc.) to give 23.4 g., (45% yield) of product, m.p. 144–148°, and a second crop of 2.5 g. (5% yield), m.p. 146–149°. The compound is not stable, as is shown by the following analyses.

Anal. Calc'd for $C_{14}H_{18}NOS \cdot HCl$: C, 58.90; H, 7.07; S, 11.21; Cl, 12.46.
Found (immediately): C, 59.37; H, 7.29; S, 11.01; Cl, 12.51.
Found (after six hours): C, 58.40; H, 7.22. Found (after ten hours): C, 57.10; H, 7.20.

The melting point of the material also decreases with time; the highest-melting samples obtained melted at 151–153.5°.

Treatment of XI with Raney nickel. The following experiment is typical. Phenyl β-(2-piperidyl)thiolpropionate hydrochloride (23 g., 0.08 mole) was dissolved in 95% alcohol (150 cc.) and to the hot stirred solution there was added 12 teaspoons of Raney nickel; the mixture was stirred and refluxed for 1.5 hours, after which time a small portion of the mixture gave no odor of thiophenol on treatment with hydrochloric acid. After removal of the nickel the filtrate was evaporated to dryness under a vacuum and the resultant residue was leached with ether to remove organic material. The ethereal extract yielded on distillation about 6 grams of material which had b.p. 84–86°/1.2 mm. and analyzed satisfactorily for 3-ketoöctahydropyrrocoline (4).

Anal. Calc'd for $C_8H_{13}NO$: C, 69.07; H, 9.35.
Found: C, 69.34; H, 9.09.

Treatment of XI with sodium bicarbonate. A mixture of the thiol ester XI (0.715 g., 2.5 millimoles) and sodium bicarbonate (0.210 g., 2.5 millimoles) suspended in 50 cc. of absolute alcohol was stirred under reflux for two hours, then cooled and the sodium chloride removed. The alcohol was removed under a vacuum and the resultant liquid residue was taken up in benzene; saturation of the benzene solution with dry hydrogen chloride gave no precipitate, indicating the absence of any of not only the original thiol ester but also of any compound with basic properties, because the hydrochlorides of any such substances would be benzene-insoluble. The benzene was washed with dilute sodium hydroxide, after which the solvent was removed under a vacuum, and the residual liquid was refluxed two hours with concentrated hydrochloric acid, washed with ether, and then evaporated to leave a solid [β-(2-piperidyl)propionic acid hydrochloride] which on recrystallization from ethanol gave ethyl β-(2-piperidyl)propionate hydrochloride, m.p. 116–120°, undepressed when mixed with an authentic sample prepared similarly from IX·HCl.

Succindialdehyde (XIV). To a hot solution of diphenyl dithiolsuccinate (47) [3.00 g., 0.010 mole, prepared from succinyl chloride (48) and thiophenol in aqueous alkali (17)] in 95% alcohol (50 cc.) there was added three teaspoons of Raney nickel and the mixture was refluxed with stirring for two hours. The nickel was removed and the filtrate was diluted with water to precipitate 0.80 g. of unchanged thiol ester. This was removed and the filtrate was added to one liter of *N* hydrochloric acid saturated with 2,4-dinitrophenylhydrazine and allowed to stand overnight. There was obtained 1.10 g. (34% yield based on unrecovered starting material) of bis-dinitrophenylhydrazone, m.p. 255–265°, m.p. raised to 268–270° after recrystallization from much ethanol (49).

Epoxysuccinyl chloride. A mixture of epoxysuccinic acid (6.6 g., 0.05 mole) [prepared in 25% over-all yield by hydrogen peroxide oxidation of hydroquinone (50)] and phosphorus pentachloride (20.9 g., 0.10 mole) was warmed until a vigorous reaction ensued; when this had subsided the mixture was heated an additional four hours at reflux (120°) and then fractionally distilled to give 5.5 g. (65% yield) of acid chloride, b.p. 104–108°/25 mm. The yellowish oily material did not give a satisfactory analysis, although the analysis did indicate the material to be as represented.

Anal. Calc'd for $C_4H_2Cl_2O_3$: C, 28.40; H, 1.18; Cl, 42.02.
Found: C, 26.50; H, 1.38; Cl, 44.86.

This material was also prepared by Schopf and Arnold (51) and reported, with no analysis at all, as having b.p. 95°/13 Torr, m.p. 36–41°, although we learned of their preparation sometime after we had made the substance.

Diphenyl dithiolepoxysuccinate (XV). Epoxysuccinyl chloride (5.1 g., 0.03 mole) was added dropwise to an ice-cold solution of thiophenol (4.4 g., 0.04 mole) in 20 cc. of 2 *N* sodium hydroxide, after which the mixture was vigorously agitated for a few minutes. A crystalline substance slowly formed and was removed and recrystallized from ethanol to give 2.1 g. (33% yield) of dithiol ester which melted, after an additional recrystallization, at 89.5–90.5°.

Anal. Calc'd for $C_{16}H_{12}O_3S_2$: S, 20.23. Found: S, 20.45.

N,N-Dimethyl β-(2-pyridyl)propionamide (XVIII). Gaseous dimethylamine was bubbled through molten β-(2-pyridyl)propionic acid (16) (100 g., 0.66 mole) maintained at 200° for a period of two hours. The cooled reaction mixture was taken up in benzene, washed with concentrated potassium carbonate solution, and then dried over potassium carbonate. After removal of the solvent, distillation gave 88.0 g. (75% yield) of the amide, b.p. 110° (0.2 mm.).

Anal. Calc'd for $C_{10}H_{14}NO$: C, 67.39; H, 7.92; N, 15.72.
Found: C, 67.25; H, 7.60; N, 15.89.

N,N-Dimethyl β-(2-piperidyl)propionamide (XIX). A solution of N,N-dimethyl β-(2-pyridyl)propionamide (41.5 g., 0.23 mole) in glacial acetic acid (100 cc.) was hydrogenated at room temperature and three atmospheres pressure in the presence of Adams' catalyst (1.0 g.). The theoretical pressure drop was 58 lbs. for 0.69 moles of hydrogen; hydrogen uptake ceased after a pressure drop of 55 lbs., at the end of 17 hours. After removal of the catalyst most of the solvent was removed under a vacuum at 40°. The residue was taken up in benzene, washed with concentrated potassium carbonate solution, and then dried over potassium carbonate. Fractional distillation gave 14.5 g. (34% yield) of product, b.p. 91–93° (0.2 mm.).

Anal. Calc'd for $C_{10}H_{20}N_2O$: C, 65.17; H, 10.94; N, 15.19.
Found: C, 65.08; H, 11.04; N, 15.35.

Lithium aluminum hydride reduction of XIX. To N,N-dimethyl-β-(2-piperidyl)propionamide (5.0 g., 0.027 mole) in dry ether (50 cc.) cooled to −70° there was slowly added, with good stirring, a solution of lithium aluminum hydride (0.55 g., 0.013 mole) in dry ether while the reaction mixture was maintained below −60°. The mixture was allowed to warm spontaneously to room temperature, then was cooled to −20° and decomposed with 1:10 hydrochloric acid (100 cc.). The ethereal layer, after drying over sodium sulfate, left a negligible residue on evaporation of the solvent. The aqueous layer was neutralized with a slight excess of sodium bicarbonate and then extracted with two 100-cc. portions of chloroform; evaporation of the chloroform left 1.0 g. of residue which was not investigated further, since pelletierine is reported (52) to not be liberated from its salts by sodium bicarbonate. The aqueous solution was then made more strongly alkaline with a considerable excess of potassium carbonate and again extracted with two 100-cc. portions of chloroform. Removal of the solvent left 1.9 g. of residue which on distillation gave 1.0 g. (20% yield) of γ-(2-piperidyl)-propyldimethylamine, b.p. 60° (10 mm.).

Anal. Calc'd for $C_{10}H_{22}N_2$: C, 70.52; H, 13.02; N, 16.47.
Found: C, 70.83; H, 12.76; N, 16.58.

A small portion of the diamine was converted to its hydrobromide which melted at 224° (dec.), after recrystallization from ethanol.

Anal. Calc'd for $C_{10}H_{22}N_2 \cdot 2\ HBr$: N, 8.43; Br, 48.2.
Found: N, 8.77; Br, 48.7.

Another small portion of the material was converted to its hydrochloride which, after recrystallization from ethanol, melted at 255° (dec.).

Anal. Calc'd for $C_{10}H_{22}N_2 \cdot 2\ HCl$: N, 11.52; Cl, 29.20.
Found: N, 11.18; Cl, 28.64.

The residue from the distillation of the diamine would not yield a crystalline hydrobromide or hydrochloride.

When the crude material was treated with hydrobromic acid, without distillation, the only crystalline product obtainable was the diamine hydrobromide.

3-Ketoöctahydropyrrocoline (XII). This was prepared by thermal dehydration of β-(2-piperidyl)propionic acid. The acid (25.2 g., 0.167 mole) was heated at 200° at atmospheric pressure for one-half hour and then slowly distilled under a vacuum (bath 230°, vapor 160°); on redistillation there was obtained 17.0 g. (73% yield) of material, b.p. 152–154° (28 mm.), n_D^{25} 1.4993. Reported (4), b.p. 126–127° (12 mm.), 263–264° atmospheric.

Lithium aluminum hydride reduction of XII. A. 3-Ketoöctahydropyrrocoline (7.0 g., 0.05 mole) was reduced with lithium aluminum hydride (0.47 g., 0.0125 mole) as described above for the reduction of XIX. The ethereal layer of the decomposed reaction mixture was separated, the aqueous layer was extracted with an additional 100 cc. of ether, and the ethereal extracts were combined and dried. Removal of the solvent left 0.8 g. of residue which was unchanged lactam. The aqueous layer of the decomposed reaction mixture was treated with sodium bicarbonate (10 g.), the gelatinous precipitate of aluminum hydroxide was removed, and the filtrate was extracted with two 100-cc. portions of chloroform. Removal of the solvent left a residue weighing 3.6 g. On distillation this material boiled at 120° (9 mm.), n_D^{25} 1.5016; this, together with the 0.8 g. obtained in the ether extracts, represents 63% of the material charged.

The aqueous layer was then made more strongly alkaline with potassium carbonate (1.0 g.) and extracted with two 100-cc. portions of chloroform. Removal of the solvent from the combined extracts left 1.5 g. (21% yield) of liquid which became more viscous with time. This was directly converted to its hydrobromide by dissolving it in a slight excess of aqueous hydrobromic acid and evaporating the resultant solution to dryness under a vacuum at room temperature. The glassy residue was taken up in dry isopropyl alcohol and reprecipitated with dry ether to give a nearly white amorphous solid, m.p. 146–148° after a second reprecipitation; the reported (7) m.p. of pelletierine hydrobromide is 140°.

Anal. Calc'd for $C_8H_{15}NO \cdot HBr$: C, 43.26; H, 7.26; N, 6.32.

Found: C, 43.79; H, 7.22; N, 6.56.

B. A repetition of the above experiment in which the reaction mixture was refluxed eight hours and then allowed to stand three days at room temperature gave a 44% recovery of starting lactam.

C. Another reduction of the lactam (13.9 g., 0.10 mole) in ether (50 cc.) by lithium aluminum hydride (1.2 g., 0.03 mole) in ether (50 cc.) was carried out by adding the lactam solution to the hydride solution at room temperature during the course of one-half hour. The mixture was then refluxed five hours and kept at room temperature for 15 hours. Decomposition was effected with ammonium acetate (7.9 g.) in water (6.5 cc.); there was still some unreacted lithium aluminum hydride in the mixture when the decomposition was started. To the decomposed mixture there was added 35 g. anhydrous sodium sulfate and the mixture was stirred for one-half hour, filtered, and the cake washed well with dry ether. Removal of the solvent left 12.0 g. of material which, on distillation through a one-foot wire-screen heated column, gave: 2.1 g. (17% yield) of octahydropyrrocoline, b.p. 60–63° (20 mm.), n_D^{25} 1.4684 [reported by Boekelheide and Rothchild (4), b.p. 71–72° (32 mm.), n_D^{25} 1.4702); 8.0 g. (58% recovery) of lactam, b.p. 146–149° (20 mm.), n_D^{25} 1.4995; and a pot residue of 1.9 g.

D. A reduction of 11.9 g. (0.086 mole) of lactam in ether (50 cc.) with 1.0 g. (0.026 mole) of hydride in ether (50 cc.) at −50° was followed by three hours' refluxing and then standing overnight at room temperature. The mixture was decomposed with ammonium acetete and then distilled at a considerably lower pressure to give: 5.0 g. (42% recovery) of lactam, b.p. 85° (1 mm.), n_D^{25} 1.5014; 0.4 g. of an intermediate fraction; 1.6 g. (14% yield) of another substance, b.p. 120–121° (1 mm.), n_D^{25} 1.5266; and 0.4 g. of pot residue.

The higher-boiling (120°) fraction gave an immediate black precipitate with Tollen's reagent. Its equivalent weight was determined by acid titration: 0.279 g. of material was dissolved in 25 cc. of 0.102 N sulfuric acid and back-titrated to neutrality, using Methyl

Red as an indicator, with 5.25 cc. of 0.102 N sodium hydroxide: $\frac{0.279 \times 1000}{19.75 \times 0.102} = 139$, equivalent weight; calculated for pelletierine, 141. About 100 mg. of the material in 3 cc. of 35% sodium hydroxide shaken with 0.2 cc. of benzoyl chloride gave a yellow amorphous solid, m.p. 73–80°; the reported (7) melting point of benzoyl pelletierine is 75°. The material, which on exposure to air was rapidly becoming gummy and resinous, formed a tacky hydrochloride and an amorphous hydrobromide (*cf.* under A).

E. Repetition of this reduction up to the point of distillation and then steam-distillation of the ethereal residue into dilute aqueous hydrobromic acid [*cf.* Hess (7)] yielded from the distillate no material corresponding with Hess' monomeric hydrobromide.

F. A reduction of 10.0 g. (0.072 mole) of lactam in 50 cc. of ether by 0.80 g. (0.021 mole) of hydride in 50 cc. of ether was carried out by adding the hydride solution to the lactam solution at −40°, followed by six hours' refluxing and then standing overnight. During decomposition of the reaction mixture with saturated ammonium acetate solution (5.6 g. of salt in 4.5 cc. of water) at 0° there was added 12.5 cc. of a solution of 0.5 g. α-tocopherol and 0.5 g. hydroquinone in 50 cc. of ether. The decomposed mixture was then stirred for 15 minutes with anhydrous sodium sulfate (20 g.), filtered, and the filter cake washed, and to the filtrate was added the remaining antioxidant solution which meanwhile had been used to rinse all parts of the distillation apparatus which was to be used. The filtrate was then made up to 200 cc. with ether and 50 cc. were removed and extracted with 25 cc. of 1:10 (48%) hydrobromic acid. The acid solution was evaporated to dryness at 0.1 mm. and under 35° to give a partially crystalline residue which, after recrystallization from acetone, melted at 155–160°; another recrystallization raised the m.p. to 164–165°, undepressed when mixed with a small sample, m.p. 162–165°, similarly prepared from authentic 3-ketoöctahydropyrrocoline.

Anal. Calc'd for $C_8H_{13}NO \cdot HBr$: Br, 36.4. Found: Br, 37.0.

The remaining 150 cc. of the ethereal solution was evaporated to leave 7.0 g. of residue (0.75 g. from the antioxidants and 6.25 g. from the reactants, corresponding to 8.5 g. for the entire reaction product) which on distillation gave: 0.7 g. (11% yield) of octahydropyrrocoline, b.p. 38–50° (10 mm.), n_D^{25} 1.4706; 4.5 g. (72% recovery) of lactam, b.p. 125–130° (10 mm.), n_D^{25} 1.5010; and 1.0 g. (16% yield) of higher-boiling material, b.p. 150–160° (1 mm.). Only the last fraction showed reducing properties toward Tollen's reagent.

SUMMARY

In an attempt to synthesize pelletierine phenyl β-(2-piperidyl)thiolpropionate was prepared and treated with Raney nickel, but none of the corresponding aldehyde was obtained; under the same conditions diphenyldithiolsuccinate yielded succindialdehyde, but no epoxysuccindialdehyde was obtained from diphenyl dithiolepoxysuccinate.

Lithium aluminum hydride treatment of N,N-dimethyl β-(2-piperidyl)propionamide gave as the only identifiable reduction product γ-(2-piperidyl)propyldimethylamine. Similar reduction of 3-ketoöctahydropyrrocoline yielded, in addition to octahydropyrrocoline, a substance which gave the reactions of an amino aldehyde and which is considered to be a polymer of pelletierine.

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