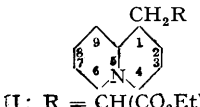
603. *Syntheses from Lupinine.*

By G. R. Clemo and J. Rudinger.

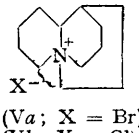
The synthesis of octahydro-1 : 5-*endo*trimethylene- and 1 : 5-*endo*ethylene-octahydro-pyridocolinium salts (V) and (IX) is described. The Hofmann degradation of the former gives two main products, identified as belonging to the aza*bicyclo*[3 : 3 : 1]nonane system (XIII) and the *epi*lupinine series (XII). The latter is formed without any of the lupinine base (XI), which shows that the new ring formed in (V) persists and that the equivalent old ring undergoes fission.

In view of the physiological interest attaching to compounds containing the 1-aza*bicyclo*[3 : 3 : 1]nonane ring system (cf. Badger, Cook, and Walker, *J.*, 1949, 1141; Prelog, Heimbach, and Seiwerth, *Ber.*, 1939, **72**, 1319; McElvain and Adams, *J. Amer. Chem. Soc.*, 1923, **45**, 2738) we have examined the possibility of obtaining a compound (XIII) possessing this structure, by the Hofmann degradation of the tricyclic quaternary ammonium bromide (V*a*) prepared from lupinine.

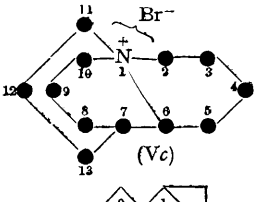
ω-Bromolupinane (Clemo, Raper, and Tenniswood, *J.*, 1931, 429), prepared in improved yield by the use of phosphorus tribromide instead of the pentabromide, condensed with ethyl sodiomalonate to give ethyl ω-lupinylmalonate (I) [Kacnelson and Kabacnik, *Compt. rend. Acad. Sci. U.R.S.S.*, 1936, **13** (4), 409] in good yield. This ester was hydrolysed and decarboxylated by boiling hydrochloric acid, and the resulting monocarboxylic acid esterified with ethanolic hydrogen chloride. Ethyl β-octahydro-1-pyridocolylpropionate (II) was



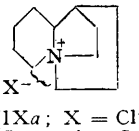
[I; R = $CH(CO_2Et)_2$]
(II; R = $CH_2{\cdot}CO_2Et$)
(III; R = $CH_2{\cdot}CH_2{\cdot}OH$)
(IV; R = $CH_2{\cdot}CH_2Br$)
(VI; R = CN)
(VII; R = CO_2Et)
(VIII; R = $CH_2{\cdot}OH$)



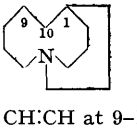
(V*a*; X = Br)
(V*b*; X = Cl)



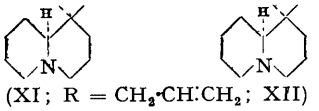
(V*c*)



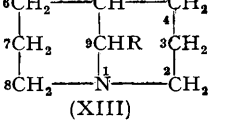
(IX*a*; X = Cl^-)
(IX*b*; X = $C_6H_2O_7N_3^-$)



(X*a*; CH:CH at 9–10)
(X*b*; CH:CH at 1–10)



(XI; R = $CH_2{\cdot}CH{:}CH_2$; XII)



(XIII)

quantitatively reduced to the propanol (III) with lithium aluminium hydride (Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 1197). On treatment with phosphorus tribromide in benzene solution this gave a benzene-soluble basic product, presumably the corresponding propyl bromide (IV), which in boiling benzene cyclised to octahydro-1 : 5-*endo*trimethylene-pyridocolinium bromide (V*a*) {1-azonia*tricyclo*[5 : 3 : 3 : $0^{1:6}$]tridecane bromide (V*c*)}. With thionyl chloride the alcohol (III) yielded the corresponding quaternary chloride (V*b*).

ω-Bromolupinane and sodium cyanide in boiling ethanol gave ω-cyanolupinane (VI) which underwent alcoholysis to ethyl octahydro-1-pyridocolylacetate (VII) on treatment with ethanolic hydrogen chloride. Reduction of this ester with lithium aluminium hydride or with sodium and alcohol gave 2-octahydro-1′-pyridocolylethanol (VIII), which, when treated with thionyl chloride in the same way as its higher homologue, afforded a highly deliquescent crystalline substance, insoluble in non-polar solvents and containing ionic chlorine, thought to be the expected 1 : 5-*endo*ethyleneoctahydropyridocolinium chloride (IX*a*) (1-azonia*tricyclo*-[5 : 3 : 2 : $0^{1:6}$]dodecane chloride). This was converted into the corresponding picrate (IX*b*) for convenience of manipulation.

Hofmann degradation of the quaternary bromide (V*a* = *c*) could theoretically yield five products. Two of these (X*a* and *b*) possess non-terminal double bonds; (XIII) belongs to the 1-azabi*cyclo*[3 : 3 : 1]nonane system; and (XI) and (XII) are based on the octahydropyridocoline system, one belonging to the lupinine, the other to the *epi*lupinine series. (The stereochemical relation between the two series has been adequately discussed by Schöpf, Schmidt, and Braun, *Ber.*, 1931, **64**, 683).

Hofmann degradation of the bromide (V*a* = *c*) produced a mixture, which under ordinary conditions gave an inseparable mixture of picrates melting at approx. 110—120°; but if the picrate preparation was carried out as described in the Experimental section, the base "A" present in maximum amount was obtained as a picrate, m. p. 114°, and the second major constituent "B" as a picrate, m. p. 132—133°; a third picrate, m. p. 140°, was isolated from the mother-liquors, but in insufficient amount for the examination of the base concerned; and even then the final picrate fraction is a mixture. The relative amounts of the bases "A" and "B" are not greatly changed by heating the bromide (V*a*) with potassium hydroxide in water or ethylene glycol instead of using the silver oxide method.

Ozonolysis of bases "A" and "B" showed the presence of a methylene group, a result confirmed by the infra-red spectra (kindly determined for us by Dr. Plíva of the Central Chemical Research Institute, Prague, Czechoslovakia). It was thus evident that "A" and "B" had two of the three structures (XI), (XII), and (XIII).

Quantitative hydrogenation readily gave the dihydro-bases which were different from the base obtained by the replacement of the bromine atom in (IV) by hydrogen, and this indicated that neither "A" nor "B" belonged to the lupinine series (XI).

Oxidation of "A" and "B" was next examined with a view to converting their $\cdot CH{:}CH_2$ groups into carboxyl and thence into carbethoxyl, whereby either "A" or "B" was expected to give the known ethyl *epi*octahydro-1-pyridocolylacetate (cf. VII). Potassium permanganate oxidised "A" smoothly in acetone, and a good yield of ester was obtained from the resulting acid, but its picrate differed from that of the *epi*-ester (VII). Thus structure (XIII) was indicated for "A". Similar oxidation of "B", however, did not proceed satisfactorily and no definite ester could be obtained from the resulting acid, but eventually, as described in the Experimental section, "B" was oxidised successfully with permanganate and the *epi*-ester was obtained. Thus "B" has the structure (XII).

Unexpected difficulty was experienced in obtaining compounds of the *epi*lupinine series. Krieg (Inaug. Diss., Marburg, 1928; cf. *Biedermanns Zentr.*, 1932, **3**, *A*, 51) states that lupinine is quantitatively converted into *epi*lupinine when heated under reflux in benzene with sodium for 3 days. This experiment has been quoted several times (Winterfeld and Holschneider, *Ber.*, 1931, **64**, 137; Schöpf, Schmidt, and Braun, *ibid.*, p. 692; Hückel and Naab, *ibid.*, p. 2137), but apparently not repeated. In our hands this method did not prove satisfactory. Only in one run out of eight was crystalline *epi*lupinine (m. p. 74—76°) obtained, in 10% yield. It is also stated by Winterfeld and Holschneider (*loc. cit.*) that Bouveault–Blanc reduction of methyl lupinate yields *epi*lupinine, but no experimental details or yields are given. We have found that this reaction yields a mixture of lupinine and *epi*lupinine, containing about 40% of the latter. It proved most convenient to convert the mixture into the mixed ω-bromo- and ω-cyano-lupinane epimers, and to effect separation by crystallisation of the ω-cyanolupinane picrates. ω-*epi*Cyanolupinane picrate was thus obtained in 10% yield. The ω-*epi*cyanolupinane recovered from the picrate was converted into ethyl *epi*octahydro-1-pyridocolylacetate. It may be noted that Krieg (*loc. cit.*) regards lupinine as the stable, and *epi*lupinine as the metastable, epimer.

Experimental.

ω-Bromolupinane.—The following modification was found more convenient than the original method [Clemo, Raper, and Tenniswood (*loc. cit.*)]. Lupinine (33 g.) and phosphorus tribromide (10 ml.) in benzene (100 ml.) were refluxed 2 hours, the excess of tribromide decomposed with ice-water, potassium hydroxide (75 g.) in water (300 ml.) added with cooling, the benzene layer separated, and the aqueous layer extracted with benzene. The combined benzene layers were dried (KOH), evaporated, and distilled, giving the bromide (38·1 g., 82%), b. p. 104°/1 mm., which yielded a *picrolonate*, golden yellow plates, m. p. 198—199° (Found: C, 48·8; H, 5·5. $C_{10}H_{18}NBr,C_{10}H_8O_5N_4$ requires C, 48·4; H, 5·3%). Use of less phosphorus tribromide gave lowered yields.

Ethyl Lupinylmalonate.—Ethyl malonate (7·9 g.) was added to sodium ethoxide in boiling ethanol [from sodium (1·2 g.) and alcohol (35 ml.)], and bromolupinane (11·4 g.) was stirred in. Boiling was continued overnight, the ethanol distilled off, the residue taken up in water, basified with 20% aqueous sodium hydroxide, and extracted with ether, and the extract dried, evaporated, and fractionated. Ethyl lupinylmalonate distilled as a clear viscous liquid (11 g., 72%), b. p. 175—178°/3 mm. (Kacnelson and

Kabačnik, *loc. cit.*, gave b. p. 199·5—200°/11 mm.) (Found : C, 65·8; H, 9·5. Calc for $C_{17}H_{29}O_4N$: C, 65·6; H, 9·3%). It afforded a *methiodide*, white prisms (from acetone–ether), m. p. 149—150° (Found : C, 47·7; H, 6·8. $C_{17}H_{29}O_4N,CH_3I$ requires C, 47·7; H, 7·1%). The use of chlorolupinane in this condensation (Kacnelson and Kabačnik, *loc. cit.*) gave a much lower yield.

Ethyl β-Octahydro-1-pyridocolylpropionate.—Ethyl lupinylmalonate (10 g.) was refluxed with hydrochloric acid (75 ml.; 1 : 1) for 5 hours, the solution taken to dryness, and the residual clear yellow gum dissolved in absolute ethanol (75 ml.), and the solution saturated with hydrogen chloride at room temperature and refluxed for 2 hours. The ethanol was distilled off and the residue taken up in water, basified with 20% sodium hydroxide solution, and extracted with ether. The extract was dried, evaporated, and distilled. The *ester* (6 g., 77%), a clear oil, b. p. 136—140°/2 mm. (Found : C, 70·4; H, 10·7. $C_{14}H_{25}O_2N$ requires C, 70·3; H, 10·5%), gave a *methiodide*, m. p. 109—111° (Found : C, 47·3; H, 7·3; N, 6·2. $C_{14}H_{25}O_2N,CH_3I$ requires C, 47·2; H, 7·3; N, 5·9%).

3-Octahydro-1′-pyridocolylpropanol.—Ethyl β-octahydro-1-pyridocolylpropionate (6 g.) in dry ether (20 ml.) was run dropwise into a stirred ethereal solution of lithium aluminium hydride (25 ml., equiv. to 1500 ml. of hydrogen), the solution set aside at room temperature overnight, and water cautiously added to decompose the excess of reagent and then sulphuric acid (20%) till the aqueous layer became clear. The solution was basified (as above) and extracted with ether, and the extract dried and evaporated. *3-Octahydro-1′-pyridocolylpropanol* (4·5 g., 93%) distilled as a colourless viscous oil, b. p. 134—136°/2 mm. (Found : N, 7·3. $C_{12}H_{23}ON$ requires N, 7·1%). It afforded a *methiodide*, white prisms (from methanol), m. p. 184° (Found : C, 46·4; H, 8·0. $C_{12}H_{23}ON,CH_3I$ requires C, 46·0; H, 7·7%).

Octahydro-1 : 5-endotrimethylenepyridocolinium Bromide (*1-Azoniatricyclo*[5 : 3 : 3 : $0^{1:6}$]*tridecane Bromide*).—3-Octahydropyridocolylpropanol (4·5 g.) in benzene (50 ml.) was treated with phosphorus tribromide (6·5 g.; *d* 2·85) and refluxed for 2 hours. Ice-water (30 ml.) was added to the cooled solution, followed by 25% sodium hydroxide solution until the mixture was strongly alkaline. The benzene layer was separated, the aqueous layer was extracted twice more with benzene, and the benzene layers were united, filtered, and evaporated to dryness. During evaporation the quaternary *bromide* was deposited as white needles (4·2 g., 70%). Crystallised from ethanol or ethanol–acetone, it had m. p. 316° (decomp.), $[\alpha]_D^{18}$ −15·53° (*c*, 7·78 in ethanol) (Found : C, 55·3; H, 8·5. $C_{12}H_{22}NBr$ requires C, 55·4; H, 8·5%).

Thionyl chloride, without a solvent or in benzene, gave the corresponding quaternary *chloride*, m. p. 318° (decomp.) (Found : C, 66·7; H, 10·1. $C_{12}H_{22}NCl$ requires C, 66·8; H, 10·2%).

Octahydro-1-n-propylpyridocoline.—3-Octahydro-1′-pyridocolylpropanol (0·7 g.) was converted into the bromide as described above; to the benzene solution was added zinc dust (2 g.) and glacial acetic acid (1 ml.). The mixture was refluxed for 6 hours, the solution separated from the zinc, which was extracted with a little benzene, and the benzene solution shaken with 25% aqueous sodium hydroxide, dried, and fractionated, giving *octahydro-1-n-propylpyridocoline* (0·35 g.), b. p. *ca.* 75°/1 mm. (Found : C, 79·2; H, 12·65. $C_{12}H_{23}N$ requires C, 79·6; H, 12·7%). The *picrate*, made in, and crystallised from, ether, formed compact, deep yellow prisms, m. p. 98—99° (Found : C, 52·9; H, 6·4. $C_{12}H_{23}N,C_6H_3O_7N_3$ requires C, 52·7; H, 6·3%). In addition, a trace of a picrate was obtained as thin, yellow prisms, m. p. 204—205°, sparingly soluble in alcohol (Found : C, 46·7; H, 5·0%).

Degradation of the Quaternary Bromide : Bases " A " and " B ".—The bromide (0·8 g.) was mixed with potassium hydroxide (1·5 g.) and water (1 c.c.) in a small Claisen flask fitted with a dropping funnel and condenser arranged to deliver the distillate into concentrated hydrochloric acid (3 ml.) and water (1 ml.) in a receiver which was connected to a water-pump. The flask was heated in a metal-bath at 245—250°, water and a basic oil being collected in the acid. Water (10 ml.) was dropped in during about 40 minutes, at the end of which no more oil distilled over. The acid solution was taken to dryness under reduced pressure, potassium hydroxide (4 g.) in water (5 ml.) was added, and the liberated bases were extracted with ether (5 times), dried (K_2CO_3), and distilled, giving mixed bases (0·45 g.), b. p. 127°/30 mm.

Picrates of " A " and " B ".—To the above bases (0·45 g.) in ether (3·5 ml.), a hot solution of picric acid (0·6 g.) in ethyl acetate (3·5 ml.) was added cautiously. After a few minutes, long, pale yellow prisms (*P*) began to separate, which amounted to 0·46 g., m. p. 110—112°, after 2 hours. By recrystallisation from ethyl acetate by the addition of an equal volume of ether, or from ethyl alcohol (10 ml.), the m. p. of this *picrate* of base " *A* " was raised to 114° (Found : C, 52·6; H, 5·8. $C_{12}H_{21}N$, $C_6H_3O_7N_3$ requires C, 52·9; H, 5·9%).

The filtrate from (*P*) was concentrated (to 2 ml.), and ether (2 ml.) added to the solution, which was then set aside, whereupon the picrate of " *B* " usually separated spontaneously; if it did not a seed was added and after 1 hour's storage at laboratory temperature, followed by ice-cooling for a few minutes, stout prisms (0·18 g.) were obtained, having m. p. 129—130°. On recrystallisation from ethyl acetate by the addition of an equal volume of ether the m. p. of this *picrate* of base " B " rose to 134° (Found : C, 52·8; H, 6·2%).

When the filtrate from the fraction of b. p. 129—130° was set aside in the refrigerator for one night, a further 0·1 g. of product separated, which melted at 100—110°; and from some batches of which a small amount of deep golden prisms, m. p. 140—141° (from ethanol) was obtained (Found : C, 52·4; H, 6·1%).

*9-But-3′-enyl-1-aza*bicyclo[3 : 3 : 1]*nonane* (*Base " A "*) (XIII).—The picrate, m. p. 114° (1·5 g.), was suspended in a solution of sodium hydroxide (5 g.) in water (10 ml.) and steam-distilled. The oily distillate was acidified (hydrochloric acid), taken to dryness, basified with potassium hydroxide (3 g. in water, 4 ml.), extracted with ether, dried (K_2CO_3), and distilled, giving *base* " A " (0·57 g.), b. p. 115°/15 mm. (Found : C, 80·7; H, 12·1. $C_{12}H_{21}N$ requires C, 80·4; H, 11·7%). The *methiodide* formed colourless well-formed prisms (from acetone), m. p. 232—233° (Found : C, 49·3; H, 7·5. $C_{12}H_{21}N,CH_3I$

requires C, 48·6; H, 7·5%). On catalytic reduction in 10% sulphuric acid over palladised charcoal at atmospheric pressure, the theoretical amount of hydrogen was absorbed in 45 minutes and the dihydro-base obtained (Found : C, 79·7; H, 12·65. $C_{12}H_{23}N$ requires C, 79·6; H, 12·7%). 9-n-*Butyl*-1-*aza*-bicyclo[3 : 3 : 1]*nonane* is stable indefinitely and forms a *picrate*, made in, and crystallised from, ether as long yellow prisms (Found : C, 53·0; H, 6·55. $C_{12}H_{23}N,C_6H_3O_7N_3$ requires C, 52·7; H, 6·3%), m. p. 84—85°, depressed to 75° by admixture with picrate of octahydro-3-*n*-propyl pyridocoline).

Oxidation. Base " A " (0·57 g.) in acetone (15 ml.) was cooled in ice and stirred, whilst powdered potassium permanganate (1·62 g.) was added during 2 hours. The stirring was continued for 4 hours, the mixture left overnight and filtered, and the manganese oxide precipitate extracted with boiling water. The aqueous extract was taken to dryness and esterified by refluxing it for 2 hours in ethyl alcohol (10 ml.) which had been saturated when ice-cold with dry hydrogen chloride. The alcoholic solution was then evaporated to dryness, saturated aqueous potassium carbonate added, and the liberated ester extracted with ether and distilled, giving 9-3′-*carboxypropyl*-1-*aza*bicylo[3 : 3 : 1]*nonane* (0·38 g.), b. p. 125°/1 mm. (Found : C, 69·15; H, 10·1. $C_{13}H_{23}O_2N$ requires C, 69·3; H, 10·2%). The derived *picrate* formed yellow prisms (from ether), m. p. 75—76° (Found : C, 49·95; H, 5·9. $C_{13}H_{23}O_2N,C_6H_3O_7N_3$ requires C, 50·2; H, 5·7%). [In the first oxidation experiment, the picrate obtained had m. p. 98—99° (Found : C, 50·7; H, 5·9%), but in all others the picrate, m. p. 75—76°, was obtained; their relation remains obscure]. The *methiodide*, colourless prisms from acetone, had m. p. 125° (Found : C, 45·8; H, 7·4. $C_{13}H_{23}O_2N,CH_3I$ requires C, 45·8; H, 7·1%).

The epi*Lupinine Base " B "* (epi-1-*Allyloctahydropyridocoline*).—This *base* was regenerated from the picrate as for base " A ", and had b. p. 123°/22 mm. (Found : C, 80·2; H, 12·2. $C_{12}H_{21}N$ requires C, 80·4; H, 11·7%). Reduction, as for " A," gave the *dihydro-base* which decomposed when kept (Found : C, 79·05; H, 12·75. $C_{12}H_{23}N$ requires C, 79·6; H, 12·7%). The *picrate*, well-formed rhombs from ether, had m. p. 131—132°, depressed to 117—120° on admixture with the picrate of " *B* " (Found : C, 52·7; H, 6·2. $C_{12}H_{23}N,C_6H_3O_7N_3$ requires C, 52·7; H, 6·3%).

Oxidation. The base (100 mg.), dissolved in 10% sulphuric acid (5 ml.) was treated with aqueous potassium permanganate at room temperature for 2 days, until the supernatant liquid remained pink; about 0·2 g. of permanganate was required. The manganese oxide precipitate was filtered off and extracted twice with hot water, and the combined filtrate and extracts were neutralised with aqueous ammonia and evaporated to dryness. The residue was evaporated twice with ethanol and then extracted with boiling absolute ethanol (4 × 5 ml.). The extracts were evaporated to half-volume and saturated with gaseous hydrogen chloride at room temperature, and the solution refluxed for 2 hours, taken to dryness in a vacuum on the water-bath. The residue was taken up in water (3 ml.), excess of potassium carbonate added, and the base extracted with ether. The extract was dried (Na_2SO_4) and evaporated, and the residue distilled; it had b. p. 80—90° (air-bath temp.) at 0·05 mm. The yield was 30 mg. The *picrate* formed bright yellow prisms (from ethanol), m. p. 137—138°, alone or mixed with ethyl *epi*octahydro-1-pyridocolylacetate picrate (Found : C, 49·95; H, 5·8; $C_{13}H_{23}O_2N,C_6H_3O_7N_3$ requires C, 50·2; H, 5·7%).

Ozonolysis of Bases " A " and " B ".—Base " A " (0·2 g.) in purified chloroform (10 ml.) was cooled in ice-salt, a 6% stream of ozone passed in for 4 hours, and the whole left overnight. The chloroform was removed in a vacuum, water (10 ml.) added to the residue, and the resulting solution heated in a Claisen flask for 1 hour on the water-bath and then distilled into an alcoholic solution of dimedone. More water (20 ml.) was gradually dropped in and distilled off. Next morning the crystalline dimedone condensation product was collected; it (0·05 g.) had m. p. 186—187°.

Base " B " gave a similar result.

ω-Cyanolupinane.—ω-Bromolupinane (5 g.) was heated under reflux overnight with potassium cyanide (2 g.) in ethanol (40 ml.), the ethanol distilled off, the residue taken up in water and extracted with ether, the extract dried and evaporated, and the *ω-cyanolupinane* distilled; it (3·85 g., 90%) had b. p. 108—112°/1 mm. (Found : C, 73·9; H, 10·5. $C_{11}H_{18}N_2$ requires C, 74·2; H, 10·1%). It gave a *picrate* m. p. 150—151° (Found : C, 50·0; H, 4·7. $C_{11}H_{18}N_2,C_6H_3O_7N_3$ requires C, 50·1; H, 5·2%), and a *methiodide*, white prisms (from methanol), m. p. 241—242° (Found : C, 45·3; H, 6·7. $C_{11}H_{18}N_2,CH_3I$ requires C, 45·0; H, 6·6%).

Ethyl Octahydro-1-pyridocolylacetate.—ω-Cyanolupinane (7·6 g.) was dissolved in absolute ethanol (150 ml.), and the solution was saturated with hydrogen chloride at room temperature and refluxed overnight. The solution was worked up as described for ethyl β-octahydro-1-pyridocolylpropionate. *Ethyl octahydro-1-pyridocolylacetate* (6 g., 62%) distilled as a colourless oil, b. p. 125—129°/3 mm. (Found : C, 68·9; H, 10·6. $C_{13}H_{23}O_2N$ requires C, 69·3; H, 10·2%). Its *picrate*, yellow needles, had m. p. 202—203° (Found : C, 50·1; H, 5·6. $C_{13}H_{23}O_2N,C_6H_3O_7N_3$ requires C, 50·2; H, 5·7%).

2-*Octahydro-1′-pyridocolylethanol.*—(*a*) Ethyl octahydro-1-pyridocolylacetate (406 mg.) in ether (5 ml.) was added to excess of ethereal lithium aluminium hydride (5 ml., equiv. to 275 ml. of hydrogen). The solution was refluxed for 1 hour, cooled, and worked up as described for 3-octahydro-1′-pyridocolylpropanol. The 2-*octahydro-1′-pyridocolylethanol* (350 mg., 97%) distilled as a clear viscous liquid at 120—130°/2 mm. (air-bath temp.) (Found : C, 71·8; H, 11·6. $C_{11}H_{21}ON$ requires C, 72·1; H, 11·5%) and gave a *methiodide* as white needles (from methanol), m. p. 205—207° (Found : C, 44·4; H, 7·6. $C_{11}H_{21}ON,CH_3I$ requires C, 44·3; H, 7·4%).

(*b*) To ethyl pyridocolylacetate (5·4 g.) in boiling absolute ethanol (150 ml.), sodium (10 g.) was added and refluxing continued until all the sodium had reacted. The solution was cooled, water (300 ml.) added with cooling, and the solution acidified (20% sulphuric acid). 250 ml. were distilled off in a vacuum. The residue was basified with 20% aqueous sodium hydroxide and extracted with ether, and the extract dried and evaporated. The alcohol (2·4 g., 55%) distilled at 124—125°/2 mm.

1 : 5-endo*Ethyleneoctahydropyridocolinium Picrate* (1-*Azonia*tricyclo[5 : 3 : 2 : $0^{1:6}$]*dodecane Picrate*).—A solution of the foregoing alcohol (1 g.) in benzene (15 ml.) was treated with thionyl chloride (3 ml.), then refluxed for 15 minutes, the benzene and excess of thionyl chloride were distilled off, the residue was taken up in water and filtered, and the filtrate basified with 20% aqueous sodium hydroxide and extracted with benzene. Evaporation of the solvent left a brown oil, insoluble in benzene or ether, which partly crystallised under acetone. It was boiled with charcoal in ethanol, and the solution evaporated to 1 ml. Ether (5 ml.) was added, and the deliquescent precipitate collected. It contained ionic chlorine, was combustible, and was considered to be the expected 1 : 5-*endo*ethyleneoctahydropyridocolinium chloride. As it was very hygroscopic, it was converted, in ethanol, into the *picrate* (90 mg., 4·5%), which was soluble in cold water, but crystallised from absolute ethanol, and decomposed at 253—257° (Found: C, 52·2; H, 6·0. $C_{11}H_{19}N,C_6H_3O_7N$ requires C, 51·8; H, 5·6%).

Reduction of Methyl Lupinate.—Methyl lupinate (6·2 g.) (Schöpf, *Annalen*, 1928, **465**, 108; Willstätter and Fourneau, *Ber.*, 1902, **31**, 1917), reduced by sodium in alcohol as described for ethyl octahydro-1-pyridocolylacetate, yielded a viscous oily mixture (4 g., 85%) of lupinine and *epi*lupinine which did not solidify on being seeded with lupinine. The specific rotation of the mixture ($[\alpha]_D^{18}$ +0·8°; *c*, 10·7 in absolute ethanol) indicated that the mixture contained 40% of *epi*lupinine, if the values for the rotations of the two epimers given by Winterfeld and Holschneider (*loc. cit.*) are accepted.

ω-epi*Cyanolupinane.*—The procedure described for the preparation of ω-bromolupinane yielded a mixture of ω-bromolupinane epimers (4 g., 73%) from the mixed lupinine epimers. Treatment of this with sodium cyanide (8 g.) in boiling ethanol (30 ml.) and working up the product by the method described for ω-cyanolupinane gave the mixed ω-cyanolupinane epimers, (2·6 g., 90%), b. p. 118—122°/2 mm. This mixture with picric acid (2·6 g.) in ethanol (50 ml.) gave mixed picrates (3·7 g.), m. p. 135—140°, clear at 165°. Fractional crystallisation from ethanol yielded ω-epi*cyanolupinane picrate* (0·46 g., 10%), m. p. 207—208° (Found: C, 50·2; H, 5·2. $C_{11}H_{18}N_2,C_6H_3O_7N_3$ requires C, 50·1; H, 5·2%). This (245 mg.) was ground with hydrochloric acid (5 ml.; 1 : 1), the picric acid filtered off, the filtrate washed with ether, basified with 20% aqueous sodium hydroxide, and extracted with ether, and the dried extract evaporated. ω-epi*Cyanolupinane* (98 mg., 91%) distilled at 120—125°/2 mm. (air-bath temp.) (Found: C, 74·2; H, 10·3. $C_{11}H_{18}N_2$ requires C, 74·2; H, 10·1%).

Ethyl epi*Octahydro-1-pyridocolylacetate.*—ω-*epi*Cyanolupinane (98 mg.) was refluxed with saturated alcoholic hydrogen chloride (10 ml.) overnight and the solution worked up as described for ethyl octahydro-1-pyridocolylacetate. The *epi*-ester (53 mg., 43%) had b. p. 120—122°/2 mm. (air-bath temp.) (Found: C, 69·2; H, 10·5. Calc. for $C_{13}H_{23}O_2N$: C, 69·3; H, 10·2%) and gave a picrate, yellow needles (from alcohol), m. p. 136—137° not depressed by admixture of the picrate of the ester obtained by the oxidation of base "B".

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