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STEREOSPECIFIC SYNTHESIS OF ϵ-CONICEINE *VIA* OPTICALLY ACTIVE SEDRIDINE

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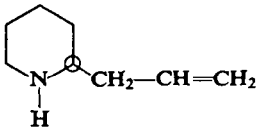
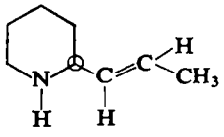
Abstract—A stereospecific synthesis of erythro-ϵ-coniceine (II) was elaborated starting with optically active picolylmethyl carbinol (VI) *via* sedridine (*threo*-VII) and *threo* O-mesyl-sedridine (X). The steric course of nucleophilic ring opening i.e. dequaternization of erythro and threo II will be studied.

THE piperidyl-propane skeleton occurs in a number of alkaloids[1,2] e.g. coniine, conhydrine and γ-coniceine in *Conium maculatum*, while sedridine[3] (I) and sedamine are present in *Sedum acre*. In a search for naturally occurring piperidinoazetidines, one of us (G.F.) found that 1,5-methylene-quinolizidinium tosylate,[4] i.e. a fused azetidinium salt, (from lupinine) on the action of sodium iodide and other nucleophiles underwent a complete cleavage–dequaternization[5]—giving rise to 1-halomethyl-, 1-methoxymethyl-, etc. quinolizidines. The conditions were mild: equivalent amounts of the reactants at 25° dissolved in aprotic solvents, e.g. acetone, chloroform.

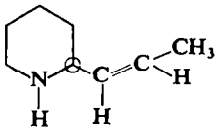


α-Coniceine
$[\alpha]_D = +18{\cdot}4°$

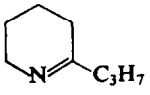


β-Coniceine
$[\alpha]_D = +50{\cdot}6°$

and

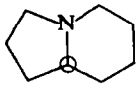


iso-allyl-piperidine
$-25{\cdot}5°$

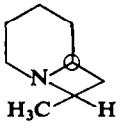


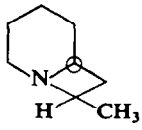
γ-Coniceine
inactive

S



δ-Coniceine
$[\alpha]_D = -7{\cdot}8°$





ϵ-coniceine
$[\alpha]_D = +67{\cdot}4°$ (42°) and $-87{\cdot}34°$

* This paper is respectfully dedicated to Sir Robert Robinson on the occasion of his 80th birthday, with our very best wishes.

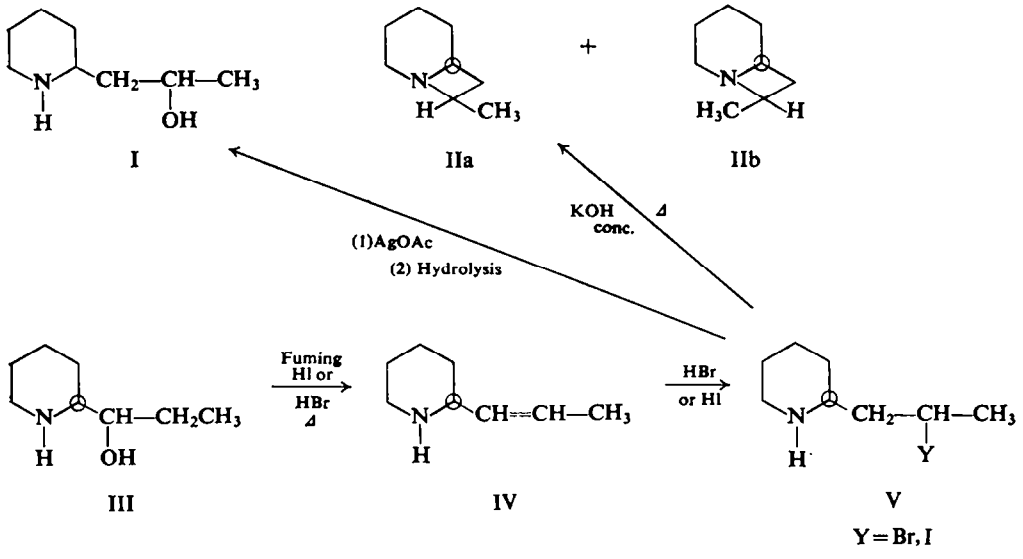
[1] L. Marion, *Pyridine Alkaloids* in: R.H.F. Manske and L. Holmes, *The Alkaloids* Vol. I; pp. 165–269 (1950); R. H. F. Manske, *The Alkaloids* Vol. 6; pp. 123–144. Academic Press, New York (1961).
[2] H. G. Boit, *Pyridin- und Piperidin-Alkaloide* in : *Ergebnisse der Alkaloid—Chemie bis* 1960. Akademie-Verlag, Berlin (1961).
[3] H. C. Beyermann and Y. M. F. Muller, *Rec. Trav. Chim.* **74**, 1568 (1955).
[4] O. E. Edwards, G. Fodor and L. Marion, *Canad. J. Chem.* **44**, 13 (1966).
[5] G. Fodor, *J. Amer. Chem. Soc.* **88**, 1040 (1966).

In order to determine the generality of this curious ring opening reaction, unknown for non-fused azetidinium salts, ϵ-coniceine[6,7] (II) was chosen as the next model.*

1,2-Piperidino-1,2-azetidinium and 1,2-pyrrolidinoazetidinium salts[8] react in a less specific way, leading to opening of either ring. Another related instance of a nucleophilic ring opening has been recorded for gelsemine.[9]

ϵ-Coniceine was obtained by heating conhydrine, i.e. (+) 2-(1-hydroxypropyl)-piperidine (III) with fuming hydriodic[6] or hydrobromic[7] acid. β-Coniceine, i.e. 2-(1-propenyl)-piperidine (IV) was assumed as an intermediate[7] which then should give by addition of HI or HBr the 2-(2-iodopropyl)- and 2-bromopropyl-piperidines (V). Ring closure of the epimeric mixture of V with boiling concentrated KOH, afforded a mixture of two diastereoisomeric non-olefinic bases to which Löffler[7] ascribed the constitution 4-epimeric-4-methyl-1,2-azetidino-1,2-piperidines (IIa and IIb) without any rigorous proof.

Reinvestigation of the work was needed to furnish evidence as to the constitution of ϵ-coniceine. Furthermore, neither the steric course of the formation of the azetidine



ring nor its opening could be adequately understood without knowledge of the complete stereochemistry of (i) the piperidylpropane derivative which serves in the penultimate step of the synthesis, and (ii) the epimeric ϵ-coniceines themselves. But first, the rather ambiguous synthesis of Löffler had to be replaced by a sterically controlled synthesis of ϵ-coniceine.

Hence, 1-(2-piperidyl)-2-propanol (I) was used as an intermediate. One isomer of the compound occurring in Nature was given the name sedridine.[3] It is probably identical with a product formed from 2-iodopropylpiperidine described by Löffler and

* Of the six coniceines only γ- and δ- are established.

[6] A. W. v. Hofmann, *Ber. Dtsch. Chem. Ges.* **18**, 9, 105 (1885).

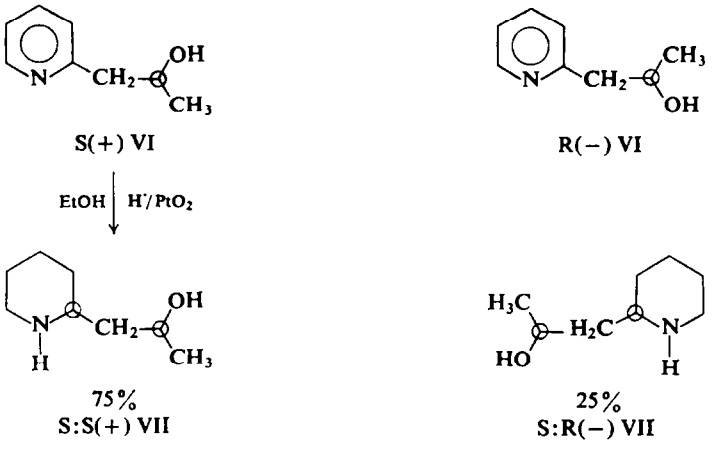
[7] K. Löffler, *Ber. Dtsch. Chem. Ges.* **42**, 948 (1909).

[8] Ebnöther und E. Jucker, *Helv. Chim. Acta.* **47**, 745 (1964).

[9] A. M. Roe and M. Gates, *Tetrahedron* **16**, 198 (1960).

Tschunke.[11] Synthesis of a mixture of both racemates by catalytic hydrogenation of racemic picolylmethylcarbinol in glacial acetic acid over platinum was described. Alternatively, the reduction was performed on the corresponding hydrochloride salt in absolute ethanol. Fractional crystallization of the picrates then gave (±) sedridine as well as (±) *allo*sedridine. The former was resolved using N-acetyl-L-leucine[12] which forms a crystalline salt with the dextrorotatory enantiomer. A more satisfactory method, but with a low yield, consisted of oxidation of the racemic hydroxypropylpiperidine to the racemic ketone (±) pelletierine[13] followed by fractional crystallization of the racemates.[10] In order to prevent the difficulties encountered in separating a mixture of *four* compounds and at the same time to increase steric selectivity, resolution of (±) picolylmethylcarbinol was achieved in our Laboratory for the first time. This compound gave both diastereoisomeric (−) dibenzoyl tartrates easily and in pure form.

Liberation of the free base enantiomers (+) and (−) VI involved no problem, both being well defined low-melting solids. Catalytic hydrogenation of each individual enantiomer gave predominantly an optically active alcohol, $[\alpha]_D = +$ or $-20°$. Since pure sedridine[3] has $[\alpha]_D = +26{\cdot}8°$ hydrogenation of the ring took place with asymmetric induction. When starting with the (+) picolylmethylcarbinol, the dextrorotatory sedridine (+) VII was obtained contaminated with very little (−) *allo*sedridine (−) VII. It gave with N-acetylleucine a 75% yield of the pure (+) sedridine salt; the diastereoisomeric salt not being known as a solid.[10] Reduction of (−) α-picolylmethylcarbinol, $[\alpha]_D - 19°$, gave the corresponding pipecolylmethyl carbinol, $[\alpha]_D - 23°$. In this way the pipecolylmethyl carbinols (VII) needed were available in optically pure form and in good yield.



As conversion of (+) or (−) sedridine into one of the alleged ϵ-coniceines (II) had to proceed under steric control, conversion of the hydroxyl into a leaving group, e.g. by acylation with aryl or alkylsulphonyl chlorides while keeping the nitrogen free was desirable. The secondary amine nitrogen could then react as an internal nucleophile in ring closure. This task proved very difficult and preliminary experiments were made

[10] H. C. Beyerman, J. Evenshuistra and W. Eveleens, *Rec. Trav. Chim.* **76**, 415 (1957).
[11] K. Löffler and R. Tschunke, *Ber. Dtsch. Chem. Ges.* **42**, 929 (1909).
[12] B. D. Dewitt and A. W. Ingersoll, *J. Amer. Chem. Soc.* **73**, 3359 (1951).
[13] H. C. Beyerman and L. Maat, *Rec. Trav. Chim.* **82**, 1033 (1963).

with the racemate. Two approaches were considered: First, protection of the nitrogen during acylation by formation of either (1) a salt or, (2) a urethane. On the other hand, activation of the hydroxyl by conversion into (3) an alkoxide ion was achieved by

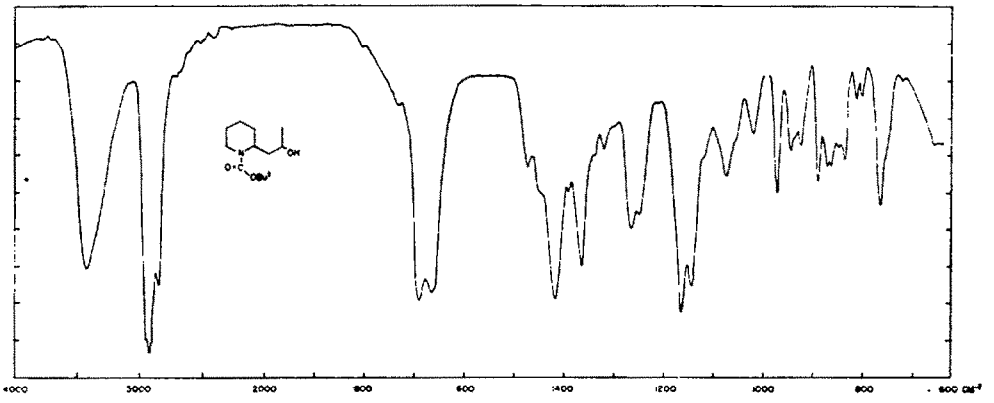


FIG. 1

reaction with sodium dispersion or sodium hydride. Only protection by N-alkoxy-carbonylation (2), with carbobenzoxy chloride or t-butoxy-carbonyl azide[14] proved successful, giving rise to VIIIa and VIIIb. Acylation of the hydroxyl in the urethane (VIII) presented serious difficulties: tosyl, brosyl and *p*-nitro-benzenesulphonyl (nosyl) chloride gave neutral products none of which had the IR bands around 1180 and 1340 cm^{-1} typical for the sulphur-oxygen double bonds. Activation of the nosyl chloride by N-methylmorpholine gave a crystalline salt-like complex containing the expected chloride ion. Nevertheless it failed to react with the obviously hindered propanol hydroxyl of VIII. Examination of IR spectra clearly revealed the presence of a split carbonyl at 1678 cm^{-1} and 1695 cm^{-1} in case of the N-t-butoxycarbonyl derivative

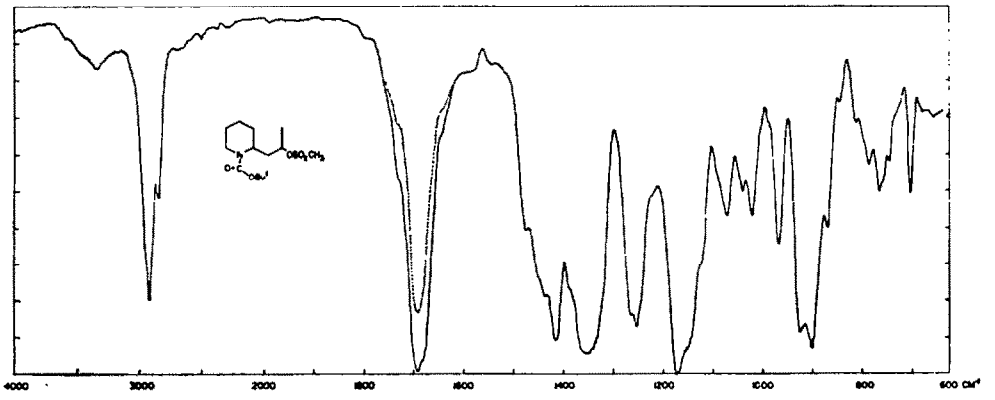


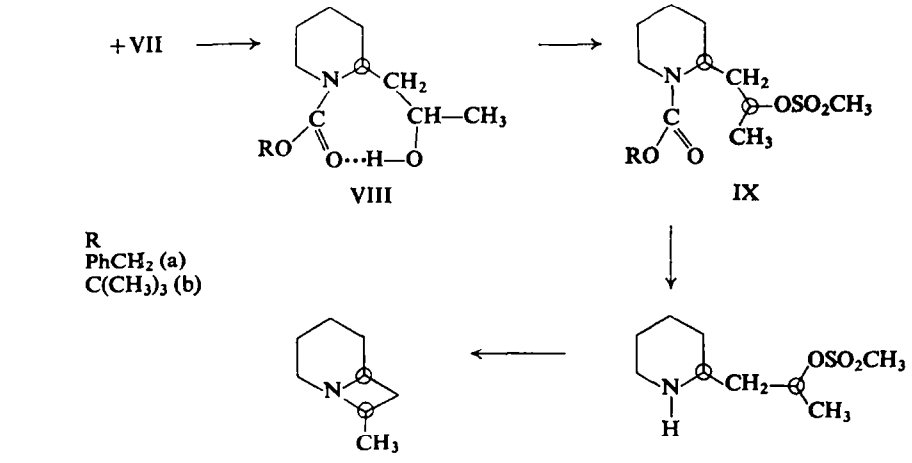
FIG. 2

(VIIIb) (Fig. 1). This band simplifies after successful acylation of the hydroxyl to a more sharp peak at 1695 cm^{-1} indicating that hydrogen bonding of the carbonyl was

[14] L. A. Carpino, *J. Amer. Chem. Soc.* **79**, 98 (1957).

responsible for the maximum at 1678 cm^{-1} (Fig. 2). Since methanesulphonyl chloride was assumed to react by a different mechanism than tosyl chloride, probably via the sulphene, mesylation of both the benzyloxycarbonyl (VIIIa) and the t-BOC- sedridines (VIIIb) was attempted, giving a good result. The N-t-butoxycarbony-O-mesylsedridine (VIIIb) was then easily cleaved in the usual way followed by lyophilization affording the O-mesylsedridine (X) hydrobromide m.p. 130–131°.

The tetraphenyloborate (precipitated in alcohol), in the IR spectrum shows no carbonyl at 1695 cm^{-1}; thus O-mesylsedridine (X), whose IR spectrum is shown in Fig. 3, is adequately characterized. Ring closure was achieved as with brosyl and tosyl lupinine, i.e. by heating in a rotating flask in a vacuum for 2 hr at 90–95°. The product, ϵ-coniceine methanesulphonate (II-mesylate) was insoluble in ether but soluble in water in contrast with the O-mesylsedridine base. It gave a tetraphenyloborate and was also converted into the free base II.



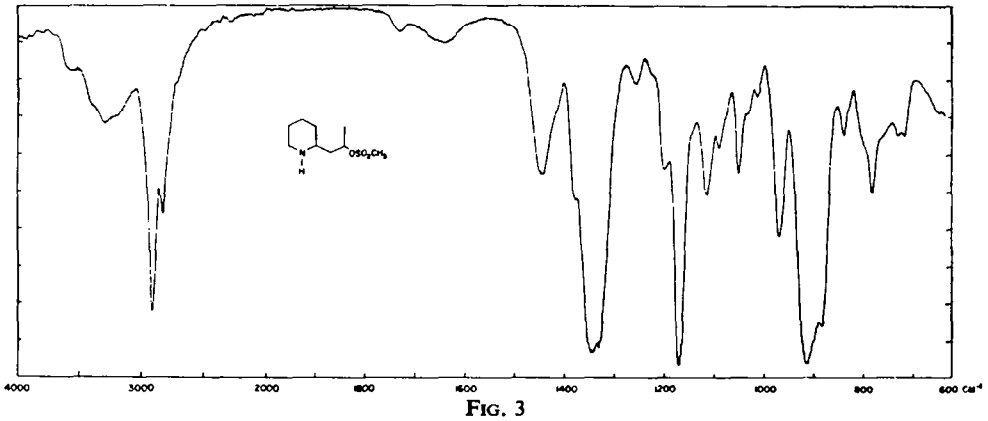


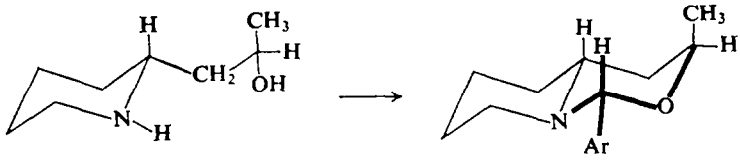
FIG. 3

The steric course of the cyclization of O-mesylsedridine (IX) can be predicted as an inversion at the carbon 2 of the side chain. The configuration of the piperidine carbon in sedridine was recently[15] correlated with L(−)pipecolinic acid. Furthermore, the

[15] H. C. Beyerman, L. Maat, A. van Veen and A. Zweistra and W. von Philipsborn, *Rec. Trav. Chim.* **84**, 1367 (1965).

NMR analysis of the epimeric tetrahydro oxazines (type XI)[16, 17] prepared from *racemic* sedridine and *allo*sedridine corresponds with the *threo* configuration for the latter.[15]

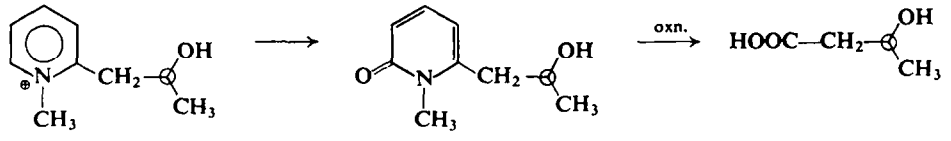
Hence the cyclized product from (*threo*) (+) O-mesylsedridine should be the *erythro* piperidino-methylazetidine, the opposite being true for the product expected by cyclizing the hitherto unknown optically active *allo*sedridines.* Although the evidence furnished[15] by deduction from principles of conformational analysis followed by application of the Karplus equation to the coupling constants of the relevant protons in the two diastereoisomers seems acceptable, a correlation of the propanol carbon in the optically active picolylmethyl carbinols with that of a natural hydroxy acid will give complete reassurance as to the absolute configuration.



(+) VII XI

For this reason degradation of the dextrorotatory carbinol (+) VI to one of the β-hydroxybutyric acid antimers (XIII) was attempted. As the first step, the carbinol VI was quaternized with methyl iodide and then treated with silver oxide in water to obtain the predictable pseudobase[18] which then should give by Decker oxidation with potassium ferricyanide[19] the α-pyridone XII or the γ-pyridone. Since in both of these the double bonds are localized, protection of the propanol carbon followed by further oxidation should lead to the desired acid.

Surprisingly, the action of silver oxide was not limited to an ion-exchange; it was accompanied by the formation of a silver mirror. Quantitative analysis of the precipitated metallic silver (iodide) by removing the excess silver oxide with ammonia and drying of the remaining silver (compound) indicated the consumption of 0·9 mole silver oxide for oxidation per mole pyridinium base. This reaction could be interpreted as leading to a pyridone.



S(+) VI methiodide XII XIII

Inversion of the propanol carbon in VIII(b) by sodium iodide should lead to the *erythro*-2-iodopropyl-N-t-BOC-2-piperidine, which on acid cleavage is expected to give *erythro*-2-iodopropyl-2-piperidine, corresponding to *allo*sedridine. Ring closure with inversion at C-2 in the propyl chain should then give *threo*-ε-coniceine. This work is in progress.

**Note added in proof*—Dr. Maat informed us recently of having succeeded in resolving *allo*sedridine, too.

[16] G. Fodor, J. Stefanowski and B. J. Kurtev, *Chem. Ber.* **98**, 705 (1965).

[17] G. Hardegger and H. Ott, *Helv. Chim. Acta* **36**, 1186 (1953).

[18] E. M. Kosower, *J. Amer. Chem. Soc.* **77**, 3883 (1955).

[19] P. Karrer and R. Widmer, *Helv. Chim. Acta* **8**, 364 (1925).

EXPERIMENTAL

IR spectra were taken on a Beckman IR4 instrument, the oils in the form of thin films, the solids in KBr pellets. NMR spectra were measured on a Varian Associates A60 NMR spectrometer with $CDCl_3$ sols and TMS internal standard. M.ps were performed in open capillaries and are uncorrected. Specific rotations were obtained with a Schmidt-Haensch instrument using 98% EtOH sols at about 25°. Values given are for the Na D line.

2-(2-*Hydroxypropyl*) *pyridine* (I).[21] This compound, although previously obtained as an oil, was found to be a solid, m.p. 31–33°, but IR and NMR data are consistent with I.

Resolution of 2-(2-*hydroxypropyl*) *pyridine* (I). Compound I (25 g, 0·183 mole) was dissolved in acetone (500 ml). To this was added a soln of (−)dibenzoyltartaric acid[22] (71 g, 0·188 mole) in acetone (500 ml). The voluminous ppt which formed was dissolved by addition of acetone (500 ml) and heating to the b.p. Slow undisturbed cooling resulted in the formation of long white needles (34·2 g, m.p. 75–82°). Three additional recrystallizations provided 17·2 g, m.p. 85–86°, $[\alpha]_D - 92{\cdot}34°$). This salt corresponds to (−)VI·(−)dibenzoyltartrate.

Concentration of the mother liquors from the initial crystallization produced after some days 13·7 g in the form of rectangular plates, m.p. 146°, $[\alpha]_D - 87°$. Further recrystallizations did not change the properties. This salt corresponds to (−)VI·(−)dibenzoyltartrate.

Difficulty was experienced in the liberation of the corresponding (+) and (−) bases due to their solubility in water. They could be obtained almost quantitatively by treatment of the salts with a paste of K_2CO_3 in water followed by extraction of the paste with ether. The two enantioners were thus obtained in the following amounts and with the following physical characteristics: (+)VI, 3·7 g, $[\alpha]_D + 15{\cdot}3°$; (−)VI, 4·5 g, $[\alpha]_D - 17{\cdot}9°$.

2-(2-*Hydroxypropyl*) *piperidine* (VII). The racemic I (10 g, 0·073 mole) was dissolved in abs EtOH (50 ml) to which was added Adams catalyst (1 g, 10%w/w). The reaction mixture was hydrogenerated at 60 psi in a Parr Apparatus for 48 hr at room temp. Work-up gave colorless crystals (10 g) of the low melting (55–60°) VII. The IR spectrum showed strong absorption at 3300 cm^{-1} (−NH, −OH) and no absorption in the region 1550–1650 cm^{-1} (absence of pyridine ring). The NMR spectrum displayed no pyridine proton resonance in the region 6·5–8 ppm.

Reduction of a sample of (−)VI with $[\alpha]_D - 19{\cdot}3°$ gave the corresponding (−)VII with $[\alpha]_D - 23{\cdot}1°$. Similarly (+)VI$[\alpha]_D + 17{\cdot}2°$) gave (+)VII$[\alpha]_D + 20{\cdot}1°$). Assuming the recorded value[23] of +26° for sedridine this indicated a 90% stereoselective reaction.

(+) *Sedridine* N-*acetylleucinate*. This salt was prepared[23] using (+)VII$[\alpha]_D + 20{\cdot}1°$, 5·4 g) After several recrystallizations from acetone containing 3% MeOH, 6·1 g of fine white needles, m.p. 168·5–170° were obtained. This represents approximately 70% recovery of the (+)VII present in the reduction product, assuming as before, $[\alpha]_D + 26°$ for (+) sedridine.

2-(2-*Hydroxypropyl*) *piperidine Bis*-p-*nitrobenzoate*. Optically inactive VII (0·5 g, $3{\cdot}5 \times 10^{-3}$ mole) was dissolved in pyridine (3 ml) and *p*-nitrobenzoyl chloride (1·29 g, $7{\cdot}0 \times 10^{-3}$ mole) was added. An exothermic reaction took place, and was stirred overnight. At the end of this period, the soln was filtered free of pyridine hydrochloride and the excess pyridine evaporated from the filtrate at red. press. The resulting viscous oil was triturated with abs EtOH to yield light yellow crystals (1·0 g, m.p. 155–160°, 88%). Several recrystallizations from abs EtOH raised the m.p. to 167·0–167·5°. The IR spectrum displayed bands at 1718 cm^{-1} (ester), 1620 cm^{-1} (amide), 1535 cm^{-1} (*p*-nitrobenzene), and no −NH or −OH absorption. (Found: C, 59·86; H, 5·29: N, 9·41. $C_{22}H_{23}O_7N_3$ requires: C, 59·82; H, 5·23; N, 9·52%).

N-*carbobenzoxy*-2-(2-*hydroxypropyl*) *piperidine* (VIII, R = $PhCH_2$—). Compound VII (3·0 g, 0·021 mole, optically inactive) was suspended in a soln of $KHCO_3$ (3·5 g) in water (50 ml). To this stirred mixture carbobenzoxychloride (3·5 g, 0·022 mole) was added and stirring continued for 1 hr. Extraction of the reaction mixture with ether, with the usual work-up, gave an oil. TLC on alumina indicated 2 components, neither of which were starting material. The IR spectrum displayed bands at 3400 cm^{-1} (—NH and/or —OH), 1750 cm^{-1} (ester), 1695 and 1680 cm^{-1} (urethane), 1590 and 1575 cm^{-1} (pyridine).

[20] E. Lellmann, *Ber. Dtsch. Chem. Ges.* **23**, 2141 (1890).

[21] L. A. Walter, *Organic Syntheses* (Edited by L. I. Smith) Vol. 23; p. 83 et seq. Wiley, New York (1943).

[22] C. L. Butter, L. H. Cretcher, *J. Amer. Chem. Soc.* **55**, 2605 (1955).

[23] H. C. Beyerman, J. Evenshuistra, W. Eveleens, A. Zweistra, *Rec. Trav. Chim.* **78**, 43 (1959).

To remove the undesirable pyridyl carbonate, the basic material was extracted from a chf soln of the crude reaction product with dil HCl. The organic soln was then dried and evaporated to yield a coloured viscous oil (4·08 g, 74%) which was chromatographically homogenous and whose IR spectrum displayed bands at 3410 cm^{-1} (—OH), 1690 and 1679 cm^{-1} (urethane).

N-t-butoxycarbonyl-2(2-hydroxypropyl) piperdine (VIII, R = t-butyl). Compound VII (2 g, 0·014 mole, optically inactive) was dissolved in purified dioxan[24] containing MgO (1·9 g). This mixture was heated, with stirring, at 55° for 1 hr. t-Butoxycarbonyl azide (3·5 g, 0·025 mole) was then added and the heating and stirring continued. The course of the reaction was monitored by TLC on silica gel, which usually indicated complete consumption of starting material after 48–60 hr at these concentrations. After the reaction was judged complete the MgO was removed by filtration and solvents evaporated at red. press. Pumping the resulting oil with a mechanical pump at less than 200 microns served to remove unreacted azide. The product was a light yellow, very viscous oil (3·1 g, 84%) which was chromatographically homogenous. The IR spectrum of VIII (R = t-butyl) is given in Fig. 1.

(−)VII, $[\alpha]_D - 23·1°$ gave an oil in good yield whose IR spectrum was identical to that obtained above and which had an $[\alpha]_D = -27·9°$.

p-*Nitrobenzenesulphonyl-N-methylmorpholinium chloride.* *p*-Nitrobenzenesulphonyl chloride (1 g, $4·5 \times 10^{-3}$ mole) was dissolved in benzene (25 ml) and added dropwise with stirring to a soln of N-methylmorpholine (10 ml) in benzene (50 ml). After several hr the reaction was filtered to yield yellow crystals (1·5 g, m.p. 124–126°, 96%). This material gave a ppt with $AgNO_3$ and was water soluble. (Found: Cl^-, 10·95. $C_{11}H_{15}O_5SClN_2$ requires: Cl^-, 11·02%). The chloride analysis makes the structural assignments virtually certain. The IR spectrum displayed 4 bands between 2750 and 2460 cm^{-1}, as well as the *p*-nitrobenzene band at 1522 cm^{-1}.

N-*carbobenzoxy-2(2-methanesulphonylpropyl) piperidine* (IX, R = $PhCH_2$—). Compound VIII (R = $PhCH_2$—; 0·210 g, $7·6 \times 10^{-4}$ mole) was dissolved in anhydrous pyridine (3 ml). To this was added redistilled methanesulphonyl chloride (0·110 g, $9·6 \times 10^{-4}$ mole) with stirring. A pink colour developed, which was discharged after 5 hr. The reaction soln was filtered free of a small amount of solid material, diluted with several volumes of ether and washed well with water. Drying and evaporating the ether gave a coloured oil (0·105 g) whose IR spectrum was essentially free of —OH absorption and which displayed bands at 1695 cm^{-1} (sharp, urethane) 1350, 1175, 900 cm^{-1} (—OMs). No attempts were made to purify or characterize this compound further.

N-t-*butoxycarbonyl-2(2-methanesulphonylpropyl) piperidine* (IX, R = t-butyl). Compound VIII (R = t-butyl; 2·95 g, 0·012 mole) was dissolved in anhydrous pyridine (25 ml) and methanesulphonylchloride (1·56 g, 0·014 mole) was added dropwise with stirring. After 12 hr, the ppt was removed by filtration. The filtrate was diluted with several volumes of ether and thoroughly washed with water. Drying and evapn of the ether gave a viscous oil (2·36 g) which was chromatographically homogeneous (TLC on silica gel). Its IR spectrum is shown in Fig. 2 and is consistent with the structure IX (R = t-butyl). The substance was decomposed by distillation *in vacuo* and also was changed during chromatography on silica gel or alumina.

This reaction was carried out on optically active VIII(R = t-butyl) derived from VII($[\alpha]_D + 25·1°$) and yielded material whose IR spectrum is the same as that in Fig. 2 and which had an $[\alpha]_D + 24·2°$.

2-(2-*Methanesulphonylpropyl) piperidine* (X, ± *Sedridine methanesulphonate*). Optically inactive IX (R = t-butyl; 2·36 g, $7·4 \times 10^{-3}$ mole) was dissolved in N HBr in glacial AcOH (120 ml, 6·56 g anhyd. HBr). and stirred at room temp for 30 min. Lyophilization of the orange soln at 20 microns and −70° afforded a light yellow powder (2·20 g). Digestion of this powder in acetone yielded a white crystalline solid (0·925 g), 25%, m.p. 130–131°)whose IR spectrum displayed bands at 2800, 2700, 2550, 2499, 2440, 2380 cm^{-1} ($(+)=N^{\oplus}H_2Br(^-)$) and 1335, 1170, 900 $cm^{\ominus 1}$ (methanesulphonate). There was no evidence of urethane absorption in the region 1750–1650 cm^{-1}. The assigned structure is X hydrobromide. Further recrystallizations for analysis raised the m.p. to 142–143° but did not change the IR spectrum. (Found: C, 35·83; H, 6·48; N, 4·42. $C_{19}H_{20}O_3NSBr$ requires: C, 35·81; H, 6·63; N, 4·64%).

± Sedridine methanesulphonate hydrobromide (0·900 g, 3×10^{-3}moles) was dissolved in water (15 ml) and added to a very vigorously stirred mixture of 50% K_2CO_3aq (50 ml) and ether (50 ml). After 1 min the ether was decanted and replaced by fresh solvent. This process was repeated three times. The ether extracts were combined, dried and evaporated to yield a light yellow viscous oil (0·630 g, 96%). This material was chromatographically homogeneous (TLC on silica gel) and its IR spectrum is shown in Fig. 3.

[24] K. B. Wiberg, *Laboratory Technique in Organic Chemistry*, p. 245. McGraw-Hill, Toronto (1960).

2-*Methyl*-1-*azabicyclo*(4.2.0)*octane*(II,ϵ-Coniceine)[6,7,20]. Compound X (0·060 g, $2·7 \times 10^{-4}$ moles) was heated at 90° and 250 microns for 5 hr. No obvious physical change in the material took place, but the product was very soluble in water. Its IR spectrum displayed prominent bands at 3430, 2750 (broad), 1350, 1190, 1020, and 930 cm^{-1}, strikingly similar to the IR spectrum of Galinovsky's brosylate.[4] Its NMR spectrum displayed bands at 4·28 δ (broad multiplet), 3·0 δ (broad), 2·99 δ (doublet, J = 1·5c/s) 2·66 δ (singlet), 2·2–1·6 δ (broad), 1·6 δ (singlet), 1·49 δ (singlet), 1·40 δ (singlet). The band at 4·28 δ is characteristic[4] of methine protons in strained azetidinium rings and provides good evidence for the existence of such a structure.

Treatment of an aqueous soln of the pyrolysis product with sodium tetraphenylboron (0·150 g) in water provided a white water-insoluble ppt which after drying under red. press. at 40° had a m.p. 132–133°. The IR spectrum of this salt (perchlorobutadiene suspension) showed no evidence of —OH or —NH absorption. There was also no absorption in the region 1600–1700 cm^{-1}, ruling out an olefinic product.

2-(2-*Hydroxypropyl*) *pyridylmethiodide* (VI·MeI). The racemic base ± VI (1·0 g, $7·3 \times 10^{-3}$moles) was dissolved in acetone to which was added MeI (1·22 g, $8·6 \times 10^{-3}$ mole). The soln was stirred at room temp overnight. Evapn of the solvent at red. press. provided a light yellow oil. This oil was dried by evaporation to dryness with benzene and finally chlorobenzene. In this way the methiodide (1·73 g, 85%) was obtained. Its IR spectrum displayed bands at 3410 cm^{-1} (—OH), 1635 and 1582 cm^{-1} (pyridine ring carrying a positive charge). The remainder of the spectrum was very similar to that of the base VI. The product gave a water-insoluble tetraphenylborate in the usual way.

Silver oxide oxidation of VI·MeI. The methiodide (5·0 g, 0·018 moles) was dissolved in water (30 ml) to which was added Ag_2O (10·34 g, 0·044 mole). The reaction mixture was stirred at room temp for 15 hr, sometimes forming a Ag mirror. At the end of this period the reaction (which in this particular experiment did not form a mirror) was filtered and the ppt collected washed thoroughly with water, dilute ammonia, and again with water. These washings were not combined with the original filtrate. Drying the ppt provided a mixture of Ag and AgI (7·63 g, 95% of the amount of Ag^0 and $Ag+^1$ expected to be produced by the oxidation).

The original filtrate was extracted with chf which on drying and evaporation yielded an oil (2·5 g, 83% based on production of the corresponding N-methyl-α- or γ- pyridone). Treatment of this oil with $AgNO_3$ soln failed to produce a ppt, indicating the absence of chloride ion. The IR spectrum of this substance displayed bands at 3300 cm^{-1} (—OH), 1665, 1690, 1570 cm^{-1} (ascribable to an N-methyl-α-pyridone). Further characterization of this substance is in progress.

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