149–155°, whose infrared spectrum (potassium bromide) was identical with that of tetrahydrocafestol. After one recrystallization from chloroform-hexane, there was obtained 26 mg. glycol (VII), m.p. 156–158°, undepressed upon admixture with authentic tetrahydrocafestol (II) and having an identical infrared spectrum (potassium bromide).

Infrared examination of the first crude samples of the synthetic glycol and its acetate, as well as of the materials recovered from various mother liquors, failed to reveal the presence of an epimeric compound.

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Synthesis of *dl*-Isoretronecanol

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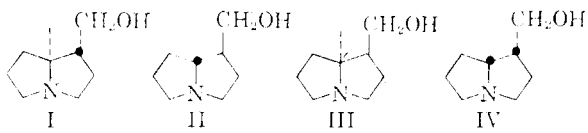
A stereospecific synthesis of *dl*-isoretronecanol is described.

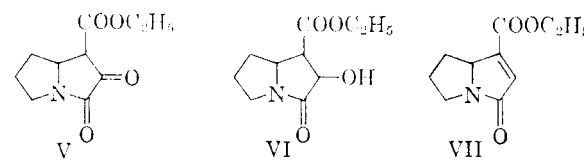
In previous papers[1,2] from this laboratory, the syntheses of 1-hydroxypyrrolizidine and 1-hydroxymethyl-2-hydroxypyrrolizidine were described. The establishment of the absolute configuration of the C-1 atom in heliotridane[3] and retronecanone[4] has permitted the deduction of the absolute configuration of the C-1 atom in a large number of naturally occurring pyrrolizidine alcohols. However, synthesis leading to a stereochemically pure hydroxymethylpyrrolizidine has been accomplished only recently.[5,6]

Altogether four 1-hydroxymethylpyrrolizidines, are known, trachelanthamidine (I), laburnine (II), isoretronecanol (III), and lindelofidine (IV).[7] As the rings in the pyrrolizidine molecule



are inclined at an angle to the plane of the paper along the C—N axis, structures I and II representing trachelanthamidine and laburnine (a pair of enantiomers) are thermodynamically more stable[8] than isoretronecanol and lindelofidine. Except for a very recently reported synthesis[9] of *dl*-isoretronecanol, all previous synthetic methods[5,10] yielded only the racemate which consisted of the thermodynamically more stable trachelanthamidine or laburnine.

We have now accomplished a stereospecific synthesis of *dl*-isoretronecanol. 2,3-Dioxo-1-carbethoxypyrrolizidine (V), prepared by the condensation of diethyl oxalate and ethyl 2-pyrrolidylacetate,[2] was reduced with 5% rhodium on alumina catalyst and hydrogen to 1-carbethoxy-2-hydroxy-3-oxopyrrolizidine (VI). Dehydration using *p*-toluenesulfonyl chloride and pyridine gave 1-carbethoxy-3-oxopyrrolizid-1,2-ene (VII) in good yield. Reduction with rhodium on alumina



catalyst and hydrogen at atmospheric pressure and temperature saturated the olefinic double bond and yielded 1-carbethoxy-3-oxopyrrolizidine. This last product upon treatment with lithium aluminum hydride in tetrahydrofuran gave in good yield 1-hydroxymethylpyrrolizidine, which was *dl*-isoretronecanol. The infrared spectrum of synthetic *dl*-isoretronecanol picrate was identical with that of *l*-isoretronecanol picrate.[11] The spectrum was very similar to but different in detail from that of *dl*-trachelanthamidine. Reaction of *dl*-isoretronecanol with benzoyl chloride yielded *dl*-1-benzoyloxymethylpyrrolizidine as a low melting solid. The infrared spectra of *dl*-1-benzoyloxymethylpyrrolizidine picrate and *l*-benzoylisoretronecanol picrate were superimposable. Treatment of *dl*-isoretronecanol with thionyl chloride yielded *dl*-chloropseudoheliotridane characterized as its picrate.

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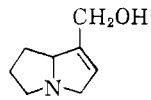
In this synthesis the hydrogen during the catalytic reduction of 1-carbethoxy-3-oxopyrrolizid-1,2-ene to 1-carbethoxy-3-oxopyrrolizidine is added stereospecifically. As would be expected, the approach of the catalyst and hydrogen has to be by necessity from the less hindered side of the pyrrolizidine nucleus thus pushing the carbethoxy function to the inside of the fold. Stereospecific catalytic reductions in the pyrrolizidine alkaloid field are well known—*e.g.*, conversion of desoxyretronecine to retronecanol,[12] isoheliotridene to heliotridane,[13] and retronecine to platynecine.[12] It is significant that in the synthesis of isoretronecanol reported[8] by the Soviet workers, the last and key step is the catalytic reduction of 1-carbethoxypyrrolid-1,2-ene to 1-carbethoxypyrrolizidine.

Attempted synthesis of the unsaturated amino alcohol supinidine (VIII) by lithium aluminum hydride treatment of 1-carbethoxy-3-oxo-pyrrolizid-1,2-ene failed. The product could not be purified. It still retained the lactam function as evidenced by its neutral character and infrared spectrum. Stepwise reduction under a variety of conditions was attempted without success.



VIII

EXPERIMENTAL

1-Carbethoxy-3-oxopyrrolizid-1,2-ene (VII). To a solution of 2.8 g. of 1-carbethoxy-2-hydroxy-3-oxopyrrolizidine[2] in 12 ml. of dry pyridine was added 5.5 (2 mole equiv.) of recrystallized *p*-toluenesulfonyl chloride. The resulting pale yellow solution was left in the ice-box for 80 hr. The pyridine hydrochloride was filtered off, washed with 3 ml. of pyridine, the filtrate acidified with 20% hydrochloric acid, and extracted repeatedly with chloroform. The crude residue which was a mixture of the tosylate and the dehydrated product was dissolved in benzene and put on a column of neutral alumina and eluted successively with benzene, ether, and 1:1 ether-chloroform. The ether and ether-chloroform eluates were evaporated and the residues consisting of colorless crystals, 1.8 g. (73%), recrystallized from *n*-hexane; m.p., 92–93°. The infrared spectrum did not show the presence of a hydroxyl or tosylate grouping.

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.60; H, 6.68; N, 7.18. Found: C, 62.08; H, 6.79; N, 7.48.

1-Carbethoxy-3-oxopyrrolizidine. A solution of 500 mg. of 1-carbethoxy-3-oxopyrrolid-1,2-ene in 15 ml. of glacial acetic acid was hydrogenated in the presence of 150 mg. of 5% rhodium on alumina at atmospheric pressure and temperature. The theoretical amount for 1 mole was absorbed in 15–20 min. The catalyst was filtered off and the solvent removed under reduced pressure. The residual oil was distilled in high vacuum to give a colorless oil, b.p. 99–100°/0.2 mm. (air bath).

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.66; N, 7.10. Found: C, 60.82; H, 7.61; N, 7.35.

dl-Isoretronecanol. To a solution of 1.2 g. of lithium aluminum hydride in 60 ml. of freshly purified tetrahydrofuran was added in drops a solution of 3.4 g. of 1-carbethoxy-3-oxopyrrolizidine in 40 ml. of tetrahydrofuran. The mixture was stirred under reflux for 3 hr., excess of hydride decomposed by cautious addition of wet tetrahydrofuran, and the precipitate filtered off through Super-cel. The filtrate was evaporated under reduced pressure and the residual oil distilled in high vacuum to yield a colorless oil, b.p., 97–98°/0.7 mm. $n^{24.5°}$ 1.5010 (lit.[11] b.p. of *l*-isoretronecanol 139–140°/8 mm.).

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.7; N, 9.91. Found: C, 68.27; H, 10.8; N, 9.95. A portion of the oil was converted into its picrate in ethanol. Recrystallization from ethanol gave needles m.p. 188–189°; (lit.[11] m.p. of *l*-isoretronecanol picrate 193–194°; *dl*-isoretronecanol picrate[9] 185.5–186.5°).

Anal. Calcd. for $C_8H_{15}NO{\cdot}C_6H_3N_3O_7$: C, 45.40; H, 4.89; N, 15.13. Found: C, 45.41; H, 4.70; N, 15.17. A picrolonate was prepared in and crystallized from ethanol to give pale yellow needles, m.p. 175.5–176° (lit.[14] m.p. of *dl*-isoretronecanol picrolonate 176–177°).

Anal. Calcd. for $C_8H_{15}NO{\cdot}C_{10}H_8N_4O_5$: C, 53.32; H, 5.71; N, 17.27. Found: C, 53.37; H, 5.70; N, 17.08. The infrared spectra of *dl*-isoretronecanol picrate and *l*-isoretronecanol picrate determined in Nujol mull and as potassium bromide discs were superimposable.

dl-Benzoylisoretronecanol. A solution of 90 mg. of *dl*-isoretronecanol in 5 ml. of reagent chloroform was shaken with 150 mg. of benzoyl chloride. The mixture was warmed on the steam bath for 15 min., cooled and ether added to turbidity. The resulting oil failed to crystallize. Most of the solvent was removed and the remaining chloroform solution shaken with 10% aqueous sodium hydroxide. The organic layer was washed once with water, dried (sodium sulfate), and evaporated to yield an oil. Distillation in high vacuum gave a colorless oil, b.p. 118–120°/0.2 mm (air bath). On cooling in Dry Ice-acetone it solidified to a low melting solid. The picrate was prepared in ethanol and crystallized from ethanol to give pale yellow needles; m.p. 138.5° (lit.[14] m.p. of *l*-benzoylisoretronecanol picrate 130–131°).

Anal. Calcd. for $C_{15}H_{19}NO_2{\cdot}C_6H_3N_3O_7$: C, 53.14; H, 4.67; N, 11.81. Found: C, 52.99; H, 4.48; N, 11.83. The infrared spectrum determined in chloroform solution was identical to that of *l*-benzoylisoretronecanol picrate.

dl-Chloroheliotridane. To 90 mg. of *dl*-isoretronecanol was added in drops with cooling 1.5 ml. of thionyl chloride and the mixture boiled under reflux for 1 hr. The excess of thionyl chloride was removed under reduced pressure and the dark residue diluted with ice-cold water, filtered, basified with 10% aqueous sodium hydroxide, and extracted with chloroform. The extract was washed once with water, dried (sodium sulfate), and evaporated to give an oil. The picrate was prepared in and recrystallized from ethanol to give needles; m.p. 188–189° (lit.[14] m.p. of *l*-chloroheliotridane picrate 185°).

Anal. Calcd. for $C_8H_{14}NCl{\cdot}C_6H_3N_3O_7$: C, 43.25; H, 4.4; N, 14.4. Found: C, 43.27; H, 4.30; N, 14.42.

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