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AN APPROACH TO NATURAL 2-ALKYL-6-METHYLPIPERIDINES VIA N-ACYLLACTAM REARRANGEMENT

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Abstract—Application of the Mundy *N*-acyllactam rearrangement to 6 - methyl - 2 - piperidone has led to a synthesis of optically active dihydropinidine, confirming the absolute configuration of the pine alkaloid pinidine, and to a new synthesis of the fire ant toxin, *Solenopsin A*.

A small subgroup of piperidine alkaloids[1] contains the 2 - alkyl - 6 - methylpiperidine skeleton **1**, the main representatives being 2,6 - dimethylpiperidine, the pine alkaloid pinidine[2] **2**, and the alkaloids of fire ant venom[3] **3–7**. Himbeline[4] is a more complex member, as are the hydroxylated alkaloids of structure **8**: carpaine,[5] cassine,[6] carnavoline[7] prosofrine and prosofrinine.[8]

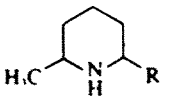
The most commonly used general synthetic route to this family is reduction of the corresponding pyridine; this approach has been applied to pinidine[9] and dihydropinidine,[2] carpaine derivatives,[10] the fire ant alkaloids,[3] and in approaches to the *Prosopis* alkaloids.[11] The nitroalkane-ketoaldehyde condensation method of Brown *et al.*[12] provides a general route to the aminoalcohols of structure **8**. It appeared to us that an alternative path to the alkaloids of skeleton **1** might proceed *via* a common intermediate containing an α-methylpiperidine ring to which various alkyl groups could then be attached at the other α-position. Such an approach might not only permit the synthesis of **3–5** from a single intermediate, but could also establish absolute configurations by leading to optically active alkaloids from a chiral intermediate.

An obvious intermediate is 6 - methyl - 2 - piperidone **9**, available in optically active form of known configuration,[13] with a carbonyl at C-2 as a handle for the introduction of alkyl groups. We report here a brief examination of the application of the Mundy *N*-acyllactam rearrangement[14] to lactam **9** which has provided a synthesis of optically active dihydropinidine, confirming the absolute configuration of pinidine, as well as a new synthesis of *Solenopsin A* **3**, the fire ant alkaloid.

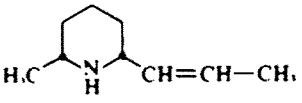
For the synthesis of dihydropinidine **14**, the recemic lactam **9** was converted to imide **10** in 67% yield using *n*-butyryl chloride and pyridine at room temperature. The Mundy rearrangement involves the pyrolysis of *N*-acyllactams with calcium oxide; in order to achieve reasonable yields in this series, we found it necessary to reflux the reaction mixture for 1.5 h before distilling. Imine **12** was isolated in 31% yield after redistillation, then hydrogenated to DL-dihydropinidine in 75% yield. Only the *cis* isomer was found, as expected for catalytic hydrogenation, and the IR spectrum of the product was identical with that of an authentic sample.

Repetition of this sequence beginning with (*S*)-(+)-**9** of 88.5% optical purity afforded (−) dihydropinidine hydrochloride, $[\alpha]_D^{25}$ − 9.1° (ethanol), while a sample of the hydrochloride derived by hydrogenation of natural pinidine had $[\alpha]_D^{25}$ + 12.7° (ethanol). This synthesis from (*S*)-**9** shows that (−) dihydropinidine hydrochloride is the (2*R*, 6*S*) isomer and that the dihydro derivative of the alkaloid is the (2*S*, 6*R*) enantiomer. Pinidine consequently has the (2*R*, 6*R*) configuration, in agreement with the absolute configuration derived earlier in this laboratory[15] by a completely different correlation.

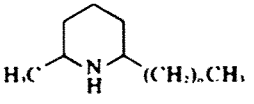
Though the Mundy method works satisfactorily for the pinidine skeleton, application to the synthesis of solenopsin-*A* **3** was plagued by poor yields. Pyrolysis of *N* - lauryl - 6 - methyl - 2 - piperidone **11** over calcium oxide gave imine **13** in about 5% yield after extensive chromatography. Reduction was effected with sodium borohydride in order to increase the proportion of *trans* product. Direct GLC comparison with authentic samples supplied by Dr. J. G. MacConnell confirmed the identity



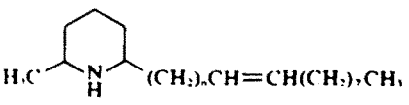
1



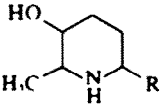
2



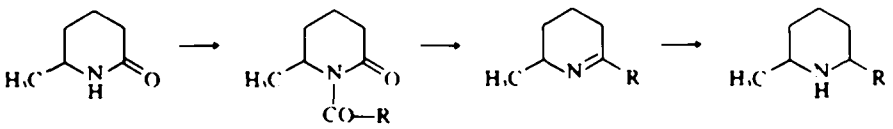
3: n = 10
4: n = 12
5: n = 14



6: n = 3
7: n = 5



8



9 **10**: R = n-C_3H_7 **12**: R = n-C_3H_7 **14**: R = n-C_3H_7
11: R = n-$C_{11}H_{23}$ **13**: R = n-$C_{11}H_{23}$ **3**: R = n-$C_{11}H_{23}$

of the synthetic product as **3** and showed it to be a 4:1 mixture of *cis* and *trans* isomers.

Thus, while the *N*-acyllactam route has provided a new synthetic approach to the fire ant alkaloids, the low yields make it unattractive for the attachment of long alkyl chains. Moreover, like previous methods which construct 2,6 - dialkylpiperidines by reduction of a pyridine ring or imine double bond, it leads predominantly to *cis* isomers, and is not a satisfactory route to the *trans* alkaloids. Other possibilities are being pursued.

EXPERIMENTAL

IR spectra were recorded on neat liquids on a Perkin-Elmer model 257 grating spectrophotometer, while NMR spectra were taken in CCl_4 solution on a Varian A-60 instrument, using TMS as an internal standard. Optical rotations were measured on a Perkin-Elmer model 141 polarimeter; c is reported as g per 100 ml. M.P.s were determined in a Thomas–Hoover oil immersion apparatus and are uncorrected.

(S)-(+)-6-Methyl-2-piperidone **9**

The optically active lactam was prepared following the procedure of Cervinka *et al.*[13] 2-Methylpiperidine (Columbia Organic Chemicals) was resolved by slow crystallization (2–3 months) of the D-tartaric acid salt as described by Leithe.[14] After four recrystallizations of the salt from ethanol–ethyl acetate the amine had $[\alpha]_D^{20}$ + 28.9° (neat, 1 dm), lit.[14] $[\alpha]_D^{20}$ + 36° (neat). Benzoylation gave the *N*-benzoyl derivative, m.p. 65–68° (ether), $[\alpha]_D^{20}$ + 37° (c 2.0, ethanol), lit.[13] m.p. 69–70°, $[\alpha]_D^{20}$ + 41° (c 2.0, ethanol) in 70% yield. Oxidation with potassium permanganate, as described by Bunzel,[15] led to *N* - benzoyl - δ - aminocaproic acid, m.p. 116–119° (water), $[\alpha]_D^{20}$ + 19.0° (c 1.99, ethanol), lit.[13] m.p. 121–122°, $[\alpha]_D^{20}$ + 22.6° (c 1.99, ethanol), in 35% yield. Cyclization at 165° for 3 h, followed by distillation, gave *N* - benzoyl - 6 - methyl - 2 - piperidone, b.p. 140–145° (6 mm) in 67% yield; the imide solidified on cooling but was directly hydrolyzed with 5% potassium carbonate solution. (*S*) - (+) - 6 - Methyl - 2 - piperidone **9**, obtained in 75% yield, had m.p. 79–80.5° (ethyl acetate), $[\alpha]_D^{20}$ + 24.6° (c 2.01, water), lit.[13] m.p. 81–82°, $[\alpha]_D^{20}$ + 27.8° (c 2.03, water).

N-n-Butyryl-6-methyl-2-piperidone **10**

In a 50-ml round-bottom flask sealed with a rubber septum was placed 1.5 g of D,L-**9**,[17] 2.1 g of dry pyridine, and 30 ml of dry benzene. While the solution was magnetically stirred and cooled in an ice bath a solution of 1.41 g of *n*-butyryl chloride in 5 ml benzene was added by syringe over 15 min; precipitation of a white solid occurred quickly. The mixture was stirred overnight at room temperature, filtered, diluted with 150 ml benzene, and washed with 10% HCl (3 × 20 ml) and 10% NaOH (20 ml). After drying over Na_2SO_4 and concentrating at reduced pressure, the residue (1.42 g) was distilled to give D,L-**10**, 1.2 g (65.6%), as a pale yellow viscous liquid, b.p. 140–145° (0.5 mm), IR 1690 (s) and 1630 (m) cm^{-1}, no absorption at 3200–3400 cm^{-1}; NMR δ 0.80 (t, 3H), 1.10 (d, 3H), 2.55 (m, 4H), 1.61 (m, 7H).

Repeating the acylation with (*S*)-(+)-**9** gave (*S*)-(+)-**10** in 67% yield, $[\alpha]_D^{20}$ + 60.1° (c 1.16, ethanol).

6-Methyl-2-n-*propylpiperideine* **12**

Following the general procedure of Mundy,[16] 1.5 g of racemic imide **10** was thoroughly mixed with an equal weight of calcium oxide and gently heated under reflux with a small flame for 1.5 h, and the mixture then distilled at atmospheric pressure over 30 min. The crude product (0.65 g) was redistilled in a Kugelrohr tube, b.p. 70–75° (oven) at 0.1 mm, giving 0.1 mm, giving 0.35 g (30%) of imine **12**, IR 1660 cm^{-1} (m), no absorption at 1690 cm^{-1}; NMR δ 0.81 (t, 3H), 1.11 (d, 3H), 1.2–1.8 (m, 7H), 2.12 (m, 4H).

In the optically active series, the imine from (+)-**10** was prepared on the same scale in 26% yield, b.p. 75–80° (oven) at 0.10 mm.

cis - 6 - *Methyl* - 2 - n - *propylpiperidine (dihydropinidine)* **14**

A solution of 278 mg of D,L-**12** in 1 ml of 10% HCl was hydrogenated at atmospheric pressure over 15 mg of 10% Pt/C. One equivalent (50 ml) of hydrogen was taken up in 35 h. After filtering the catalyst, the filtrate was neutralized with cold 50% KOH and extracted with ether (3 × 20 ml). The dried (Na_2SO_4) extracts were distilled (Kugelrohr) to yield 210 mg (74.5%) of D,L-**14**, b.p. 175–180° (lit.[2] b.p. 176–177°); NMR δ 0.85 (t, 3H), 1.11 (d, 3H), 3.3 (broad m, 2H), 3.3 (broad m, 2H), 1.4–2.2 (m, 11 H). The IR spectrum was identical with that of authentic dihydropinidine.

The hydrochloride, prepared by passing HCl gas into an ether solution, was recrystallized twice from 2:1 ethyl acetate–ethanol to furnish colorless needles, m.p. 210–213° (lit.[2] m.p. 219–220°). Its IR spectrum was identical with that of authentic dihydropinidine hydrochloride.

(2*R*,6*S*)-**14**, prepared similarly in 76.5% yield by hydrogenation of the optically active imine, had b.p. 175–180°. Its hydrochloride, m.p. 215–220°, showed $[\alpha]_D^{25}$ – 9.1° (c 1.03, ethanol). The IR spectra of both the free base and hydrochloride were identical with those of authentic samples.

Authentic dihydropinidine **14**

A sample of *N*-benzoylpinidine[15] was hydrogenated in ethanol solution over 10% Pd/Cat atmospheric pressure; one equivalent of hydrogen was taken up in 6 h. Concentration of the filtered solution left *N*-benzoyldihydropinidine as a viscous oil, IR 1630, 1600, 1580, 1490 cm^{-1}, no absorption at 965 cm^{-1}. The amide (400 mg) was heated overnight at 95–100° with 2 ml of conc. HCl in 2 ml of glacial acetic acid. The mixture was neutralized with cold 50% KOH and extracted with ether (3 × 30 ml). Disillation of the extracts gave 185 mg (79%) of dihydropinidine, b.p. 175–180°. Its hydrochloride had m.p. 215–220° (lit.[2] m.p. 244–246°), $[\alpha]_D^{20}$ + 12.8° (c 1.07, ethanol), lit.[2] $[\alpha]_D^{25}$ + 12.7° (c 1.07, ethanol).

6 - *Methyl* - 2 - n - *undecypiperidine (solenopsin A)* **3**

N - Lauryl - 6 - methyl - 2 - piperidone **11** was prepared from D,L-**9** and lauryl chloride by the same procedure used for **10**. After chromatography over silica gel in benzene, the viscous imide had IR 1700 cm^{-1}, NMR δ 0.91 (t, 3H), 1.11 (d, 3H), 1.25 (narrow m, 18H). Pyrolysis of 1.25 g of **11** with calcium oxide, as described above for **12**, gave 250 mg of crude product; the IR spectrum showed it to be a mixture of imine **13** and unreacted imide **11**. The mixture was chromatographed on 40 g of silica gel; ether eluted the unreacted imide, while elution with methanol yielded imine **13** (50 mg) as a pale yellow liquid, IR 1660 cm^{-1}.

Reduction of **13** with sodium borohydride in ethanol gave amine **3**, whose IR spectrum showed no absorption at 1660 cm^{-1}. G.L.C. analysis was carried out on a Varian Aerograph instrument with flame ionization detector, using 5% SE-30 on Chromosorb W, 60–80 mesh, column temp. 180°, He flow rate 60 ml/min. The product showed two peaks in a 4:1 ratio with retention times of 4.25 and 4.70 min, identical with the retention times of authentic *cis* and *trans* 6 - methyl - 2 - *n* - undecylpiperidines[3] under the same conditions.

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