τ 8.91, 9.03 (*endo*-CH—CH_3), singlet (3H) τ 8.80 p.p.m. (C—CH_3). Ultraviolet and mass spectra of compounds **8** and **9** were identical. Compound **9** was hydrogenated on 10% palladium on charcoal in ethanol. The diketo ketal **12** (m.p. 319 °C) was obtained in a quantitative yield. This material was identical (t.l.c., i.r., n.m.r., and mass spectra) with the corresponding optically active compound of the same structure (m.p. 245–248 °C) obtained from napelline (3).

We wish to thank the National Research Council, Ottawa, and the Hoffmann-La Roche Company, Dorval, Quebec, and Nutley, New Jersey (U.S.A.) for the generous support of these investigations.

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The Total Synthesis of Racemic Napelline

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Received April 19, 1974

Karel Wiesner, Pak-Tsun Ho, Connie Shii Jeou (Pan) Tsai, and Yiu-Kuen Lam. Can. J. Chem. **52**, 2355 (1974).

Lucidusculine **1** was converted into the lactame **5**. This compound is identical with the corresponding racemate described in the accompanying Communication. The synthesis of napelline **2** from the lactame **5** is discussed. The process completes the first (formal) total synthesis of a racemic hexacyclic polysubstituted aconite alkaloid.

Karel Wiesner, Pak-Tsun Ho, Connie Shii Jeou (Pan) Tsai et Yiu-Kuen Lam. Can. J. Chem. **52**, 2355 (1974).

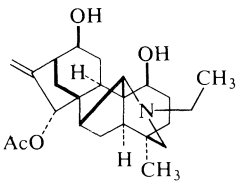
On transforme la lucidusculine **1** en la lactame **5**. Ce composé est identique au racémate correspondant décrit dans la communication qui accompagne cet article. On présente une discussion de la synthèse de la napelline **2** à partir de la lactame **5**. Le processus complète la première synthèse totale (formelle) de l'alcaloïde aconite polysubstitué hexacyclique et racémique. [Traduit par le journal]

In the accompanying Communication (1) we have described the total synthesis of the racemic hexacyclic lactames **5** and **8**. We report now the preparation of the optically active form of these compounds from lucidusculine (2) **1** and the conversion of (optically active) **5** to the alkaloid napelline **2** (2).

Lucidusculine **1** was converted quantitatively to napelline **2** (m.p. 165 °C) by reduction with lithium aluminum hydride in tetrahydrofuran at 0 °C. Hydrogenation of napelline with platinum oxide in acetic acid gave dihydronapelline **3** (2) (m.p. 175 °C) in a yield of 70%. Treatment of **3** with mercuric acetate in aqueous acetic acid at 60 °C for 3 h gave a mixture of products which was oxidized with chromium trioxide in pyridine at room temperature for 36 h. The triketolactam **4**[1] (m.p. 284 °C) was isolated in a yield of 16.5%; i.r.: 3400 (NH), 1742 (five-membered ketone), 1706 (six-membered ketone), 1672 cm^{-1} (lactam); n.m.r.: singlet (3H) τ 8.74 (C—CH_3), doublet (3H) τ 8.99 p.p.m. (*endo*-CH—CH_3).

The diketo ketal **5** (m.p. 248 °C) was prepared by treatment of **4** with *p*-toluenesulfonic acid and ethylene glycol in boiling benzene for 2 h in a yield of 71%; i.r.: 1738 (five-membered ketone), 1710 (six-membered ketone), 1670 cm^{-1} (lactam); n.m.r.: broad singlet (4H) τ 5.96 (dioxolane protons), singlet (3H) τ 8.85 (C—CH_3), doublet

[1]The i.r., n.m.r., and mass spectra of all compounds have been recorded and are in agreement with the structures assigned. All crystalline compounds gave correct elemental analyses.



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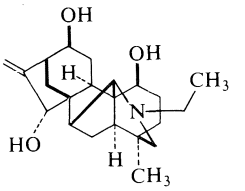

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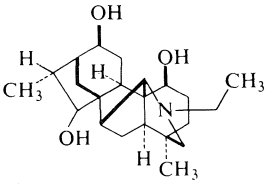

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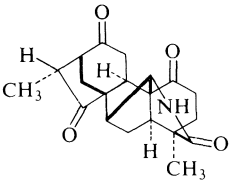

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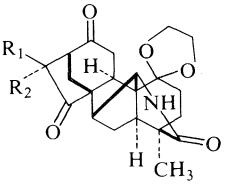
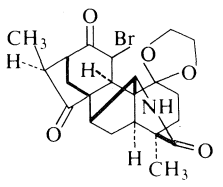


5 $R_1 = H$; $R_2 = CH_3$
6 $R_1 = CH_3$; $R_2 = H$



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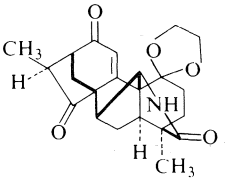

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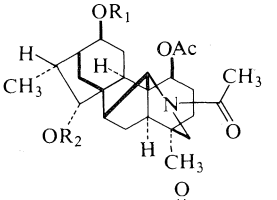
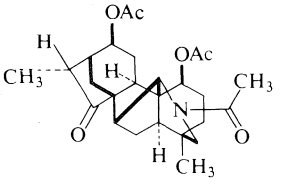


9 $R_1 = R_2 = C(=O)-CH_3$
10 $R_1 = R_2 = H$
11 $R_1 = C(=O)-CH_3$, $R_2 = H$



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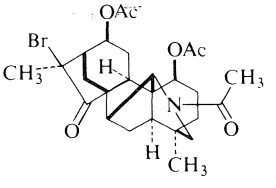
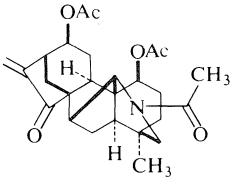


13



14

(3H) τ 8.99 p.p.m. (*endo*-CH—CH_3). The identity of this optically active material and the synthetic racemic compound (m.p. 319 °C) is reported in the accompanying Communication (1).

Refluxing with methanolic potassium hydroxide, converted the diketo ketal **5** to an equilibrium mixture (4:6, separated by preparative t.l.c.) of the starting material and the epimer **6** (m.p. 249 °C); n.m.r.: singlet (3H) τ 8.78 (C—CH_3), doublet (3H) τ 8.83 p.p.m. (*exo*-CH—CH_3). Compound **6** was brominated with bromine in a mixture of ether and chloroform in the presence of hydrogen chloride at 0 °C. The monobromo ketone **7** (m.p. 229 °C) was obtained in a yield of 92%; n.m.r.: doublet (1H) τ 5.03 (CH—*CH*—Br), doublet (3H) τ 8.79 p.p.m. (*exo*-CH—CH_3). Dehydrobromination of **7** with lithium bromide and lithium carbonate in dimethylformamide at 140 °C for 1 h gave 85% of the unsaturated ketone **8** (m.p. 208 °C); i.r.: 1745 (five-membered ketone), 1672 cm^{-1} (lactam and α,β-unsaturated ketone); n.m.r.: singlet (1H) τ 4.10 (vinyl proton), doublet (3H) τ 8.73 (*exo*-CH—CH_3), singlet (3H) τ 8.81 p.p.m. (C—CH_3); u.v.: λ_{max}(EtOH) 232, 272 nm (ε =

8234, 5553). (For the identity of compound **8** and the corresponding totally synthetic racemate *cf.* (1).) Hydrogenation of **8** on 10% palladium on charcoal in ethanol gave back quantitatively the diketone **6**.

In order to complete the synthesis of napelline, compound **5** was converted to the triketone **4** in 60% aqueous acetic acid at 80 °C in a quantitative yield. Reduction of **4** with lithium aluminum hydride in boiling dioxane under nitrogen for 22 h yielded a trihydroxyamine, which was immediately acetylated with acetic anhydride in pyridine and gave compound **9** (m.p. 189 °C) in a yield of 20% (after recrystallization); i.r.: 1730 (acetate), 1626 cm^{-1} (amide); n.m.r.: two singlets (3H) τ 7.82, 7.88 (—N(—CO—CH_3)—), singlets (3H each) τ 7.91, 7.93, 7.98 (3-O—CO—CH_3), doublet (3H) τ 9.08 (CH—CH_3), singlet (3H) τ 9.14 p.p.m. (C—CH_3).

Alkaline hydrolysis of **9** with potassium carbonate in aqueous methanol at room temperature gave a mixture from which the oily dihydroxy acetate **10** was isolated by preparative t.l.c. in a yield of 45%; i.r.: 1733 (acetate), 1625 cm^{-1} (amide); n.m.r.: broad singlet (1H) τ 4.93 (—C*H*—OAc), singlet (3H) τ 7.92 p.p.m. (—O—CO—CH_3). Compound **10** was acetylated with acetic anhydride in pyridine at 5 °C for 7 h. The oily hydroxy diacetate **11** was obtained in an almost quantitative yield and it was purified by preparative t.l.c.; n.m.r.: singlet (3H) τ 7.93 (—O—CO—CH_3), singlet (3H) τ = 8.00 (—O—CO—CH_3), doublet (3H) τ 8.96 (CH—CH_3), singlet (3H) τ 9.14 p.p.m. (C—CH_3).

Compound **11** was oxidized with chromium trioxide – pyridine in methylene dichloride at room temperature. The oily ketone **12** was obtained in a yield of 77% and was homogeneous by t.l.c. in several solvent systems; i.r.: 1739 (five-membered ketone and acetate), 1633 cm^{-1} (amide); n.m.r.: singlet (3H) τ 7.91 (—O—CO—CH_3), singlet (3H) τ 7.94 (—O—CO—CH_3), doublet (3H) τ 8.80 p.p.m. (CH—CH_3). Compound **12** was dissolved in a mixture of ether and chloroform containing hydrogen chloride and treated with bromine at room temperature to yield 82% of the oily bromo ketone **13**; n.m.r.: singlet (3H) τ 8.04 p.p.m. (—CBr—CH_3). Dehydrobromination of **13** with lithium bromide and lithium carbonate in dimethylformamide at 145 °C for 1 h led to the formation of the unsaturated ketone **14** in a yield of 62%. It was homogeneous in t.l.c.; i.r.: 1735 (acetate), 1731 (α,β-unsaturated ketone), 1643 (double bond), 1628 cm^{-1} (amide); n.m.r.: two broad singlets (2H) τ 3.91, 4.39 p.p.m. (methylenic protons); u.v.: λ_{max}(EtOH) 225 nm (ε = 11 830).

Finally, reduction of **14** with lithium aluminum hydride in dioxane at 60 °C for 2 h yielded napelline **2** (m.p. 165 °C). The synthetic compound was identical (mixture m.p., t.l.c., i.r. in KBr, n.m.r., and mass spectrum) with an authentic sample of napelline **2**. Thus, the first total synthesis of napelline is formally completed.

We wish to thank the National Research Council of Canada, and the Hoffmann-La Roche Company, Dorval, Quebec, and Nutley, New Jersey (U.S.A.) for the generous support of these investigations. We also thank Professor Shô Itô, Tohoku University, Japan, for providing us with the large amount of lucidusculine needed for these studies.

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