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SYNTHESIS OF (+)-HUPEOL FROM (–)-CYTISINE: TRANSFORMATION OF A CYCLIC IMINE INTO A CYCLIC HEMIACETAL

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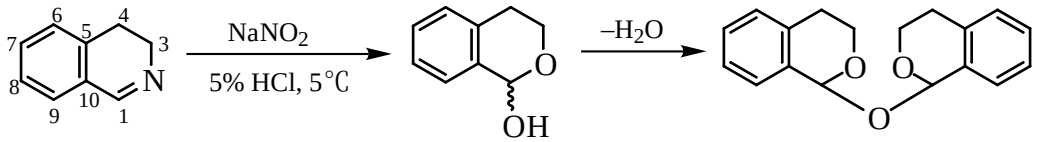
Abstract – A possible intermediate in the metabolism of lupin alkaloids, (+)-hupeol, was synthesized from (–)-cytisine by transformation of a cyclic imine into a cyclic hemiacetal by treatment with HNO_2. The absolute stereochemistry of (+)-hupeol was confirmed to be 7*S*, 9*R*, which is the same as that of (–)-cytisine.

In our phytochemical study of lupin alkaloids, we recently reported the isolation and structural determination of (+)-hupeol together with lupin alkaloids from *Maackia hupehensis*.[1] (+)-Hupeol, in which 12-N of (–)-cytisine is replaced by oxygen, is structurally similar to (–)-cytisine, but it is not an alkaloid because it does not possess a basic amino group. (+)-Hupeol is the first possible metabolite in the metabolism of lupin alkaloids to non-basic compounds.[1] If (–)-cytisine, a major base in *M. hupehensis*, was to be metabolized oxidatively to (+)-hupeol, the absolute stereochemistries of these two compounds must agree. To determine whether their absolute stereochemistries agree, we investigated the synthesis of the hemiacetal (+)-hupeol from the secondary amine (–)-cytisine by treating a cyclic imine with HNO_2. We describe a novel method for transformation of a cyclic imine into a cyclic hemiacetal and its application to the synthesis of (+)-hupeol from (–)-cytisine.

A solution of the cyclic imine 3,4-dihydroisoquinoline (**1**) in 5% HCl was treated with $NaNO_2$ at 5℃ for 24 h to give bis(3,4-dihydro-1*H*-benzopyran-1-yl) ether (**3**) in 84% yield (Scheme 1).

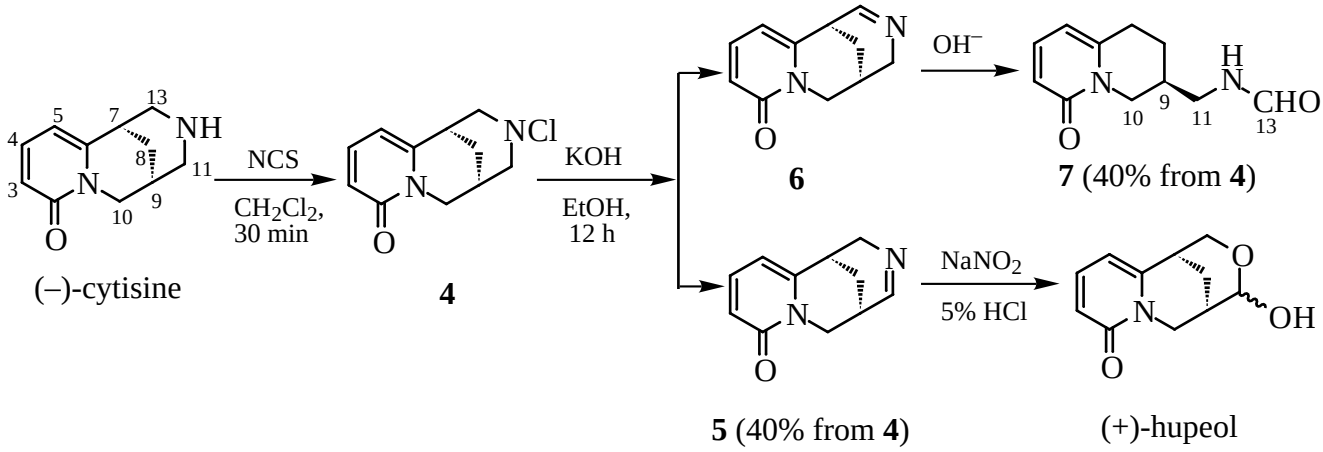


1 **2** **3**

Scheme 1

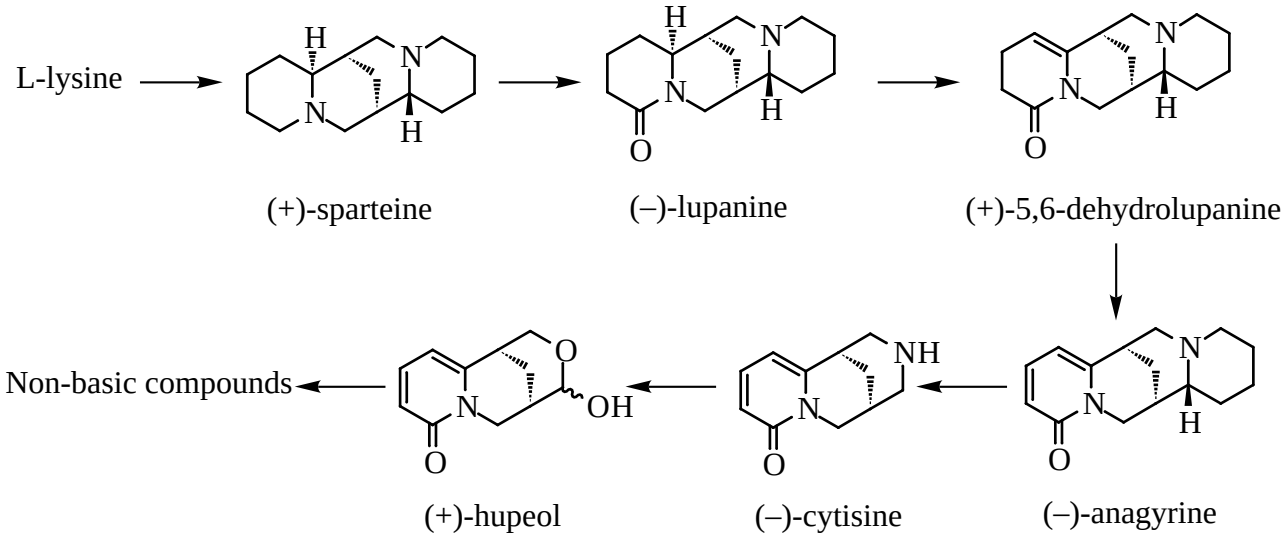
The formation of ether (**3**) indicates that 3,4-dihydro-1*H*-benzopyran-1-ol (**2**) was formed as an intermediate, since ether (**3**) is known to be formed readily by dehydration of the two molecules of hemiacetal (**2**).[2] Thus, it was proved that a cyclic imine was transformed into a cyclic hemiacetal only by treatment with HNO_2.

12-Chlorocytisine (**4**)[3] was derived from (–)-cytisine quantitatively simply by stirring (–)-cytisine with *N*-chlorosuccinimide (NCS) for 30 min in CH_2Cl_2 at room temperature. In dehydrochlorination of **4**, we expected to obtain 11,12-dehydrocytisine (**5**)[4] and 12,13-dehydrocytisine (**6**). Contrary to our expectation, compounds (**5**, **7**) were both obtained in yields of 40% by treatment of **4** with KOH-EtOH for 12 h. Compound (**7**)[5] was likely transformed from **6**.



Scheme 2

11,12-Dehydrocytisine (**5**, 75 mg, 0.4 mmol) was treated with $NaNO_2$ (34 mg, 0.5 mmol) in a manner similar to that described above to give (+)-hupeol (63 mg, 0.3 mmol) in 77% yield (Scheme 2). Thus, the absolute stereochemistry of (+)-hupeol was confirmed to be 7*S*, 9*R*, which is the same as that of (–)-cytisine.



Scheme 3

It is universally accepted in the biosynthesis of lupin alkaloids that tetracyclic sparteine-type alkaloids are metabolized oxidatively to tricyclic cytisine-type alkaloids *via* tetracyclic anagyrine-type alkaloids. (–)-Cytisine is considered to be the ultimate metabolite in the biosynthetic pathway of lupin alkaloids (Scheme 3).[6] That the absolute stereochemistries of (+)-hupeol and (–)-cytisine are the same suggests that (–)-cytisine might be metabolized to non-basic compounds *via* (+)-hupeol.

Experimental Procedure for the Transformation

3,4-Dihydroisoquinoline[7] (**1**, 131 mg, 1.0 mmol) was dissolved in 10 mL of 5% HCl and cooled to 5 ℃. Sodium nitrite (90 mg, 1.3 mmol) was added to the solution. The reaction mixture was allowed to stand at 5 ℃ for 24 h. The product (**3**, 60 mg, 84%) crystallized from the solution. The crystals of **3** were separated from the mixture by filtration and recrystallized from *n*-hexane.

Bis(3,4-dihydro-1*H*-2-benzopyran-1-yl) ether (3): mp 143-144 ℃ (lit.,[2] mp 143-144 ℃). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 27.9 (4-C), 58.1 (3-C), 92.7 (1-C), 126.3 (6-C), 127.5 (9-C), 128.0 (7-C), 128.4 (8-C), 133.8 (5-C), 134.1 (10-C). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.63 (1H, dm, *J* = 16.6 Hz), 3.10 (1H, ddd, *J* = 16.6, 12.4, 6.1 Hz), 4.06 (1H, ddd, *J* = 11.8, 6.1, 1.3 Hz), 4.34 (1H, ddd, *J* = 12.4, 11.8, 3.3 Hz), 6.11 (1H, s), 7.20 (4H, m). $C_{18}H_{18}O_3$ from HRMS, found 282.0459, calcd for 282.0456. MS (EI, 70 eV): *m/z* (%) 282 (60), 146 (75), 134 (92), 133 (100).

(+)-Hupeol: mp 216 ℃, $[\alpha]_D$ +33° (EtOH, *c* 0.4). These physical properties and the spectral data were identical with those of natural (+)-hupeol.

REFERENCES AND NOTES

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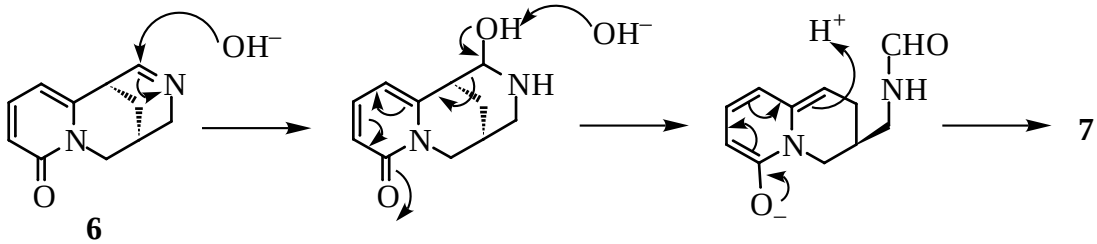
5. Compound (**7**) is considered to be transformed from **6** by the following possible mechanism in which the α-pyridone ring participates in cleavage of the $C_7 - C_{13}$ bond.



6

Data for **7**. Oil; ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 22.9 (8-C), 28.1 (7-C), 33.5 (9-C), 41.0 (11-C), 43.4 (10-C), 105.4 (5-C), 116.5 (3-C), 139.3 (4-C), 161.9 (13-C), 163.6 (6-C), 165.0 (2-C). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.34 (1H, m), 2.05 (1H, m), 2.32 (1H, m), 2.80 (2H, m), 2.91 (1H,

m), 3.56 (1H, m), 3.86 (1H, dd, *J* = 14.4, 7.9 Hz), 4.16 (1H, dd, *J* = 14.4, 4.9 Hz), 6.06 (1H, dd, *J* = 6.9, 1.0 Hz), 6.43 (1H, dd, *J* = 9.0, 1.0 Hz), 7.00 (1H, br), 7.26 (1H, dd, *J* = 9.0, 6.9 Hz), 8.21 (1H, br). $C_{11}H_{14}N_2O_2$ from HRMS, found 206.1058, calcd for 206.1056. MS (EI, 70eV): *m/z* (%) 206 (35), 177 (10), 160 (12), 148 (100), 146 (10), 134 (14).

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