[Chem. Pharm. Bull. 21(7)1410—1414(1973)] UDC 547.94.02 : 581.192

Alkaloids of *Corydalis incisa* Pers. III.[1] The Structures of Corydamine Hydrochloride and N-Formyl Corydamine

Genichiro Nonaka and Itsuo Nishioka

Faculty of Pharmaceutical Sciences, Kyushu University[2]

(Received November 11, 1972)

Two new alkaloids, corydamine hydrochloride, $C_{20}H_{19}O_4N_2Cl$, mp 235—239° (decomp.) and N-formyl corydamine, $C_{21}H_{18}O_4N_2$, mp 159.5—160.5°, were isolated from *Corydalis incisa* Pers. (Papaveraceae) and their structures were established to be II and IX, respectively, by spectroscopic analyses and their chemical conversion to coptisine iodide and anhydrodihydroprotopine-B.

Corydamine hydrochloride and N-formyl corydamine are noted as the first naturally occurring alkaloids having the 3-phenyl isoquinoline skeleton.

In the course of our investigation on the alkaloids of *Corydalis incisa* Pers. (Papaveraceae), we have isolated eight unknown alkaloids together with five known,[3] and in a previous paper[1] the structure of corydalic acid methyl ester (I) was characterized to be a novel alkaloid with the 3-phenyl tetrahydroisoquinoline skeleton.

This paper concerns the structures of two other unknown alkaloids named corydamine hydrochloride (TN-23)[3] and N-formyl corydamine (TN-12).[3]

Corydamine hydrochloride (II) was obtained as pale brown needles, mp 235—239° (decomp.), $C_{20}H_{19}O_4N_2Cl$. II shows on an infrared (IR) spectrum absorption bands at 3420 cm^{-1} (broad, NH), 2440 cm^{-1} (ammonium) and 1580, 1570 cm^{-1} (-C=C- and/or -C=N-), and its ultraviolet (UV) spectrum shows maxima at 245 mμ (log ε: 4.51), 312 mμ (log ε: 4.18) and 380 mμ (log ε: 3.59), suggesting the presence of the highly conjugated system in II.

On treatment with acetic anhydride, II readily afforded an acetate (III), mp 180.5—181.5°, $C_{22}H_{20}O_5N_2$, which depicts on the IR spectrum the absorption of the amide group at 1640 cm^{-1}.

Reductive methylation of II with formaldehyde and sodium borohydride gave a N-methylate (IV).

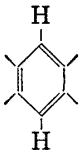
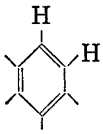
On the nuclear magnetic resonance (NMR) spectra (Tables I and II), the respective methine proton of -CH=N- group in III and IV shows almost the same chemical shift with that of II, while the N-methyl signal of III is observed at the relatively lower field than that of II, and the purturbed multiplet due to four methylene protons of II appears as the symmetrical A_2B_2-type multiplet in the lower field than that of IV.

These findings reveal that acetylation or methylation occurred only at the nitrogen atom bearing a methyl group, and the ethylene group of II is adjacent to $-NHCH_3$ group at one end and to the carbon bearing no hydrogen atom at the other. The mass spectrum of II shows an intense fragment ion peak at *m/e* 306 $(M\text{-}HCl\text{-}CH_3NHCH_2)^+$ and this fragment ion indicates II to be a monohydrochloride and $CH_3NHCH_2CH_2$- group being attached to the aromatic ring.[5]

1) Part II: G. Nonaka, Y. Kodera, and I. Nishioka, *Chem. Pharm. Bull.* (Tokyo), **21**, 1020 (1973).
2) Location: *Katakasu, Higashi-ku, Fukuoka.*
3) G. Nonaka, H. Okabe, I. Nishioka, and N. Takao, *Yakugaku Zasshi*, **93**, 87 (1973).
4) *a*) K. Isobe, A. Ukai, and Y. Tsuda, The 92 nd Annual Meeting of Pharmaceutical Society of Japan, Osaka, April, 1972. Abst. II, p. 207; *b*) Y. Tsuda, A. Ukai, and K. Isobe, *Tetrahedron Letters*, **1972**, 3153.
5) S. Agurell, *Lloydia*, **32**, 40 (1969).

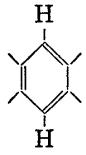
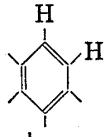
The NMR spectrum of II exhibits the signals of two *ortho*- and two *para*-coupled protons and protons of two methylenedioxy groups. The presence of these functional groups suggests II to be a compound closely related to the other non-phenolic alkaloids of *Corydalis incisa*, except for one more nitrogen atom in II.

Table I. NMR Spectral Data of III, IV and IX[a)]

	III	IV	IX
>N-C(=O)-CH_3	1.82, 1.97 (3H in total)[b)]		
>N-CH_3	2.76(3H, s)	2.11 (6H, s) (-N<CH_3 CH_3)	2.68, 2.72 (3H in total)[b)]
Ar-CH_2-	2.50—3.15 (2H, m)	2.24—2.64 (2H, m)	—3.10 (m)[c)]
>N-CH_2-	3.15—3.70 (2H, m)	2.64—3.04 (2H, m)	3.15—3.70 (2H, m)
-OCH_2O-	6.00 (2H, s) 6.26 (2H, s)	5.93 (2H, s) 6.19 (2H, s)	6.00 (2H, s) 6.24 (2H, s)
	6.73, 6.84 (1H in total[b)] 6.92 (1H, d, J=1.0 Hz)	6.80 (1H, s) 6.88 (1H, s)	6.74, 6.86 (1H in total)[b)] 6.93 (1H, d, J=1.5 Hz)
	7.44 (2H, s)	7.33 (2H, s)	7.41 (2H, s)
Ar-CH=C<	7.64, 7.71 (1H in total, br. singlets[b)]	7.57 (1H, br. s)	7.62, 7.68 (1H in total, br. singlets)[b)]
>N-C(=O)-H			7.80, 7.92 (1H in total, br. singlets)[b)]
Ar-CH=N-	9.35 (1H, br. s)	9.35 (1H, br. s)	9.28 (1H, br. s)

a) The spectra were determined at 60 MHz in $CDCl_3$ with TMS as an internal standard and chemical shifts are on δ scale (s: singlet, br: broad, d: doublet, m: multiplet).
b) These signals were observed as singlets when determined at higher temperatures (III: 76°, IX: 123°)[4)].
c) A part of the signal in the higher field are overlapped by that of N-methyl protons.

Table II. NMR Spectral Data of II[a)]

	solvent		
	CF_3COOH	$(CD_3)_2SO$	D_2O
>N-CH_3	2.88 (t, J=6 Hz)	overlapped by $(CH_3)_2SO$	2.63 (s)
-CH_2CH_2-	2.70—3.80 (m)	3.50—4.50 (m)	2.90—3.20 (m)
-OCH_2O-	6.10 (s) 6.48 (s)	6.10 (s) 6.36 (s)	6.10 (s) 6.38 (s)
	6.95 (s) 6.97 (s)	7.04 (s) 7.06 (s)	6.77 (s) 7.00 (s)
	7.78 (d, J=9 Hz) 7.95 (d, J=9 Hz)	7.56 (d, J=9 Hz) 7.71 (d, J=9 Hz)	7.49 (d, J=9 Hz) 7.63 (d, J=9 Hz)
-CH=C<	8.18 (broad s)	7.92 (broad s)	7.78 (broad s)
-CH=N-	9.51 (broad d, J=7 Hz)	9.38 (broad s)	9.24 (broad s)

a) The spectra were determined at 60 MHz and chemical shifts are given in ppm from TMS as an internal standard for CF_3COOH and $(CD_3)_2SO$ solutions and external one when measured in D_2O (s: singlet, d: doublet, t: triplet, m: multiplet).

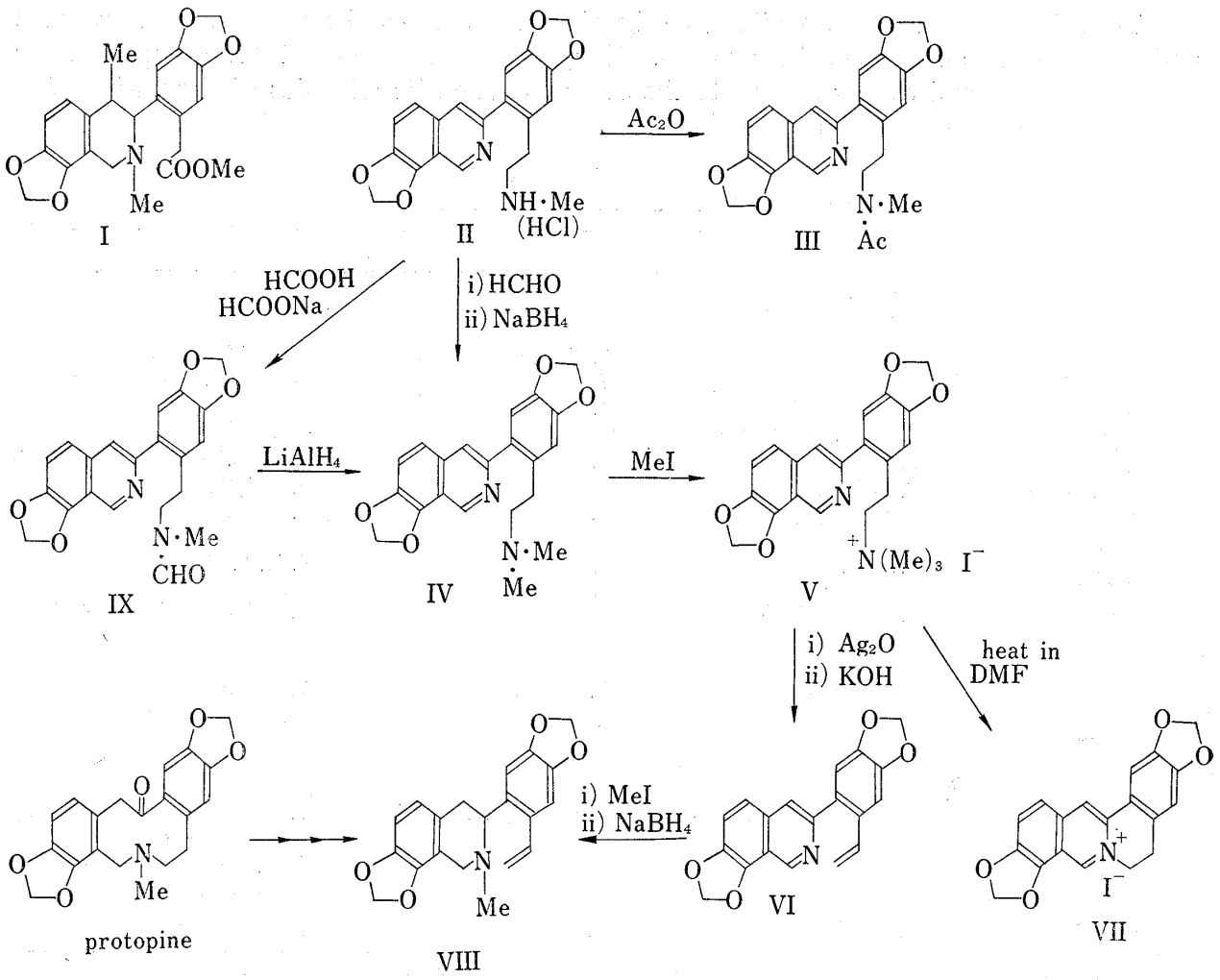


Chart 1

In order to eliminate the nitrogen atom in the side chain, IV was further methylated with methyl iodide in benzene and the resulting methiodide (V), $C_{22}H_{23}O_4N_2I$, mp 215° (decomp.), was then subjected to Hofmann degradation to afford a methine base (VI), mp 166—167°. In the NMR spectrum of VI, the signal of four methylene protons in IV disappeared and is observed the ABX-type signal of typical olefinic protons in the styrene (δ 5.11, q, J_{AB}=1.5, J_{AX}=10.5 Hz; δ 5.59, q, J_{AB}=1.5, J_{BX}=17.0 Hz; δ 6.68, q, J_{AX}=10.5, J_{BX}=17.0 Hz).

When heated in dimethyl formamide at 140—150°, V gave orange needles (VII) releasing trimethylamine. The IR and UV spectra of VII are identical with those of coptisine iodide. These results suggest that II possesses the N-methyl phenethylamine moiety at position-3 of the isoquinoline ring system.

Therefore the conversion of VI to the known base, anhydrodihydroprotopine-B was attempted.

On treatment with methyl iodide in a sealed tube, VI gave the corresponding methiodide, which was then subjected to sodium borohydride reduction to afford a base (VIII), mp 139—140°. VIII was identified with anhydrodihydroprotopine-B prepared from protopine,[6] by the comparison of the spectral data.

On the basis of the chemical and spectral data, the structure of corydamine hydrochloride was established to be II.

6) *a*) S. Osada, *Yakugaku Zasshi*, **47**, 547 (1927); *b*) *Idem, ibid.*, **47**, 727 (1927).

N-Formyl corydamine (IX), mp 159.5—160.5°, $C_{21}H_{18}O_5N_2$, depicts remarkably similar UV spectrum to that of II showing the absorption maxima at 244 mμ (log ε: 4.06), 309 mμ (log ε: 4.14) and 376 mμ (log ε: 3.53). The IR spectrum shows the absorption band of carbonyl group at 1670 cm^{-1}, and on the NMR spectrum (Table I) the signals due to an N-methyl group, four methylene protons, two methylenedioxy groups, six protons in the aromatic proton region and an aldehyde proton are observed.

These spectral data suggest that IX has the same skeleton with corydamine and the nitrogen bearing a methyl group is formylated. On treatment with lithium aluminium hydride, IX gave a brown oil and it was identified as IV by TLC and IR spectrum.

These results apparently indicate that IX has an N-formyl group.

When II and equal mole of sodium formate were heated in formic acid, the corresponding formate was obtained and it was identified as IX by the direct comparison of IR (KBr) and UV spectra and mixed melting point.

Accordingly, N-formyl corydamine is represented by the formula IX.

Corydamine hydrochloride and N-formyl corydamine are the first naturally occurring alkaloids having the aromatic ring at position-3 of the isoquinoline ring system and they are probably originated from coptisine. This assumption may be supported by the co-existence of coptisine in the same plant.[7]

Experimental[8]

Corydamine Hydrochloride (II)——Pale brown needles (MeOH), mp 235—239° (decomp.). *Anal.* Calcd. for $C_{20}H_{19}O_4N_2Cl$: C, 62.09; H, 4.92; N, 7.24. Found: C, 62.14; H, 5.00; N, 7.03. UV λ_{max}^{MeOH} mμ (log ε): 245 (4.51), 312 (4.18), 380 (3.59). IR ν_{max}^{KBr} cm^{-1}: 3420 (NH), 2440 (ammonium), 1580, 1570 (>C=C< and/or >C=N-). Mass Spectrum *m/e*: 350 $(M\text{-}HCl)^+$, 306 (base peak) $(M\text{-}C_2H_7NCl)^+$, 44 $(C_2H_6N)^+$.

Formation of III from II——II (250 mg) was dissolved in acetic anhydride (5 ml) and was warmed at 90° for 20 min. After the solvent being evaporated *in vacuo* to dryness, the residue was recrystallized from MeOH to afford a pale brown powder (III) (180 mg); mp 180.5—181.5°. *Anal.* Calcd. for $C_{22}H_{20}O_5N_2$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.50; H, 5.12; N, 7.05. UV λ_{max}^{MeOH} mμ (log ε): 244 (4.61), 309 (4.20), 378 (3.67). IR λ_{max}^{KBr} cm^{-1}: 1640 (C=O), 1580, 1570 (>C=C< and/or >C=N-). Mass Spectrum *m/e*: 392 $(M)^+$, 318 (base peak) $(M\text{-}C_3H_8ON)^+$, 306 $(M\text{-}C_4H_8ON)^+$.

Formation of IV from II——The solution of II (300 mg) in MeOH (10 ml) and 37% formaldehyde (3 ml) was refluxed for 45 min and then $NaBH_4$ (260 mg) was added to the ice-cooled reaction mixture. After stirring at room temperature for 30 min, the mixture was diluted with H_2O, extracted with $CHCl_3$ and the $CHCl_3$ layer was washed, dried and evaporated. The brown residue was purified ove a silica gel column using $CHCl_3$–MeOH (97: 3) to give IV (272 mg) as a brown oil: UV λ_{max}^{MeOH} mμ: 244.5, 312, 380. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1585, 1578 (>C=C< and/or >C=N-). Mass Spectrum *m/e*: 364 $(M)^+$, 318 $(M\text{-}C_2H_8N)^+$, 58 (base peak) $(C_3H_8N)^+$.

Formation of V from IV——To a solution of IV (190 mg) in dry benzene (6 ml) was added CH_3I (1 ml). After standing at room temperature for 20 min, the pale brown precipitates were filtered, washed with benzene and recrystallized from MeOH to give V (131 mg) as pale brown needles, mp 210° (decomp.). *Anal.* Calcd. for $C_{22}H_{23}O_4N_2I$: C, 52.17; H, 4.58; N, 5.54. Found: C, 52.23; H, 4.60; N, 5.46.

Hofmann Degradation of V——To a stirred solution of V (92 mg) in MeOH (10 ml) was added freshly prepared Ag_2O (60 mg). Stirring was continued for 10 min, then the excess of Ag_2O and AgI were filtered off and the solvent was evaporated *in vacuo*. To the residue 20% methanolic KOH was added and heated for 90 min, and then the reaction mixture was diluted with water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried and evaporated. The residue was recrystallized from acetone–MeOH to give VI (31 mg) as pale brown sands, mp 166—167°, UV λ_{max}^{MeOH} mμ (log ε): 232 (4.68), 328 (4.17), 343 (sh. 4.03), 384 (3.69). NMR (δ): 5.11 (1H, q, J_{AX}=10.5, J_{AB}=1.5 Hz; $\underline{H}$>C=C<$\underline{H}$), 5.59 (1H, q, J_{BX}=17.0, J_{AB}=1.5 Hz; $\underline{H}$>C=C<$\underline{H}$), 6.68 (1H, q, J_{AX}=10.5, J_{BX}=17.0 Hz; $\underline{H}$>C=C<$\underline{H}$), 6.00 (2H, s, $-OCH_2O-$), 6.20 (2H, s, $-OCH_2O-$), 7.02, 7.10 (each 1H, s, aromatic proton), 7.33 (2H, s, aromatic proton), 7.56 (1H, broad s, Ar-CH=C<), 9.35 (1H, broad s, Ar-CH=N-).

Formation of Coptisine Iodide from V——A solution of V (14 mg) in dimethyl formamide (3 ml) was heated at 140—150° for 1 hr. The solvent was evaporated *in vacuo*, and the residue was recrystallized

7) C. Tani and N. Takao, *Yakugaku Zasshi*, **82**, 598 (1961).
8) Refer to Part II for general methods.

from MeOH to give orange needles, mp 290°<, which was identified as coptisine iodide by the comparison of IR (KBr) and UV spectra.

Formation of Anhydrodihydroprotopine-B from VI——A solution of VI (32 mg) in acetone–MeOH and CH_3I (0.3 ml) was heated in a sealed tube at 90° for 2 hr. The solvent was evaporated and the residue was recrystallized from acetone–MeOH to give reddish brown prisms (37 mg), mp 240° (decomp.). To the solution of the product in MeOH (4 ml) and H_2O (0.2 ml) was added a solution of $NaBH_4$ (100 mg) in MeOH. After stirring at room temperature for 1 hr, the reaction mixture was diluted with H_2O, extracted with ether, and the ether layer was washed with H_2O, dried and evaporated to give a brown oily residue, which was chromatographed on silica gel. The benzene eluate gave colorless prisms (MeOH) (11 mg), mp 139—140°, which was identified as anhydrodihydroprotopine-B by the comparison on TLC and IR ($CHCl_3$) spectrum.

N-Formyl Corydamine (IX)——Brown prisms (MeOH), mp 159.5—160.5°. *Anal.* Calcd. for $C_{21}H_{18}O_5N_2$: C, 66.66; H, 4.80; N, 7.40. Found: C, 66.21; H, 4.88; N, 7.32. UV λ_{max}^{MeOH} mμ (log ε): 244 (4.60), 309 (4.14), 376 (3.53). IR ν_{max}^{KBr} cm^{-1}: 1670 (>NCHO), 1586, 1573 (>C=C< and/or >C=N-). Mass Spectrum *m/e*: 378 $(M)^+$, 318 (base peak) $(M\text{-}C_2H_6ON)^+$, 306 $(M\text{-}C_3H_6ON)^+$.

Formation of IV from IX——To a stirred solution of IX (50 mg) in dry tetrahydrofuran (THF) (3 ml) was added $LiAlH_4$ (20 mg in dry THF) and the reaction mixture was allowed to stand at 0° for 30 min. An excess of $LiAlH_4$ was decomposed by adding AcOEt, and then the reaction mixture was extracted with AcOEt. The AcOEt solution was washed with water, dried and evaporated to give a brown residue, which was chromatographed over a silica gel column. The $CHCl_3$–MeOH (96: 4 to 93: 7) eluate gave a brown oil (11 mg), which was identified as IV by TLC and IR ($CHCl_3$) spectrum.

N-Formylation of II——A solution of II (193 mg) and sodium formate (34 mg) dissolved in formic acid (3 ml) was refluxed for 5 hr. The reaction mixture was diluted with water, neutralized with NH_4OH and extracted with AcOEt. The AcOEt solution was washed, dried and evaporated. The brown residue was chromatographed on alumina (Merck, neutral, Grade I, 20 g). The $CHCl_3$ eluate gave brown prisms (MeOH) (110 mg), mp 158—159°, which was identified as IX by the mixed melting point determination and IR (KBr) and UV spectral comparison.

Acknowledgement The authors are grateful to Prof. N. Takao, Kobe Womens' College of Pharmacy for his kind encouragement, and to Dr. S. Saeki and Dr. H. Okabe of this Faculty for valuable discussion. Thanks are also due to Mr. Y. Tanaka, Mr. H. Matsui, Miss K. Soeda and Miss M. Kawamura for IR, UV, NMR and mass spectral measurements, and to the members of the Central Analysis Room of this University for microanalysis.