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Hexahydro-dibenz[*d*,*f*]azecines: Existence of Two Conformational Isomers of the 6-Oxo Derivatives in Solution[1)]

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New hexahydro-dibenz[*d*,*f*]azecines, **11** and **12**, were synthesized from the homoerythrinan-enone **3**. Their 6-oxo derivatives were shown to exist in two conformations in solution due to the rotational isomerism of the ten-membered lactam group. An example of remarkably large separation of two methylenedioxy protons in the proton nuclear magnetic resonance spectrum due to their non-equivalence is also presented.

Keywords——dibenz[*d*,*f*]azecine alkaloid; homoerythrinan-enone; hexahydro-dibenz[*d*,*f*]-azecine; tetrahydro-dibenz[*d*,*f*]azecin-6(5*H*)-one; conformational isomer; rotational isomerism; ten-membered lactam; methylenedioxy group; ^{1}H-NMR

Alkaloids with a dibenz[*d*,*f*]azecine skeleton are attracting much interest, since they are regarded as the biosynthetic precursors of homoerythrinan alkaloids.[2)] Although only one example of the natural occurrence of such an alkaloid, dysazecine **1**,[3)] is known at present, many others may exist. We report here a synthesis of two such alkaloids and show that the 6-oxo derivatives (tetrahydro-dibenz[*d*,*f*]azecin-6(5*H*)-ones) exist in two conformations in solution.

During our studies on the total synthesis of homoerythrinan alkaloids[4)] we have observed that, on demethoxycarbonylation of the enone **2** by $CaCl_2$–DMSO, the dibenz[*d*,*f*]azecin-6-one **5** is always obtained as a by-product together with the major product, the non-conjugated enone **3**. This is in remarkable contrast to the erythrinan series, since from the erythrinan-enone **6**, the conjugated enone **8** is always obtained as a by-product together with the non-conjugated enone **7**.[5)] This means that the conjugated enone **4** is labile under the reaction conditions, being decomposed into the aromatized compound **5** through a β-elimination. In fact, **3** directly gave the dibenz[*d*,*f*]azecin-6-one **5** on treatment with NaOH or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), while the corresponding erythrinan-enone **7** quantitatively isomerized into the conjugated ketone **8** on heating with DBU.[5)]

Methylation of **5** with diazomethane gave the *O*-methyl ether **9**, which, on further methylation with methyl iodide and sodium hydride, afforded the *N*,*O*-dimethyl derivative **10**. Reduction of **9** and **10** with $LiAlH_4$–$AlCl_3$ afforded 5,6,7,8,9,10-hexahydro-2-methoxy-12,13-methylenedioxy-dibenz[*d*,*f*]azecines, **11** and **12**, in quantitative yields, respectively.

The tetrahydro-dibenz[*d*,*f*]azecin-6(5*H*)-ones showed interesting behavior in the proton nuclear magnetic resonance (^{1}H-NMR) spectra. For example, the lactam **5** exhibited a set of peaks attributable to two isomers in a ratio of 3:2 in $CDCl_3$–CD_3OD; these signals were assignable as shown in Fig. 1-a. This ratio was solvent-dependent, and changed to 3:1 in DMSO-d_6 (Fig. 1-b). However, the pattern was not affected on addition of an acid (methanesulfonic acid) or a base (triethylamine). The *O*-methyl derivative **9** also showed peaks corresponding to two isomers in a ratio of 3:2 in $CDCl_3$ (Fig. 2-a). This collapsed into the spectrum of a single compound with broadening of the peaks on heating at 100 °C. The

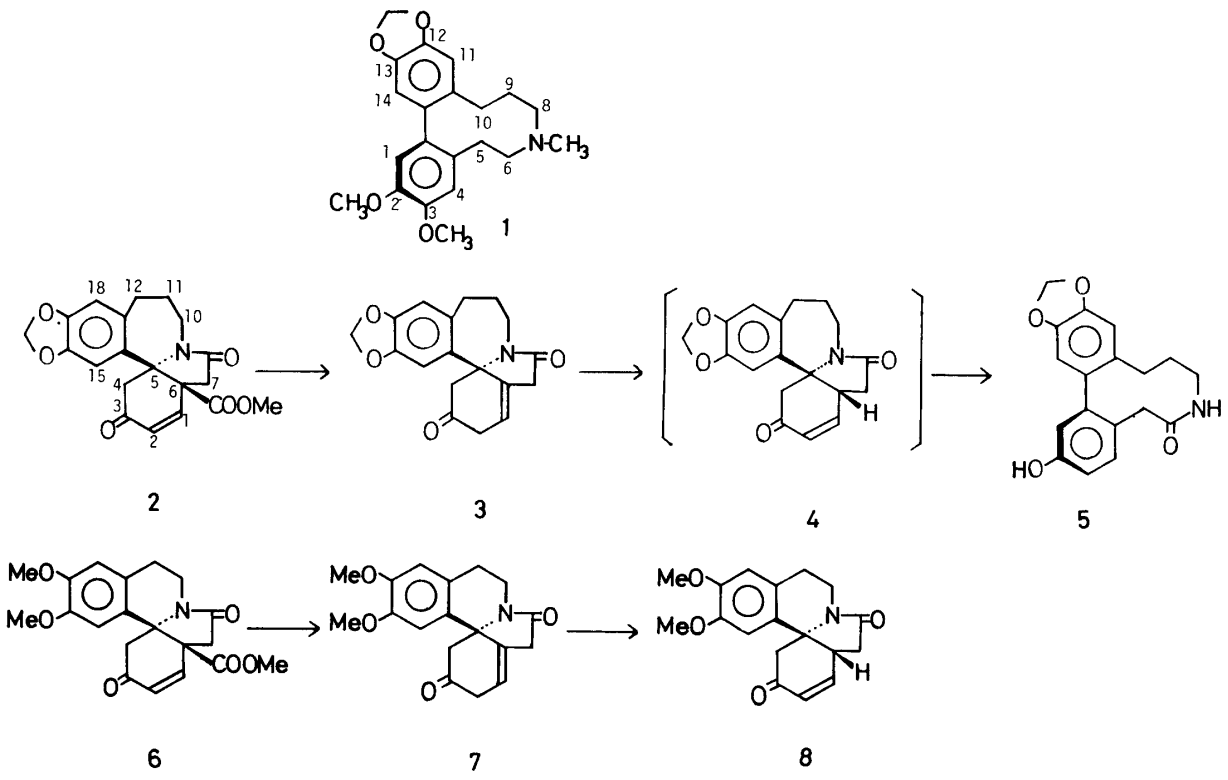

Chart 1

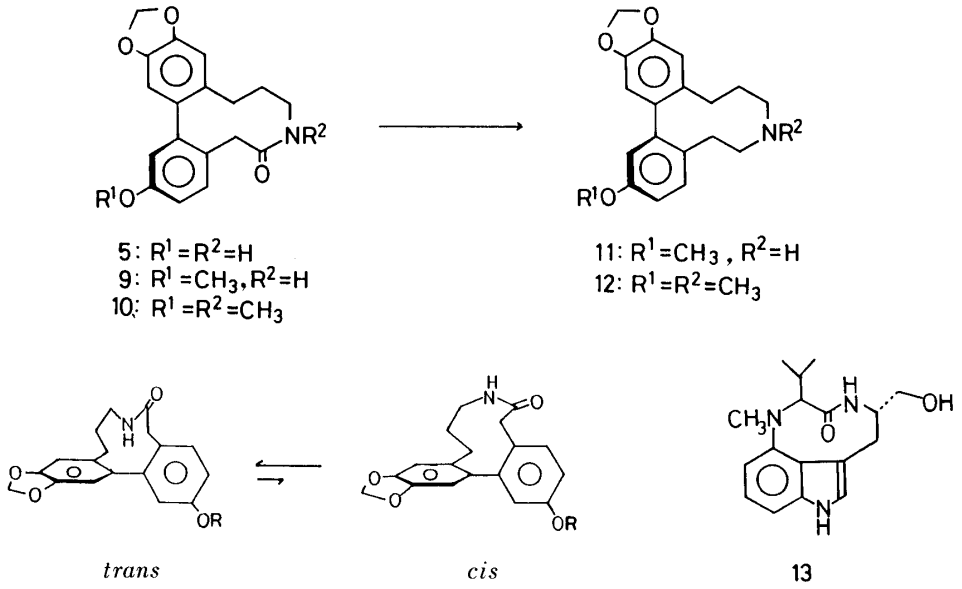

Chart 2

complexity of the spectra diminished in the amines, **11** and **12**, which each exhibited peaks corresponding to a single isomer. Therefore the origin of the above complexity is attributable to an equilibrium of two conformational isomers of the ten-membered lactam ring in **5** and **9**. Molecular models indicate that the *trans* conformer arising from the rotational isomerism of the amide group is more stable than the *cis* conformer, thus implying that the major component in the spectra is the *trans* conformer (see Chart 2). The lactam **10** exhibits the spectrum of a single isomer, suggesting that it exists as a single conformer (maybe *trans*) in

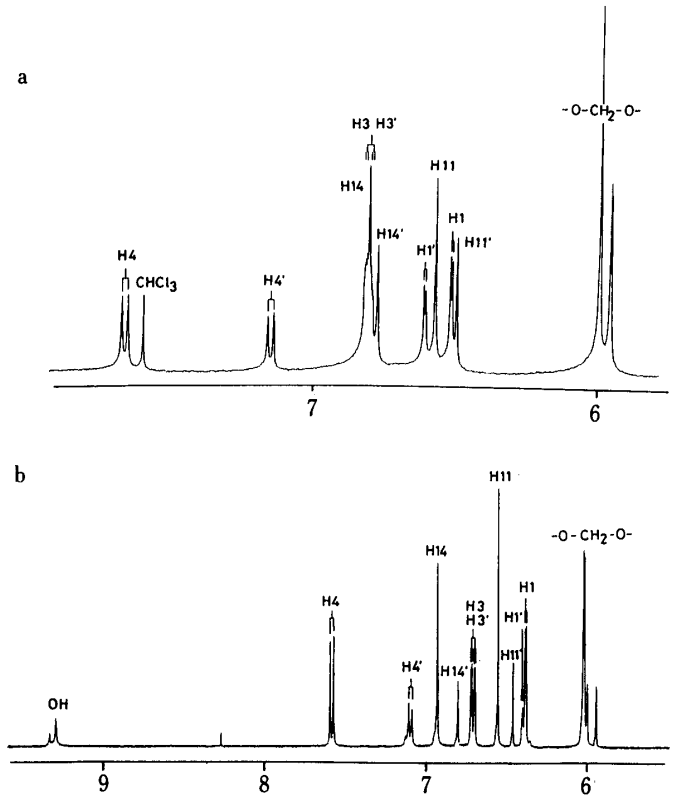

Fig. 1. 400 MHz ^{1}H-NMR Spectra of the Tetrahydro-dibenz[*d*, *f*]azecin-6(5*H*)-one **5** at 25 °C

a: In $CDCl_3$–CD_3OD. b: In DMSO-d_6.

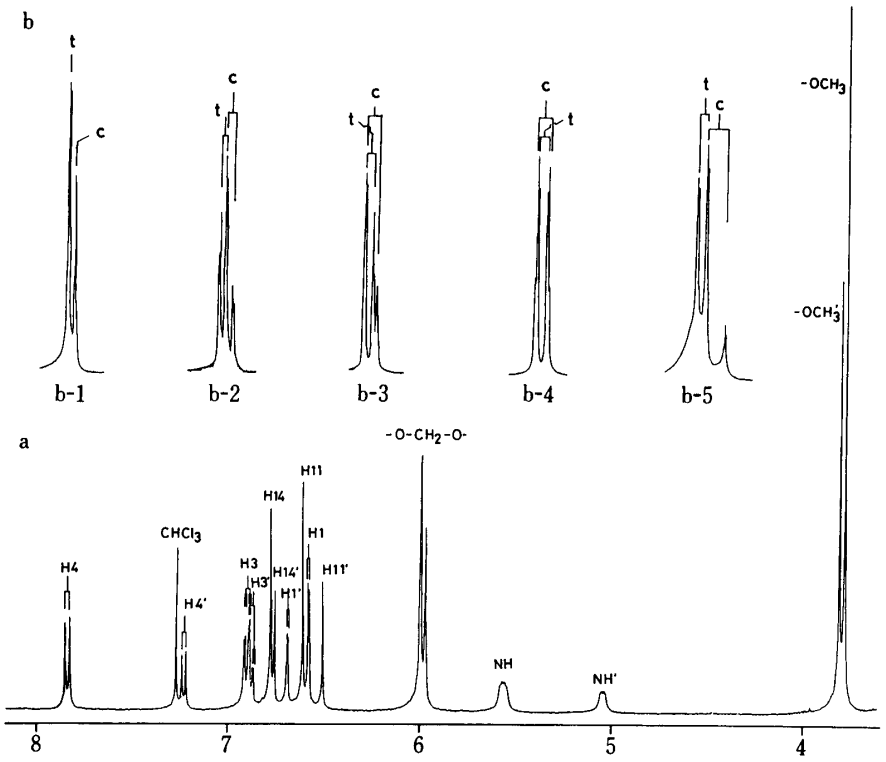

Fig. 2. 400 MHz ^{1}H-NMR Spectra of the *O*-Methyl Derivative **9** at 25 °C

a: The spectrum in $CDCl_3$.

b: Methylenedioxy proton signals in $CDCl_3$–benzene-d_6 mixtures of various proportions (parenthetical values are separations of the two peaks, Hz). t: *trans* isomer. c: *cis* isomer.

b-1, $CDCl_3$ only (t–0, c–0); b-2, 3 : 1 (t–4.8, c–6.4); b-3, 1 : 1 (t–7.2, c–12.8); b-4, 1 : 2 (t–8.4, c–12.8); b-5, benzene-d_6 only (t–8.4, c–16.4).

solution. A similar equilibrium was reported in the nine-membered lactam compound **13** (related to a tumor promotor, teleocidin B), where the *trans* (sofa) conformer was shown to be more stable than the *cis* (twist) isomer by means of molecular mechanics calculations.[6]

Another interesting observation on the lactams **5** and **9** is that not only did the ratio of the two isomers change depending on the solvent polarity, but also the signals of the methylenedioxy group were markedly affected by the solvent used. For example, hhe methylenedioxy group of **5** in DMSO-d_6 (Fig. 1-b) appeared as three peaks, one large and two small. The latter peaks are separated by 20 Hz (0.05 ppm) at 400 MHz with a further small coupling of *ca.* 1 Hz. This separation varied proportionally to the magnetic field indicating that it originates from the non-equivalence of the methylenedioxy protons, particularly in the *cis* conformer. The two peaks of the methylenedioxy group of **9** in $CDCl_3$ also showed complex changes on addition and increase in proportion of benzene-d_6, as shown in Fig. 2-b.

The reported spectra of dibenz[*d*,*f*]azecin-8-one derivatives are rather complex.[7] This phenomenon must, at least partly, arise from factors similar to those discussed above.

Experimental[8]

7,8,9,10-Tetrahydro-2-hydroxy-12,13-methylenedioxy-dibenz[*d*,*f*]azecin-6(5*H*)-one (5)——The enone **2** (40 mg) in 1 N NaOH (2 ml) and methanol (3 ml) was stirred at room temperature for 2 h. The mixture was diluted with $CHCl_3$, washed with brine, dried, and concentrated to dryness. The residue was crystallized from methanol to give **5** (40 mg, 100%) as colorless needles, mp 253—255 °C. IR: 1640 in KBr and 1650 in $CHCl_3$. HRMS *m/z*: 311.1157 Calcd for $C_{18}H_{17}NO_4$ (M^+). Found: 311.1180. *Anal.* Calcd for $C_{18}H_{17}NO_4 \cdot CH_3OH$: C, 66.45; H, 6.16; N, 4.08. Found: C, 66.49; H, 6.00; N, 3.97.

7,8,9,10-Tetrahydro-2-methoxy-12,13-methylenedioxy-dibenz[*d*,*f*]azecin-6(5*H*)-one (9)——Compound **5** (30 mg) and an excess of diazomethane in methanol were kept at room temperature for 2 h. Evaporation of the solvent and crystallization of the residue from methanol gave the *O*-methyl ether **9** (31 mg, 100%) as colorless needles, mp 204—205 °C. IR (KBr): 1670. HRMS *m/z*: 325.1312 Calcd for $C_{19}H_{19}NO_4$ (M^+). Found: 325.1291.

7,8,9,10-Tetrahydro-2-methoxy-7-methyl-12,13-methylenedioxy-dibenz[*d*,*f*]azecin-6(5*H*)-one (10)——The *O*-methyl derivative **9** (25 mg) and NaH (60% in oil, 4 mg) in tetrahydrofuran (THF) (10 ml) were refluxed for 1 h under argon, then CH_3I (1 ml) was added, and reflux was continued for a further 1 h with stirring. After being quenched with AcOH and H_2O, the mixture was extracted with $CHCl_3$. The extract was dried and concentrated to give **10** (22 mg, 84%), colorless needles from MeOH, mp 234—235 °C. IR: 1635. UV (EtOH): 235 (13000), 286 (6700). ^{1}H-NMR (100 MHz) δ: 1.90 (2H, m, H-9), 2.37 (2H, m, H-10), 2.88 (3H, s, NCH_3), 3.02 and 3.52 (each 1H, m, H-8), 3.08 and 3.65 (each 1H, d, J=13 Hz, H-5), 3.76 (3H, s, OCH_3), 5.96 (2H, s, OCH_2O), 6.54 (1H, d, J=3.0 Hz H-1), 6.58 (1H, s, H-11), 6.76 (1H, s, H-14), 6.87 (1H, dd, J=3.0, 9.0 Hz, H-3), 7.87 (1H, d, J=9.0 Hz, H-4). HRMS *m/z*: 339.1469 Calcd for $C_{20}H_{21}NO_4$ (M^+). Found 339.1484.

5,6,7,8,9,10-Hexahydro-2-methoxy-12,13-methylenedioxy-dibenz[*d*,*f*]azecine (11)——The *O*-methyl ether **9** (22 mg) in THF (4 ml) and $LiAlH_4$–$AlCl_3$ in THF–ether (3 ml) (prepared from 76 mg of $LiAlH_4$ and 248 mg of $AlCl_3$ in 6 ml of THF and 4 ml of ether) were mixed, and the mixture was stirred at room temperature for 3 h. After being quenched with ice-water, the mixture was basified with 5% NH_4OH and extracted with ether. The extract was washed with brine, dried, and concentrated to give the amine **11** (21 mg, 100%) as an oil. ^{1}H-NMR (400 MHz) δ: 1.66, 2.07, 2.35, 2.43—2.62, 2.70—2.94 (2H, 1H, 1H, 3H, 3H, each m, H-5, 6, 8, 9, 10), 3.78 (3H, s, OMe), 5.97 and 5.98 (each 1H, d, J=1 Hz, OCH_2O), 6.51 (1H, s, H-11), 6.60 (1H, d, J=3.0 Hz, H-1), 6.73 (1H, s, H-14), 6.91 (1H, dd, J=3.0, 8.5 Hz, H-3), 7.18 (1H, d, J=8.5 Hz, H-4). HRMS *m/z*: 311.1520 Calcd for $C_{19}H_{21}NO_3$ (M^+). Found: 311.1525.

5,6,7,8,9,10-Hexahydro-2-methoxy-7-methyl-12,13-methylenedioxy-dibenz[*d*,*f*]azecine (12)——The *N*, *O*-dimethyl derivative **10** (10 mg) in THF (6 ml) and ether (4 ml) was treated with $LiAlH_4$–$AlCl_3$ in THF–ether (3 ml) as described for **11** to give the amine **12** (12 mg, 83%) as an oil. UV (EtOH): 289 (5800). ^{1}H-NMR (100 MHz) δ: 1.44—1.92 and 2.16—2.80 (10H, m, H-5, 6, 8, 9, 10), 2.04 (3H, s, NCH_3), 3.74 (3H, s, OCH_3), 5.93 (2H, s, OCH_2O), 6.48 (1H, s, H-11), 6.52 (1H, d, J=3.0 Hz, H-1), 6.72 (1H, s, H-14), 6.82 (1H, dd, J=3.0, 8.4 Hz, H-3), 7.14 (1H, d, J=8.4 Hz, H-4). HRMS *m/z*: 325.1676 Calcd for $C_{20}H_{23}NO_3$ (M^+). Found 325.1673.

References and Notes

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8) Melting points were taken on a Yanagimoto micro hot-stage apparatus, and are uncorrected. Ultraviolet (UV) spectra were recorded on a Hitachi-323 spectrophotometer and are given in λ max nm (ε). Infrared (IR) spectra were taken on a JASCO IR-G spectrometer and are given in cm^{-1}. The 100 MHz ^{1}H-NMR spectra were measured on a JEOL FX-100 and the 400 MHz ^{1}H-NMR on a JEOL GX-400 spectrometer, both in $CDCl_3$ solutions with tetramethylsilane as an internal standard. High-resolution mass spectra (HRMS) were obtained on a Hitachi M-80 machine. Fuji-Davison BW-820 MH (silica gel) was used for column chromatography. For thin layer chromatography (TLC), Macherey-Nagel SIL G-25 UV_{254} plates were used, and spots were observed by spraying 1% ceric sulfate in 10% H_2SO_4 followed by heating at 100 °C until coloration appeared.