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Quinolizidines. XXIV.[1] Syntheses of Ankorine Congeners in Different Oxidation States

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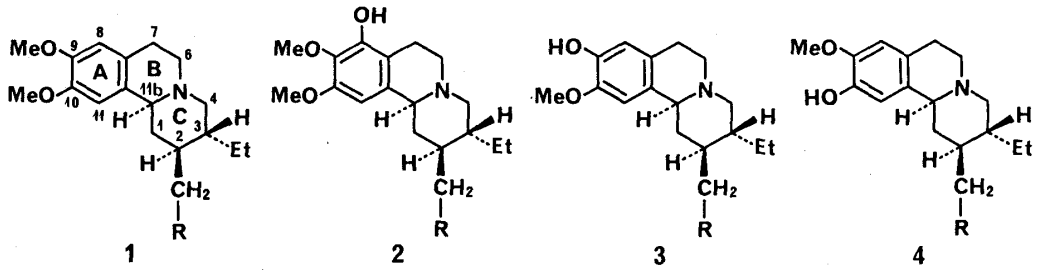
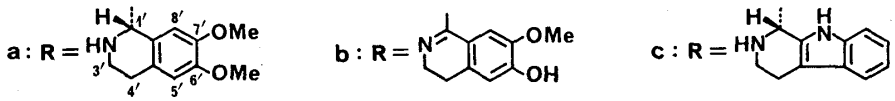
8-Hydroxyprotoemetine [(−)-**2f**], an aldehyde of biogenetic interest, has been synthesized for the first time from the tricyclic ester (−)-**5** through the intermediate (−)-**6**. Wolff–Kishner reduction of (−)-**2f** produced the 2-ethyl congener (−)-**2g**. As a result of these syntheses, the circular dichroism (CD) spectra of (−)-**2f**·$HClO_4$ and (−)-**2g** in 0.1 N aqueous HCl and in EtOH, together with those of the *Alangium* alkaloids ankorine (**2d**) and alancine (**2e**), are now available.

Keywords——hydroxyprotoemetine; deoxyankorine; benzyl ether hydrogenolysis; diisobutylaluminum hydride ester reduction; Wolff–Kishner reduction; *Alangium* alkaloid CD

Nineteen benzo[*a*]quinolizidine alkaloids isolated so far from *Alangium* plants (Alangiaceae) are structurally classified into four types (**1**—**4**) (R=CH_2OH, CO_2H, or a heterocyclic ring)[2] according to their substitution patterns in the aromatic ring A.[3,4] Type **2** includes four alkaloids, alangicine (**2b**),[1,5] alangimarckine (**2c**),[1,6] ankorine (**2d**),[1,6a,7] and alancine (**2e**),[1,8] all isolated from *A. lamarckii*. Interestingly, the latter two bases are





d: R = CH_2OH **e**: R = CO_2H **f**: R = CHO **g**: R = Me

equivalent to the aldehydic base **2f** which has not been isolated yet from the same plant. On the other hand, protoemetine (**1f**), the corresponding tricyclic aldehyde of **1**-type, was actually isolated from *Cephaelis ipecacuanha* (Rubiaceae),[3c,9] and its probable intermediacy has been assumed in the biogenetic transformation of the precursor deacetylisoipecoside into other ipecac alkaloids such as cephaeline (**1a**: 6′-OMe replaced by OH) and emetine (**1a**).[3a,10,11] It is, therefore, not unreasonable to postulate 8-hydroxyprotoemetine (**2f**) to be a possible intermediate for the biosynthesis of the **2**-type alkaloids **2b**—**e** in *A. lamarckii*. The availability of synthetic reference samples would greatly facilitate the search for this aldehyde

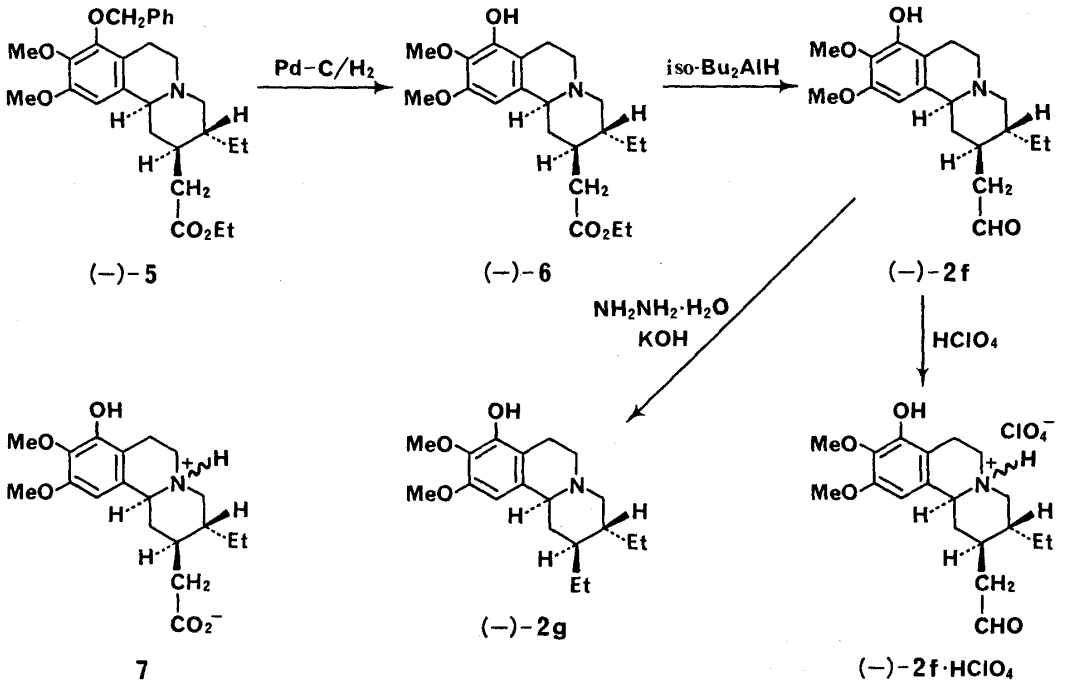


Chart 1

as a natural product and the testing of this speculation. Furthermore, the availability of the 2-ethyl analogue **2g** should complete a series of ankorine congeners (**2d**—**g**) differing in oxidation state at the side chain. This led us to synthesize **2f** and **2g** for the first time in the present work.

The first target selected for synthesis was 8-hydroxyprotoemetine (**2f**), the desired tricyclic aldehyde, which was expected to be accessible from the known tricyclic ester (−)-**5**, a common key intermediate utilized in our previous syntheses of ankorine (**2d**),[1,7c,f] alangicine (**2b**),[1,5c,d] alangimarckine (**2c**),[1,6c,d] and alancine (**2e**).[1,8b,c] Thus, debenzylation of (−)-**5** was effected in EtOH by using hydrogen and 10% Pd–C catalyst at 24 °C for 1 h, giving the phenolic base (−)-**6** in 96% yield. On reduction with diisobutylaluminum hydride in CH_2Cl_2–hexane at −78 °C, (−)-**6** afforded the desired aldehyde (−)-**2f** in 85% yield. The aldehyde was unstable as the free base, but formed a crystalline perchlorate [(−)-**2f**·$HClO_4$] in 91% yield when treated with aqueous $HClO_4$. For the synthesis of the second target structure **2g**, Wolff–Kishner reduction of (−)-**2f** was then carried out by means of the Huang–Minlon modification to give the deoxyankorine (−)-**2g** in 80% yield.

Now that all four functional members in the ankorine series had become available, it was possible to measure their circular dichroism (CD) spectra. It may be seen from Fig. 1 that **2d**,[7c,f] **2e**,[8b,c] (−)-**2f**·$HClO_4$, and (−)-**2g** showed similar CD curves in 0.1 N aqueous HCl with the exception that the curve of (−)-**2f**·$HClO_4$ has an additional shoulder at 300 nm. In EtOH (Fig. 2), however, the free base (−)-**2g** exhibited a CD curve similar to that reported[8c] for ankorine (**2d**), and those of the salts **2e**·HCl[8b,c] and (−)-**2f**·$HClO_4$ were similar to each other, but different from that of the free base (−)-**2g** or **2d**. Interestingly, the shape of the CD curve of alancine (**2e**) in EtOH suggests the presence of the dipolar ion form (**7**) in a certain proportion in ethanolic solution. The existence of this dipolar ion form in the solid state has already been demonstrated by infrared (IR) spectroscopy.[8c]

With the completion of the above syntheses and characterization of the hydroxyprotoemetine (−)-**2f** and the deoxyankorine (−)-**2g**, the search for these substances in plants will be facilitated.

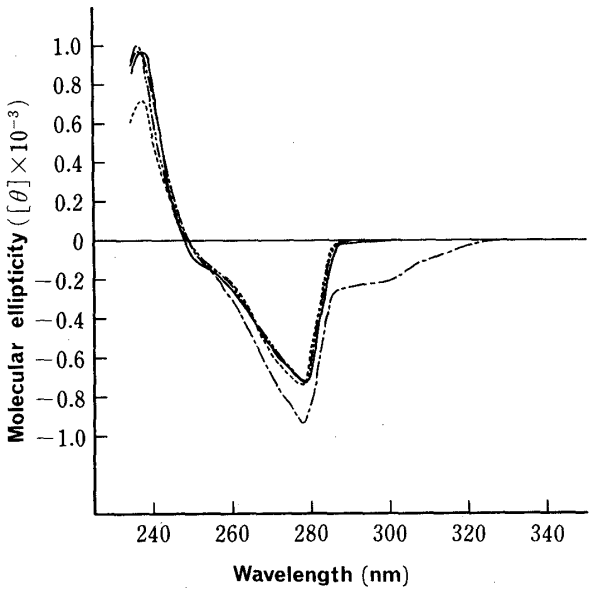


Fig. 1. CD Curves of Ankorine (**2d**) and Its Congeners in 0.1 N Aqueous HCl

——: **2d** ($c=4.66\times10^{-4}$ M) at 22 °C. ——: **2e** ($c=4.68\times10^{-4}$ M) at 20 °C. —·—: (−)-**2f**·$HClO_4$ ($c=4.70\times10^{-4}$ M) at 22 °C. ----: (−)-**2g** ($c=4.70\times10^{-4}$ M) at 20 °C.

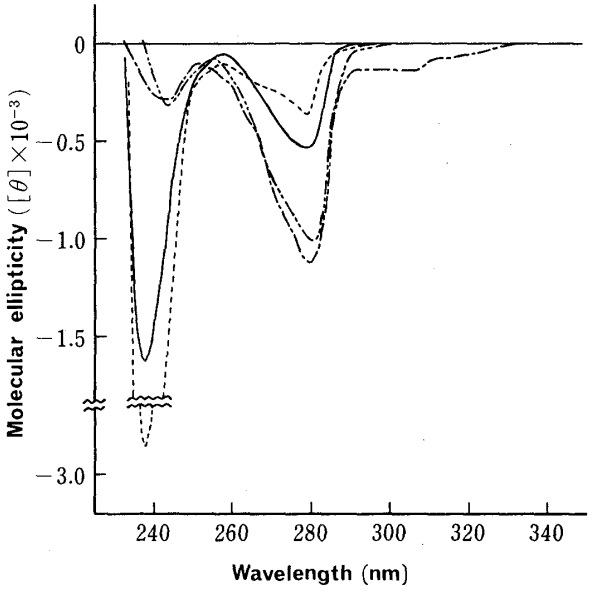


Fig. 2. CD Curves of Alancine (**2e**) and Its Congeners in 99% Aqueous EtOH

——: **2e** ($c=2.65\times10^{-4}$ M) at 20 °C. ——: **2e**·HCl ($c=4.13\times10^{-4}$ M) at 22 °C. —·—: (−)-**2f**·$HClO_4$ ($c=4.05\times10^{-4}$ M) at 20 °C. ----: (−)-**2g** ($c=3.10\times10^{-4}$ M) at 20 °C.

Experimental

General Notes——All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are corrected. See ref. 8*c* for details of instrumentation and measurements. Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, dd = doublet-of-doublets, q = quartet, s = singlet, t = triplet.

(2*R*,3*R*,11b*S*)-3-Ethyl-1,3,4,6,7,11b-hexahydro-8-hydroxy-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-acetic Acid Ethyl Ester [(−)-6]——A solution of (−)-**5**[1,7c,f] (561 mg, 1.2 mmol) in EtOH (20 ml) was hydrogenated over 10% Pd–C (200 mg) at ordinary pressure and 24 °C for 1 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to leave a yellow oil. Purification of the oil by means of flash chromatography[12] [Silica gel 60 (E. Merck, No. 9385), AcOEt–hexane (1 : 1, v/v)] afforded (−)-**6** (433 mg, 96%) as a faintly yellowish oil, $[\alpha]_D^{20}$ −35.6° ($c=0.50$, EtOH); MS *m/z*: 377 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540 (OH), 2810, 2760 (*trans*-quinolizidine ring),[13] 1727 (ester CO); NMR ($CDCl_3$) δ: 0.91 (3H, t, $J=6.5$ Hz, $CCH_2\underline{Me}$), 1.28 (3H, t, $J=7$ Hz, $OCH_2\underline{Me}$), 3.81 and 3.86 (3H each, s, two OMe's), 4.17 (2H, q, $J=7$ Hz, $OC\underline{H}_2Me$), 5.80 (1H, s, OH), 6.28 [1H, s, H(11)].

(2*R*,3*R*,11b*S*)-3-Ethyl-1,3,4,6,7,11b-hexahydro-8-hydroxy-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-acetaldehyde (8-Hydroxyprotoemetine) [(−)-2f]——A stirred solution of (−)-**6** (403 mg, 1.07 mmol) in CH_2Cl_2 (12 ml) was cooled to −78 °C in an atmosphere of N_2, and a 1.0 M solution (2.4 ml, 2.4 mmol) of diisobutylaluminum hydride in hexane was added dropwise over 15 min. After the mixture had been stirred at −78 °C for 1 h, the reaction was quenched by adding MeOH (0.5 ml). The resulting mixture, after addition of 10% aqueous Rochelle salt (10 ml), was stirred at 0 °C for 30 min. Then, the pH of the aqueous layer was adjusted to *ca.* 7 with 10% aqueous HCl. The CH_2Cl_2 layer was separated from the aqueous layer, which was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a yellow glass. The glass was purified by means of flash chromatography[12] [Silica gel 60 (E. Merck, No. 9385), AcOEt–hexane (3 : 1, v/v)] to give (−)-**2f** (302 mg, 85%) as a pale yellow, unstable glass, $[\alpha]_D^{18}$ −42.9° ($c=0.50$, $CHCl_3$)[14]; MS *m/z*: 333 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540 (OH), 2810, 2760 (*trans*-quinolizidine ring),[13] 1724 (aldehyde CO); NMR ($CDCl_3$) δ: 0.92 (3H, dull t, $J=6.5$ Hz, $CCH_2\underline{Me}$), 3.82 and 3.86 (3H each, s, two OMe's), 5.81 (1H, br, OH), 6.27 [1H, s, H(11)], 9.87 (1H, dd, $J=2$, 1.5 Hz, CHO).

(2*R*,3*R*,11b*S*)-3-Ethyl-1,3,4,6,7,11b-hexahydro-8-hydroxy-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-acetaldehyde Perchlorate (8-Hydroxyprotoemetine Perchlorate) [(−)-2f·$HClO_4$]——A solution of 70% aqueous $HClO_4$ (89 mg, 0.62 mmol) in H_2O (1 ml) was added to an ice-cooled solution of (−)-**2f** (207 mg, 0.62 mmol) in EtOH (1 ml). The mixture was then concentrated *in vacuo* to a volume of *ca.* 1 ml, and the precipitate that resulted was filtered off, washed with H_2O, and dried to give (−)-**2f**·$HClO_4$·H_2O (254 mg, 91%). Recrystallization from H_2O–EtOH (8 : 1, v/v) and drying over P_2O_5 at 2 mmHg and 100 °C for 4 h furnished an analytical sample as colorless minute needles,

mp 216—217 °C; $[\alpha]_D^{25}$ −23.0° [c=0.50, 70% (v/v) aqueous EtOH]; CD (Figs. 1 and 2); IR ν_{max}^{Nujol} cm^{-1}: 3550, 3480 (OH, H_2O), 1726 (aldehyde CO); NMR (Me_2SO-d_6) δ: 0.86 (3H, t, J=7 Hz, $CH_2\underline{Me}$), 3.67 and 3.77 (3H each, s, two OMe's), 4.37 [1H, dull t, J=9.5 Hz, H(11b)], 6.43 [1H, s, H(11)], 9.25 (1H, s, OH or N^+H), 9.4 (1H, br, N^+H or OH), 9.77 (1H, s, CHO). *Anal.* Calcd for $C_{19}H_{28}ClNO_8 \cdot H_2O$: C, 50.50; H, 6.69; N, 3.10. Found: C, 50.71; H, 6.40; N, 2.98.

(2*R*,3*R*,11b*S*)-2,3-Diethyl-1,3,4,6,7,11b-hexahydro-8-hydroxy-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine [(−)-2g] ——A stirred mixture of (−)-**2f** (123 mg, 0.37 mmol), ethylene glycol (1 ml), 80% aqueous hydrazine hydrate (50 mg, 0.80 mmol), and KOH (75 mg) was heated under N_2 in an oil bath kept at 120 °C for 1 h. Then, the temperature of the oil bath was slowly raised to 190 °C in 30 min, and the mixture was further heated at 190—195 °C with stirring for 3 h. After cooling, the reaction mixture was poured into H_2O (5 ml), and the resulting solution was neutralized with 10% aqueous HCl and then extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a brown glass. Purification of the glass was carried out by flash chromatography[12] [Silica gel 60 (E. Merck, No. 9385), AcOEt–hexane (1 : 2, v/v)] to afford (−)-**2g** (94 mg, 80%) as a colorless solid, mp 107—108 °C. Recrystallization from hexane yielded an analytical sample as colorless scales, mp 108—108.5 °C; $[\alpha]_D^{20}$ −79.5° (c=0.51, EtOH); MS m/z: 319 (M^+); CD (Figs. 1 and 2); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 2815, 2760 (*trans*-quinolizidine ring);[13] NMR ($CDCl_3$) δ: 0.91 (6H, t, J=6.5 Hz, two $CH_2\underline{Me}$'s), 3.85 and 3.87 (3H each, s, two OMe's), 5.78 (1H, s, OH), 6.34 [1H, s, H(11)]. *Anal.* Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.38. Found: C, 71.30; H, 9.28; N, 4.39.

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