

REACTION OF *N*-ACYLATED ISOFEBRIFUGINE WITH ACID

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Abstract - The reaction of *N*-acylated isofebrifugine with hydrochloric acid is discussed. Although the corresponding deprotected compound was not isolated, three new heterocyclic compounds were obtained. Based on these findings, new furan and pyrrole derivatives were prepared.

Febrifugine (*d*-1) is an antimalarial agent that was isolated from *Dichroa febrifuga* and *Hydrangea umbellata* along with isofebrifugine (*d*-2).^{1a-c} Although several methods for synthesizing *d*-1^{2a, b} and its racemate (**1**)^{3a-d} have been reported, there are few methods for *d*-2^{2b} and its racemate (**2**)^{3b} (Figure 1). Recently, we developed a new method of synthesizing **1** via **2**.⁴ In this method, an isofebrifugine derivative (**3**) protected by a benzyloxycarbonyl group (*Z*) afforded **2** in moderate yield by hydrogenolysis. On the other hand, it was known that the alkoxy carbonyl group in the febrifugine derivative was successfully deprotected by acid hydrolysis.^{2b, 3b} We attempted reacting **3** with acid to improve the yield of the deprotection.

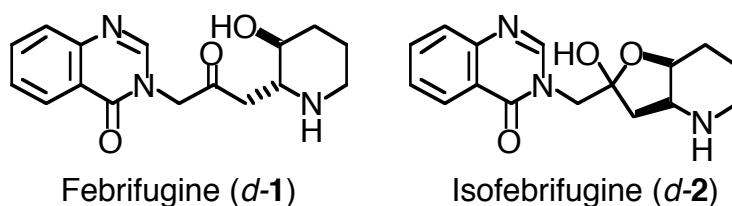
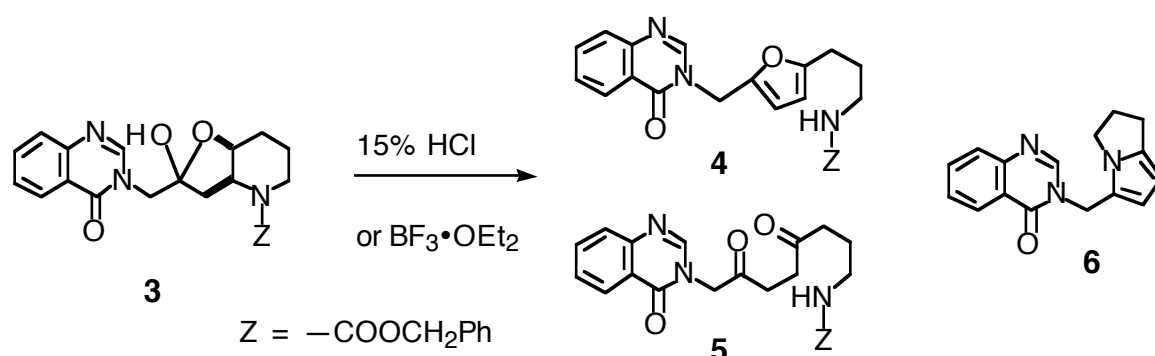


Figure 1

Although we could not find **2** in the reaction mixture of **3** and 15% hydrochloric acid in acetonitrile under reflux for 0.5 h, we were able to isolate the furan derivative (**4**) in 36% yield and the 1,4-diketone derivative (**5**) in 4% yield (Scheme 1). Even when the reaction time was prolonged to 2 h, **2** was not detected, but a new compound (**6**) was obtained in 6% yield along with **4** and **5**. The structure of this compound was determined from analytical data to include a condensed pyrrole ring. These results indicate that opening of the piperidine ring occurred before deprotection of the acyl group in the reaction of *Z*-protected isofebrifugine with hydrochloric acid. Using boron trifluoride etherate instead of hydrochloric acid in the reaction of **3** afforded **4** in 74% yield.



Scheme 1

We thought that **3** would successively produce **4**, **5**, and **6** in order and that new furan or pyrrole derivatives could be prepared using this reaction. As a convenient model of **3**, we selected **7**, which is **3** without the quinazoline ring (Scheme 2). Using molecular orbital calculations, Uesato *et al.* predicted that compound (**7**) with a deprotecting Z group would exist in the hemi-ketal form (**7**) rather than the keto form (**8**).⁵ We calculated that a stable structure (**9**) would form when the benzyl group of **7** or **8** with a methyl group by the PM3 method.⁶ Our calculations supported Uesato's prediction⁵ that the hemi-ketal forms (**7a**, **b**) were significantly more stable than the keto form (**8a**) (Figure 2).

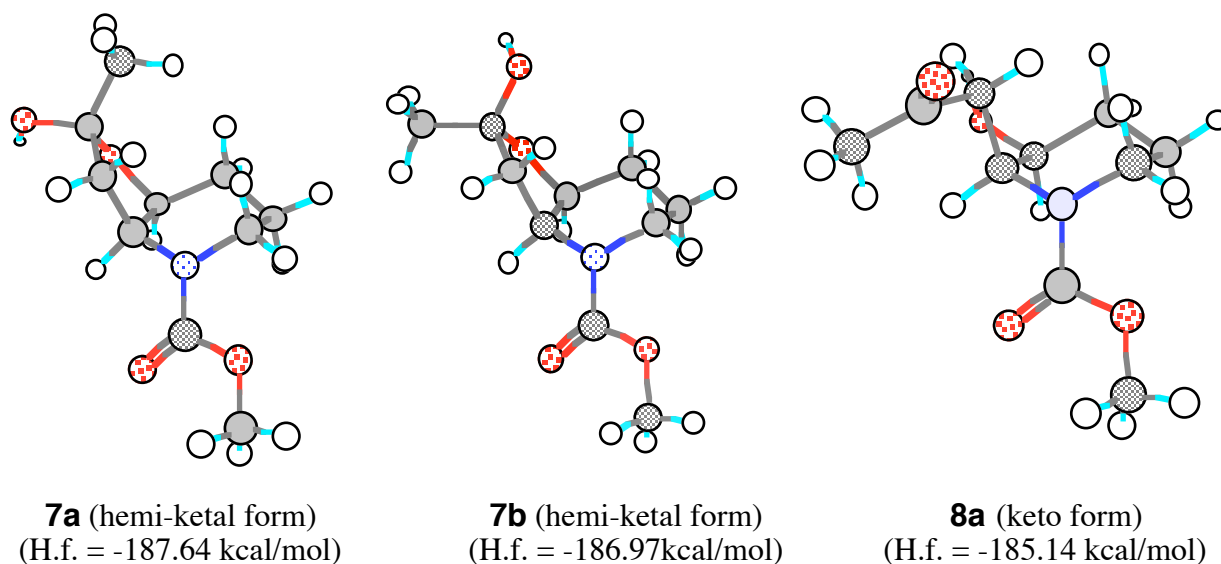
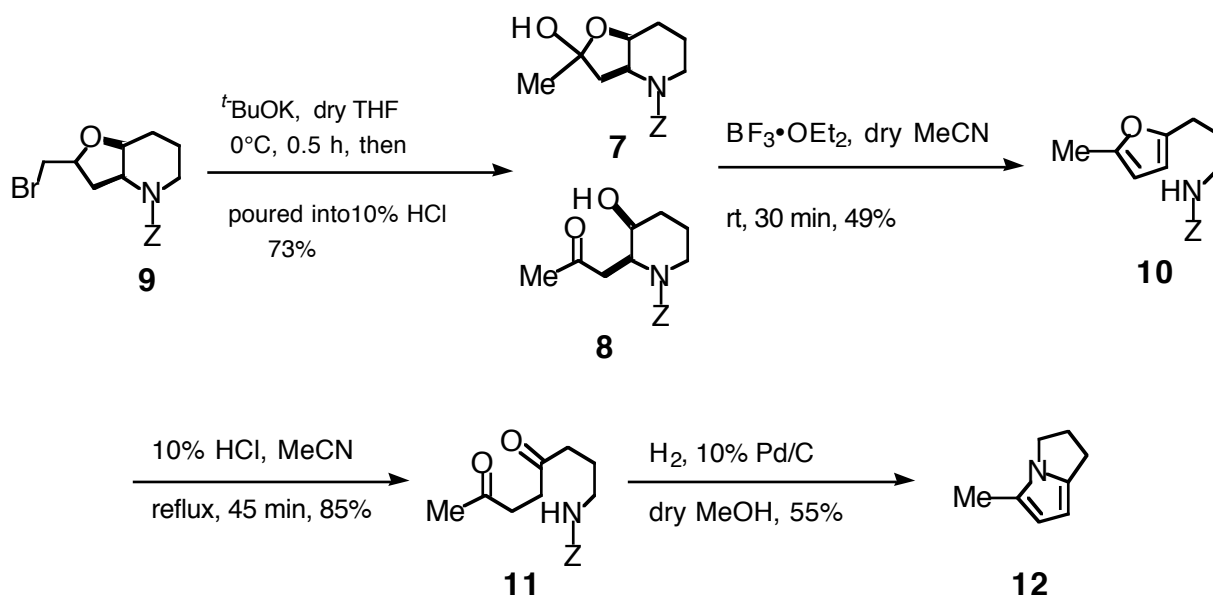


Figure 2

In contrast with the calculations, dehydrobromination of **9**⁴ with potassium *tert*-butoxide followed by treatment with acid afforded **8**, whose methyl proton was observed as a singlet peak at δ 2.07 ppm in DMSO- d_6 with ^1H -NMR. However, an additional peak was observed at δ 1.50 ppm in CDCl_3 with ^1H -NMR and two peaks were observed at δ 207.3 and δ 102.7 ppm with ^{13}C -NMR. From these results, we concluded that **8** would rapidly afford a mixture of **7** and **8** in CDCl_3 . The reaction of a mixture of **7** and **8**

with borontrifluoride etherate afforded the furan derivative (**10**) in 49% yield. The reaction of **10** with hydrochloric acid gave the 1,4-diketone derivative (**11**) in 85% yield. Removal of the Z group of **11** by hydrogenolysis followed with the condensation reaction afforded the pyrrole derivative (**12**), which was identified by comparing the ¹H-NMR data with reported ¹H-NMR data (Scheme 2).^{7a, b}



Scheme 2

EXPERIMENTAL

General: Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO A-102 spectrophotometer. MS spectra were recorded on a VG-70SE spectrometer. ¹H-NMR spectra were run on a Hitachi R-1500 (60 MHz) spectrometer. Merck silica gel 60 (230-400 mesh) was employed for column chromatography.

Reaction of **3** with Hydrochloric acid in MeCN.

A mixture of **3** (1.01 g, 2.32 mmol) and 5*N*-HCl (5 mL) in MeCN (15 mL) was heated at reflux for 0.5 h. The mixture was made basic with 10% NaOH and extracted with AcOEt (100 mL x 2). AcOEt layer was washed with brine (100 mL), dried over anhydrous MgSO_4 , and the solvent was evaporated off. The residue was chromatographed (SiO_2). The first eluant (AcOEt:hexane = 2:1) gave benzyl *N*-[3-[5-[(4-oxo-3(4*H*)-quinazoliny]methyl]-2-furyl]propyl]carbamate (**4**, 0.35 g, 36%) as a colorless oil. IR (neat) cm^{-1} : 3340, 1710, 1680, 1260. ¹H-NMR (CDCl_3) δ : 1.68–1.92 (m, 2H), 2.63 (t, 2H, $J = 7.5$ Hz), 3.21 (q, 2H, $J = 6.5$ Hz), 4.71 (br s, 1H), 5.09 (s, 4H), 5.96 (d, 1H, $J = 3.1$ Hz), 6.34 (d, 1H, $J = 3.1$ Hz), 7.33 (s, 5H), 7.52–7.79 (m, 3H), 8.15 (s, 1H), 8.32 (dd, 1H, $J = 7.6, 1.2$ Hz). HRMS (FAB) Calcd for $\text{C}_{24}\text{H}_{24}\text{N}_3\text{O}_4$ (MH)⁺: 418.1767. Found: 418.1780. The second eluant (AcOEt) gave benzyl *N*-[4,7-dioxo-8-(4-oxo-3(4*H*)-quinazoliny]octyl]carbamate (**5**, 0.038 g, 4%) as colorless needles, mp

137–138°C (AcOEt and hexane). IR (KBr) cm^{-1} : 3320, 1710, 1690, 1280. $^1\text{H-NMR}$ (CDCl_3) δ : 1.66–2.00 (m, 2H), 2.51 (t, 2H, $J = 6.6$ Hz), 2.79 (s, 4H), 3.19 (q, 2H, $J = 6.5$ Hz), 4.85 (s, 2H), 5.09 (s, 2H), 7.34 (s, 5H), 7.42–7.82 (m, 3H), 7.92 (s, 1H), 8.28 (dd, 1H, $J = 7.3, 1.5$ Hz). MS (FAB, positive ion mode) m/z : 436 (MH)⁺. Anal. Calcd for $\text{C}_{24}\text{H}_{25}\text{N}_3\text{O}_5$: C, 66.20; H, 5.79; N, 9.65. Found: C, 66.11; H, 5.49; N, 9.62.

Reaction of **3** with Hydrochloric Acid.

A mixture of **3** (0.99 g, 2.27 mmol) and 5*N*-HCl (15 mL) was heated at reflux for 2 h. The mixture was made basic with 10% NaOH and extracted with AcOEt (100 mL x 2). AcOEt layer was washed with brine (200 mL), dried over anhydrous MgSO_4 , and the solvent was evaporated off. The residue was chromatographed (SiO_2). The first eluant (AcOEt:hexane = 1:1) gave 3-[(2,3-dihydro-1*H*-6-pyrrolo[1,2-*a*]pyrrolyl)methyl]-4(3*H*)-quinazolinone (**6**, 0.037 g, 6%) as colorless needles, mp 148–149°C (hexane). IR (CHCl_3) cm^{-1} : 1650. $^1\text{H-NMR}$ (CDCl_3) δ : 2.45–2.81 (m, 4H), 3.89 (t, 2H, $J = 6.5$ Hz), 5.15 (s, 2H), 5.77 (d, 1H, $J = 3.4$ Hz), 6.30 (d, 1H, $J = 3.4$ Hz), 7.49–7.76 (m, 3H), 8.09 (s, 1H), 8.33 (dd, 1H, $J = 8.8, 1.2$ Hz). HRMS (FAB) Calcd for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}$ (M)⁺: 265.1215. Found: 265.1212. Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.58; H, 5.80; N, 15.25. The second eluent (AcOEt:hexane=2:1) gave **4** (0.023 mg, 2%) and The third eluent (AcOEt) gave **5** (0.023 mg, 2%).

Benzyl *N*-[3-[5-[(4-Oxo-3(4*H*)-quinazolinyl)methyl]-2-furyl]propyl]carbamate (**4**)

To a solution of **3** (1.53 g, 3.51 mmol) in MeCN (10 mL), $\text{BF}_3 \cdot \text{OEt}_2$ (0.45 mL, 3.55 mmol) was added. The mixture was heated at reflux for 0.5 h. The mixture was made basic with saturated KHCO_3 and extracted with AcOEt (100 mL). AcOEt layer was washed with brine (100 mL), dried over anhydrous MgSO_4 , and the solvent was evaporated off. The residue was chromatographed (SiO_2 ; hexane:AcOEt = 2:1) to give **4** (1.08 g, 74%).

(2*S**,3*S**)-Benzyl 3-Hydroxy-2-(2-oxo)propyl-1-piperidinecarboxylate (**7**) and (3*aS**,7*aS**)-Benzyl 2-hydroxy-2-methylhexahydrofuro[3,2-*b*]pyridine-4(2*H*)-carboxylate (**8**)

To a solution of (3*aS**,7*aS**)-benzyl 2-(bromomethyl)hexahydrofuro[3,2-*b*]pyridine-4(2*H*)-carboxylate (**9**, 0.50 g, 1.41 mmol) in dry THF (5 mL), KOBU^t (0.32 g, 2.85 mmol) was added at 0°C and the mixture was stirred at the same temperature for 0.5 h. The mixture was poured into water (100 mL), made acidic with 10% HCl, and extracted with AcOEt (100 mL x 2). The AcOEt layer was washed with brine (100 mL), dried over anhydrous MgSO_4 , and the solvent was removed. The residue was chromatographed (SiO_2 , AcOEt:hexane = 1:1) to give a mixture of **7** and **8** (0.30 g, 73%) as a colorless oil. HRMS (FAB) Calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_4$ (MH)⁺: 292.1548. Found: 292.1532.

Benzyl *N*-[3-(5-methyl-2-furyl)propyl]carbamate (**10**)

To a solution of a mixture (0.74 g, 2.50 mmol) of **7** and **8** in dry MeCN (5 mL), $\text{BF}_3 \cdot \text{OEt}_2$ (0.32 mL, 2.50 mmol) was added dropwise and the mixture was heated at reflux for 0.5 h. The mixture was poured into

saturated KHCO₃ solution (50 mL) and extracted with AcOEt (50 mL x 2). The AcOEt layer was washed with brine (100 mL), dried over anhydrous MgSO₄, and the solvent was removed. The residue was chromatographed (SiO₂, AcOEt:hexane = 1:4) to give **10** (0.34 g, 49%) as a colorless oil. IR (neat) cm⁻¹: 3340, 2950, 1700, 1250. ¹H-NMR (CDCl₃) δ: 1.68–2.00 (m, 2H), 2.23 (s, 3H), 2.61 (t, 2H, *J* = 6.8 Hz), 3.23 (q, 2H, *J* = 6.5 Hz), 4.70 (br s, 1H), 5.10 (s, 2H), 5.85 (s, 2H), 7.34 (s, 5H). HRMS (FAB) Calcd for C₁₆H₁₉NO₃ (M)⁺: 273.1365. Found: 273.1359. Calcd for C₁₆H₂₀NO₃ (MH)⁺: 274.1443. Found: 274.1385.

Benzyl *N*-(4,7-Dioxooctyl)carbamate (11**)**

A mixture of **10** (0.80 g, 2.93 mmol) and 10% HCl (5 mL) in MeCN (10 mL) was heated at reflux for 45 min. The mixture was made basic with 10% NaOH solution and extracted with AcOEt (100 mL x 2). The AcOEt layer was washed with brine (200 mL), dried over anhydrous MgSO₄, and the solvent was removed. The residue was chromatographed (SiO₂, AcOEt:hexane = 1:1) to give **11** (0.73 g, 85%) as colorless plates, mp 32–33°C. IR (KBr) cm⁻¹: 3330, 1700, 1270. ¹H-NMR (CDCl₃) δ: 1.66–2.00 (m, 2H), 2.16 (s, 3H), 2.52 (t, 2H, *J* = 6.5 Hz), 2.66 (s, 4H), 3.19 (q, 2H, *J* = 6.5 Hz), 4.90 (br s, 1H), 5.10 (s, 2H), 7.34 (s, 5H). HRMS (FAB) Calcd for C₁₆H₂₂NO₄ (MH)⁺: 292.1549. Found: 292.1521.

Dihydro-6-methyl-1*H*-pyrrolo[1,2-*a*]pyrrole (12**)**

A mixture of **11** (0.72 g, 2.46 mmol) and 10% Pd/C (0.12 g) in dry MeOH (10 mL) was stirred at the rt for 24 h under the atmosphere of H₂. The mixture was filtered off and the solvent was removed. The residue was chromatographed (SiO₂, AcOEt:hexane = 1:30) to give **12** (0.16 g, 55%) as a colorless oil. ¹H-NMR data of this compound were identified with those of reported data^{7a,b}: ¹H-NMR (CDCl₃) δ: 2.19 (s, 3H), 2.30–3.00 (m, 4H), 3.79 (t, 2H, *J* = 6.7 Hz), 5.67 (d, 1H, *J* = 3.2 Hz), 5.86 (d, 1H, *J* = 3.2 Hz).

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