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Studies on the Syntheses of Heterocyclic Compounds. CDLXXXVI.[1] Behavior of the Erythrinadienone and Its Relatives in Acidic Medium

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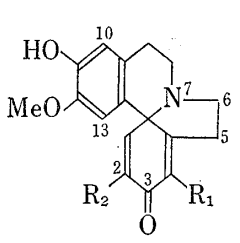
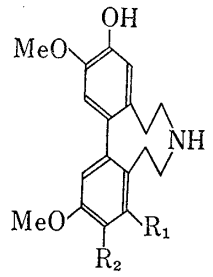
The reductive rearrangement of the dienol (V), derrived from erythrinadienone (III), did not give the proposed dibenzazonine analog (IV), but V was converted to the dibenzazonine (VI) in methanolic hydrochloric acid solution. The catalytic hydrogenation of (III) has also been examined.

As mentioned by Barton and his co-workers,[3] the reductive rearrangement of the erythrinadienone (I) with chromous chloride in 3% hydrochloric acid proceeded to give the dibenzazonine (II) in fairly good yield. This suggests that the dienol derived from the erythrinadienone would be also converted to the appropriate dibenzazonine analog under the reductive conditions, accompanying the dehydroxylation at the 3-position with the cleavage of C_{13b}-N bond in the dienol.

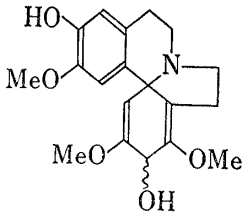
Based on the above aspect, we have studied on some reactions of 11-hydroxy-2,4,12-trimethoxyerythrinadienone (III) in acidic medium, which was synthesized by the phenolic oxidative coupling of N-(3-hydroxy-4-methoxyphenethyl)-3-hydroxy-2,4-dimethoxyphenethylamine,[4] in the expectation of the formation of the protostephanine precursor, 6,7,8,9-tetrahydro-3-hydroxy-2,10,12-trimethoxy-5H-dibenz[d,f]azonine (IV). During the course of our investigation, unexpected results were obtained and herein we wish to report these results.



I : R_1=H, R_2=OMe
III : R_1=R_2=OMe



II : R_1=H, R_2=OH
IV : R_1=OMe, R_2=H
VI : R_1=OMe, R_2=OH



V

Chart 1

Firstly, the reduction of the dienol (V), derived from the erythrinadienone III by sodium borohydride reduction, was attempted according to a method similar to that described by Barton[3]; compound (V) was treated with an excess of chromous chloride in 3% methanolic hydrochloric acid at room temperature. This attempt to obtain IV resulted in failure, and the starting material (V) was recovered. Furthermore, treatment of V with chromous chloride in boiling methanolic hydrochloric acid solution afforded no expected compound (IV), but

1) Part CDLXXXV: T. Kametani, T. Honda, M. Ihara, H. Shimanouchi, and Y. Sasads, *Tetrahedron Letters*, in press.
2) Location: *Aobayama, Sendai.*
3) D.H.R. Barton, R. James, G.W. Kirby, D.W. Turner, and D.A. Widdowson, *J. Chem. Soc.* (*C*), **1968**, 1529.
4) T. Kametani and T. Kohno, *Chem. Pharm. Bull.* (Tokyo), **19**, 2102 (1971).

gave VI. Also, the same treatment of V in boiling methanolic hydrochloric acid solution in the absence of chromous chloride gave VI in comparatively good yield (50%). It was suggested that the protonation to the nitrogen atom occurred preferentially, followed by the C-N bond cleavage to give dibenzazonine ring system under the boiling conditions. This fact was different from Mondon's report,[5] in which the dienol, derived from the dienone (I) by sodium borohydride reduction, was converted mainly to the enone (VII) under the acidic conditions without accompanying the same type of protonation of the dienol as in our case. It has been well known that the dienone-phenol and dienol-benzene rearrangements gave the different type of products depending on the reagent and the reaction condition used in these reactions.[6,7] The formation of the different type of compound in both cases would be due to the reagent and reaction condition, which had not been reported in Mondon's work. All the physical and spectral data of VI were identical with those of the authentic specimen, which was prepared by chromous chloride reduction of the erythrinadienone (III). The compound (VI) was also convertible to III by potassium ferricyanide oxidation.[3]

Secondly, hydrogenolysis of the dienone (III) over palladium-charcoal was examined. As mentioned by Kametani,[8] hydrogenolysis of norerythrinadienone over palladium-charcoal afforded the dibenzazocine analog. However, only the enone (VIII) was obtained as a hydrogenated product in the case of the erythrinadienone. Infrared (IR) spectrum of VIII exhibited characteristic absorptions due to the enone system at 1675 and 1660 cm^{-1}. Nuclear magnetic resonance (NMR) spectrum (τ) showed two methyl protons due to two methoxyl groups on the aromatic ring and 4-position as singlets at 6.19 and 6.25, methyl protons attributable to the methoxyl group on the 2-position as singlet at 6.67, and the absence of the olefinic proton. Mass spectrum showed the molecular ion peak at *m/e* 345. These spectral data supported the enone system (VIII) except the stereochemistry of the methoxyl group at the 2-position of VIII.

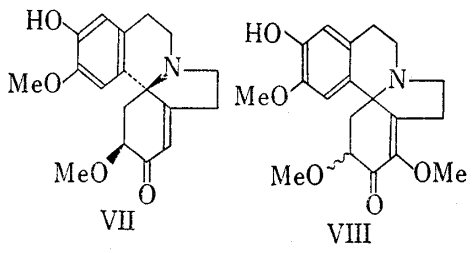


Chart 2

Thus, we have succeeded in an approach to the dibenzazonine derivatives by the acid-catalyzed reaction of the dienol (V).

Experimental[9]

3,5,8,9-Tetrahydro-3,11-dihydroxy-2,4,12-trimethoxy-6*H*-indolo[7a,1-a]isoquinoline (V)——To a solution of 50 ml of the dienone (III) in 100 ml of MeOH was added 25 mg of $NaBH_4$ with stirring under cooling in an ice-bath and the stirring was continued for 1.5 hr. After an additional stirring for 1.5 hr at room temperature, the mixture was evaporated to dryness *in vacuo*. The residue was agitated with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4, and evaporated to give 45 mg of an oily dienol (V) as an epimeric mixture. IR ($CHCl_3$) cm^{-1}: 1655 (C=C). NMR ($CDCl_3$) τ: 3.44, 3.67 (1H×2, each s, aromatic protons), 4.95 (1H, s, olefinic proton), 5.10 (1H, s, >CHOH), 6.18, 6.24, 6.42 (3H×3, each s, OCH_3×3).

Chromous Chloride Reduction of V——A mixture of 60 mg of V and 10 ml of $CrCl_2$ solution (0.95 m mole of $CrCl_2$) in 100 ml of 3% methanolic HCl solution was gently refluxed for 40 min under a current of N_2 and the air was bubbled in the mixture. The mixture was adjusted to pH 9 with $NaHCO_3$ and concentrated *in vacuo* to give the residue, which was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and evaporated to give 50 mg of a dark brown

5) A. Mondon and M. Ehrhardt, *Tetrahedron Letters*, **1966**, 2557.
6) A.H. Jackson and J.A. Martin, *J. Chem. Soc.* (*C*), **1966**, 2222.
7) M. Shamma and W.A. Slusarchyk, *Chem. Commum.*, **1965**, 528.
8) T. Kametani, K. Takahashi, S. Shibuya, and K. Fukumoto, *J. Chem. Soc.* (*C*), **1971**, 1800.
9) Melting points are not corrected. The IR spectra were taken with a Hitachi EPI-S_2 spectrophotometer in chloroform and NMR spectra were measured on a Hitachi H-60 in deuteriochloroform using TMS as an internal standard. Mass spectra were measured on a Hitachi RMU-7 (80 eV).

solid, which was recrystallized from MeOH to afford 40 mg of VI as colorless needles, mp 213—215°, undepressed on an admixture with the authentic sample. Spectral data were also identical with those of the authentic sample.

6,7,8,9-Tetrahydro-3,11-dihydroxy-2,10,12-trimethoxy-5H-dibenz[d,f]azonine (VI)——(a) To a solution of 50 mg of the dienone (III) in 100 ml of 3% methanolic HCl solution was added 10 ml of $CrCl_2$ solution (0.95 m mole of $CrCl_2$) under a current of N_2. The mixture was kept aside for 40 min at room temperature and the air was bubbled in the mixture. The reaction mixture was adjusted to pH 9 and concentrated *in vacuo*. The residue was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and evaporated. The resulting brown oil was triturated with MeOH to afford 20 mg of VI. Recrystallization from MeOH gave colorless needles, mp 213—215°. *Anal.* Calcd. for $C_{19}H_{23}O_5N$: C, 66.07; H, 6.71. Found: C, 65.91; H, 6.53. IR ($CHCl_3$) cm^{-1}: 3500 (OH). NMR ($CDCl_3$) τ: 3.27, 3.36, 3.52 (1H×3, each s, aromatic protons), 6.13 (3H, s, $OC\underline{H}_3$), 6.15 (3H×2, s, $OC\underline{H}_3\times2$), 6.90—7.80 (8H, m, $-C\underline{H}_2-C\underline{H}_2-\times2$).

(b) A solution of 10 mg of the dienol (V) in 15 ml of 3% methanolic HCl solution was refluxed for 40 min under a current of N_2. After the same treatment of the reaction mixture as in case of (a), 5 mg of VI was obtained as colorless needles, mp 213—215°, the spectral data of which were identical with those of an authentic sample prepared by method (a).

Oxidation of VI——To a solution of 58 mg of VI in 240 ml of $CHCl_3$ was added 15 ml of 5% $NaHCO_3$ aqueous solution containing 90 mg of $K_3Fe(CN)_6$. After stirring for 30 min at room temperature, the $CHCl_3$ layer was separated and the resulting aqueous layer was extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with H_2O, dried over Na_2SO_4 and evaporated. The resulting pale brown solid was recrystallized from MeOH to afford 45 mg of the dienone (III) as colorless needles, mp 213—216° (decomp.), the spectral data of which were identical with those of the authentic sample.

Catalytic Hydrogenation of III——A mixture of 50 mg of the dienone (III) and 50 mg of 10% palladium-charcoal in 150 ml of tetrahydrofuran was shaken at room temperature under a current of H_2. After an absorption of the calcurated amount of H_2, the mixture was filtered and the filtrate was evaporated. The remaining brown solid (45 mg) was chromatographed on silicic acid (1 g) with MeOH–$CHCl_3$ (1: 99) as eluant to give 10 mg of VII as colorless needles (from MeOH–ether), mp 188—190°. *Anal.* Calcd. for $C_{19}H_{23}O_5N$: C, 66.07; H, 6.71. Found: C, 66.29; H, 6.49. IR ($CHCl_3$) cm^{-1}: 3500 (OH), 1670 (C=C). NMR ($CDCl_3$) τ: 3.28, 3.44 (1H×2, each s, aromatic protons), 6.19, 6.25, 6.67 (3H×3, each s, $OC\underline{H}_3\times3$). Mass Spectrum *m/e*: 345 (M^+).

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