[Chem. Pharm. Bull. 19(10)2102—2105(1971)]

UDC 547.56.04 : 547.94.057

Synthesis of Erythrinadienone by Phenol Oxidation of Bisphenethylamine (Studies on the Synthesis of Heterocyclic Compounds. CDXLV[1])

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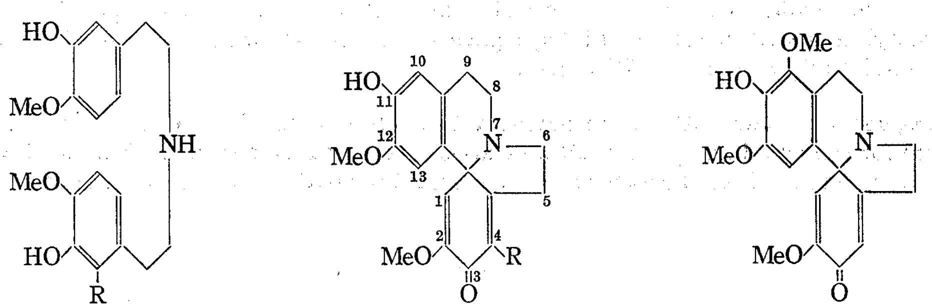
(Received March 27, 1971)

Phenolic oxidative coupling of N-(3-hydroxy-4-methoxyphenethyl)-3-hydroxy-2,4-dimethoxyphenethylamine (III) with alkaline potassium ferricyanide in two-phase system (water–chloroform) was investigated. Cyclization of III proceeded preferentially to give the erythrinadienone (IV).

The chemical oxidation of phenolic bisphenethylamine is the most synthetically useful method to the erythrinan ring system as indicated by Scott[3] and Mondon[4]; the oxidation of bis(3-hydroxy-4-methoxyphenethyl)amine (I) with alkaline potassium ferricyanide afforded the erythrinadienone (II) in 35% yield. In addition, Mondon[4] and Barton[5] reported on the acid-catalyzed rearrangement of the dienol derived from II and the reductive rearrangement of II with chromous chloride in hydrochloric acid, respectively. The former gave the enone analogue as the major product and the latter afforded the dibenzazonine in high yield.



I : R=H
III : R=OMe

II : R=H
IV : R=OMe

V

Chart 1

Based on the above facts, we examined the phenol oxidation of N-(3-hydroxy-4-methoxyphenethyl)-3-hydroxy-2,4-dimethoxyphenethylamine (III), as this was the first step of our synthetic approach to the dibenzazonine analogue through the reductive rearrangement of the dienol which would be furnished from the appropriate erythrinadienone. In the course of our investigation it was found that cyclization of III proceeded preferentially to give the erythrinadienone (IV), while two possibilities of cyclization were conceivable to IV and/or V. Herein we wish to report these results.

The synthesis of the starting material (III) for the phenol oxidation was carried out as follows. 3-Benzyloxy-2,4-dimethoxybenzaldehyde (VI), which was prepared by a method similar to that described by Kametani,[6] was oxidized to the corresponding acid (VII)(76%

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1) Part CDXLIV: T. Kametani, S. Hibino, and S. Takano, *Chem. Commun.*, **1971**, 925.
2) Location: *Aobayama, Sendai.*
3) J.E. Gervay, F. McCapra, T. Money, G.M. Sharma, and A.I. Scott, *Chem. Commun.*, **1966**, 142.
4) A. Mondon and M. Ehrhardt, *Tetrahedron Letters*, **1966**, 2557.
5) D.H.R. Barton, R.B. Boar, and D.A. Widdowson, *J. Chem. Soc.* (*C*), **1970**, 1208.
6) T. Kametani and K. Fukumoto, *J. Chem. Soc.*, **1968**, 2156.

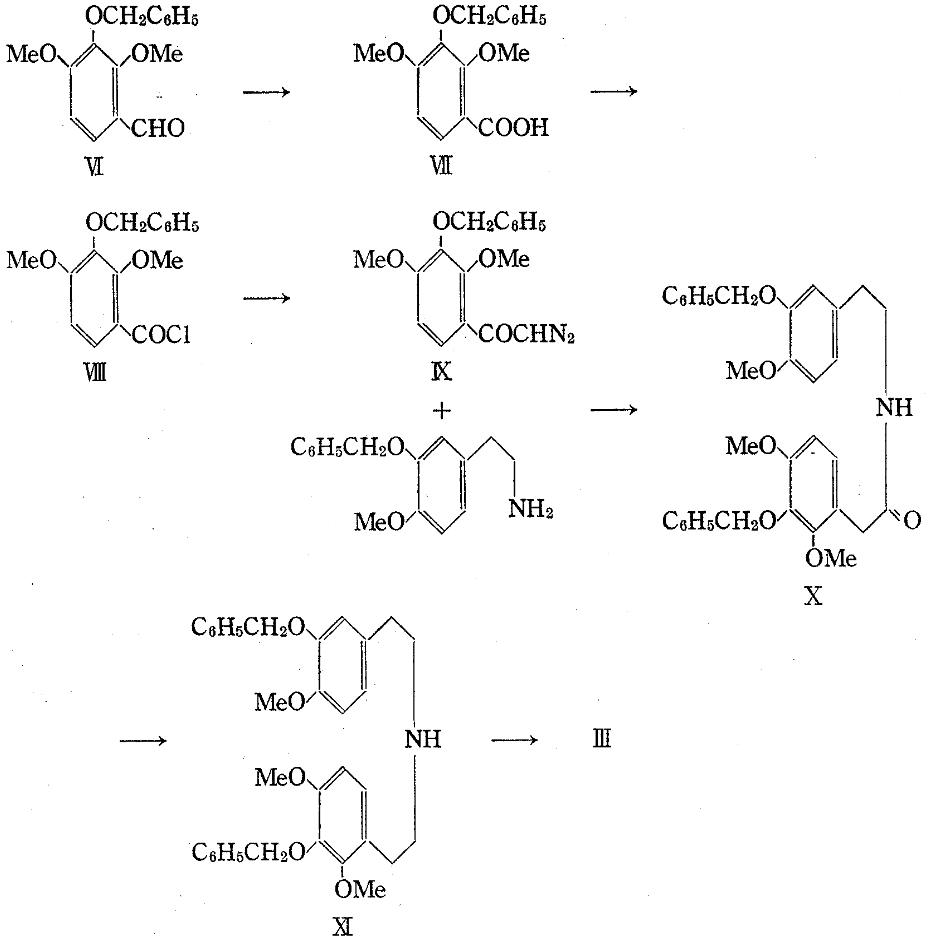

Chart 2

yield), mp 103—105°, with silver nitrate and sodium hydroxide. The acid, considerably resistant to chlorination with phosphorus pentachloride, was converted into the unstable acid chloride (VIII) with thionyl chloride in the presence of pyridine. The treatment of VIII with an excess of ethereal diazomethane gave quantitatively 3-benzyloxy-2,4-dimethoxy-ω-diazoacetophenone (IX) as a yellowish oil. The infrared (IR) spectrum of IX exhibited a characteristic peak due to the diazo group at 2075 cm^{-1}. The Arndt–Eistert condensation reaction of 3-benzyloxy-4-methoxyphenethylamine with the diazoketone (IX) afforded N-[2-(3-benzyloxy-4-methoxyphenyl)ethyl]-2-(3-benzyloxy-2,4-dimethoxyphenyl)acetamide (X), mp 104.5—106° (47% yield). Reduction of X with lithium aluminum hydride in tetrahydrofuran gave N-(3-benzyloxy-4-methoxyphenethyl)-3-benzyloxy-2,4-dimethoxyphenethylamine (XI), mp 156—158° as the oxalate. The nuclear magnetic resonance (NMR) spectrum (τ) of XI showed two methylene protons due to two benzyl groups as singlets at 4.94 and 5.04, three methyl protons due to three methoxy groups as singlets at 6.19, 6.23, and 6.26, and four methylene protons ($2H \times 4$) as singlet at 7.27.

Catalytic debenzylation of the secondary amine (XI) with hydrogen over palladium-charcoal gave N-(3-hydroxy-4-methoxyphenethyl)-3-hydroxy-2,4-dimethoxyphenethylamine (III). As mentioned by Barton,[5)] the effective conditions of the phenol oxidation to the erythrinadienone involved a two-phase system of chloroform and aqueous potassium ferricyanide in the presence of sodium hydrogen carbonate at room temperature for 40 min. By this method the erythrinadienone (IV), mp 212.5—215.5°, which was isolated with silica gel chromatography, was preferentially obtained in 5.8% yield. IR spectrum of IV exhibited the characteristic absorption of the dienone at 1660 and 1620 cm^{-1}. NMR spectrum (τ)

showed two aromatic protons as singlets at 3.37 (C_{13}-H)⁷⁾ and 3.64 (C_{10}-H), olefinic proton as singlet at 4.00 (C_1-H), methyl protons as singlet at 6.15 (C_{12}-$OC\underline{H}_3$), two methyl protons as singlets at 6.28 and 6.38 (C_2,C_4-$OC\underline{H}_3$), and aliphatic protons (8H) as multiplet at 6.50—7.60. Furthermore, mass spectrum (M^+ at *m/e* 343) and microanalysis supported the erythrinadienone system (IV).

Experimental⁸⁾

3-Benzyloxy-2,4-dimethoxybenzoic Acid (VII)——To a stirred mixture of 17 g of 3-benzyloxy-2,4-dimethoxybenzaldehyde (VI), 51 g of $AgNO_3$, and 100 ml of H_2O was added dropwise 60 ml of 40% NaOH aq. solution at 80°. After stirring for 2 hr at 90°, the reaction mixture was diluted with 200 ml of hot water and filtered. The filtrate was washed with ether and acidified with conc. HCl. The resulting precipitate was extracted with ether. The ethereal extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The residual solid was recrystallized from aq. EtOH to give 13 g of colorless rods (VII), mp 105—106°. *Anal.* Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.77; H, 5.42. IR ($CHCl_3$) cm^{-1}: 1730 (C=O). NMR ($CDCl_3$) τ: 2.15 (1H, doublet, $J=9.0$ Hz, C_6-H), 3.24 (1H, doublet, $J=9.0$ Hz, C_5-H), 5.01 (2H, singlet, $OC\underline{H}_2C_6H_5$), 5.94 (3H, singlet, C_2-$OC\underline{H}_3$), 6.12 (3H, singlet, C_4-$OC\underline{H}_3$).

3-Benzyloxy-2,4-dimethoxybenzoic Acid Chloride (VIII)——To a cooled solution of 12 g of VII in 200 ml of dry ether was added 7.2 g of $SOCl_2$ and 0.5 ml of pyridine. The mixture was refluxed for 10 hr and then left standing overnight at room temperature. The ethereal layer was separated by decantation. Evaporation of ether left a yellowish oil, which, after treatment with C_6H_6 followed by evaporation, gave 12 g of the expected acid chloride (VII) as an oil. IR ($CHCl_3$) cm^{-1}: 1755 (C=O). The acid chloride (VIII) thus obtained was used for the following step without further purification.

N-[2-(3-Benzyloxy-4-methoxyphenyl)ethyl]-2-(3-benzyloxy-2,4-dimethoxyphenyl)acetamide (X)——A solution of 12 g of VIII in 100 ml of dry ether was added dropwise to an excess of ethereal diazomethane, derived from 50 g of *p*-toluenesulfonyl-N-methyl-N-nitrosoamide, at ice-bath temperature. The solution was set aside overnight, and then evaporation of the solution gave 14 g of 3-benzyloxy-2,4-dimethoxy-ω-diazoacetophenone (IX) as a yellowish oil, IR ($CHCl_3$) cm^{-1}: 2075, 1600 (diazoketone).

To a stirred mixture of 14 g of the diazoketone (IX) and 14 g of 3-benzyloxy-4-methoxyphenethylamine in 150 ml of dry C_6H_6 was added in portions 9 g of freshly prepared Ag_2O at 60°. After vigorous gas evolution had ceased, the stirring was continued for an additional 3 hr at 75°. The mixture was cooled, diluted with 300 ml of C_6H_6, and filtered. The filtered solution was washed with 10% HCl, H_2O, satd. $NaHCO_3$, and H_2O and dried over Na_2SO_4. The remaining oil obtained upon evaporation of the solvent was chromatographed on silica gel (100 g) with 1% MeOH–$CHCl_3$ as eluant to give a pale brown solid. Recrystallization from ligroin (bp 75—120°) afforded 10 g of colorless needles (X), mp 104.5—106°. *Anal.* Calcd. for $C_{33}H_{35}O_6N$: C, 73.17; H, 6.51; N, 2.59. Found: C, 73.02; H, 6.29; N, 2.66. IR ($CHCl_3$) cm^{-1}: 3380 (NH), 1660 (C=O). NMR ($CDCl_3$) τ: 2.50—2.84 (10H, multiplet, aromatic protons), 3.13—3.55 (5H, multiplet, aromatic protons), 4.98, 5.08 (2H × 2, each singlet, $OC\underline{H}_2C_6H_5 \times 2$), 6.23 (9H, singlet, $OC\underline{H}_3 \times 3$), 6.61 (2H, singlet, -$C\underline{H}_2$-CO-NH), 6.71 (2H, distorted triplet, $J=7$ Hz, -CH_2-$C\underline{H}_2$-NH), 7.40 (2H, distorted triplet, $J=7$ Hz, -$C\underline{H}_2$-CH_2-NH).

N-(3-Benzyloxy-4-methoxyphenethyl)-3-benzyloxy-2,4-dimethoxyphenethylamine (XI)——To a stirred suspension of 3 g of $LiAlH_4$ in 100 ml of dry tetrahydrofuran(THF) was added dropwise a solution of 10 g of the amide (X) in 100 ml of dry THF at ice-bath temperature. The mixture was then heated under reflux for 4 hr and allowed to stand overnight at room temperature. This was follwed by treatment with about 50 ml of 40% KOH at 0°. The THF layer was separated and the water layer was extracted with $CHCl_3$. After removal of THF under reduced pressure, the residue was combined with the $CHCl_3$ extract, then washed with H_2O, dried over Na_2SO_4 and evaporated. Chromatography of the resulting dark yellow oil over silica gel (15 g) and eluate with $CHCl_3$ afforded 5 g of a solid (XI), which gave the oxalate, mp 156—158° (ether–MeOH). *Anal.* Calcd. for $C_{33}H_{37}O_5N \cdot C_2H_2O_4$: C, 68.05; H, 6.36; N, 2.27. Found: C, 67.91; H, 6.13; N, 2.46. NMR (free base in $CDCl_3$) τ: 2.40—2.90 (10H, multiplet, aromatic protons), 3.20—3.59 (5H, multiplet, aromatic protons), 4.94, 5.04 (2H × 2, each singlet, $OC\underline{H}_2C_6H_5 \times 2$), 6.19, 6.23 and 6.26 (3H × 3, each singlet, $OC\underline{H}_3 \times 3$), 7.27 (8H, singlet, (-$C\underline{H}_2$-$C\underline{H}_2$)$_2$NH).

N-(3-Hydroxy-4-methoxyphenethyl)-2,4-dimethoxy-3-hydroxyphenethylamine (III)——A mixture of 2 g of the amine (XI) and 0.1 g of 10% $PdCl_2$ on charcoal in 200 ml of EtOH was shaken at 40° under the

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7) Each position of substituents on the erythrinadienone ring was indicated according to the nomenclature of "The Ring Index, 2nd. edition" (American Chemical Society).

8) Melting points are not corrected. The IR spectra were taken in chloroform with a Hitachi EPI-S2 spectrophotometer, and NMR spectra were measured on a Hitachi R-20 in deuteriochloroform using TMS as an internal standard. Mass spectrum was measured on a Hitachi RMU-7.

atmospheric pressure of H_2 for 20 hr. The reaction mixture was filtered, then evaporated to give 1.3 g of the diphenolic amine (III), which was treated as usual and used for the following step without further purification. IR ($CHCl_3$) cm^{-1}: 3500 (OH). NMR ($CDCl_3$)τ: 3.18—3.60 (5H, multiplet, aromatic protons), 6.25 (6H, singlet, $OC\underline{H}_3 \times 2$), 6.29 (3H, singlet, $OC\underline{H}_3$), 6.70—7.25 (8H, broad singlet, $(C\underline{H}_2\text{-}C\underline{H}_2)_2NH$).

Erythrinadienone (IV)——A solution of 1.3 g of the diphenolic amine (III) in 1 liter of $CHCl_3$ was added to a solution of 14 g of $K_3Fe(CN)_6$ in 1 liter of 5% $NaHCO_3$ with vigorous stirring under N_2. After stirring for 40 min, the $CHCl_3$ layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel (20 g) with 1% MeOH–$CHCl_3$ as eluant, to give a pale brown solid, which was recrystallized from MeOH to give 70 mg of colorless needles (IV), mp 212.5—215.5° (decomp.). *Anal.* Calcd. for $C_{19}H_{21}O_5N$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.40; H, 6.09; N, 4.22. IR ($CHCl_3$) cm^{-1}: 1660, 1620 (dienone). NMR ($CDCl_3$) τ: 3.37 (1H, singlet, C_{13}-H), 3.64 (1H, singlet, C_{10}-H), 4.00 (1H, singlet, C_1-H), 6.15 (3H, singlet, $C_{12}\text{-}OC\underline{H}_3$), 6.28, 6.38 ($3H \times 2$, each singlet, $C_2\text{-}OC\underline{H}_3$ and $C_4\text{-}OC\underline{H}_3$), 6.50—7.60 (8H, multiplet, aliphatic protons). Mass Spectrum: M^+ at *m/e* 343.

Acknowledgement We thank Miss A. Kawakami and Miss T. Yoshida for microanalysis, Miss T. Tadano for the NMR spectral measurement, and Mr. T. Ouchi for the mass spectral measurement.