Communications to the Editor

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EFFECTIVE TOTAL SYNTHESIS OF FAGARONINE[1]: ANTILEUKEMIC PHENOLIC BENZO[*c*]PHENANTHRIDINE ALKALOID

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Fagaronine (1), an antileukemic benzo[*c*]phenanthridine alkaloid bearing a phenol group, was synthesized from the chalcone (4) according to the synthesis sequence shown in Chart 1. The phenol group was protected as an isopropoxy group during synthesis works.

KEYWORDS— fagaronine; phenolic benzo[*c*]phenanthridine alkaloid; total synthesis; protecting group of a phenol; isopropoxy group; isopropoxy-1-tetralone; intramolecular Friedel-Crafts reaction; phosphorus oxychloirde; concentrated sulfuric acid in acetic acid

In 1972, Farnsworth *et al.*[2] isolated fagaronine (1) from *Fagara zanthoxyloides* Lam. as a phenolic benzo[*c*]phenanthridine alkaloid which acts strongly against L-1210 and P-388 leukemia in mice. Later, according to the Kessar method,[3] Stermitz *et al.*[4] synthesized fagaronine (1) through the photocyclization of the anil derivative prepared by condensation of 6-isopropoxy-7-methoxy-1-naphthylamine and 2-bromoveratraldehyde.

On the other hand, in the course of studies on the structural establishment of naturally occurring benzo[*c*]phenanthridine alkaloids bearing five alkoxy functions in their molecules, we[5] needed to establish a versatile method for total synthesis of benzo[*c*]phenanthridine alkaloids in general. Occasionally, we succeeded in establishing the synthetic sequence (Chart 1) which gave the desired benzo[*c*]phenanthridine alkaloids in reasonable yields, and prepared various non-phenolic alkaloids according to this method. However, in order to apply this method to the synthesis of phenolic bases, selection of the protecting group for the phenol groups becomes an important task. A benzyloxy group is not suitable for this purpose, because it would be cleaved at the step of hydrogenolysis of a ketonic function to a methylene on a 2,4-bisaryl-4-oxobutyric acid. Actually, all trials to find the condition under which debenzylation could not take place during the hydrogenolysis failed. We also found that the subsequent intramolecular Friedel-Crafts cyclization of 2,4-bisarylbutyric acids to 2-aryl-1-tetralone derivatives after re-benzylation of the resulting phenolic 2,4-bisarylbutyric acids did not give good results.[6] The situation challenged us to synthesize fagaronine (1) and other phenolic benzo[*c*]phenanthridine alkaloids. In this report, we describe the successful synthesis of fagaronine (1).

After some preliminary attempts, an isopropoxy group[7] was developed to protect the phenol function in our synthetic sequence. Thus, 3-isopropoxy-4-meth-

oxyacetophenone (2), mp 55.5-56.5°C (Et_2O-hexane) (lit.[8] mp 56°C), one of the starting materials, was prepared by the Grignard reaction of 3-isopropoxy-4-methoxybenzaldehyde[9] with methylmagnesium iodide followed by oxidation with Jones reagent in 62.3% yield. Aldol condensation of the acetophenone (2) with veratraldehyde (3) with sodium hydroxide in aqueous ethanol gave the oily chalcone (4), quantitatively. Hydrocyanation of the chalcone (4) with potassium cyanide and acetic acid in ethyl cellosolve gave the keto-nitrile[10] (5), colorless prisms, mp 148-149°C ($CHCl_3$-MeOH), in 75.5% yield. The direct hydrolysis of the keto-nitrile (5) with sodium hydroxide in aqueous ethanol for 7.5 h under reflux afforded the keto-acid[10] (6), colorless prisms, mp 135-137°C (benzene-hexane), in 95.9% yield. Catalytic hydrogenation of the keto-acid (6) over 10% palladium-charcoal[11] provided the isopropoxy-acid[10] (7), colorless needles, mp 103-104°C (Et_2O-hexane), quantitatively.

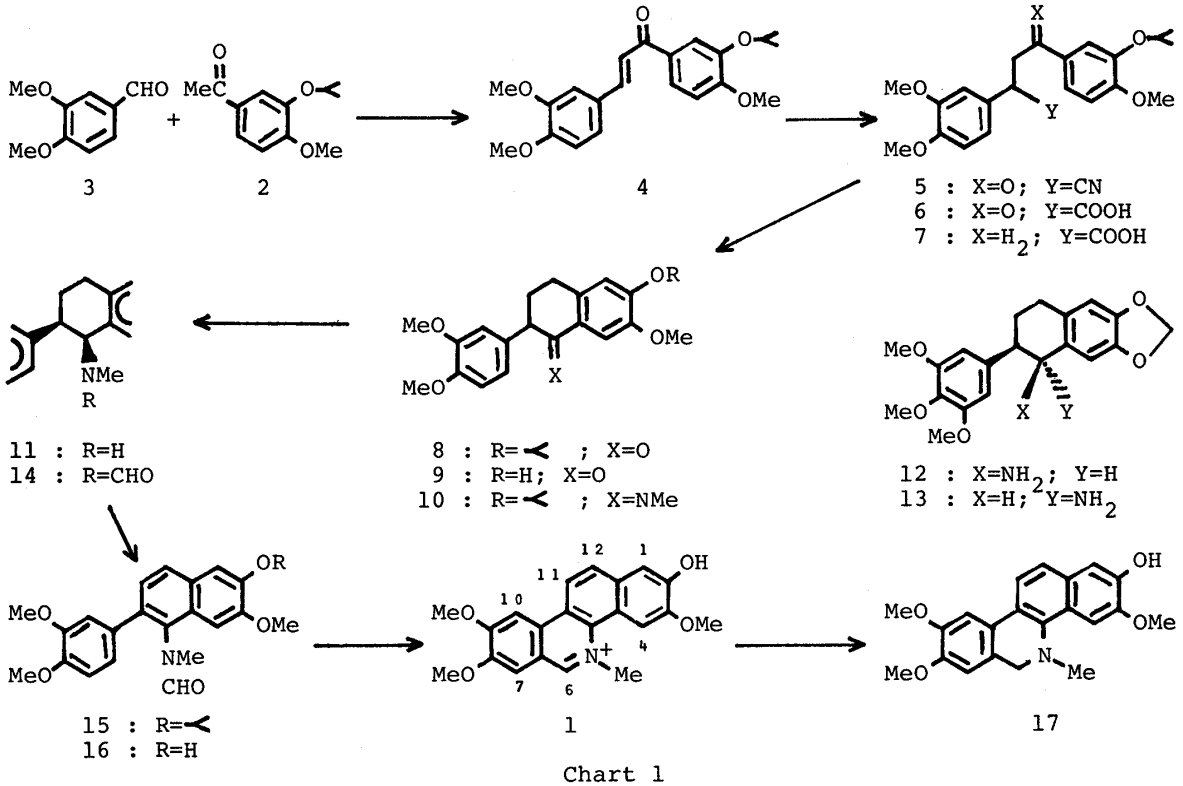

Chart 1

The intramolecular Friedel-Crafts reaction of the isopropoxy-acid (7) with phosphorus oxychloride in chloroform was carefully achieved at 80°C for 2.5 h. The mixture of products was separated into two fractions, neutral and phenolic, in 71.0% and in 5.8% yield, respectively. The desired isopropoxy-1-tetralone (8), colorless prisms, mp 121-122°C (benzene-hexane) [$C_{22}H_{26}O_5$, IR ν_{max}^{Nujol} cm^{-1}: 1670 (CO), PMR ($CDCl_3$) δ: 1.43 (6H, d, J=6.0 Hz, $CH\underline{Me}_2$), 2.20-2.60 (2H, m, C_3-H_2), 2.80-3.17 (2H, m, C_4-H_2), 3.70 (1H, t, J=8.0 Hz, C_2-H), 3.85 (6H, s, OMe × 2), 3.88 (3H, s, OMe), 4.67 (1H, septet, J=6.0 Hz, $OC\underline{H}Me_2$), 6.60-6.86 (4H, m, arom. H × 4), 7.57 (1H, s, C_8-H)], was obtained from the neutral fraction. The phenolic fraction provided another 2-aryl-1-tetralone (9) having a phenolic function, instead of an isopropoxy group, indicating that the isopropoxy group of the former tetralone (8) was cleaved under the condition of the cyclization to give the hy-

droxy-1-tetralone (9), colorless prisms, mp 170-172°C (MeOH) [$C_{19}H_{20}O_5$, IR ν_{max}^{Nujol} cm^{-1}: 3410 (OH) and 1665 (CO), PMR ($CDCl_3$) δ: 2.20-2.60 (2H, m, C_3-H_2), 2.77-3.15 (2H, m, C_4-H_2), 3.68 (1H, t, J=8.0 Hz, C_2-H), 3.84 (6H, s, OMe × 2), 3.92 (3H, s, OMe), 6.14 (1H, br s, OH), 6.60-6.84 (4H, m, arom. H × 4), 7.56 (1H, s, C_8-H)]. These results demonstrate that an isopropoxy group was available as a protecting group for a phenol function in our reaction sequence.

Treatment of a solution of the isopropoxy-1-tetralone (8) in anhydrous chloroform containing titanium tetrachloride with methylamine gas at -5 - 0°C afforded the labile Schiff base (10) which led directly to an oily amine[10] (11) by treatment with sodium borohydride without purification, in 99.1% yield. In the proton magnetic resonance (PMR) spectrum, the oily amine (11) shows a 1H double triplet (J=12.0 and 3.5 Hz) due to the C_2-proton at δ 3.17 and a 1H doublet (J=3.5 Hz) due to the C_1-proton at δ 3.61, respectively. The J value (3.5 Hz) of the coupling constant between the C_1- and the C_2- protons demonstrates the *cis*-configuration of the resulting amine (11), because those of the related *cis*- (12) and *trans*- (13) amines[1b] were observed as 3.4 Hz in the former (12) and 9.6 Hz in the latter (13).

A solution of the amine (11) in chloroform was treated with freshly prepared chloral[5b,12] to give the *cis*-formamide[10] (14), colorless prisms, mp 148-150°C[13] (benzene-hexane), in 88.1% yield. Dehydrogenation of the *cis*-formamide (14) with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) in benzene provided the aromatized formamide[10] (15), colorless prisms, mp 181-183°C ($CHCl_3$-MeOH), in 87.1% yield. When treated with conc. sulfuric acid in acetic acid or with boron trichloride in methylene chloride, the isopropoxy group of the aromatized formamide (15) was selectively cleaved under a moderate condition to give the phenolic formamide[10] (16), colorless prisms, mp 209-210°C (MeOH-Et_2O), in 80.7% or in 56.2% yield, respectively.

The Bischler-Napieralski reaction of the resulting phenolic formamide (16) with phosphorus oxychloride in acetonitrile gave fagaronine (1) chloride as yellow needles, mp 276°C (193-195°C[14]) (MeOH-AcOEt) [lit. mp 255°C (202°C[14])[2a]; mp 260-261°C (198-200°C[14])[4a]] [IR ν_{max}^{KBr} cm^{-1}: 3375 (OH), PMR (CF_3CO_2H) δ: 4.22 (6H, s, OMe × 2), 4.33 (3H, s, OMe), 5.07 (3H, s, N^+Me), 7.69, 7.73, 8.10, and 8.19 (each 1H, s, arom. H), 8.16 (1H, d, J=9.0 Hz, C_{12}-H), 8.52 (1H, d, J=9.0 Hz, C_{11}-H), 9.38 (1H, s, C_6-H)], in 87.1% yield. This material (1) was characterized as dihydrofagaronine (17), colorless prisms, mp 196-200°C ($CHCl_3$-MeOH) [IR ν_{max}^{Nujol} cm^{-1}: 3400 (OH), PMR ($CDCl_3$) δ: 2.61 (3H, s, NMe), 3.92, 3.97, and 4.03 (each 3H, s, OMe), 4.13 (2H, s, C_6-H_2), 6.02 (1H, br s, OH), 6.77 and 7.62 (each 1H, s, C_7- and C_4-H), 7.22 and 7.29 (each 1H, s, arom. H), 7.44 and 7.68 (each 1H, d, J=8.5 Hz, C_{12}- and C_{11}-H)], which was easily obtained in 67.8% yield by treatment with sodium borohydride. The synthetic fagaronine (1) was completely identical with an authentic sample of naturally occurring fagaronine,[2a] a gift from Prof. N. R. Farnsworth and Dr. J. M. Pezzuto, University of Illinois at Chicago.

Finally, it should be added here that Stermitz *et al.*[4] synthesized fagaronine (1) from 2,3-dihydroxynaphthalene as a starting material in 5.2% overall yield, while our synthetic sequence provided it in 15.1% overall yield based on the starting isovanillin.

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9) S. Sugasawa and K. Kakemi, Yakugaku Zasshi, 55, 1283 (1935). We prepared isopropylisovanillin by treating a suspension of isovanillin, isopropyl bromide, and potassium carbonate in dimethylformamide in 88.0% yield.

10) This compound gave satisfactory elemental analysis and the structure was supported by spectral data (PMR and IR).

11) An aqueous solution of $PdCl_2$ and a corresponding amount of Norit for preparation of 10% Pd/C were added to a solution of the keto-acid (5) in AcOH. Then, the suspension[6] was hydrogenated.

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13) This compound has two melting points (mp 181-183°C and mp 148-150°C) due to dimorphism.

14) This material melted at this temperature at once followed by resolidification, then melted again.

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