Practical Preparation of Coralyne Chloride

KWANG YUEN ZEE-CHENG and C. C. CHENG▲

Abstract □ Coralyne chloride was prepared by a convenient process which can be adapted to large-scale synthesis of this antileukemic alkaloid.

Keyphrases □ Coralyne chloride—procedure adaptable for large-scale synthesis □ Antileukemic alkaloids—process for the large-scale synthesis of coralyne chloride

Although berbinium salts and related compounds have been known for a long time, studies on their cytotoxic effects and neoplasm inhibitory action have only been reported during the last decade (1, 2). Among the berbinium salts, coralyne chloride (I, 5,6,7,8,-13,13a - hexadehydro - 8 - methyl - 2,3,10,11 - tetramethoxyberbinium chloride or 8-methyl-2,3,10,11-tetramethoxydibenzo[*a*,*g*]quinolizinium chloride), was found to possess antileukemic activity against both the P-388 and L-1210 strains[1].

In connection with the search for a practical, large-scale synthesis of this alkaloid, existing methods for the synthesis of coralyne and related compounds (3–25) were examined and modified, and a convenient preparation of coralyne chloride has now been realized. This compound can be prepared in five steps from commercially available materials in 56% overall yield. Certain intermediates and the final product were also properly characterized.

DISCUSSION

Condensation of β-(3,4-dimethoxyphenyl)ethylamine (homoveratrylamine) (5) with (3,4-dimethoxyphenyl)acetyl chloride (prepared by the treatment of homoveratric acid with thionyl chloride) in base gave 95% yield of *N*-(3,4-dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)acetamide (II), m.p. 123–125°. Cyclization of II to 1 - (3,4 - dimethoxybenzyl) - 6,7 - dimethoxy - 3,4 - dihydroisoquinoline (III) was smoothly carried out in 87% yield with phosphorus pentachloride in chloroform. This method was preferred rather than the conventional phosphorus oxychloride condensation since the yield was higher and the desired product was more readily isolated and purified. Aromatization of III with 10% palladium-on-charcoal in tetralin readily afforded 1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (IV, papaverine) in 82% yield. This was cyclized in 83% yield in a mixture of sulfuric acid and acetic anhydride to form the sulfoacetate of coralyne (V). The latter was quantitatively converted into coralyne chloride (I) by means of sodium chloride (Scheme I).

EXPERIMENTAL

N-(3,4-Dimethoxyphenethyl)-2 - (3,4 - dimethoxyphenyl)acetamide (II)—To a stirred solution of 39.2 g. (0.20 mole) of homoveratric acid [(3,4-dimethoxyphenyl)acetic acid] (5, 26) in 250 ml. of dry chloroform (molecular sieve 4A) was added dropwise, with ice cooling, 72 g. (0.61 mole) of thionyl chloride. The reaction mixture was heated between 45 and 50° on a water bath for 2 hr., after which it was allowed to stand overnight at room temperature. The solvent and excess thionyl chloride were removed under reduced pressure at <50°. The resulting residue (about 44 g. of the acid chloride) was dissolved in 600 ml. of anhydrous ether. The solution was then added dropwise, under nitrogen with ice cooling, to a stirring mixture of 44 g. (0.24 mole) of homoveratrylamine [β-(3,4-dimethoxyphenyl)ethylamine] (5) in 900 ml. of aqueous 1 *N* KOH and 200 ml. of ether. The addition took approximately 20 min. The reaction mixture was stirred continuously in an ice bath for 3 hr. The resulting solid was collected by filtration and washed thoroughly with 3 × 100 ml. of water. It was dried *in vacuo* to give 69.2 g. (95% yield) of II, m.p. 122–124°, sufficiently pure for use in the next step. Recrystallization of 1.5 g. of the crude product from a mixture of 20 ml. of ethanol and 40 ml. of water gave 1.2 g. of analytically pure product, m.p. 123–125° [lit. (5) m.p. 124°]; $\lambda_{max.}^{EtOH}$: 233 (log ε 4.16) and 277 nm. (log ε 4.08).

Anal.—Calc. for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.02; N, 3.90. Found: C, 67.02; H, 7.02; N, 3.86.

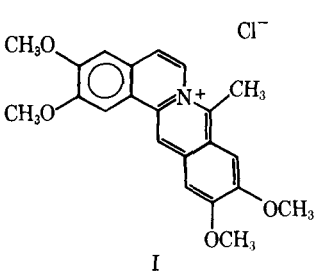
1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy - 3,4 - dihydroisoquinoline (III)—A solution of 44 g. (0.122 mole) of II in 320 ml. of dry chloroform was slowly added (about 15 min.), under nitrogen with ice cooling, to a stirred suspension of 52 g. (0.25 mole) of phosphorus pentachloride in 150 ml. of dry chloroform. After the addition was complete, the mixture was stirred in an ice bath for 2 hr., yielding a light-brown solution. It was allowed to stir continuously at room temperature for 2 days under nitrogen while protected from moisture. The hydrochloride salt of the product started to precipitate after several hours. The mixture was then diluted with 800 ml. of anhydrous ether, and the salt was collected by filtration. It was washed with 2 × 300 ml. of ether and dried *in vacuo* to give 60 g. of crude product.

One-half of this amount (30 g.) was dissolved in 300 ml. of chloroform and filtered into 1200 ml. of ether while stirring in an ice bath. The white hydrochloride salt of the dihydroisoquinoline was collected by filtration, washed with 2 × 80 ml. of ether, and dried to give 20 g. (87% yield) of the purified hydrochloride salt of III, m.p. 178–180°; $\lambda_{max.}^{EtOH}$: 236 (log ε 4.26), 306 (log ε 3.98), and 360 nm. (log ε 3.94).

Anal.—Calc. for $C_{20}H_{23}NO_4 \cdot HCl$: C, 63.57; H, 6.40; N, 3.71. Found: C, 63.22; H, 6.57; N, 3.67.

The remaining half (30 g.) of the crude product was suspended in 400 ml. of ice water. The pH of the mixture was adjusted to 8 with 100 ml. of 25% aqueous ammonia, and the mixture was extracted with 5 × 350 ml. of chloroform. The extract was washed with 4 × 150 ml. of water and dried (potassium carbonate). Chloroform was then removed *in vacuo* to yield 18 g. of the free base, III, m.p. 100–110° [lit. (5) m.p. 105°]. This was used for the following dehydrogenation process without further purification. Since the free base is readily oxidizable to an aminoketone, exposure of the free base in air should be avoided as much as possible. The product should be stored under nitrogen or another inert atmosphere.

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline (IV)—Under a stream of dry nitrogen, a stirred mixture of 18 g. (0.053 mole) of the aforementioned free base III and 4 g. of 10% palladium-on-charcoal in 60 ml. of freshly distilled tetralin was heated in an oil bath at 220–230° for 3 hr. (The reaction flask was fitted with an air



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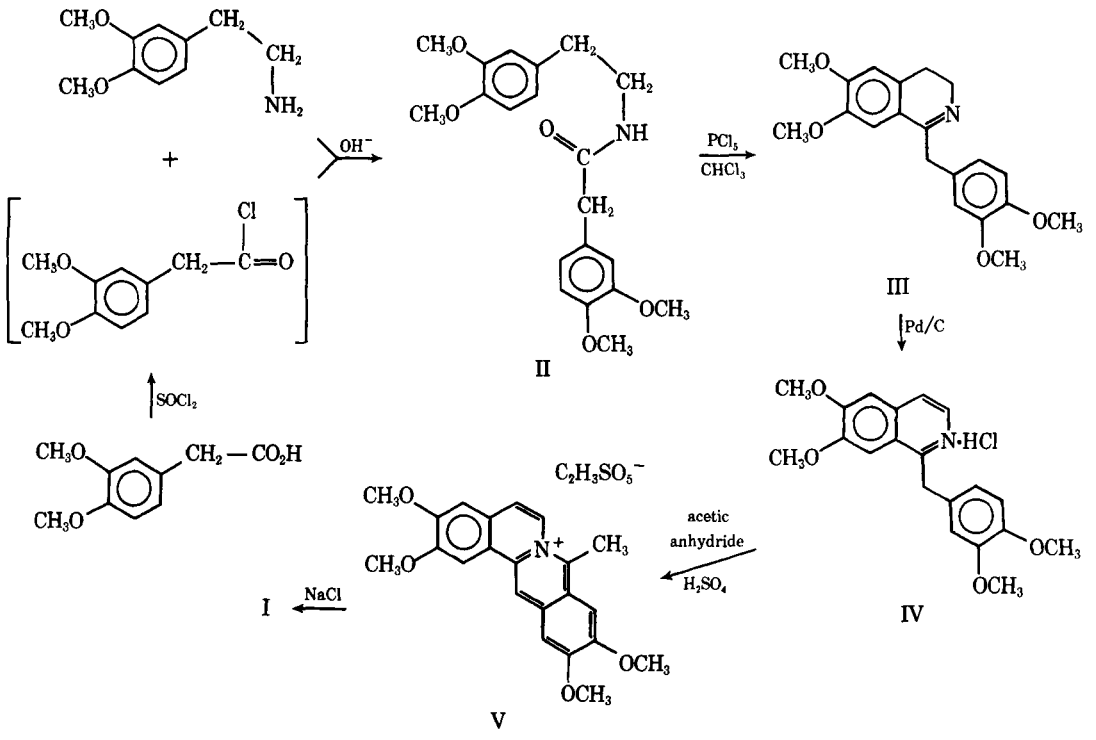
[1] Dr. Harry B. Wood, Jr., personal communication.



Scheme I

condenser, and the latter was connected to a drying tube.) The reaction mixture was cooled to approximately 160–180°, and the catalyst was separated by filtration under nitrogen. The original reaction flask and the catalyst were rinsed and washed with 2 × 25 ml. of ethanol, and the washings were combined with the cooled filtrate. With cooling and stirring, the mixture was acidified to pH 1 with 40 ml. of 20% ethanolic hydrogen chloride. The resulting dark-brown mixture was filtered, and the filtrate was quickly added to 1200 ml. of ether with stirring. The precipitated salt of the isoquinoline was collected by filtration, washed with 2 × 100 ml. of anhydrous ether, and dried to give 16.3 g. (82% yield) of the hydrochloride salt of IV, m.p. 222–224° dec. [lit. (5) m.p. 231°; lit. (27) m.p. 225–226°]; $\lambda_{max.}^{EtOH}$: 239 (log ε 4.68), 280 (log ε 3.86), 311 (log ε 3.81), and 326 nm. (log ε 3.81); λ_{sh}^{EtOH}: 252 nm. (log ε 4.49).

Coralyne Sulfoacetate (V)—To 36 ml. of acetic anhydride was added dropwise, with stirring, 7.2 ml. of concentrated sulfuric acid. The mixture was heated at 80–90° until a red-wine color was noted (about 10 min.). To this was added 9 g. of IV. The resulting dark-brown solution was heated at 85–90° on a water bath until solids started to appear (about 30 min.). The mixture was then cooled and to it was slowly added, with stirring, 150 ml. of methanol. Stirring was continued for 20 min. following the addition. The mixture was chilled in an ice bath for 30 min. and the solid product was collected by filtration. The product was washed with 2 × 20 ml. of methanol and 2 × 50 ml. of ether and dried to give 9.1 g. (76% yield) of bright-yellow crystals, m.p. 278–280°. An additional 1 g. was isolated from the mother liquor after standing to raise the total yield to 83%. An analytical sample was prepared by recrystallization from methanol, m.p. 278–280° [lit. (4) m.p. 277°]; $\lambda_{max.}^{EtOH}$: 220 (log ε 4.39), 233 (log ε 4.37), 243 (log ε 4.32), 286 (log ε 4.59), 300 (log ε 4.74), 310 (log ε 4.78), 326 (log ε 4.66), 361 (log ε 3.94), 405 (log ε 4.17), and 425 nm. (log ε 4.29); IR: 1735 cm.$^{-1}$ (acetate carbonyl); NMR (CF_3CO_2H): τ 1.62 (1s, H_1), 2.30 (1s, H_4), 2.00 (1d, H_5), 1.20 (1d, H_6), 6.53 (3s, CH_3), 2.14 (1s, H_9), 2.40 (1s, H_{12}), 0.63 (1s, H_{13}), and 5.71 and 5.80 (6d, OCH_3); J H_5,H_6 = 8 Hz.; *m/e* 363 (M^+—$C_2H_4SO_5$).

Anal.—Calc. for $C_{24}H_{25}NO_9S$: C, 57.25; H, 5.00; N, 2.78. Found: C, 57.52; H, 4.82; N, 2.98.

Coralyne Chloride (I)—To a stirred yellow solution of 3 g. of V in 250 ml. of water was added 300 ml. of 10% sodium chloride. Fine, yellow crystals of the chloride I gradually separated from the stirring mixture. After 2 hr. of stirring and cooling, the product was collected by filtration and washed with 2 × 10 ml. of dilute salt solution followed by 2 × 50 ml. of ether. After drying at 100° *in vacuo*, 2.5 g. (approximately 100% yield) of I was obtained, m.p. 248–250° dec. (At about 240°, the color of the solid changed from yellow to red.) An analytical sample was prepared by either: (*a*) dissolving 0.1 g. of the product in 100 ml. of water and reprecipitating it with 5 ml. of 15% hydrochloric acid, or (*b*) recrystallization of 0.1 g. of product from 80 ml. of ethanol, m.p. 250–252°. The IR of this compound did not show the acetate carbonyl peak at 1735 cm.$^{-1}$; $\lambda_{max.}^{EtOH}$: 234 (log ε 4.36), 241 (log ε 4.32), 284 (log ε 4.46), 300 (log ε 4.72), 310 (log ε 4.77), 325 (log ε 4.66), 360 (log ε 3.84), 405 (log ε 4.17), and 425 nm. (log ε 4.28).

Anal.—Calc. for $C_{22}H_{22}ClNO_4 \cdot {}^1/_2H_2O$: C, 64.62; H, 5.70; N, 3.43. Found: C, 64.35; H, 5.57; N, 3.25.

The melting-point, IR, UV, and NMR characteristics of this compound were found to be identical with those of the plant product provided by the National Cancer Institute.

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▲ To whom inquiries should be directed.

Synthesis of Acyl Dihydroxyacetone Phosphates and Related Derivatives

CLAUDE PIANTADOSI*▲, KUN CHAE*, KHALID S. ISHAQ*, and FRED SNYDER†

Abstract □ The chemical syntheses of 1-*O*-palmitoyl- and 1-*O*-acetyl-2,2-dimethoxypropane-3-phosphate cyclohexylammonium salt and 1-*O*-palmitoyl-2,2-dimethoxypropane-3-*O*-phosphorylethanolamine are reported. The acyl dihydroxyacetone phosphates can serve as intermediates in the pathway for the biosynthesis of phosphatidic acid, phosphatidylcholine, phosphatidylethanolamine, and alkyl glycerolipids.

Keyphrases □ Acyl dihydroxyacetone phosphates and related derivatives—synthesis for use as biosynthesis intermediates □ Dihydroxyacetone phosphates (acyl) and related derivatives—synthesis for use as biosynthesis intermediates

Studies directed toward the chemical synthesis of *O*-alkyl dihydroxyacetone and its derivatives were reported by Piantadosi *et al.* (1, 2). In a series of papers, Snyder *et al.* (3–6) and Wykle and Snyder (7, 8) reported studies on a sequence of reactions involved in the biosynthetic pathway for *O*-alkyl glycerolipids in which dihydroxyacetone phosphate was an obligatory precursor. Other investigators (9, 10) also demonstrated the presence of the *O*-alkyl ether-synthesizing enzymes in other systems. In 1970, Snyder *et al.* (4) isolated and described a microsomal enzymic system from Ehrlich ascites cells which, in the cell-free system, is capable of synthesizing *O*-alk-1-enyl glycerolipids (plasmalogens).

DISCUSSION

In a continuation of this research, we now report on synthetic studies involving the acyl analog, which is an important intermediate in the biosynthetic scheme. Acyl dihydroxyacetone phosphate was characterized by Hajra and Agranoff (11) and found to occur in guinea pig liver. It is formed (12) enzymatically by acylation of dihydroxyacetone phosphate in the presence of acyl CoA, ATP, and Mg^{+2} as cofactors. This keto intermediate can then be reduced in mitochondria by NADPH (13) and further acylated to form phosphatidic acid. Agranoff and Hajra (14) also reported on the participation of the acyl dihydroxyacetone phosphate pathway in mouse liver and Ehrlich ascites tumor cells, and they suggested that this pathway plays an important role in these cells. Furthermore, Hajra (9) and Wykle *et al.* (15) found that acyl dihydroxyacetone serves as a precursor of *O*-alkyl glycerolipids.

In this paper, we describe the complete chemical synthesis of acyl dihydroxyacetone phosphates which is based on an earlier procedure (2) used for the synthesis of 1-*O*-alkyl dihydroxyacetone derivatives. The cyclohexylammonium salts of 1-*O*-palmitoyl-2,2-dimethoxypropane-3-phosphate (VIII, Scheme I), 1-*O*-acetyl-2,2-dimethoxypropane-3-phosphate (XII, Scheme II), and 1-*O*-palmitoyl-2,2-dimethoxypropane-3-phosphorylethanolamine (XVI, Scheme III) were prepared. In the synthesis of palmitoyl derivatives (VIII and XVI), 3-*O*-benzylglycerol (Compound I) was used as the starting material. Compound I was acylated with palmitoyl chloride in the presence of pyridine at −20°, resulting in a crude mixture of II which contained over 70% of the monopalmitoyl derivative as determined by TLC. The Compound II mixture was then subjected to the Pfitzner–Moffatt (16) oxidation to III in a solution of dicyclohexylcarbodiimide–dimethyl sulfoxide, containing a proton source such as pyridinium phosphate or pyridinium trifluoroacetate, in a manner similar to that described by Hartman (17) for the synthesis of 3-haloacetol phosphates. In this oxidation reaction, dimethyl sulfoxide is converted into a labile intermediate which facilitates the attack at the sulfur atom by the β-hydroxy group of benzylglycerol. Trifluoroacetic acid was used to initiate the reaction, while dicyclohexylcarbodiimide was used as a polarizing agent (2).

The keto compound, III, was ketalized to IV, which was debenzylated with palladium black to V. Compound V was phosphorylated with diphenyl chlorophosphate to VI and then treated with platinum oxide to remove the phenyl groups resulting in VII. Compound VII was subsequently treated with cyclohexylamine and isolated as the salt, VIII.

Compound V was also phosphorylated with phenyl phosphorodichloridate (Scheme III) to XIII, which was then reacted with carbobenzoxyethanolamine, resulting in XV. The protecting groups were removed by hydrogenation with platinum oxide and palladium black at room temperature to XVI. The acetyl derivative (IX),