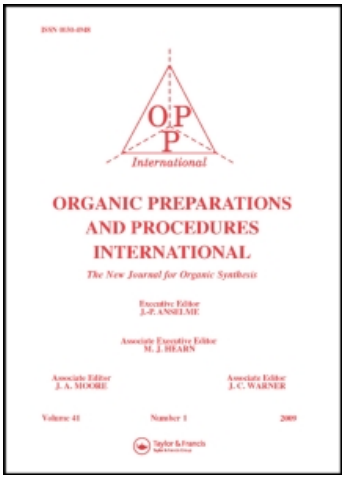

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SYNTHESIS OF (±)-NORCORALYDINE AND (±)-TETRAHYDROPALMATINE

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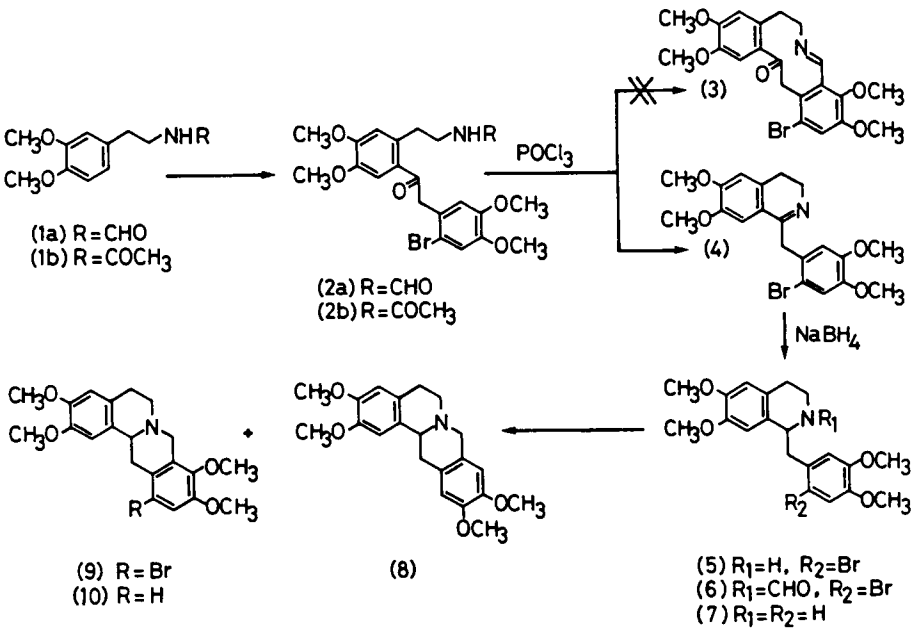
Recently, the facile two-step generation of 3,4-dihydroisoquinoline ring system via the Friedel-Crafts acylation of N-acetylhomoveratrylamine (1b) has been reported.[1] The present paper describes the results of the Friedel-Crafts acylation reaction of N-formylhomoveratrylamine (1a), and further elaboration of the 2-acylated product 2a leading to the titled isoquinoline alkaloids 8 and 10.



As described for the Friedel-Crafts acylation of N-acetylhomoveratrylamine (1b), formamide 1a was warmed with 2-bromo-4,5-dimethoxyphenylacetyl chloride (3 mol) in the presence of aluminium chloride (2 mol) in nitrobenzene at 35° for 2 hr. After steam distillation to remove nitrobenzene from the reaction mixture, the deoxybenzoin 2a was isolated in good yield (87%). In the hope that the Bischler-Napieralski reaction might convert 2a to the dibenz[c,g]azecine ring system, characteristic of the protopine alkaloid, 2a was then treated with phosphorus oxychloride. However, the reaction did not give any 10-membered ring imino compound such as 3, but resulted in the quantitative formation (97%) of the dihydroisoquinoline 4, which could be also obtained by acid-catalyzed hydrolysis of 2a. Sodium borohydride reduction of 4 in the usual manner gave the tetrahydroisoquinoline 5 (95%). When 5 was heated with formalin-hydrochloric acid, the Mannich type ring closure accompanied with the displacement of bromine atom proceeded smoothly to give (±)-norcoralydine (8) as a single product; this alkaloid had been prepared on treatment of tetrahydropapaverine (7) under Mannich conditions, by several groups since 1916.[2-6]

The Bischler-Napieralski cyclization of the formamide 6, derived from 5, was also examined. Treatment of 6 with phosphorus oxychloride in boiling toluene gave the iminium salt which was then treated with sodium borohydride. Separation of the crude products by preparative TLC furnished the aforementioned alkaloid 8 and (±)-12-bromotetrahydropalmatine[7,8] (9) in a molar ratio of 3.8:1 in 92% yield. The formation of 9 clearly shows that the cyclization occurred at the C_6 position of 6 by the fact that the C_2 is blocked with bromine atom and this is similar to the observation of Tani et al. in the use of the 2-bromo-4,5-methylenedioxybenzyl derivative.[9] In view of the previous conversion of bromide 9 to (±)-tetrahydropalmatine 10,[8] our results constitute also a formal synthesis of the alkaloid 10.

EXPERIMENTAL SECTION

Mps, determined on a Laboratory Devices MEL-TEMP, and bps. are uncorrected. IR spectra were recorded on a Hitachi Perkin-Elmer Model 125 spectrophotometer. ^{1}H NMR spectra were run in $CDCl_3$ solution with Me_4Si as an internal standard (δ=0 ppm) and resistered on a 90 M Hz Hitachi R-22 spectrometer. Preparative thin layer chromatography (TLC) was run on Merck silica gel PF-254 (No.7749).

N-β-[2-(2-bromo-4,5-dimethoxyphenylacetyl)-4,5-dimethoxyphenethyl]formamide (2a).- To a stirred solution of N-β-(3,4-dimethoxyphenethyl)formamide 1a (1.52 g, 7.27 mmol) and 2-bromo-4,5-dimethoxyphenylacetyl chloride (6.40 g, 21.9 mmol)[10] in nitrobenzene (20 ml) in a flask fitted with a cotton wool tube in an ice-water bath was added freshly powdered $AlCl_3$ (1.93 g, 14.05 mmol). The mixture was warmed in an oil bath at 35±1° for 2.5 hr, then poured into ice-water (100 ml), and subjected to steam distillation in order to remove nitrobenzene. The residue was cooled and extracted with methylene chloride (20 ml × 3). The extracts were washed with 0.5N NaOH (30 ml × 2) and water (30 ml), dried over anhydrous Na_2SO_4, and evaporated to dryness. Crystallization of the crude product from benzene-ether gave 2a (2.92 g, 86%), mp. 130-132°. Recrystallization from the same solvents afforded an analytical sample, mp. 133°. IR (nujol): 3310, 1660, 1600 cm^{-1}; ^{1}H NMR: δ 3.02 (2H, t, J = 7Hz, CH_2CH_2N), 3.53, 3.60 (each 1H, t, J = 7Hz, CH_2N), 3.87, 3.89 (each 3H, s, 2 OCH_3), 3.96 (6H, s, 2 OCH_3), 4.35 (2H, s, CH_2CO), 6.70 (1H, br s, NH), 6.85, 6.86, 7.12, 7.40 (each 1H, s, aromatic Hs), 8.14 (1H, s, CHO).

Anal. Calcd for $C_{23}H_{28}O_6NBr$: C, 54.09; H, 5.19; Br, 17.13; N, 3.00

Found: C, 54.13; H, 5.38; Br, 17.32; N, 2.96

Reaction of 2a with Phosphorus Oxychloride.- A mixture of 2a (160 mg, 0.32 mmol) and phosphorus oxychloride (153 mg, 1.00 mmol) in dry benzene (2 ml) was refluxed under an atmosphere of nitrogen for 2 hr. After cooling, the mixture was poured into ice-water, basified with 2N NaOH, and extracted

with methylene chloride (10 ml × 2). The extracts were washed with water, dried over anhydrous Na_2SO_4, and evaporated to leave an oil (140 mg, 97%). The hydrochloride was crystallized from chloroform-ether and melted at 224-225°, lit.[1] mp. 224-225°, lit.[11] the oxalate mp. 192-193°. IR and ^1H NMR spectra were identical in all respects with those of an authentic sample of 1-(2-bromo-4,5-dimethoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline hydro chloride 4, derived from N-β-[2-(2-bromo-4,5-dimethoxyphenylacetyl)-4,5-dimethoxyphenethyl]acetamide[1] 2b or N-β-(3,4-dimethoxyphenethyl)-2-bromo-4,5-dimethoxyphenylacetamide.[4,11]

Hydrolysis of 2a.- A mixture of 2a (150 mg), 1N HCl (3 ml) and ethanol (4 ml) was refluxed with stirring for 18 hr, and then the solvent was evaporated. The residue was crystallized twice from chloroform-ether to give the hydrochloride 4 (140 mg, 92%), mp. 224-225°.

(±)-Norcoralydine (8) and (±)-12-Bromotetrahydropalmatine (9).- Compound 4 (840 mg, 2 mmol) in methanol (20 ml) was treated with $NaBH_4$ (38 mg, 1 mmol) at room temperature for 1 hr. After evaporation of the solvent, the residue was diluted with water (20 ml) and extracted with methylene chloride (20 ml × 2). The methylene chloride layer was dried and evaporated to leave the crude amine 5 (804 mg), whose ^1H NMR spectrum displayed peaks at δ 2.5-4.5 (7H, m, CH and CH_2), 3.83, 3.86 (each 3H, s, 2 OCH_3), 6.66, 6.72, 6.87, 7.13 (each 1H, s, aromatic Hs). This oil was heated with formic acid (98-100%, 200 mg, 4.36 mmol) at 150° in an oil bath for 5 hr. To the cooled mixture, water (20 ml) and methylene chloride (15 ml × 2) were added. The extracts were washed with 0.5N NaOH (10 ml) and water (20 ml) and then dried over anhydrous Na_2SO_4. Evaporation of the solvent left the oily formamide 6 (728 mg). A solution of this amide (600 mg, 1.3 mmol) and phosphorus oxychloride (612 mg, 4 mmol) in dry benzene (5 ml) was heated to reflux under nitrogen or 2 hr. The mixture was

evaporated to leave an oily residue, which was dissolved in methanol (15 ml). To this, $NaBH_4$ (51 mg, 1.33 mmol) was added portionwise. After the mixture was stirred at room temperature for 2 hr, the methanol was evaporated. Water (20 ml) and methylene chloride (15 ml × 2) were added. The methylene chloride extracts were washed with water, dried and evaporated to leave an oil (500 mg), which was separated by preparative TLC on silica gel developing with 3% methanol-methylene chloride. The mobile fraction (Rf. 0.6) was crystallized from MeOH to give white crystals (110 mg, 19%), mp. 160-162°, Lit.[7] mp. 162°, Lit.[8] mp. 161-162°, whose IR and 1H NMR spectra were identical with those of 12-bromotetrahydropalmatine 9.[8] The less mobile fraction (Rf. 0.4) was crystallized from chloroform-ether to gave (±)-norcoralydine (xylopine) 8 (340 mg, 73 %), mp. 156-158°, lit.[2,12] mp. 157-158°, lit.[3] mp. 151.5-152.5°, lit.[4] mp. 158-159°. The melting point was undepressed on admixture with an authentic sample prepared from (±)-tetrahydropapaverine hydrochloride 7 according to Craig and Tarbell's method.[4] The IR and NMR spectra [IR ($CHCl_3$): 2800-2700 cm^{-1} (trans-quinolizideine structure), 1606 cm^{-1}; ^1H NMR: δ 2.4-4.6 (9H, m, CH and CH_2), 3.86, 3.88 (9H, 3H, each s, four OCH_3), 6.62, 6.65, 6.70, 6.78 (each 1H, s, aromatic Hs)] were also superimposable on those of an authentic sample.

Reaction of 5 with Formaldehyde.- A mixture of 5 (420 mg, 1 mmol), 37% HCHO (1 ml), H_2O (4 ml) and conc. HCl (0.5 ml) was heated to reflux for 1 hr. The cooled reaction mixture was diluted with H_2O (20 ml), basified with 5% Na_2CO_3 solution, and extracted with methylene chloride (15 ml × 2). Drying over anhydrous Na_2SO_4 followed by evaporation of the solvent left an oil, which did not show even a trace of the compound 9 on the TLC plate. Purification and crystallization in the same manner as noted above afforded 8 (300 mg, 87%), mp. 156-158°.

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