Synthesis of the Novel Isoquinoline Enamide Alkaloid Polycarpine

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The synthesis of the novel enamide isoquinoline alkaloid polycarpine, (*Z*)-1-(2′-hydroxy-3′,4′-dimethoxybenzylidene)-3,4-dihydro-6,7-dimethoxy-2-(1H)isoquinolinecarboxaldehyde, proceeding from commercially available 2′,3′,4′-trimethoxyacetophenone in seven steps is described. The *O*-methyl and *O*-benzyl derivatives were also obtained.

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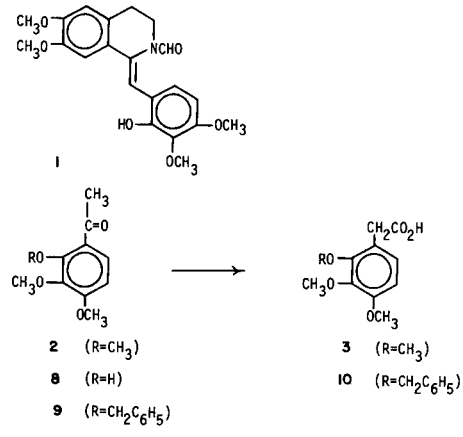
The family of alkaloids derived from benzylisoquinoline is very large and has been growing each year as isolation and identification techniques have improved (1). One of the potential types which has hitherto not been found is that of the enamides which could be readily formed by acylation of an intermediate 1-benzyl-3,4-dihydroisoquinoline. The enamide functionality has been used in the benzylisoquinoline series as a starting point for the synthesis of a wide variety of alkaloids and alkaloid analogs (2). Thus, it was particularly gratifying when Cavé and Leboeuf reported the occurrence of the novel isoquinoline enamide alkaloid polycarpine **1** in the bark of the tree *Enantia polycarpa* Engl. et Diels which is found in the dense rain forests of the Ivory Coast (3). Although this type of enamide system was originally synthesized by Baxter and Swan (4) and subsequently used by Lenz for the photochemical synthesis of protoberberine alkaloids (5), the occurrence of the free phenolic hydroxyl group in polycarpine made this an intriguing molecule, especially considering the sensitivity of the enamide functionality to hydrolysis by weak acids (6). Because of this and the reported biological activity of the plant extracts (3), we were interested in devising an efficient synthesis of polycarpine from commercially available materials. After this work was completed a report appeared by Shamma on a biogenetically patterned synthesis of polycarpine using peracid oxidation of the naturally occurring protoberberine alkaloid palmatine (7).

The synthesis of the alkaloid was dependent on finding an efficient method for the preparation of the appropriately substituted phenylacetic acid. The method selected was recently reported rearrangement of acetophenones using thallium trinitrate supported on Montmorillinite clay (8); a reagent which is superior to thallium trinitrate in methanol (9). As a model compound, we selected 2′,3′,4′-trimethoxyacetophenone **2** which would eventually lead to *O*-methylpolycarpine **7**. Although the rearrangement of the acetophenone **2** was very slow at 0°, it was very fast at room temperature. Subsequent saponification of the non-isolated ester yielded 2′,3′,4′-trimethoxyphenylacetic acid **3** in 73% yield (10). Thermal condensation in refluxing xylene (5) of the acid **3** with β-(3,4-dimethoxyphenyl)-ethylamine formed the amide **4** in 96% yield. Cyclization of amide **4** with polyphosphoric ester (11) in refluxing ether gave the dihydroisoquinoline **5** (12) in 92% yield. The free base **5** was very reactive towards oxygen and even in the solid state rapidly formed the benzoyl compound **6**. The nitrogen in **5** was formylated, with the concomitant double bond shift, using mixed formic-acetic anhydride (13) to form *O*-methylpolycarpine **7** in 90% yield.



1

2 (R=CH_3)

8 (R=H)

9 (R=$CH_2C_6H_5$)

3 (R=CH_3)

10 (R=$CH_2C_6H_5$)

The *Z*-configuration of *O*-methylpolycarpine **7** was assigned because of a uv maximum at 326 nm and the absence of any shielded methoxyl group hydrogens in the nmr spectrum (5).

The synthesis of polycarpine **1** also started from acetophenone **2**. Selective demethylation of the *ortho*-methoxyl group in **2** was achieved using boron trichloride (14) in methylene chloride at ice bath temperature to yield **8** in 88% yield (15). *O*-Benzylation of **8** proceeded uneventfully using potassium carbonate and benzyl bromide in acetone to obtain **9** (16). Supported thallium trinitrate rearrangement and subsequent saponification yielded the phenylacetic acid derivative **10** in 48% yield. Thermal condensation with β-(3,4-dimethoxyphenyl)ethylamine in refluxing xylene yielded, in 94% yield, the amide **11**. The dihydroisoquinoline **12** was formed with phosphorus oxychloride in refluxing toluene (17). The dihydroisoquinoline was not characterized but was immediately condensed with mixed formic-acetic anhydride to obtain *O*-benzylpolycarpine **13** in 83% yield based on starting amide. In order to remove the protecting benzyl group under the mildest possible

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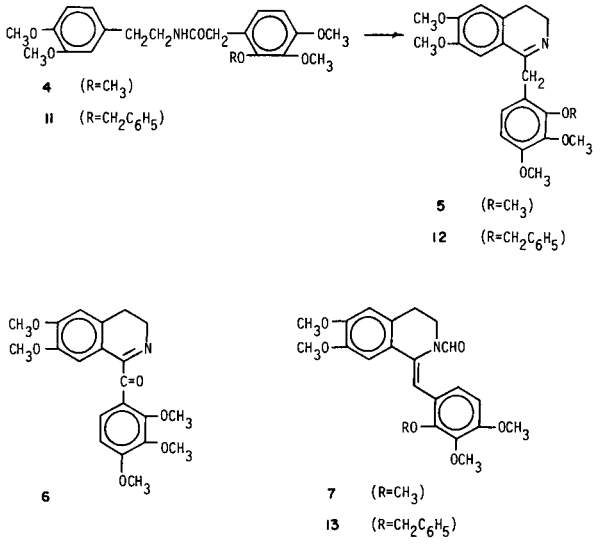
hydrogenation conditions, palladium on strontium and barium catalysts were tried but to no avail. Cleavage of the protecting group in **13** was accomplished using hydrogen and palladium on calcium carbonate to yield polycarpine **1** in 76% yield after recrystallization from methanol. The polycarpine thus obtained was identical with an authentic sample of **1** kindly provided by Professor Leboeuf.



EXPERIMENTAL

General.

Melting points were taken on a Thomas-Hoover Unimelt capillary apparatus and are uncorrected. Infrared spectra were recorded in potassium bromide pellets, and ultraviolet and visible spectra were run in methanol unless otherwise noted. A Varian Associates A-60 or EM-390 nmr spectrometer was used and the spectra were run in deuterochloroform using tetramethylsilane as an internal standard. The nmr data are given by the chemical shift, followed by the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; followed by the coupling constant in Hertz, where appropriate, and the integrated signal intensity. Microanalyses were determined by Searle Laboratories Microanalytical Department under the supervision of Mr. E. Zielinski. Glc analyses were run on a Perkin-Elmer 900 gas chromatograph.

2,3,4-Trimethoxyphenylacetic Acid (**3**).

To a solution of 5.325 g. (25.32 mmoles) of 2,3,4-trimethoxyacetophenone **2** (Aldrich) in 200 ml. of methylene chloride at 0°, was added 44.12 g. (29.1 mmoles) of thallium trinitrate on K-10 reagent (8). At ice bath temperature the rearrangement is extremely slow but is very rapid upon warming to room temperature. The reaction was judged over when a potassium iodide-starch test was negative. The solid was filtered using Celite and the filter cake subsequently was washed with additional methylene chloride. The combined filtrates were washed with dilute potassium carbonate and dried over sodium sulfate. The solvent was evaporated to yield a yellow oil which was taken up in 80 ml. of methanol. After the addition of 3 g. of sodium methoxide and 20 ml. of water, the solution was allowed to stand overnight. After acidification and dilution with water the solution was extracted three times with chloroform. After drying with sodium sulfate, the chloroform was evaporated to yield an oil which rapidly crystallized to yield 4.15 g. (73%) of 2,3,4-trimethoxyphenylacetic acid (**3**) (10), m.p. 101-102° (ether-petroleum ether); ir: 1722 cm^{-1}, 1705; nmr: δ 6.85 (d, J = 9 Hz, 1H), 6.60 (d, J = 9 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H); the methylene group lies under the methoxyl resonances.

N-3,4-Dimethoxyphenylethyl-2,3,4-trimethoxyphenylacetamide (**4**).

A mixture of 5.0 g. (22.1 mmoles) of 2,3,4-trimethoxyphenylacetic acid **3** (10) and 4.01 g. (22.1 mmoles) of 3,4-dimethoxyphenylethylamine in 150 ml. of xylene were refluxed under nitrogen overnight. Water was separated using a Dean-Stark trap. After cooling, the solvent was evaporated to yield a white solid which was recrystallized from water to yield the amide **4**, 8.3 g., 21.3 mmoles (96%), m.p. 95-96° (methanol-water); ir: 3285 cm^{-1}, 1650, 1605, 1595, 1520; nmr: δ 6.5-6.9 (m, 5H), 5.73 (1H, NH), 3.84, 3.82, 3.81 (s, 15H), 3.43 (s, 3H), 3.40 (t, 2H), 2.66 (t, 2H).

1-(2,3,4-Trimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**5**).

A solution of 7.4 g. (19.0 mmoles) of amide **4** was dissolved in 150 ml. of ether and 74 g. of polyphosphoric ester (11) and refluxed for two days under nitrogen. It was then poured into ice and water and after warming to room temperature, the ether was separated and the aqueous acidic solution made basic with potassium hydroxide. The dihydroisoquinoline **5** precipitated and was collected by filtration. After drying **5** weighed 6.5 g. (17.4 mmoles, 92%) and could be recrystallized from ether, although as the free base it reacted very rapidly with oxygen to form 1-(2,3,4-trimethoxybenzoyl)-6,7-dimethoxy-3,4-dihydroisoquinoline **6**, m.p. 198-200° (ether); ir: 1665 cm^{-1}, 1590, 1520; nmr: δ 7.61 (d, J = 9 Hz, 1H), 7.02 (s, 1H), 6.73 (d, J = 9 Hz, 1H), 6.76 (s, 1H), 3.93, 3.83, 3.72 (s, 15H), ~3.85 (m, 2H), 2.78 (m, 2H).

Anal. Calcd. for $C_{21}H_{23}NO_6$: C, 65.43; H, 6.03; N, 3.63. Found: C, 65.43; H, 6.17; N, 3.62.

1-(2,3,4-Trimethoxybenzylidene)-6,7-dimethoxy-3,4-dihydro-2-(1*H*)isoquinolinecarboxaldehyde (**7**).

To a solution of 1.0 g. (2.7 mmoles) of isoquinoline **5** in 30 ml. of mixed formic-acetic anhydride (13) at 0° was added 3 g. of sodium acetate. After stirring overnight, the mixture was poured into 400 ml. of water containing 50 ml. of pyridine. After extracting three times with chloroform, the combined extracts were washed with water and then dilute citric acid. After drying with sodium sulfate, the residue, after evaporation of solvent, was flash chromatographed (18) using 1:4-ethyl acetate-methylene chloride to yield 975 mg. 2.44 mmoles (90%) of the enamide **7**, m.p. 152-154.5° (methanol-ether); ir: 1680 cm^{-1}, 1520; uv: 248 nm (sh, ε 13,800), 268 (min, 11,200), 302 (sh, 15,600), 326 (20,100); nmr: δ 8.10 (s, 1H), 7.24 (s, 1H), 7.02 (d, J = 9 Hz, 1H), 6.87 (s, 1H), 6.64 (d, J = 9 Hz, 1H), 6.59 (s, 1H), 3.97 (t, 2H), 3.95, 3.92, 3.90, 3.88, 3.85 (s, 15H), 2.87 (t, 2H).

Anal. Calcd. for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 65.81; H, 6.33; N, 3.60.

2'-Hydroxy-3',4'-dimethoxyacetophenone (**8**).

A 0° solution of 16.3 g. (77.5 mmoles) of **2** in 100 ml. of methylene chloride was contained in a three necked flask equipped with an argon inlet, a condenser connected to a bubbler and a graduated addition funnel fitted with a rubber septum. Boron trichloride (1.3 equivalents) as a 1 molar solution in methylene chloride (100 ml.) was transferred to the addition funnel using a two feet long flex needle and a positive nitrogen pressure. The boron trichloride solution was added to the acetophenone under argon and reacted for 15 minutes at 0° and then carefully quenched with sodium acetate solution (gas evolution). The organics were washed two additional times with sodium acetate and then dried with sodium sulfate. After treating with decolorizing carbon and filtration through Celite, the solvent was removed and the residue crystallized from ether-cyclohexane to yield 13.4 g. (68.3 mmoles, 88%) of **8** (15), m.p. 72-76°; ir: 1640 cm^{-1}, 1615, 1520; nmr: δ 7.52 (d, J = 9 Hz, 1H), 6.51 (d, J = 9 Hz, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 2.55 (s, 3H).

2'-Benzyloxy-3',4'-dimethoxyacetophenone (**9**).

A solution of 5.8 g. (29.6 mmoles) of **8** was dissolved in 100 ml. of acetone and 10.11 g. (59.1 mmoles) of benzyl bromide and 8.99 g. (65.1 mmoles) of potassium carbonate added. The mixture was stirred and refluxed overnight. After cooling, toluene was added and the precipitated

solids were filtered. The solvents were evaporated and the residue was flash chromatographed (18) using 3:97 ethyl acetate-toluene to yield 6.4 g of **9** (16) as an oil which slowly crystallized; m.p. 47-48°; ir: 1675 cm^{-1}, 1595; uv: 220 nm (ϵ 27,000), 245 (min, 4500), 270 (13,500); nmr: δ 7.50 (d, J = 9.5 Hz, 1H), 7.38 (m, 5H), 6.70 (d, J = 9.5 Hz, 1H), 5.13 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 2.50 (s, 3H).

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.19; H, 6.44.

2'-Benzyloxy-3',4'-dimethoxyphenylacetic Acid (**10**).

To a solution of 5.87 g. (19.8 mmoles) of **9** in 300 ml. of methylene chloride at 0° was added 35 g. (23 mmoles) of thallium trinitrate on K-10 reagent (8). The stirred mixture was allowed to warm to room temperature over an hour and then filtered. The organic solution was washed with potassium carbonate solution, dried and evaporated. The residue was taken up in 200 ml. of methanol and 20 ml. of water. After the addition of 6 g. of sodium methoxide, the solution was stirred overnight. The methanol was removed on a rotary evaporator and the aqueous solution was extracted with toluene. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with chloroform. The organics were dried with sodium sulfate and evaporated. The residue was crystallized from ether-petroleum ether to yield 2.9 g. (9.6 mmoles, 48%) of the acid **10**, m.p. 108-111°.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.69; H, 5.90.

N-β-(3,4-dimethoxyphenyl)ethyl-2'-benzyloxy-3',4'-dimethoxyphenylacetamide (**11**).

To a solution of 2.75 g. (9.11 mmoles) of acid **10** in 100 ml. of xylene was added an equivalent of *N*-β-(3,4-dimethoxyphenyl)ethylamine, 1.65 g. After refluxing for 18 hours, the solution was cooled and extracted with sodium bicarbonate and citric acid solutions. After drying with sodium sulfate, the solvent was evaporated and the residue crystallized from ether-petroleum ether to yield 4.0 g. (8.6 mmoles, 94%) of amide **11**, m.p. 102.5-103.5°; ir: 3330 cm^{-1}, 1660, 1525; uv 230 nm (ϵ 16,000), 251 (min, 1100), 277 (4000); nmr: δ 7.33 (s, 5H), 6.5-7.0 (m, 5H), 5.02 (s, 2H), 3.87, 3.83, 3.82, 3.78 (s, 12H), 3.30 (t, 2H), 2.58 (t, 2H), the acetamide benzyl protons are under the methoxyls by integration.

Anal. Calcd. for $C_{27}H_{31}NO_6$: C, 69.66; H, 6.71; N, 3.01. Found: C, 69.40; H, 6.72; N, 3.08.

O-Benzylpolycarpine (**13**).

A solution of 2.3 g. (4.94 mmoles) of amide **11** in 250 ml. of toluene was brought to reflux and dried using a Dean-Stark trap. The hot solution was cooled slightly and 9 ml. of phosphorus oxychloride added. After 2 hours of reflux, the mixture was cooled under nitrogen and made basic with aqueous sodium hydroxide. The organic layer was separated, dried with sodium sulfate and evaporated to yield approximately 3 g. of an oil which was the dihydroisoquinoline **12** by tlc in 1:9-methanol-chloroform. To the oil was added 5 g. of sodium acetate and then 30 ml. of mixed formic-acetic anhydride (13) at 0° under nitrogen. After warming to rt overnight, the mixture was again cooled in an ice bath and slowly diluted with water to give an oil. The aqueous mixture was extracted with methylene chloride which was, in turn, washed with sodium bicarbonate, dried and evaporated. The residue was flash chromatographed (18) using 1:4 ethyl acetate-methylene chloride to yield 1.95 g. (4.10 mmoles, 83%) of (*Z*)-1-(2'-benzyloxy-3',4'-dimethoxybenzylidene)-3,4-dihydro-6,7-dimethoxy-2-(1*H*)isoquinolinecarboxaldehyde (*O*-benzylpolycarpine) (**13**) m.p. 153-155.5° (ether); ir 1675 cm^{-1}; 1605, 1510; uv: 225 nm (ϵ 33,500), 276 (min, 10,000), 328 (20,400); nmr: δ 7.86 (s, 1H), 6.5-7.5 (m, 10H), 5.09 (s, 2H), 3.91 (s, 3H); 3.87 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 2.83 (t, 2H), the α-formamide methylene protons are under the methoxyl resonances by integration.

Anal. Calcd. for $C_{28}H_{29}NO_6$: C, 70.72; H, 6.15; N, 2.95. Found: C, 70.75; H, 6.11, N, 3.11.

Polycarpine (**1**).

A solution of 1.102 g. of *O*-benzylpolycarpine (2.32 mmoles) in 100 ml. of tetrahydrofuran was hydrogenated at room temperature and atmospheric pressure in the presence of 0.11 g. of 5% palladium on calcium carbonate. After 6 hours, an equivalent of hydrogen had been consumed and the reaction solution was filtered from catalyst and evaporated. Addition of a small amount of methanol caused immediate crystallization to yield 673 mg. (1.75 mmoles, 76%) of (*Z*)-1-(2'-hydroxy-3',4'-dimethoxybenzylidene)-3,4-dihydro-6,7-dimethoxy-2-(1*H*)isoquinolinecarboxaldehyde **1** (polycarpine), m.p. 179-180°, lit. (3) m.p. 178-180°, ir: 3400 cm^{-1} (broad), 1675, 1610, 1520; uv: 262 nm (ϵ 12,000), 280 (min, 10,700), 328 (19,400); nmr: δ 8.09 (s, 1H), 7.22 (s, 1H), 6.98 (d, J = 9 Hz, 1H), 6.84 (s, 1H), 6.56 (s, 1H), 6.43 (d, J = 9 Hz, 1H), 3.96 (t, 2H), 3.92, 3.89, 3.83 (s, 12H), 2.85 (t, 2H).

Anal. Calcd. for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.01; N, 3.63. Found: C, 65.09; H, 6.16; N, 3.52.

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