[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, GEORGIA INSTITUTE OF TECHNOLOGY]

New Synthetic Approach to the Berberine Alkaloids

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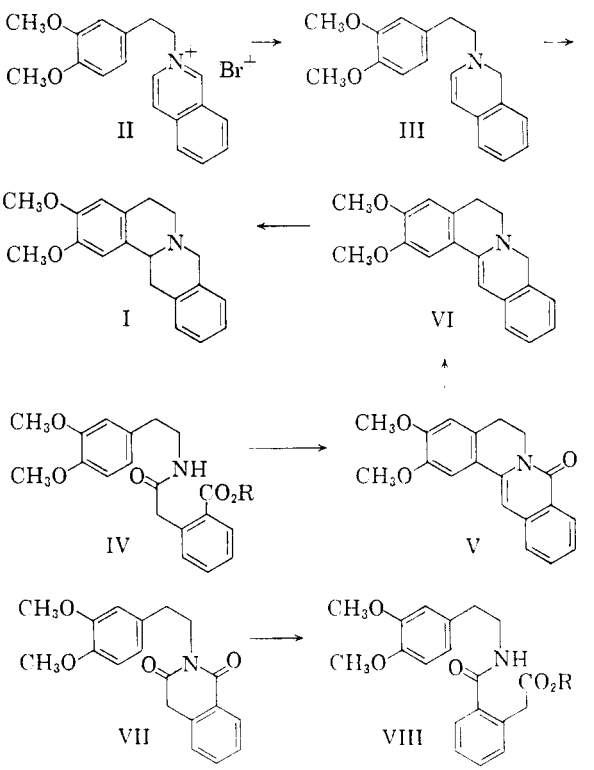
2-[2-(3,4-Dimethoxyphenyl)ethyl]isoquinolinium bromide has been reduced with lithium aluminum hydride to the dihydroisoquinoline, which on acid treatment affords 2,3-dimethoxyberbine. The same berbine derivative has been prepared by the classical berberine alkaloid synthesis, from homoveratryl amine and homophthalic anhydride.

Although a number of synthetic routes to the berberine alkaloids have been thoroughly investigated,[1] all of those using readily available starting materials fail to give rise to the naturally occurring compounds without multistep reaction sequences.[2] With the recent elucidation of the course of the reductive cyclization of indolylethylisoquinolinium salts to dehydroyohimbanes[3] a new synthetic approach *via* substituted β-phenylethylisoquinolinium salts appeared feasible. The goal chosen for our synthetic efforts was 2,3-dimethoxyberbine (I) to be obtained from 2-[2-(3,4-dimethoxyphenyl)ethyl]isoquinolinium bromide (II) on treatment with lithium aluminum hydride followed by acid.

The salt (II) was prepared from 3,4-dimethoxyphenylethyl alcohol,[4] followed by treatment with phosphorus tribromide, and heating of the crude bromide with isoquinoline, the method used for the preparation of the parent phenylethylisoquinolinium salt.[5] Reduction of the salt with lithium aluminum hydride in ether gave 2-[2-(3,4-dimethoxyphenyl)ethyl]-1,2-dihydroisoquinoline (III), as an unstable oil, which gave the desired 2,3-dimethoxyberbine (I) as the hydrochloride on heating with hydrochloric acid. Although the yield on this conversion is low (18% for the two steps), from a standpoint of steps involved this appears to be the shortest and most general synthetic approach to the berberine alkaloids yet devised.

For comparison with the sample of I prepared by reductive cyclization we attempted to prepare this compound from 1-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline by the method used for the preparation of berbine.[6] Although there were no difficulties encountered in the preparation of 1-benzyl-3,4-dihydro-6,7-dimethoxyisoquinoline,[7] we were unable to repeat the reduction of this compound with zinc and sulfuric acid.[8] We finally obtained the tetrahydroisoquinoline by catalytic hydrogenation of the dihydro compound; however all attempts to convert it to I met with failure.



The route which ultimately led to the dimethoxyberbine derivative was a modification of that employed in the classical total synthesis of the berbine alkaloids.[9]

(1) T. A. Henry, *The Plant Alkaloids*, Blakiston, Philadelphia, Pa., 1949, pp. 334–336.

(2) C. K. Bradsher and J. H. Jones, *J. Org. Chem.*, **23**, 430 (1958), have recently investigated what appears to be a very promising "short" synthesis of these alkaloids.

(3) J. W. Huffman, *J. Am. Chem. Soc.*, **80**, 5193 (1958).

(4) F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.*, 4252 (1956) have prepared this compound from veratryl lithium and ethylene oxide, and also lithium aluminum hydride reduction of 3,4-dimethoxyphenylacetic acid. Although the yields on the reduction are low (in our hands 30%), the commercial availability and relatively low cost of this acid make this the method of choice for the preparation of modest quantities of this alcohol.

(5) J. L. Hartwell and S. R. L. Kornberg, *J. Am. Chem. Soc.*, **68**, 868 (1946).

(6) (a) W. Leithe, *Chem. Ber.*, **62**, 2343 (1930). (b) L. E. Craig and D. S. Tarbell, *J. Am. Chem. Soc.*, **70**, 2783 (1948).

(7) G. Tsatsas, *Ann. pharm. franc.*, **10**, 61 (1952); *Chem. Abstr.*, **46**, 11208 (1952).

(8) R. A. Robinson, *J. Org. Chem.*, **16**, 1911 (1951).

(9) (a) R. D. Haworth, W. H. Perkin, and H. S. Pink, *J. Chem. Soc.*, **127**, 1709 (1925). (b) R. D. Haworth, J. B. Koepfli, and W. H. Perkin, *J. Chem. Soc.*, 549 (1927). (c) J. B. Koepfli and W. H. Perkin, *J. Chem. Soc.*, 2989 (1928).

Homoveratrylamine with homophthalic anhydride in boiling benzene afforded the amido acid (IV. R = H) which was converted by diazomethane to the methyl ester (IV. R = CH_3). In an effort to obtain the acid (III) in greater yield, an attempt was made to accomplish the hydrolysis of the homophthalimide, obtained from homoveratryl amine and homophthalic anhydride (VII). Although hydrolyses of this type have been reported to occur exclusively at the benzamide side of the imide ring,[9,10] the only solid product obtainable by this reaction in our hands was an acid isomeric with IV (R = H), undoubtedly the amido acid (VIII. R = H). The hydrolysis product gave an ester (VIII. R = CH_3) isomeric with, but not identical to IV (R = CH_3).

The assignment of structures IV and VIII is based on the following observations:

The acid IV (R = H) showed infrared absorption bands in the carbonyl region at 5.86 μ and 6.00 μ, while its isomer (VIII. R = OH) had bands at 5.74 μ and 6.17 μ.[11] The methyl ester of IV has carbonyl bands at 5.82 μ (benzoate ester), and 6.00 μ. A secondary argument favoring our assignment of structures is the observation that homophthalic anhydride has been shown to react preferentially at the aliphatic carbonyl group with alcohols and under Friedel-Crafts conditions.[12]

Amido ester (IV. R = CH_3) with phosphorus oxychloride in toluene afforded 2,3-dimethoxy-5,6-dihydro-8-oxo-8*H*-dibenzo[*a*,*g*]quinolizine (V). V was reduced with lithium aluminum hydride to the corresponding dihydroisoquinoline, (VI), which was treated directly with sodium borohydride[3] to give I identical to that obtained *via* reductive cyclization.

EXPERIMENTAL[13]

2-[2-(3,4-Dimethoxyphenyl)ethyl]isoquinolinium bromide. To a solution of 1.50 g. of 2-(3,4-dimethoxyphenyl)ethyl alcohol in 90 ml. of dry ether at 0° was added 1.5 g. of phosphorus tribromide. The reaction mixture was allowed to stand 24 hr. at room temperature, washed with water, 5% sodium bicarbonate, dried and the solvent removed at room temperature and reduced pressure, leaving 1.20 g. of yellow oil. The crude bromide was mixed with 0.75 g. of isoquinoline and heated 2 hr. on the steam bath, during which time the reaction mixture set to a crystalline mass. Recrystallization from ethanol–ethyl acetate gave 1.1 g. (36%) of pale yellow crystals m.p. 209–210°. The compound was crystallized for analysis from ethanol–ethyl acetate, and had m.p. 210–211°.

Anal. Calcd. for $C_{19}H_{20}BrNO_2$: C, 61.11; H, 3.74; N, 5.38. Found: C, 61.53; H, 3.86; N, 5.33.

2-Carboxy-N-[2-(3,4-dimethoxyphenyl)ethyl]phenylacetamide. To a solution of 4.0 g. of homoveratryl amine[14] in 100 ml. of benzene was added 3.2 g. of homophthalic anhydride, and the mixture heated under reflux 2 hr. On cooling the product separated as fine white needles, which were collected, and washed with two small portions of benzene. Recrystallization from cyclohexane–ethyl acetate gave 4.82 g. (67%) of material, m.p. 142–144°. Several recrystallizations from the same solvent pair gave an analytical sample, m.p. 148–149°.

Anal. Calcd. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.57; H, 6.32; N, 4.32.

2-Carbomethoxy-N-[2-(3,4-dimethoxyphenyl)ethyl]phenylacetamide. To a solution of 2.0 g. of the homophthalamic acid dissolved in 100 ml. of a chloroform-methanol mixture was added 100 ml. of an ethereal diazomethane solution, prepared from 3.3 g. of nitrosomethylurea. Following the rapid evolution of nitrogen the solution was allowed to stand 3 hr. at room temperature, and then concentrated to dryness at reduced pressure, leaving a pale yellow oil. Trituration with cyclohexane afforded a white solid, which on recrystallization from a cyclohexane–ethyl acetate mixture gave 1.84 g. (88%) of fluffy white needles, m.p. 100–102°. Additional recrystallizations from the same solvent pair gave an analytical sample m.p. 102–103°.

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.84; H, 6.75; N, 4.35.

2,3-Dimethoxy-5,6-dihydro-8-oxo-8H-dibenzo-[a,g]-quinolizine. To a solution of 1.0 g. of the above amido ester in 20 ml. of toluene was added 20 ml. of phosphorus oxychloride, and the mixture was heated under reflux for 2 hr. After cooling, ice water was added and the aqueous layer drawn off, and shaken with ether. After washing with water, drying and removal of the solvent *in vacuo* a small amount of dark colored oil was obtained which could not be induced to crystallize. The acidic aqueous phase was made basic with 10% aqueous sodium carbonate, and extracted with five portions of ether. The ethereal extracts were washed with water, dried, and the solvent removed at reduced pressure leaving a pale yellow solid. Recrystallization from ethyl acetate gave 0.34 g. (40%) of small yellow crystals, m.p. 187–189°. Several recrystallizations from ethyl acetate gave material m.p. 189–190°.

Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.24; H, 5.35; N, 4.67.

2,3-Dimethoxyberbine. a. To a suspension of 0.2 g. of lithium aluminum hydride in 20 ml. of boiling dry tetrahydrofuran was added slowly a solution of 0.1 g. of the dibenzooxoquinolizine in 5 ml. of tetrahydrofuran. The reaction was heated under reflux 2 hr., cooled with an ice bath and a solution of ethyl acetate in moist ether added slowly to decompose the excess hydride. Following the addition of several drops of water the aluminum salts were removed by filtration through a sintered glass funnel. After washing the precipitate thoroughly with tetrahydrofuran, the filtrate was concentrated to dryness at the water pump, leaving a pale yellow glass. This was dissolved in 4 ml. of methanol, treated with 0.1 g. of sodium borohydride and heated at reflux 30 min. After cooling and dilution with water the solution was first made acidic with 10% hydro-

(10) K. T. Potts and R. Robinson, *J. Chem. Soc.*, 2675 (1955).

(11) We have no rational explanation for this abnormally high amide band. *N*-homoveratryl benzamide [H. J. Harwood and T. B. Johnson, *J. Am. Chem. Soc.*, **56**, 468 (1934)] shows normal amide absorption at 6.00 μ.

(12) N. P. Buu-Hoi, *Compt. rend.*, **209**, 562 (1932); *Bull. soc. chim.*, **11**, 338 (1944). That the reactions of homophthalic anhydride with amines is not completely selective is evidenced by the isolation of a small amount of acid (VIII) from the saponification of impure IV (R = CH_3). In view of the known hydrolysis rates of aliphatic *versus* aromatic esters (J. Hine, *Physical Organic Chemistry*, McGraw-Hill, New York, 1956, p. 274). It is surprising that the earlier workers (Refs. 9 and 10) obtained acids similar to (IV) in hydrolyses of homophthalimides.

(13) All melting points were determined on a Fischer-Johns block, and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer model 137 spectrophotometer, using chloroform as a solvent. Analyses were carried out by Galbraith Analytical Laboratories, Knoxville, Tenn.

(14) We would like to thank Dr. S. F. Kern of Eli Lilly and Company for a generous sample of homoveratryl amine.

chloric acid and then basic with 10% sodium carbonate. Extraction with chloroform, drying, and removal of the solvent *in vacuo* gave a viscous pale yellow oil. This oil was boiled with several 10-ml. portions of hexane, which were combined and concentrated to a small volume, however no solid could be obtained. Removal of the hexane and treatment of the oily residue with concentrated hydrochloric acid afforded 0.021 g. (25%) of the base hydrochloride, m.p. 236–238 (dec.). Recrystallization from ethanol–ethyl acetate gave material m.p. 237–239 (dec.).

Anal. Calcd. for $C_{19}H_{21}NO_2 \cdot HCl$: C, 68.76; H, 6.68; N, 4.22. Found: C, 68.67; H, 6.89; N, 4.31.

b. To a stirred suspension of 0.4 g. of lithium aluminum hydride in 50 ml. of dry ether was added slowly 0.46 g. of 2-[2-(3,4-dimethoxyphenyl)ethyl]isoquinolinium bromide, and the mixture was stirred at room temperature overnight. The excess reducing agent was decomposed with ethyl acetate, and finally water and 10% sodium carbonate were added. The aqueous layer was drawn off and extracted with two portions of ether. The ethereal extracts were combined, dried, and the solvent removed at reduced pressure and room temperature giving 0.28 g. (77%) of crude dihydroisoquinoline as a red oil. This oil was taken up in 50 ml. of concentrated hydrochloric acid and heated on the steam bath 4 hr., with an additional 5 ml. of acid being added hourly. The pale yellow solution was concentrated to a small volume and on cooling deposited 0.071 g. (18% based on bromide, 23% on crude reduction product) of white powder, m.p. 225–235 (dec.). Recrystallization from ethanol–ethyl acetate gave a white powder m.p. 236–238 (dec.), undepressed on mixture with material prepared in part *a*. The infrared spectra of the free base from this material and from material in part *a*. were identical.

N-[2-(3,4-dimethoxyphenyl)ethyl]homophthalimide. A mixture of 0.8 g. of homophthalic anhydride and 1.0 g. of homoveratrylamine were heated at 180° for 2 hr. On cooling the molten mass solidified, and was recrystallized from chloroform-methanol to give 0.8 g. (45%) of small needles m.p. 145–147°. The analytical sample was crystallized from the same solvent pair and had m.p. 147–148°.

Anal. Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.88; N, 4.31. Found: C, 70.26; H, 5.86; N, 4.28.

2-[N-(2-[3,4-dimethoxyphenyl]ethyl)carboxamido]phenylacetic acid. a. To 12 ml. of 2*N* sodium hydroxide was added 0.6 g. of the homophthalimide, and the mixture was heated at 100° for 12 hr. Addition of water, treatment with charcoal, filtration and acidification gave 0.43 g. of white slightly gummy solid, m.p. 146–153°. Recrystallization from ethyl acetate–cyclohexane afforded 0.13 g. of small white needles, m.p. 159–162°. No additional solid material could be obtained from the mother liquors. The analytical sample, m.p. 162–163°, was obtained by several recrystallizations from ethyl acetate–cyclohexane.

Anal. Calcd. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.33; H, 6.13; N, 4.15.

b. A suspension of 50 mg. of crude 2-carbomethoxy-*N*-[2-(3,4-dimethoxyphenyl)ethyl]phenylacetamide in 1 ml. of 10% sodium hydroxide was heated on the steam bath 30 min. Acidification with dilute hydrochloric acid gave a small amount of solid, which on crystallization from ethyl acetate gave a few crystals of material m.p. 160–161°, undepressed with material from part *a*. above.

2-Carbomethoxymethyl-N-[2-(3,4-dimethoxyphenyl)ethyl]-benzamide. To a solution of 0.08 g. of the substituted phenylacetic acid in 10 ml. of chloroform was added 10 ml. of an ethereal solution of diazomethane prepared from 0.15 g. of nitrosomethyl urea. After standing 3 hr. at room temperature, the solvent was removed *in vacuo*, leaving a colorless oil, which on crystallization from cyclohexane–ethyl acetate afforded 0.05 g. (60%) of small white needles, m.p. 92–93°, unchanged on additional recrystallizations. A mixed melting point with the other homophthalamic ester was 79–90°.

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49. Found: C, 67.67; H, 6.75.

1-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline. A solution of 2.2 g. of 1-benzyl-3,4-dihydro-6,7-dimethoxyisoquinoline in 25 ml. of ethanol was added to 0.1 g. of prehydrogenated platinum oxide in 25 ml. of ethanol and hydrogenated at atmospheric pressure until the uptake of hydrogen ceased, when 1.32 mol. had been absorbed. The catalyst was filtered off, and the filtrate evaporated at reduced pressure leaving a brown oil. Treatment of 0.1 g. of this oil with ethanolic picric acid gave a gummy picrate which after several recrystallizations had m.p. 100–102°, resolidifying at about 120° followed by melting at 160–165°. The remainder of the oil was dissolved in benzene and chromatographed on 75 g. of Merck alumina. Elution with benzene-chloroform mixtures gave several fractions of pale yellow oils whose picrates behaved as above. These fractions were combined to give 1.40 g. (61%) of the desired product. The picrate after several recrystallizations from ethanol had m.p. 102–104°, resolidification, m.p. 163–165°.

Anal. Calcd. for $C_{24}H_{24}N_4O_9$: C, 56.25; H, 4.72; N, 10.93. Found: C, 56.34; H, 4.54; N, 10.87.

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