STEREOSPECIFIC SYNTHESIS OF A DIBENZO[*a*,*g*]QUINOLIZINE ANALOG OF 18-HYDROXYALLOYOHIMBANE

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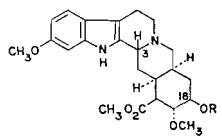
Received April 7, 1965

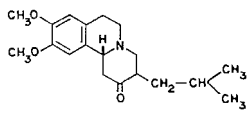
ABSTRACT

Starting from 4-cyclohexene-*cis*-1,2-dicarboxylic acid, the stereospecific synthesis of the dibenzo[*a*,*g*]quinolizine analog IV of epialloyohimbane is described. The synthetic method of approach is outlined in Chart 1. As the trimethoxybenzoic acid ester, the base IV proved to be devoid of significant pharmacological properties.

The alkaloid reserpine (I, R = 3,4,5-trimethoxybenzoyl) and several 18-ester analogs possess unique physiological properties, the most striking being their ability to interfere with the storage mechanism of the catecholamine hormones and serotonin (1). Other



I



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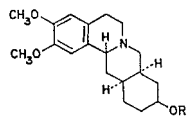
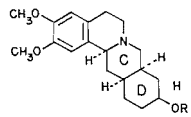


III



IV

types of analogs such as the 18-ethers (I, R = alkyl) share this property (1) but differ in one important respect: whereas the action of reserpine is protracted, that of the ether derivatives is of shorter duration (1). It seems therefore that an acyl function at position 18 may be essential for prolonged in vivo activity. Quantitatively, reserpine produces effects that are characteristic of irreversible inhibitors such as the alkylating adrenergic blocking agents of the Dibenamine class of drugs (2). It is conceivable that reserpine may be a prototype of selective acylating agents, a hypothesis which readily accounts for the irreversibility characteristics of its action.

Some time ago, it was discovered that a simple benzoquinolizidine derivative (II) known under the name of Tetrabenazine displays reserpine-like activity (3). However, in contrast to reserpine, it is a short-acting compound, a feature which is in accord with the non-acylating properties of the molecule. Evidence is thought to have been produced that Tetrabenazine interacts with the same physiological receptors that serve to bind reserpine (4). This was surprising to us in view of the remote structural analogy between these two drugs. It is apparent that should the same receptors mediate the physiological effects of both reserpine and Tetrabenazine, the formal transformation of the latter to an acylating agent ought to markedly intensify its reserpine-like properties. To this end,

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a close structural analogy to reserpine should be maintained, and accordingly, we elected to synthesize a trimethoxybenzoyl ester of the 3,4-dimethoxyphenyl analog of 18-hydroxy-epialloyohimbane (III). It is the purpose of this communication to report on a stereo-specific approach which led to the synthesis of the isomeric alloyohimbane analog IV (R = 3,4,5-trimethoxybenzoyl). The synthesis of the desired epiallo isomer III was eventually accomplished as described in an accompanying communication (5).

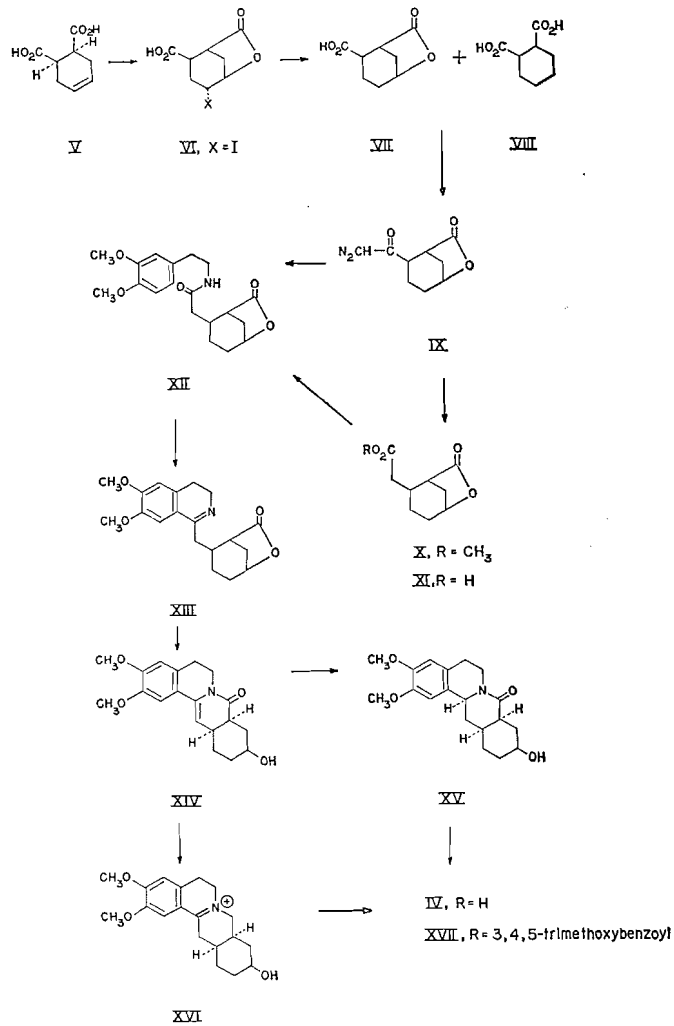

CHART 1.

Our synthetic approach (Chart 1) was based on the readily available starting material *cis*-Δ^4-tetrahydrophthalic acid (V) which provided for the desired *cis* fusion of rings C and D in the end product III. Iodolactonization of V proceeded normally (6) to give iodolactone acid (VI). The lactone VI has recently been described by others (7). Absorption in the infrared at 1 750 cm^{-1} confirmed the exclusive formation of a γ-lactone ring in which the potential 18-hydroxyl function of III assumes the proper configuration.

Catalytic hydrogenolysis of the iodolactone acid afforded the lactone acid VII accompanied in various proportions by *cis*-hexahydrophthalic acid (VIII). On a preparative scale, the separation of the hydrogenolysis mixture presented some difficulty. The formation of *cis*-hexahydrophthalic acid was unexpected; it seems probable on the basis of related experiments (5) that the lactone acid VII is the immediate precursor of the diacid VIII. It has been noted before that γ-lactones with an axial ring oxygen can be susceptible to hydrogenolysis (8). However, this process is slower than reductive dehalogenation. Homologation of the lactone acid VII by way of the intermediate diazoketone IX followed by Wolff rearrangement in the presence of homoveratrylamine offered directly the lactone homoamide XII in good yield. The Wolff rearrangement is known to proceed with retention of configuration (9). Alternatively, the rearrangement was carried out in methanol whereupon the methyl ester X was formed; saponification gave the homoacid lactone XI from which the same oily amide XII could be readily prepared. Bishler–Napieralsky ring closure of the amide led to the dihydroisoquinoline lactone XIII in high yield. It was initially characterized as the picrate but the hydrochloride was later obtained in pure form (5). Cyclization of XIII to the tetracyclic ene-lactone XIV was accomplished in moderate yield by boiling in xylene for several hours. The infrared spectrum of the lactam XIV was in agreement with expectations (see Experimental). Conversion of the ene-lactam XIV to the corresponding reduced base IV involved either catalytic hydrogenation of the double bond to give the reduced lactam XV followed by lithium aluminium hydride reduction to IV or hydride treatment to give the intermediate XVI followed by reduction to IV. Thus, reduction of the iminium ion XVI with lithium aluminium hydride, sodium borohydride, zinc and hydrochloric acid, or with sodium in liquid ammonia – *t*-butanol uniformly produced the same tetracyclic base in a homogeneous state. Surprisingly, zinc – acetic acid reduction, a method which is successful in the yohimbane series (10), led only to unchanged starting material. The reasons for this are not clear. The tetracyclic base IV was readily oxidized to the imine XVI by mercuric acetate (10).

Since it has been shown that the sodium – liquid ammonia – *t*-butanol system leads to the thermodynamically more stable isomer in the analogous yohimbane series (11), it follows that the tetracyclic base obtained by us in this manner must possess the configuration IV in which both the phenyl and 18-hydroxyl substituents are equatorial. In agreement with this conclusion, the tetracyclic base IV gave rise to Bohlmann bands (12) in the region 2 800 – 2 700 cm^{-1} of the infrared spectrum; the stable conformation of IV which places the phenyl and hydroxyl substituents in the equatorial orientation has the electron pair on the nitrogen *trans* to two axial α-hydrogens in accord with the spectroscopic characteristics. Reaction of the base IV with 3,4,5-trimethoxybenzoyl chloride gave the corresponding 18-ester XVII in moderate yield.

It was evident at this point that to obtain the desired isomeric tetracyclic base III (epiallo configuration), an alternative approach had to be sought. More gratifying results are reported in an accompanying paper (5). Since 3-isoreserpine (allo configuration as in the base IV) is devoid of reserpine-like activity (1), the analog XVII would be expected to be also inactive. Dr. M. Pindell of Bristol Laboratories, Syracuse, has confirmed this expectation using a variety of standard tests.

EXPERIMENTAL

Melting points and boiling points are uncorrected. The infrared spectra were determined with an Infracord instrument or a Perkin-Elmer spectrometer model 112G using chloroform as the solvent unless otherwise

noted. The sentence "was worked up in the usual manner" signifies that the reaction mixture was extracted with ether or chloroform and, wherever appropriate, the extract was washed with dilute acid or dilute base followed by drying and evaporation *in vacuo*. Microanalyses by Midwest Microlab, Indianapolis, Indiana.

4-Hydroxy-5-iodo-cis-cyclohexane-1,2-dicarboxylic Acid γ-Lactone (VI)

To a stirred suspension of Δ^4-cyclohexene-*cis*-1,2-dicarboxylic acid in 500 ml of water, 29 g of sodium hydrogen carbonate was added, followed by the addition in portions of a solutions of 29 g of iodine in 200 ml of water containing 112 g of potassium hydroxide. After stirring for 1 h at room temperature some sodium thiosulfate was added until the solution became colorless, and the mixture was acidified with conc. hydrochloric acid. The solution was filtered without delay whereupon a crystalline mass separated from the filtrate. After 1 h at 0°, the solid was collected and recrystallized from ethanol–hexane; m.p. 158–160° (reported (7): 161–162°), yield: 74–80%.

Anal. Calcd. for $C_8H_9IO_4$: C, 32.45; H, 3.06; I, 42.86; Found: C, 32.67; H, 3.30; I, 44.00. Infrared: λ_{max} (Nujol mull) 3 100, 1 750, 1 710 cm^{-1}.

The iodolactone acid VI was further characterized as the crystalline *diethylamine salt*; after recrystallization from methanol – ethyl acetate, the m.p. was 122–124°.

Anal. Calcd. for $C_{12}H_{20}INO_4$: C, 39.04; H, 5.46; I, 34.38; Found: C, 39.02; H, 5.43; I, 35.04.

4-Hydroxy-cis-1,2-cyclohexanedicarboxylic Acid γ-Lactone (VII)

A solution of 25.3 g of the iodolactone acid in 190 ml of methanol containing 12.5 ml of diethylamine was hydrogenated at 85 p.s.i. of hydrogen over 25 g of freshly prepared Raney nickel. After a pressure drop of about 6.5 pounds, the reaction was stopped and the catalyst was removed by filtration. The filtrate was treated with 17.0 g of freshly precipitated silver carbonate, and the suspension was shaken for 20 min and filtered through Florex XXX. The colorless filtrate was evaporated *in vacuo* and the residue was dissolved in 50 ml of 3 *N* aqueous sulfuric acid; some insoluble silver sulfate was removed by filtration and the filtrate was extracted five times with 50 ml portions of ethyl acetate. The combined extracts were dried and evaporated *in vacuo*, and the residue was crystallized from 100 ml of dry ether. This first crop weighed 6.0 g and had m.p. 142–143°. The filtrate was taken to dryness and the residue was partitioned between equal volumes (100 ml) of ether and water. The distribution coefficients of the lactone acid VII and the diacid VIII in this solvent system were 0.1 and 2.0 respectively. After equilibration, the aqueous phase was twice extracted with 100 ml portions of ether. The aqueous phase was saturated with ammonium sulfate and extracted with five 50 ml portions of chloroform. The combined extracts were dried and evaporated, and the residue was crystallized from ethyl acetate – ether to give an additional 0.30 g of lactone acid VII m.p. 140–141°. Total yield: 6.3 g or 47% of the theoretical. After recrystallization from benzene, the m.p. was 143–144°.

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.61; H, 5.91. λ_{max}: 1 755, 1 700 cm^{-1}.

From the ether extracts and mother liquors there was isolated from 2 to 4 g of the *cis*-cyclohexane-1,2-dicarboxylic acid (VIII) which was characterized by mixture m.p. determination and comparison of its infrared spectrum with that of an authentic specimen.

Diazoketone IX from Lactone Acid VII

To a cooled solution of 6.78 g of the lactone acid VII in 220 ml of dry benzene containing 6.5 ml of triethylamine was added dropwise 8.6 ml of oxalyl chloride. After standing for 3.5 h, the suspension was filtered and the filtrate was treated with a freshly prepared ethereal solution of diazomethane (from 26 g of *N*-nitrosomethyl urea, 52 ml of 45% aqueous potassium hydroxide, and 370 ml of ether). After standing overnight, the mixture was filtered and the filtrate was evaporated *in vacuo*. The residue (7.4 g or 96% of theory) crystallized spontaneously. It was used as such without further purification.

λ_{max}: 2 140, 1 760, and 1 640 cm^{-1}.

(A) Wolff Rearrangement in Methanol

A quantity of diazoketone equivalent to 0.955 g of lactone acid VII was dissolved in boiling methanol and some freshly precipitated silver oxide was added. The mixture was boiled for 3 h, cooled, and filtered through Celite. The filtrate was evaporated *in vacuo* and the residue was distributed between 6 *N* aqueous sulfuric acid and ether. The ether extract was worked up in the usual manner to give 563 mg of semisolid residue. Repeated extraction of the aqueous layer with chloroform and isolation in the usual manner yielded an additional 110 mg of methyl ester. The total yield of crude ester X was 60%.

λ_{max}: 1 753, 1 725 cm^{-1}.

The *lactone homoacid* XI was obtained through saponification of the preceding crude ester X (542 mg) in boiling 5% methanolic potassium hydroxide. The solution was evaporated to dryness, the residue was taken up in 6 *N* aqueous sulfuric acid, and the resulting solution was saturated with ammonium sulfate and repeatedly extracted with chloroform. The extract was dried and evaporated to give an oil (390 mg or 77% of theory) which was dissolved in benzene and purified by chromatography on silicic acid (6 g). Ether eluted 333 mg of an oil which crystallized from benzene–pentane, m.p. 119–120°. Other crystalline forms of m.p. 111–116° exhibiting changes of crystal form at 100–110° were more frequently observed. These varied forms had superimposable infrared spectra in chloroform.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 59.10; H, 6.53. λ_{max}: 1 750, 1 700 cm^{-1}.

N-(3',4'-dimethoxy-β-phenethyl)-cis-2-carboxy-4-hydroxy-cyclohexane-1-acetamide γ-Lactone (XII)

(A) From the Diazoketone IX

To a solution of 6.87 g of homoveratrylamine in 25 ml of pure dioxane, some freshly precipitated silver oxide was added and the suspension was heated to boiling. Heating was discontinued and a solution of 7.41 g of the crude diazoketone IX in 30 ml of dioxane was added dropwise whereupon a vigorous evolution of nitrogen ensued. At intervals, 13.4 g of silver oxide was added in portions over a period of 1 h. The suspension was then heated under reflux for 3 h, cooled, and filtered through a bed of Florex XXX. The precipitate was washed with acetone, and the washings and filtrate were combined and evaporated. The residue was taken up in chloroform; the solution was washed with dilute aqueous sulfuric acid and then with saturated sodium bicarbonate solution; the chloroform solution was finally filtered through a column of 100 g of aluminium oxide (Woelm, activity II) and the column was thoroughly washed with chloroform. Removal of the solvent *in vacuo* afforded 13.2 g of the crude homoamide lactone XII as an uncrystallizable oil. It was used as such in the next step.

λ_{max}: 2 125, 1 765, 1 640 cm^{-1}.

(B) From the Homoacid Lactone XI

The homoacid lactone acid chloride was prepared by treatment of the acid triethylamine salt in benzene with oxalyl chloride as described above in the case of the preparation of the diazoketone IX. The benzene solution of the acid chloride was treated with excess homoveratrylamine in the cold, and the mixture was worked up in the usual manner to give in high yield the oily homoamide lactone XII identical in the infrared with the amide obtained through the application of method A above.

1-[(cis-2'-Carboxy-4'-hydroxy)-1'-cyclohexylmethyl]-3,4-dihydro-6,7-dimethoxyisoquinoline γ-Lactone (XIII)

The preceeding homoamide lactone XII (13.0 g) was heated under reflux and under an oxygen-free nitrogen atmosphere in 100 ml of dry toluene containing 25 ml of freshly distilled phosphorous oxychloride. After 75 min, the solution was evaporated to dryness *in vacuo*. The residual syrup was taken up in chloroform and the solution was washed twice with saturated sodium bicarbonate, dried, and evaporated to give 12.1 g (97% of theory) of a clear deep-yellow oil.

λ_{max}: 1 750, 1 600, 1 555, 1 500 cm^{-1}.

The *picrate* crystallized from methanol; recrystallization from acetone – ethyl acetate gave yellow crystals m.p. 193–194°; recrystallization from acetone–chloroform gave another form m.p. 175–176°. The two forms are interconvertible.

Anal. Calcd. for $C_{25}H_{26}N_4O_{11}$: C, 53.76; H, 4.69. Found: C, 53.48; H, 4.92.

Ring Closure of XIII to the Tetracyclic Ene-lactam XIV

A solution of 12 g of the preceeding base XIII in 200 ml of dry xylene was heated under reflux for 24 h under an atmosphere of oxygen-free nitrogen. The hot mixture was decanted from some insoluble gum and the solvent was removed *in vacuo*. The residue was dissolved in chloroform and the solution was worked up in the usual manner to give an oil which crystallized from 70 ml of boiling toluene. The yield was 5.1 g (42% of theory). Recrystallization from benzene gave white crystals m.p. 195–196°.

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.83; H, 6.89; N, 4.40. λ_{max}: 3 400, 1 640, 1 500 cm^{-1}.

Catalytic Hydrogenation of XIV to the Decahydrodibenzo[a,g]quinolizinone XV

A solution of 1.41 g of the preceeding ene-lactam XIV in 20 ml of ethanol containing 0.5 ml of 75% aqueous perchloric acid was shaken in a hydrogen atmosphere at atmospheric pressure in the presence of 300 mg of Adam's catalyst. After 6 min, the theoretical amount of hydrogen was adsorbed; the catalyst was removed and the solvent was evaporated. The residue was dissolved in chloroform and the solution was worked up in the usual manner to give a solid which on recrystallization from benzene afforded 1.14 g (80% of theory) of the lactam XV, m.p. 217–219°. Depending on the rate of heating the m.p. varied from 213–216° to 217–219°. Additional recrystallizations did not alter the m.p. The product was homogeneous as ascertained by thin-layer chromatography (silicic acid; chloroform–methanol).

Anal. Calcd. for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60. Found: C, 68.81; H, 7.72. λ_{max}: 3 400, 1 620, 1 500 cm^{-1}.

Reduction of XV to the Tetracyclic Base IV

To a suspension of 1 g of lithium aluminium hydride in 30 ml of dry ether was added dropwise a solution of 1.44 g of the preceeding lactam XV in 100 ml of dry tetrahydrofuran. After 3 h of heating under reflux, the mixture was cooled and treated successively with 1 ml of water, 0.75 ml of 20% aqueous sodium hydroxide, and 3.5 ml of water. The salts were filtered off, the filtrate was evaporated, and the residue was partitioned between 16 ml of 3 *N* aqueous sulfuric acid and 50 ml of ether. The aqueous phase was made alkaline and extracted with ether. The ether was dried and evaporated and the residue was crystallized from acetone–water to give 1.22 g (89% of theory) of the base IV, m.p. 178–180°. Recrystallization from acetone did not change the m.p.

Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57. Found: C, 71.92; H, 8.40. λ_{max}: 2 800, 2 760 cm^{-1} (Bohlmann bands); 3 400, 1 500 cm^{-1}.

Treatment of the base with a 10% excess of mercuric acetate in acetic acid at 60° gave an immediate precipitate of mercurous acetate. After working up the mixture in the usual manner (excess mercuric ions being removed with H_2S), the dehydrobase XVI was isolated as the chloride salt in the form of an uncrystallizable yellow oil identical in the infrared with a sample prepared as described below.

λ_{max}: 3 400, 1 720, 1 500 cm^{-1}.

Reduction of Ene-lactam XIV to the Dehydrobase XVI

The ene-lactam XIV (400 mg) was reduced with lithium aluminium hydride by the same method described above in the case of the reduction of XV to IV. After isolation in the usual manner, the free base (which is sensitive to air) was converted to the oily chloride XVI which was identical in the infrared with a sample obtained by mercuric acetate dehydrogenation of IV (see above).

Attempted reduction of this dehydrobase XVI by zinc in acetic acid led to unchanged starting material. Reduction with boiling hydrochloric acid and zinc gave in good yield the base IV (identity established by mixed m.p. determination and infrared); similar results were obtained using either lithium aluminium hydride or sodium borohydride (in aqueous ethanol). The reduced base was obtained in good yield (75–90%) in each instance.

Reduction with sodium – liquid ammonia – *t*-butanol (using the procedure of Stork and Hill (11)) also gave the base IV in high yield.

3,4,5-Trimethoxybenzoic Acid Ester XVII of the Base IV

The method of Lucas *et al.* (13) was applied. Thus, 317 mg of the base IV was treated in 15 ml of dry pyridine with 920 mg of 3,4,5-trimethoxybenzoyl chloride. After 4 days at room temperature, the mixture was poured onto ice-cold dilute ammonia and the precipitate was collected. After several recrystallizations from methanol, the pure ester XVII (100 mg) had m.p. 149–150°.

Anal. Calcd. for $C_{29}H_{37}NO_7$: C, 68.10; H, 7.24; N, 2.74. Found: C, 67.80; H, 7.24; N, 2.95. λ_{max}: 1 700, 1 590 cm^{-1}.

ACKNOWLEDGMENTS

The financial support of this work by the National Research Council of Canada is gratefully acknowledged.

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