The Synthesis of 5,6-Dimethoxycyclopentano[*h*]-isoquinoline and Derivatives

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The synthesis of the previously unreported 5,6-dimethoxycyclopentano[*h*]isoquinoline (**1**) by way of a Pomeranz Fritsch ring closure of the diethyl acetal of 4,5-dimethoxy-7-indanylidene aminoacetaldehyde (**3**) is reported. Acetylation of the *N*-oxide of **1** yielded the corresponding *N*-acetyl-1-isoquinolone, which readily converted to the 1-isoquinolone on exposure to atmospheric moisture. Several diesters of the dihydroxy analog of **1** are reported.

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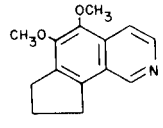
The synthesis of cyclopentanoisoquinolines as potential cardiovascular agents has been a continuing interest of our laboratory (1-3). Thus far, the compounds we have reported have been based on the cyclopentano[*f*]- and cyclopentano[*h*]-1,2,3,4-tetrahydroisoquinoline nucleus. The synthesis of the more highly unsaturated 5,6-dimethoxycyclopentano[*h*]isoquinoline (**1**) ring system as a more efficient precursor than the previously reported cyclopentano[*h*]-1,2,3,4-tetrahydroisoquinoline and as a more versatile intermediate for the development of more complex structures is described.



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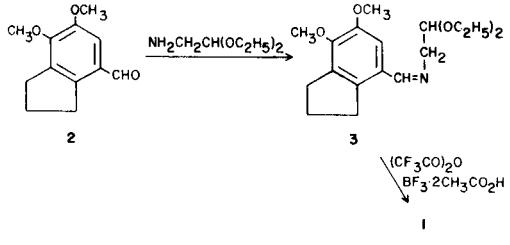
The synthesis of **1** was accomplished by the route outlined in Scheme I.

Scheme I

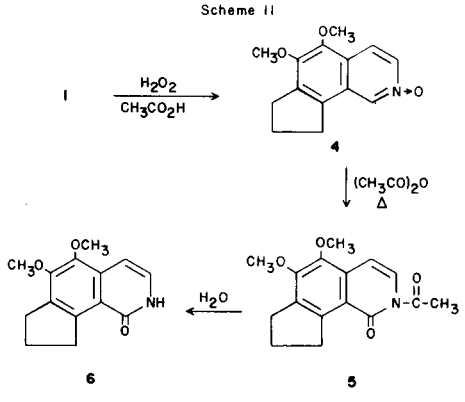


The precursor aldehyde (**2**) was prepared by methods reported previously by our laboratory (1). The Bevis (4) modification of a Pomeranz-Fritsch ring closure of the Schiff's base **3** proceeded without difficulty and readily afforded the desired compound **1** in excellent yield.

As a means to more complex structures, some preliminary reactions of this new ring system were investigated.

The *N*-oxide (**4**) of **1** was prepared by a standard procedure and some of its chemistry was investigated (Scheme II).

Scheme II



Treatment of **4** with acetic anhydride yielded the *N*-acetyl-1-isoquinolone (**5**). However, exposure of **5** to atmospheric moisture resulted in a rapid conversion to the 1-isoquinolone derivative **6**. Robison and Robison (5) have reported that isoquinoline *N*-oxide yields *N*-acetyl-1-isoquinolone (*N*-acetylisocarbostyril) when reacted with acetic anhydride and that this compound is also readily converted to 1-isoquinolone by atmospheric moisture.

The nmr spectrum of **5** gave a singlet at δ 2.81 for the 2-acetyl methyl group. The ir spectrum yielded intense bands at 1710 and 1675 cm^{-1} and additional bands at 1635 and 1525 cm^{-1}. The spectrum data is consistent with the *N*-acetyl-1-isoquinolone structure given. McKillop, *et al.* (6), assigned chemical shift values of δ 2.76 and 2.29, respectively to the acetyl groups of *N*-acetyl-2-pyridone and 2-pyridyl acetate. Robison and Robison (5) reported infrared absorption bands for *N*-acetyl-1-isoquinolone at 1705 and 1665 cm^{-1} (assigned to the two carbonyl groups) and 1625 and 1597 cm^{-1} (assigned as ring absorption bands).

It seems apparent from the spectral data presented that a resonance structure, such as **7**, contributes significantly to the chemical properties of the *N*-acetyl-1-isoquinolones. Energy required for separation of opposite charges would at least be partially compensated for by the resonance energy gained from aromatic ring formation.

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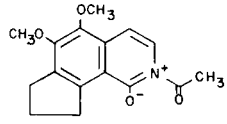

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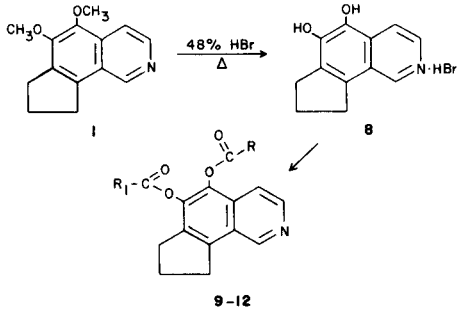
Structure **7** explains the reactivity of the acetyl group toward atmospheric moisture (the positive charge on nitrogen increases the electrophilicity of the carbonyl carbon) and accounts for the farther than anticipated down-field shift of the *N*-acetyl methyl group in the nmr spectrum. Simple examples from the literature (7) indicate that either an aromatic ring or an atom of increased electronegativity bonded to the carbonyl carbon of the acetyl group will cause a down-field shift of the methyl singlet, *e.g.*, *N*-*n*-butylacetanilide, δ 1.87 and *N*,*N*-dimethylacetamide, δ 2.08 as compared with acetyl chloride, δ 2.67 and acetophenone δ 2.59. It is well known that compounds such as 2-pyridone, 2-pyrimidone and uracil possess aromatic properties and for example, are not hydrolyzed by hot aqueous base or acid and undergo electrophilic substitution. At the same time, it has been shown that the aromatic properties of these compounds do no arise from keto-enol tautomerisation but are the results of resonance of the type indicated in structure **7** (8).

The preparation of some simple diesters of 5,6-dihydroxycyclopentano[*h*]isoquinoline (**7**) is outlined in Scheme III. The *o*-hydroquinone hydrobromide **8** precipitated after a short period of heating **1** in 48% hydrobromic acid solution. Reaction of **8** with acetic anhydride, butyryl chloride or benzoylchloride in the presence of an excess of a base (pyridine or triethylamine) yielded the desired esters. The diesters **9** and **10**, however, proved to be somewhat unstable in the presence of air and light; discoloration occurred and a strong odor of acetic (**9**) and butyric acids (**10**) was apparent. However, it was possible to obtain the necessary data for structural confirmation.

Scheme III



9 R=R$_1$=CH$_3$
10 R=R$_1$=CH$_3$CH$_2$CH$_2$
11 R=R$_1$=C$_6$H$_5$
12 R=R$_1$=3,4,5-(CH$_3$O)$_3$C$_6$H$_2$

EXPERIMENTAL

All melting points were determined on a Swissco melting point apparatus and are uncorrected. Ir spectra were recorded on a Beckman IR-33 infrared spectrophotometer. Vapor phase chromatograms were recorded on a Varian Autoprep model 700 chromatograph. Nmr spectra were recorded on Varian A-60 and Perkin-Elmer R24 spectrometer. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tennessee.

4,5-Dimethoxy-7-indanylidene Aminoacetaldehyde Diethylacetal (**3**).

A solution of 20.0 g. (0.097 mole) of 4,5-dimethoxy-indan-7-aldehyde (**2**), 16 ml. (0.110 mole) of aminoacetaldehyde diethylacetal and 200 ml. of benzene was refluxed overnight with removal of water in a Dean-Stark trap. The solvent was removed on the rotary evaporator yielding 31.8 g. (crude) of **3** as an orange oil; ir (liquid film): 2820-3000 (C-H), 1640 and 1600 (-CH=N- and aromatic -CH=CH-), 1115, 1060 cm^{-1} (C-O). This compound was utilized in the subsequent reaction without further purification.

5,6-Dimethoxycyclopentano[*h*]isoquinoline (**1**).

Cyclization of **3** to yield the title compound **1** was carried out according to the procedure of Bevis (4) with slight modifications. To 25.0 g. (0.078 mole) of the imine **3** in a 3-necked round bottom flask fitted with a pressure equalizing funnel, condenser, and drying tube, 100 g. of trifluoroacetic anhydride was added dropwise (exothermic) with stirring and cooling in an ice bath. In a similar manner, 100 g. of trifluoroacetic anhydride was added to 50.4 g. of 40% (W/W) boron trifluoride/glacial acetic acid (prepared by passing boron trifluoride gas into glacial acetic acid). After slowly adding the solution of the imine to the boron trifluoride solution, at a temperature of 4-9°, the reaction was allowed to warm to room temperature and stand for 30 hours. The reaction mixture was then poured into ice water. An excess of concentrated ammonium hydroxide and 30 g. of sodium hydroxide in water was added and the mixture was allowed to stand overnight. Saturation of the mixture with sodium hydroxide was then followed by extraction with ether. The ether solution was then extracted with five 100 ml. portions of 5% hydrochloric acid. The acid solution was made basic by addition of ammonium hydroxide and sodium hydroxide and the resulting alkaline aqueous solution was extracted again with ether. After drying and thorough removal of the solvent by rotary evaporation, 15.3 g. of colored solid was obtained which yielded **1** as yellow crystals from acetonitrile, 9.94 g. (55%), m.p. 92-94°. Removal of acetonitrile from the filtrate gave a dark oil which yielded a further crop of **1** when eluted from an alumina column with ether. Further recrystallization of **1** from acetonitrile yielded colorless prisms, m.p. 93-95°; ir (potassium bromide): 2860 and 2880-3040 (C-H), 1617, 1580 (aromatic-CH=CH-) and 1060, 1085 cm^{-1} (C-O).

Anal. Calcd. for $C_{14}H_{15}O_2N$: C, 73.34; H, 6.59; N, 6.10. Found: C, 73.43; H, 6.44; N, 6.04.

Note.

The product may be extracted with chloroform but the isolation procedure must be modified. The hydrochloride salt of the product is soluble in chloroform to such an extent that aqueous hydrochloric acid solutions will extract it from chloroform only with extreme difficulty.

5,6-Dimethoxycyclopentano[*h*]isoquinoline *N*-Oxide (**4**).

After stirring 4.70 g. (0.020 mole) of **1** in 10 ml. of acetic acid and 6 ml. of 30% hydrogen peroxide at room temperature for 1 hour the solution was refluxed for 2 hours. An additional 4 ml. of 30% hydrogen peroxide was added and stirring was continued for 1 hour at room temperature followed by gentle heating for 1.5 hours. After making the reaction mixture basic with sodium carbonate solution, the *N*-oxide was extracted with chloroform giving 3.08 g. of solid material which recrystallized well from acetonitrile giving 2.03 g. (40%) of **4** as very fine needles, m.p. 171-173°.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.59; H, 6.42; N, 5.88.

N-Acetyl-5,6-dimethoxycyclopentano[*h*]-1-isoquinolone (**5**).

A solution of 2.03 g. (0.008 mole) of **4** in 25 ml. of acetic anhydride was refluxed 50 minutes and cooled to room temperature. After standing at room temperature 2 hours, the dark reaction mixture yielded a crystalline material which was filtered, washed with a small quantity of anhydrous ether and carefully dried giving 0.78 g. (37%) of **5** as slightly pink needles, m.p. 135-137°, ir (potassium bromide): 1710 (s), 1675 (s), 1635 (s) cm^{-1}; nmr (deuteriochloroform): δ 7.83 (d, 1, 3=CH-), 6.70 (d, 1, 4=CH-), 4.00 (s, 3, 5 CH_3O), 3.85 (s, 3, 6 CH_3O), 3.48 (t, 2, 9-CH_2), 2.99 (t, 2, 7-CH_2), 2.81 (s, 3, CH_3-C(=O)-) and 2.15 (m, 2, 8-CH_2).

Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.87. Found: C, 67.05; H, 5.89; N, 4.74.

5,6-Dimethoxycyclopentano[*h*]-1-isoquinolone (**6**).

Samples of **5** which stood in the presence of atmospheric moisture or which were refluxed in an aqeuous solution gave a single carbonyl stretching absorption in the ir (1650 cm^{-1}) and showed a complete loss of the methyl singlet (δ 2.81) in the nmr spectrum. A sample was recrystallized from absolute ethanol yielding needles, m.p. 201-202°; ir (potassium bromide): 1650 cm^{-1}.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.27; H, 6.01; N, 5.67.

5,6-Dihydroxycyclopentano[*h*]isoquinoline Hydrobromide (**8**).

In a round bottom flask fitted with a condenser, 8.74 g. (0.038 mole) of **1** and 90 ml. of 48% hydrobromic acid were refluxed for 45 minutes. After the first 20 minutes of refluxing, a yellow precipitate consisting of small fine needles began to form. During the total reflux period, the reaction mixture became thick with precipitate which was finally filtered. The precipitate was washed into a flask with water. After removing the water on the rotary evaporator, the solid was dried for two hours at 60° in a vacuum oven. Recrystallization was carried out by dissolving the compound in a large volume of absolute alcohol and then reducing the volume by about half causing some of the material to precipitate. This mixture yielded 7.45 g. (68%) of **8**, m.p. greater than 245° with decomposition; ir (potassium bromide): 3600 cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}BrO_2N$: C, 51.08; H, 4.28; Br, 28.32; N, 4.96. Found: C, 51.24; H, 4.18; Br, 28.27; N, 4.90.

5,6-Dihydroxycyclopentano[*h*]isoquinoline Diacetate Ester (**9**).

In 15 ml. of pyridine and 3 ml. of acetic anhydride, 1.0 g. (0.0035 mole) of **8** was stirred for 2 hours at room temperature. The reaction was slightly exothermic. After shaking the reaction mixture with ice and water and extracting with several portions of 400 ml. of ether, the combined ether extracts were washed with ammonium carbonate solution. The ether extract was dried over anhydrous magnesium sulfate and then evaporated at reduced pressure giving 612 mg. (61%) of **9** as a tan crystalline solid. A small sample was recrystallized several times from ethyl acetate giving prisms, m.p. 164-167°. After standing several days, this compound possessed a strong odor of acetic acid; ir (potassium bromide): 1730 cm^{-1}.

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.35; H, 5.29; N, 4.90. Found: C, 67.47; H, 5.32; N, 4.82.

5,6-Dihydroxycyclopentano[*h*]isoquinoline Di-*n*-butyrate Ester (**10**).

To 118 ml. of pyridine, 7.90 g. (0.028 mole) of **8** and 24 ml. of butyric anhydride were added and the mixture was stirred for 4.5 hours at room temperature. After pouring the reaction mixture into ice and water, shaking well and saturating with sodium hydroxide, extraction was carried out with small volumes of ether (a total of 1 l.). The ether extract was washed with ammonium carbonate solution and dried over anhydrous magnesium sulfate. After evaporation of the solvent, a crude oil was obtained which was distilled through a short path distillation apparatus at approximately 30 μ pressure and 192°. The distillate solidified on standing overnight and the solid was recrystallized from 90-120° b.p. ligroin. Charcoal was utilized to remove color and prolonged periods of cooling the solution (room temperature) had to be avoided because a second white powdery substance formed on the surface of the heavier prisms of diester. The second substance appeared to be a monoester. Thus, 2.87 g. (30%) of the diester was obtained, m.p. 83-85°. After standing for several days, this compound always possessed the odor of butyric acid; ir (potassium bromide): 1730 cm^{-1}.

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.49; H, 6.63; N, 4.01.

5,6-Dihydroxycyclopentano[*h*]isoquinoline Dibenzoate Ester (**11**).

In a round bottom flask fitted with a condenser and drying tube, 5.97 g. (0.021 mole) of **8**, 20.3 ml. (0.176 mole) of benzoyl chloride and 50 ml. of pyridine were heated at 70-80° for about 45 minutes. After cooling to room temperature, volatile materials were removed on the rotary evaporator giving a cherry red oil which was stirred with many portions of petroleum ether. The petroleum ether removed excess benzoyl chloride and/or other impurities and caused the oil to solidify giving 6.21 g. of a pink powder. Two recrystallizations of the powder from acetonitrile yielded 4.01 g. (47%) of **11** as slightly colored heavy crystals, m.p. 188-189°; ir (potassium bromide): 1730 cm^{-1}.

Anal. Calcd. for $C_{26}H_{19}O_4N$: C, 76.27; H, 4.67; N, 3.42. Found: C, 76.07; H, 4.62; N, 3.34.

5,6-Dihydroxycyclopentano[*h*]isoquinoline Bis(3,4,5-trimethoxybenzoate) Ester (**12**).

In 60 ml. of pyridine, 3.00 g. (0.011 mole) of **8** and 9.33 g. (0.041 mole) of 3,4,5-trimethoxybenzoyl chloride were heated at 60-70° for 30 minutes and then allowed to cool slowly to room temperature. After removing the pyridine by evaporation *in vacuo*, the solid obtained was heated twice in 200 ml. of 30-60° boiling petroleum ether followed by decantation of the solvent. The solid was dried, stirred in 400 ml. of 6% (W/W) ammonium carbonate solution for 50 minutes filtered and dried. An ir spectrum indicated the presence of an anhydride as well as the ester. The solid was then refluxed several times in petroleum ether or ligroin. Each time the hot solution was filtered removing some of the more soluble anhydride in the filtrate and finally leaving only the ester, 3.60 g. (15%). A small sample was recrystallized from acetonitrile yielding **12** as shiny needles, m.p. 217-218°; ir (potassium bromide): 1730 cm^{-1}.

Anal. Calcd. for $C_{32}H_{31}O_{10}N$: C, 65.18; H, 5.29; N, 2.37. Found: C, 65.11; H, 5.31; N, 2.13.

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