An Alternate Route for the Synthesis of Cyclopentano[*h*]-1,2,3,4-tetrahydroisoquinolines

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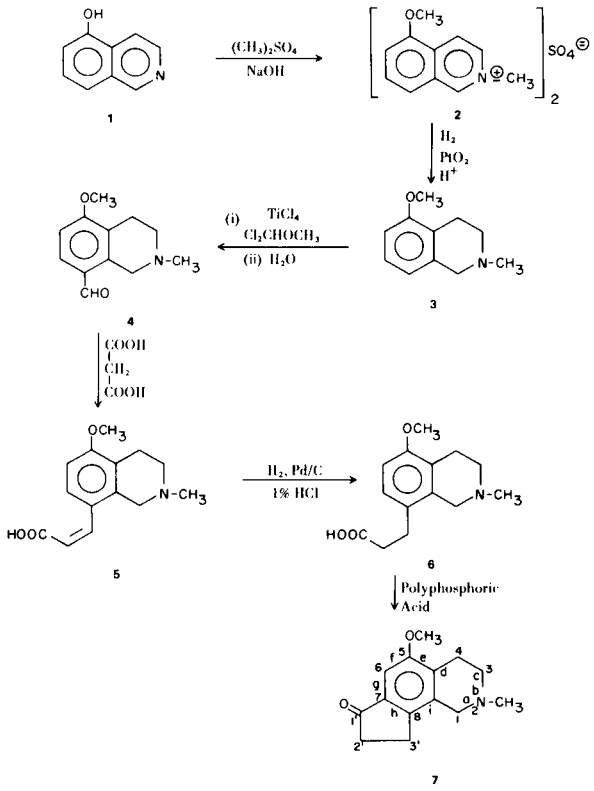
In a continuation of our established interest (1) in variously reduced isoquinolines and in particular in the recent synthesis (2) of the previously unreported cyclopentano[*h*]-1,2,3,4-tetrahydroisoquinolines, an attempt was made to synthesize this ring system from an isoquinoline derivative. Our earlier studies involved the addition of the nitrogen containing ring to a substituted indane. While this route was successful it comprised many steps (**9**) including the separation of positional isomers produced at one stage of the reaction sequence. It was our feeling that the pathway could be improved by utilizing a substituted tetrahydroisoquinoline as the starting material.

The initial attempts involved the very obvious Friedel-Crafts type reactions on 5-bromoisoquinoline using various chloracyl chlorides, or β-propiolactone, with aluminum chloride as the Lewis acid. These proved unsuccessful and appreciable quantities of starting material were isolated. The formylation of 5-bromoisoquinoline by the method of Rieche (3) using the titanium tetrachloride catalyzed reaction with α,α-dichloromethyl methyl ether was also unsuccessful. The acylation of 5-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**3**) at the 8-position was attempted using the titanium tetrachloride catalyzed introduction of (a) β-propiolactone and (b) β-chloropropionyl chloride but also proved to be impractical. A final attempt to formylate 3, using α,α-dichloromethyl methyl ether, was successful and laid the foundation for the synthesis, accomplished as outlined in Figure 1.

Figure 1



5-Hydroxyisoquinoline (**1**) was methylated with dimethyl sulfate using a procedure outlined by Hiers and Hager (4) to produce **2**. Catalytic hydrogenation of **2** yielded the desired 5-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (3) as expected. Treatment of **3** with α,α-dichloromethyl methyl ether using titanium tetrachloride as catalyst according to the method of Rieche (3) introduced the aldehyde group into the aromatic ring (**4**) in good yield (74%). The location of this group at the 8-position in **4** was assigned by nmr spectroscopy. Compound **3** showed an absorption for the 1-CH_2- grouping at 3.57 δ as a well defined singlet, clearly separated from the 5-OCH_3 (3.80 δ). The subject aldehyde **4**, on the other hand, showed these protons to be downfield at 3.88 δ, in close proximity to the 5-OCH_3 (3.90 δ) signal. This evidence strongly supports the assignment of the aldehyde grouping to the 8-position since if, indeed, the alternate 6 position had been formylated, then no change in the position of the 1-CH_2- grouping would have been expected. Furthermore, addition of the shift reagent Eu(DPM)$_3$ to aldehyde **4** resulted in a downfield shift of the 1-CH_2- signal to 9.27 δ. This shift in signal position would be expected if the aldehyde is located at position 8, since the 1-CH_2- would be effected by the binding of the reagent to both the heteroatom and the aldehyde grouping. In the alternate situation (*i.e.*, aldehyde at position 6) the 1-CH_2- would be effected only by the binding at the heteroatom

and a signal shift comparable to that observed for the 3 and 4 -CH_2- protons of **4** would be observed, *i.e.*, 4.6-5.0 δ. The aldehyde signal of **4** taken in conjunction with the aldehyde signals of *o*-methoxybenzaldehyde (OMB) and *p*-methoxybenzaldehyde (PMB) was also of significance in assigning the structure. Aldehyde **4** gave a signal at 9.85 δ while a peak was noted for OMB at 10.42 δ, and at 9.84 δ for PMB thus indicating a similar location of the functional grouping in PMB and **4** (*i.e.*, aldehyde at position 8 in **4**). Examination of the aromatic proton signals, including the addition of the shift reagent, did not contribute additional evidence for the structure elucidation.

Treatment of **4** with malonic acid according to the Doebner (5) modification of the Perkin reaction afforded the unsaturated acid **5** in good yield. Purification of **5** proved extremely difficult; however, reduction in the presence of acid to the corresponding saturated amino acid **6** allowed purification more readily. Ring closure of **6** using polyphosphoric acid (6) yielded the desired ring system in 65% yield. Infrared and nmr spectral data coupled with microanalytical evidence confirmed the structure of **7**.

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 Varian Autoprep model 700 chromatograph. Nmr spectra were recorded on Varian HA-60 and Perkin-Elmer R24 spectrometers. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tennessee and Chemalytics, Tempe, Arizona.

5-Methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**3**).

Into a flask equipped with a mechanical stirrer, reflux condenser, and an equilibrium addition funnel, was placed a solution prepared by the addition of 5-hydroxyisoquinoline (**1**) (25.0 g., 0.172 mole) to water (100 ml.) in which sodium hydroxide (6.9 g., 0.172 mole) had previously been dissolved. The contents of the flask were cooled to 0° and stirred. During a 1 hour period, dimethyl sulfate (43.5 g., 0.345 mole) was added. The reaction mixture was maintained at 70° for 30 minutes, and a second solution of **1** (25.0 g., 0.172 mole), prepared as described above, was added during a 15 minute period. The reaction mixture was refluxed overnight. Dilute (10%) hydrochloric acid was added to the cooled reaction mixture until it became acidic (a large excess of acid was avoided). The resulting quaternary salt, 5-methoxy-2-methylisoquinolinium salt(s) (2), was reduced in the acidic solution over platinum oxide (2.5 g.) using a low pressure Paar Hydrogenation Apparatus. The filtrate obtained from the hydrogenation was made basic with excess sodium hydroxide (20%) and saturated with sodium chloride. The product was extracted with diethyl ether, and the ether extract dried over sodium sulfate. Removal of the ether afforded the crude product which was vacuum distilled (b.p., 80-85°/0.4 mm) resulting in pure **3** (26.8 g., 49%) ν max (thin film): 1256 (C-N), 1082 (C-O-C) cm^{-1}, δ (deuteriochloroform): 6.55-7.30 (m, 3H, 6, 7, and 8 -CH=), 3.80 (s, 3H, 5 -OCH_3), 3.57 (s, 2H, 1 -CH_2), 2.56-3.02 (m, 4H, 3 and 4 -CH_2-), 2.45 (s, 3H, 2 -CH_3). The hydrochloride salt of **3** melted at 222° (lit. (7) m.p. 221°).

5-Methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-8-carboxaldehyde (**4**).

Into a flask equipped with a mechanical stirrer, an equilibrium addition funnel, and a condenser fitted with a calcium chloride drying tube, were placed methylene chloride (150 ml.) and **3** (15.0 g., 0.085 mole). The solution was cooled to 0° and stirred. Titanium tetrachloride (51.6 g., 0.272 mole) was added gradually, followed by the rapid dropwise addition of α,α-dichloromethyl ether (9.8 g., 0.085 mole). After the reaction mixture was allowed to warm to room temperature, it was refluxed for 7 hours. The titanium chloride complex of the product was decomposed with water and ice, and the resulting solution kept cool as it was made basic with excess sodium hydroxide (20%). The resulting suspension was extracted with chloroform. The extract was dried over sodium sulfate and the solvent removed, affording the crude product which was vacuum distilled (b.p. 122°/0.1 mm) to yield 13.0 g. (74%), 5-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-8-carboxaldehyde (**4**). The hydrochloride salt of **4** melted at 244-245° after recrystallization from absolute ethanol; ir ν max (thin film of the free base): 1680 (C=O), 1580 (C=C), 1263 (C-N), 1081 (C-O-C) cm^{-1}; nmr δ (carbon tetrachloride): 9.85 (s, 1H, 8 -CHO), 7.50 (d, 1H, J = 8 cps, 7 -CH=), 6.73 (d, 1H, J = 8 cps, 6 -CH=) 3.90 (s, 3H, 5 -OCH_3), 3.88 (s, 2H, 1 -CH_2-), 2.55-2.9 (m, 4H, 3 and 4 -CH_2-), 2.45 (s, 3H, 2 -CH_3).

Anal. Calcd. for $C_{12}H_{13}ClNO_2$: C, 59.6; H, 6.7; N, 5.8; Cl, 14.7. Found: C, 59.8; H, 6.8; N, 5.8; Cl, 14.4.

β-(5-Methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-8)propenoic Acid Hydrochloride (**5**).

Into a flask (100 ml.) were placed malonic acid (12.0 g., 0.116 mole) and dry pyridine (25 ml.). The contents of the flask were heated until solution occurred. After the solution had cooled to room temperature, **4** (12.0 g., 0.058 mole) was added. Piperidine (25 drops) was added as a catalyst. The reaction mixture was warmed for 30 minutes at 80° followed by a 2.5 hour refluxing. After the solution had cooled, it was poured into cold water (200 ml.) and slowly acidified with dilute (10%) hydrochloric acid. The precipitated product (**5**) was collected by filtration and dried (4 hours, 110°); it was then ground and further dried (2 hours 110°) in a vacuum oven. The filtrate was successively concentrated and cooled until no additional product precipitated. The crude product (**5**), m.p. 260-265° (11.5 g., 70%), was not purified; ir ν max (potassium bromide): 1670 (C=O), 1590 (C=C) cm^{-1}.

β-(5-Methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-8)propanoic Acid Hydrochloride (**6**).

Into a hydrogenation bottle (500 ml.) were placed 5% palladium on charcoal (0.5 g.) and a suspension of **5** (5.7 g., 0.028 mole) in dilute (1%) hydrochloric acid (250 ml.). Compound **5** was reduced during a 20 hour period in a low pressure Paar Hydrogenation Apparatus. After removal of the catalyst by filtration, the filtrate was successively concentrated and cooled until no further product precipitated. The portions of the product (**6**) were collected by filtration and dried (4 hours, 110°) in a vacuum oven. If the dry product (**6**) (4.8 g., 84%) had a melting point less than 210°, it was recrystallized from water (m.p. 212°); ir ν max (potassium bromide): 1708 (C=O) cm^{-1}.

Anal. Calcd. for $C_{14}H_{20}ClNO_3$: C, 58.8; H, 7.1; N, 4.9; Cl, 12.4. Found: C, 58.9; H, 7.0; N, 4.7; Cl, 12.2.

5-Methoxy-2-methyl-7,8-cyclopentano[*h*]-1,2,3,4-tetrahydroisoquinoline-1′-one (**7**).

Into a flask (500 ml.) which was heated to 55° with an oil bath and equipped with a mechanical stirrer, calcium chloride drying

tube, and a thermometer, were placed preheated (steam bath) polyphosphoric acid (PPA) (100 g.) and compound **6** (7.4 g., 0.026 mole). The mixture was stirred as the temperature of the oil bath was gradually raised. At an internal temperature of 60° the reaction commenced, as evidenced by a light green color. The internal temperature was raised to 78° over a 15 minute period and maintained there for a further 20 minutes. The reaction mixture became dark green during this time. The PPA complex formed was then decomposed with ice and water after the contents of the flask had cooled to room temperature. The solution was kept at room temperature or cooler during basification with sodium hydroxide (20%) by the addition of large amounts of ice. The resulting suspension was extracted with diethyl ether and the extract dried over sodium sulfate. Removal of the ether afforded the crude product (**7**) which was recrystallized (m.p. 151-152°) from diethyl ether (3.9 g., 65%); ir ν max (potassium bromide): 1690 and 1300 (C=O); 1078 (C-O-C) cm^{-1}; nmr δ (deuteriochloroform): 7.07 (s, 1H, 6 -CH), 3.88 (s, 3H, 5 -OCH_3), 3.57 (s, 2, 1 -CH_2-), 2.60-3.03 (m, 8H, 3, 4, 2′ and 3′ -CH_2-), 2.52 (s, 3H, 2 -CH_3).

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.7; H, 7.4; N, 6.1. Found: C, 72.5; H, 7.5; N, 5.9.

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