

Studies on the Syntheses of Heterocyclic Compounds. Part DCXLIV (1).  
Catalytic Reduction of Homoproorphine Related Compounds

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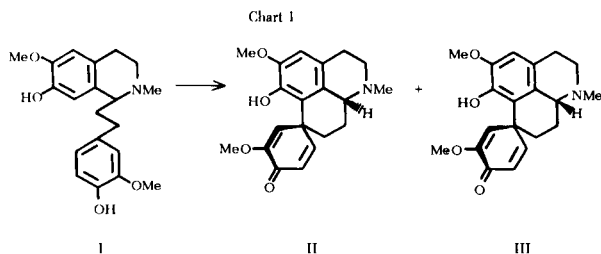
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Received September 8, 1975

Hydrogenation of the homoproorphine (IV) over platinum oxide gave a mixture of the cyclohexanols VIIa and VIIb. In contrast, reduction of IV on palladium provided the cyclohexanone VI, which was also obtained from VIIb by oxidation. Treatment of the cyclohexanols VIIa and VIIb under hydrogen on platinum oxide afforded the same mixture of VIIa and VIIb.

Previously we have reported a synthesis of the homoproorphine alkaloid ( $\pm$ )kreysiginone (II) (3) and its epimer III by phenolic oxidation of diphenolic phenethylisoquinoline (I) by biogenetic pattern (4) and determination of the configuration of homoproorphine at the spiro-center by chemical and spectral studies (5,6). Recently, we have also described the novel epimerization of the hydrogen at C<sub>6a</sub> position of the homoproorphines in the catalytic hydrogenation of ( $\pm$ )kreysiginone (II) and epimer III on platinum catalyst (7). In this paper we wish to report hydrogenation of the homoproorphine IV derived from III.



( $\pm$ )Kreysiginone epimer (III) was subjected to dienone-phenol rearrangement with concentrated hydrochloric acid in glacial acetic acid at 20-25° for 24 hours to give the homoaporphine (V), m.p. 241-243° [lit. (5), m.p. 241-242°] and the cyclohexenone IV, m.p. 197-198° [lit. (5), m.p. 197-198°] in 5% and 62% yield, respectively, and the latter product showed a cyclohexenone system at 1690 cm<sup>-1</sup> but not a hydroxyl group in ir spectrum. The nmr spectrum revealed an aliphatic *O*-methyl resonance at  $\delta$  3.61, and two doublets having  $J = 10.5$  Hz at 5.93 (C<sub>10</sub>-H) and 6.90 (C<sub>9</sub>-H), the latter doublet of which suffered a further long-range coupling ( $J = 2$  Hz) through the ring with C<sub>13</sub>-protons resonated at 2.0.

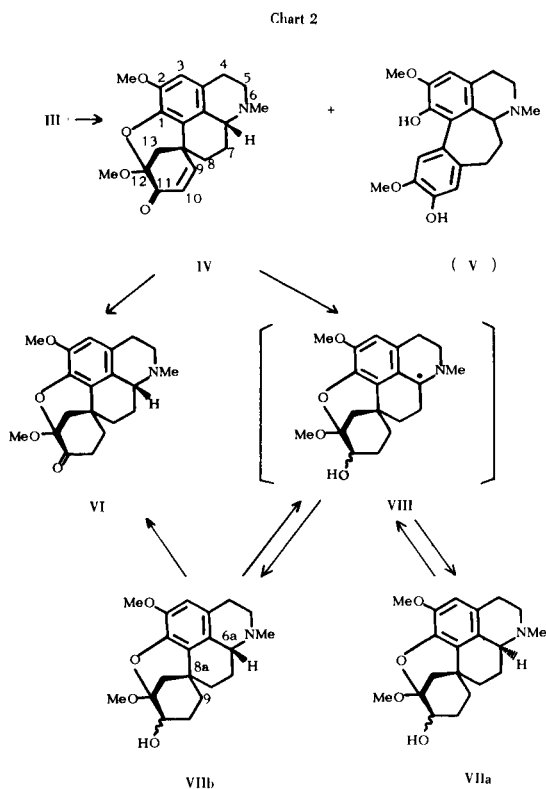
Catalytic hydrogenation of the cyclohexenone IV in the presence of 20% palladium on charcoal in ethanol at atmospheric pressure and room temperature afforded, in 63% yield, the cyclohexanone VI characterized as its methiodide, m.p. 255-257° dec., whose free base showed a six-membered ketone at 1730 cm<sup>-1</sup> in the ir spectrum and no olefinic protons in the nmr spectrum.

On the other hand, catalytic reduction of the same cyclohexenone IV in methanol on platinum oxide at room temperature and atmospheric pressure gave a mixture of the cyclohexanols VIIa and VIIb in a ratio of 1:2, which was separated by silica gel column chromatography. The first eluate afforded one of the cyclohexanols VIIa as colorless prisms, m.p. 113-115°, and the second eluate gave the other cyclohexanol VIIb, characterized as its methiodide as colorless prisms, m.p. 250-252° dec. The ir spectrum of the first base VIIa lacked a carbonyl group and showed a hydroxyl band at 3560 cm<sup>-1</sup> and the nmr spectrum revealed three methyl resonances at 2.42 (NCH<sub>3</sub>, s), 3.40 (aliphatic OCH<sub>3</sub>, s) and 3.83 (aromatic OCH<sub>3</sub>, s) and an aromatic proton at 6.57, but olefinic protons could not be observed. The ir and nmr spectra of the second product VIIb were closely similar [ $\nu$  max 3560:  $\delta$  2.36 (3H, s), 3.36 (3H, s), 3.80 (3H, s) and 6.52 (1H, s)] to those of the first one.

The oxidation of the second cyclohexanol VIIb with chromic anhydride-pyridine complex in methylene chloride at room temperature for 15 minutes provided the cyclohexanone (VI), whose methiodide was identical with the sample prepared from IV as above. However, oxidation product of the first cyclohexanol VIIa under the same conditions as above was different from VI. Treatment of the cyclohexanol VIIa with hydrogen on platinum oxide

in methanol gave a mixture of the first cyclohexanol VIIa and the second cyclohexanol VIIb in a ratio of 1:2, which was also formed in the same ratio from the second cyclohexanol VIIb in the same reaction as the case of VIIa.

It has been known that catalytic hydrogenation over platinum oxide catalyst abstracts the C<sub>1</sub>-hydrogen on 1-monosubstituted 1,2,3,4-tetrahydroisoquinoline ring to generate a radical which is then hydrogenated to afford a mixture of the starting isoquinoline and its C<sub>1</sub>-epimer (7-9). Therefore, the second cyclohexanol could be assigned structure VIIb which had the relative configuration between the C<sub>6a</sub> hydrogen and the C<sub>8a</sub>-C<sub>9</sub> bond to be *trans*, and the first cyclohexanol to structure VIIa, but the stereochemistry of the hydroxyl group remained unclear. Moreover, the intermediate in a reduction of the cyclohexenone IV to the cyclohexanols VIIa and VIIb and in conversion between VIIa and VIIb, in case of hydrogenation, would be a radical VIII which formed by an absorption of the substrate on the catalyst and then a homolytic removal of the hydrogen at the C<sub>6a</sub> position of homoproaporphine system.



Recently, Šantavý (10) has isolated a new phenethylisoquinoline alkaloid kesselringine and assigned structure IX, which is closely similar to our reduction product VII. Therefore, the cyclohexanone VI or the cyclohexanols VII would be intermediates in the biogenesis of kesselringine (IX) from kreysiginine (I) and dihydrokreyssiginine (X) (11).

The above hydrogenations provide the second example of novel epimerization of homoproaporphines in the presence of platinum catalyst.

#### EXPERIMENTAL

All melting points are uncorrected. The ir spectra were measured with a Hitachi-215 recording spectrophotometer, nmr spectra with a JNM-MH 60 spectrometer (TMS as an internal standard and deuteriochloroform as the solvent) and mass spectra with a Hitachi RMU-7 spectrometer.

#### Acidic Treatment of the Homoproaporphine III.

A solution of 500 mg. of the homoproaporphine III in 5 ml. of concentrated hydrochloric acid and 120 ml. of glacial acetic acid was allowed to stand for 24 hours at 20-25°. The reaction mixture was then basified with ammonia under ice cooling and extracted with 400 ml. of chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to leave a colorless caramel, which was chromatographed on 15 g. of silica gel. Evaporation of the chloroform-methanol (v/v 99.5:0.5) eluate, followed by recrystallization from methanol, gave 310 mg. of the cyclohexenone (IV) as colorless needles, m.p. 197-198°, ir  $\nu$  max (potassium bromide): 1690  $\text{cm}^{-1}$  (C=O); nmr,  $\delta$ , 2.17 (2H, d,  $J = 2.0$  Hz, C<sub>13</sub>-H<sub>2</sub>), 2.42 (3H, s, NCH<sub>3</sub>), 3.61 (3H, s, OCH<sub>3</sub>), 3.77 (3H, s, OCH<sub>3</sub>), 5.93 (1H, d,  $J = 10.5$  Hz, C<sub>10</sub>-H), 6.56 (1H, s, C<sub>3</sub>-H), and 6.90 (1H, dd,  $J = 10.5$  and 2.0 Hz, C<sub>9</sub>-H); mass (m/e): 341 (M<sup>+</sup>).

Anal. Calcd. for C<sub>20</sub>H<sub>23</sub>NO<sub>4</sub>: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.05; H, 6.71; N, 3.85.

The second eluate with chloroform-methanol (v/v 99:1) afforded 25 mg. of the homoaporphine (V) as colorless needles from methanol, m.p. 241-243° [lit. (5), m.p. 241-242°]; ir  $\nu$  max (potassium bromide): 3470  $\text{cm}^{-1}$  (OH); nmr (deuteriochloroform-deuteriomethanol):  $\delta$ , 2.35 (3H, NCH<sub>3</sub>), 3.89 (3H, s, OCH<sub>3</sub>), 3.92 (3H, s, OCH<sub>3</sub>), 6.67 (1H, s, ArH), 6.83 (1H, s, ArH), and 7.14 (1H, s, ArH).

#### Catalytic Hydrogenation of the Cyclohexenone IV on Palladium-Charcoal.

A mixture of 300 mg. of the cyclohexenone IV and 200 mg. of 20% palladium-charcoal in 50 ml. of ethanol was shaken in a current of hydrogen at room temperature and atmospheric pressure. After the absorption of a calculated amount of hydrogen, a catalyst was filtered off and the solvent was evaporated to give a residue which was dissolved in water and the resulting solution was made alkaline with ammonia and then extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give a pale yellow caramel, which was subjected to silica gel (9 g.) chromatography. The chloroform-methanol (v/v 99:1) eluate afforded 190 mg. of the cyclohexanone (VI) as a colorless syrup; ir  $\nu$  max (chloroform): 1730  $\text{cm}^{-1}$  (C=O); nmr:  $\delta$ , 2.39 (3H, s, NCH<sub>3</sub>), 3.56 (3H, s, OCH<sub>3</sub>), 3.79 (3H, s, OCH<sub>3</sub>), and 6.53 (1H, s, ArH), whose

methiodide (13) formed colorless prisms (from chloroform-acetone), m.p. 251-252° dec. ir  $\nu$  max (potassium bromide): 1740  $\text{cm}^{-1}$  (C=O).

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{28}\text{NO}_4$ : C, 51.97; H, 5.81; N, 2.89. Found: C, 51.67; H, 5.86; N, 2.96.

Catalytic Hydrogenation of the Cyclohexenone IV on Platinum Oxide.

A mixture of 500 mg. of the cyclohexenone IV, 300 mg. of platinum oxide and 50 ml. of methanol was shaken in a current of hydrogen at room temperature and atmospheric pressure for 1 hour, and worked up as above to leave a colorless caramel. This was chromatographed on 15 g. of silica gel and the first eluate with chloroform-methanol (v/v 99:1) afforded 120 mg. of the cyclohexanol VIIa as colorless prisms after recrystallization from acetone-petroleum ether, m.p. 113-115°, ir  $\nu$  max (potassium bromide): 3560 and 3370  $\text{cm}^{-1}$  (OH); nmr:  $\delta$ , 2.42 (3H, s,  $\text{NCH}_3$ ), 3.40 (3H, s,  $\text{OCH}_3$ ), 3.83 (3H, s,  $\text{OCH}_3$ ), and 6.57 (1H, s, ArH).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{27}\text{NO}_4 \cdot \text{O} \cdot 5\text{H}_2\text{O}$ : C, 67.74; H, 7.96; N, 3.95. Found: C, 67.86; H, 7.93; N, 3.82.

The second eluate with chloroform-methanol (v/v 98.5:1.5) gave 280 mg. of the cyclohexanol VIIb as a colorless syrup,  $\nu$  max (chloroform): 3560  $\text{cm}^{-1}$  (OH); nmr:  $\delta$ , 2.36 (3H, s,  $\text{NCH}_3$ ), 3.36 (3H, s,  $\text{OCH}_3$ ), 3.80 (3H, s,  $\text{OCH}_3$ ), and 6.52 (1H, s, ArH), whose methiodide was obtained as colorless prisms (from methanol-acetone), m.p. 250-252°.

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{30}\text{INO}_4$ : C, 51.75; H, 6.20; N, 2.87. Found: C, 51.75; H, 6.26; N, 2.73.

Oxidation of the Cyclohexanol VIIb.

A mixture of 80 mg. of the cyclohexanol VIIb and chromic anhydride-pyridine complex [prepared from 90 mg. of chromic anhydride and 150 mg. of pyridine (12)] in 5 ml. of methylene chloride was stirred for 15 minutes at room temperature and then poured into water. The mixture was basified with ammonia and extracted with methylene chloride. The extract was washed with water, dried over sodium sulfate and evaporated to give 50 mg. of a brown caramel, which was chromatographed on 1 g. of silica gel. The chloroform-methanol (v/v 99:1) eluate afforded 10 mg. of the cyclohexanone VI as a colorless syrup, which gave its methiodide, m.p. 254-256° dec., as colorless prisms (from methanol). This methiodide was identical with the authentic sample prepared by palladium-charcoal reduction of IV in ir spectral comparison.

Oxidation of the Cyclohexanol VIIa.

Thirty mg. of the cyclohexanol VIIa was mixed with chromic anhydride-pyridine complex [prepared from 150 mg. of chromic anhydride and 240 mg. of pyridine] in 5 ml. of methylene chloride, and stirred for 20 minutes at room temperature. Work-up and purification of silica gel as above gave a resinous oil, whose structure could not be determined.

Isomerization of the Cyclohexanol VIIa.

A mixture of 10 mg. of the cyclohexanol VIIa and 10 mg. of platinum oxide in 20 ml. of methanol was shaken in a current of hydrogen at room temperature and atmospheric pressure for 1

hour. After filtration and removal of the solvent, the residue was extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to leave 8 mg. of a pale pink syrup, which was chromatographed on 300 mg. of silica gel. Evaporation of the chloroform-methanol (v/v 99:1) eluate gave 1 mg. of the starting cyclohexanol VIIa, whose m.p. and ir spectrum were identical with those of the authentic sample.

The second eluate of chloroform-methanol (v/v 98:2) afforded 2 mg. of the isomeric cyclohexanol VIIb, whose methiodide, m.p. 251-253° dec., was identical with the authentic sample in ir spectral comparison.

Isomerization of the Cyclohexanol VIIb.

A mixture of 30 mg. of the cyclohexanol VIIb, 20 mg. of platinum oxide and 10 ml. of methanol was shaken in a current of hydrogen and worked up as above to give 2 mg. of the isomeric cyclohexanol VIIa and 4 mg. of the starting cyclohexanol VIIb after chromatography on silica gel. The cyclohexanol VIIa and methiodide of VIIb were identical with the authentic samples in m.p. and ir spectral comparisons, respectively.

Acknowledgement.

We thank President A. Yanagisawa and Director O. Takagi, Grelan Pharmaceutical Co. Ltd., for their grateful encouragement. We also thank Miss R. Kato, Miss R. Suenaga, Miss E. Nagaoka, Miss Y. Yokohama, Mrs. A. Sato, Mrs. C. Koyanagi, and Mr. K. Kawamura for spectral measurements and microanalyses.

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- (13) Recrystallization of this methiodide from methanol gave the compound having an enolic form, m.p. 255-257° dec., ir  $\nu$  max (potassium bromide) 3430  $\text{cm}^{-1}$  (OH).  
*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{28}\text{NO}_4 \cdot \text{CH}_3\text{OH} \cdot \text{H}_2\text{O}$ : C, 49.35; H, 6.40; N, 2.62. Found: C, 49.63; H, 6.57; N, 2.46.