Deamination of 5-Aminodecahydroisoquinolines. An Improved Synthesis of *cis*-5,9,10-H- and *trans*-9,10-*trans*-5-H-5-Hydroxydecahydroisoquinolines

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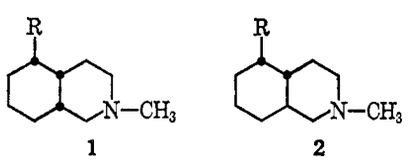
The stereochemistry of some previously unreported 5-amino-2-methyldecahydroisoquinolines, and their derivatives, has been elucidated by relation to the 5-hydroxy-2-methyldecahydroisoquinolines (**1a** and **2a**). The isomeric 5-amino-2-methyldecahydroisoquinolines were prepared by a one-step reduction of 5-nitro-2-methylisoquinolinium *p*-toluenesulfonate and converted into their acetamide derivatives which allowed convenient separation of the *cis*-9,10 (**1c**) and *trans*-9,10 (**2c**) isomers. Acid hydrolysis of these separated acetamides subsequently yielded pure *cis*-5,9,10-H- (**1b**) and *trans*-9,10-*trans*-5-H-5-amino-2-methyldecahydroisoquinolines (**2b**). The hydrolysis of **1c** proceeded at a faster rate than **2c**. Conversion of **1b** and **2b** by deamination with nitrous acid into the corresponding alcohols in high yield supports the equatorial nature of the 5 substituents. A small amount (2%) of inversion was observed during the deamination of **2b**.

An investigation of the effects on the cardiovascular system induced by various stereoisomers of substituted decahydroisoquinolines led us to develop an improved method of producing reduced isoquinolines of known stereochemistry at the ring junction, *i.e.*, *cis*-9,10 and *trans*-9,10. The stereochemistry of decahydroisoquinoline[1] and 5-hydroxy-2-methyldecahydroisoquinolines[2,3] has previously been studied. No previous work has been reported on the 5-amino-2-alkyldecahydroisoquinolines and their derivatives, the stereochemistry of which we have now related to the hydroxy analogs.



1 **2**

a, R = OH
b, R = NH_2
c, R = $NHCOCH_3$

Witkop[1] showed that direct, low pressure, platinum-catalyzed hydrogenation of isoquinoline in acidic media produced a 2:1 mixture of *cis*- and *trans*-decahydroisoquinolines. We have found, under similar conditions, the addition of a 5-hydroxy substituent to the isoquinoline nucleus does not significantly alter the 2:1 *cis* to *trans* ratio of 5-hydroxydecahydroisoquinolines produced, as demonstrated by vapor phase chromatography of the crude reaction products. Quaternization of 5-hydroxyisoquinoline with methyl *p*-toluenesulfonate and hydrogenation of the resulting product under identical acidic conditions to those previously reported[4] yielded 5-hydroxy-2-methyldecahydroisoquinolines; the *cis*/*trans* ratio is unaltered from that reported by Witkop[1] for isoquinoline. The yield, in our hands, approximated 25% alcohols [*cis* and *trans*, predominantly as the acetate ester(s) as shown by infrared spectra] and 25% decahydroisoquinolines, *cis* and *trans* in a 2:1 ratio, as shown by vapor phase chromatography.[5] Kimoto and Okamoto[2] report only *cis*-9,10-5-acetoxy-2-methyldecahydroisoquinoline and *cis*-9,10-2-methyldecahydroisoquinoline from the platinum-catalyzed reduction of 5-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline. A similar reduction[3] of 5-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline did not produce the acetate (although the work-up may have obscured its presence) nor any hydrogenolysis products, but did yield two alcohols, the *cis* alcohol being the predominant isomer.

We have been able to avoid or minimize the problems of hydrogenolysis and ester formation and to improve the yield during hydrogenation, by reducing 5-nitro-2-methylisoquinolinium *p*-toluenesulfate, under the same acidic conditions, to the previously unreported *cis*-5,9,-10-H- (**1b**) and *trans*-9-10-*trans*-5-H-5-amino-2-methyldecahydroisoquinolines (**2b**). Vapor phase chromatography of the crude reaction products indicated 85–90% 5-amino-2-methyldecahydroisoquinolines **1b**–**2b** (2:1) and only 10–12% hydrogenolysis products. The lower boiling hydrogenolysis products were separated from the 5-amino isomers by distillation, and vapor phase chromatography of the 5-amino isomers showed only two components. Efficient separation of these isomers was not possible by distillation on spinning-band columns. The 5-amino isomeric mixture was converted into a mixture of the corresponding acetamides. It is possible by differences in water solubility to separate the *cis*-5,9,10-H- (**1c**) and *trans*-9,10-*trans*-5-H-5 acetamido (**2c**) derivatives. Hydrolysis of the amides afforded pure *cis*-5,9,10-H- (**1b**) and pure *trans*-9,10-*trans*-5-H-5-amino-2-methyldecahydroisoquinolines (**2b**) in quantitative yield. Hydrolysis of the pure acetamide isomers proceeded at markedly different rates. The *cis* acetamide hydrolyzed readily on refluxing with 15% w/v sulfuric acid over 1 day; the *trans* isomer, however, required up to 6 days refluxing with 20% w/v sulfuric acid before complete hydrolysis was achieved—a rate difference of approximately six to ten. Examination of Dreiding molecular models of the equatorial isomers reveals little hindrance to the water molecule attacking the protonated amide function. We speculatively suggest that this marked difference in hydrolytic rates between the isomers to be due to the flexibility of the *cis* isomer as opposed to the rigidity of the *trans* isomer. The formation of the tetrahedral carbon intermediate required by the hydrolytic mechanism[6] may be more readily accommodated by the flexible *cis* ring system. We are unaware of any studies of comparable hydrol-

(1) B. Witkop, *J. Amer. Chem. Soc.*, **70**, 2617 (1948).
(2) S. Kimoto and M. Okamoto, *Yakugaku Zasshi*, **85**, 371 (1965).
(3) S. Durand-Henchoz and R. C. Moreau, *Bull. Soc. Chim. Fr.*, 3424 (1966).
(4) I. W. Mathison, *J. Org. Chem.*, **30**, 3558 (1965).
(5) The stereochemistry in this hydrogenation is developed at the same point as hydrogenations outlined by Kimoto and Okamoto[2] and Durand-Henchoz and Moreau;[3] the experimental details are therefore not reported in this paper.
(6) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, pp 328, 329.

ysis differences in similar cyclic systems. These differences suggest the possibility of separating the *cis* and *trans* isomers by selective hydrolysis.

We have demonstrated the equatorial conformation of the 5-amino substituent of the separated 5-amino-2-methyldecahydroisoquinolines (and therefore their aceamides) by deamination with nitrous acid in high yield to the corresponding alcohols (see Experimental Section). These conclusions are based upon the work of Dauben, *et al.*,[7] who reported that in the decalylamines high conversions (100%) were obtained only with the equatorial conformers; axial amino substituents on deamination with nitrous acid yielded small amounts of alcohol (27%) and large amounts of olefins. The stereochemical assignments for the alcohols produced during our deaminations are based on the work of Durand-Henchoz and Moreau,[3] who related spectrally the decahydroisoquinolinols with the corresponding known decalols.[7]

Additionally, we observed some inversion during the deamination of the *trans*-9,10-*trans*-5-H-5-amino (**2b**) isomer. A small quantity of *trans*-9,10-*cis*-5-H-5-hydroxy-2-methyldecahydroisoquinoline (2%) was isolated from the deamination of *trans*-9,10-*trans*-5-H-5-amino-2-methyldecahydroisoquinoline (**2b**). Dauben did not report any evidence for this type of inversion in the corresponding decalylamines. Hückel,[8] however, demonstrated the production of 13% inverted product from the deamination of the equatorial amino grouping in 4-*t*-butylcyclohexylamine.

The advantages of our above-noted procedure for the synthesis of the decahydroisoquinolinols are twofold, namely, increased over-all yield over previously reported procedures[2-4] and the elimination of time-consuming chromatographic techniques for purification of the various isomers, especially the *trans* isomer.

Experimental Section

All melting points were determined using a Swissco melting point apparatus and are corrected. Ir spectra were recorded on a Perkin-Elmer Model 137 B Infracord spectrophotometer and a Perkin-Elmer Model 421 infrared spectrophotometer. Vapor phase chromatograms were recorded on a Varian Aerograph Model 700 Autoprep chromatograph. Nmr spectra were recorded on a Varian A-60 spectrometer. Elemental analyses were carried out by Drs. G. Weiler and F. B. Strauss, Oxford, England.

5-Nitro-2-methylisoquinolinium *p*-Toluenesulfonate.—Methyl *p*-toluenesulfonate (49.5 g) and 5-nitroisoquinoline[9] (46.1 g) were mixed in dimethylformamide (130 ml). After warming to get all the 5-nitroisoquinoline in solution, the mixture was allowed to stand 48 hr. The dimethylformamide was decanted and the crystalline cake was washed with EtAc. A second crop of crystals was obtained when the dimethylformamide decantate was diluted with EtAc. The two combined crops recrystallized from EtAc–EtOH gave 76.6 g, mp 145–146°. An analytical sample melted at 146.5–147.5°.

Anal. Calcd for $C_{17}H_{16}N_2O_5S$: C, 56.65; H, 4.48; N, 7.78; S, 8.90. Found: C, 56.58; H, 4.62; N, 7.92; S, 8.98.

5-Amino-2-methyldecahydroisoquinoline.—5-Nitro-2-methylisoquinolinium *p*-toluenesulfonate (25 g) was dissolved in glacial acetic acid (150 ml), concentrated H_2SO_4 (0.6 ml) was added, and the mixture was hydrogenated over platinum oxide (4 g) at 50 psi. In 25 min the color changed from yellow-brown to colorless, and the rate of hydrogen uptake dropped markedly; during this stage the temperature rose to approximately 60–70°. After 120 hr, the uptake of hydrogen was very slow though only 90–95% of the theoretical amount had been absorbed. After removal, *in vacuo*, of most of the acetic acid, the residue was made alkaline with aqueous base and the free amine extracted with ether. The weight of recovered material after removal of the ether was 95% of the calculated amount based on 5-amino-2-methyldecahydroisoquinoline. Vapor phase chromatography (column, 20 ft, 30% SE-30 on Chromosorb W) showed two 5-amino products, 29% *trans* 9,10-*trans*-5-H- (**2b**) and 59% *cis*-5,9,10-H (**1b**) (shown by hydrolysis of acetamides), and two products of shorter retention time, presumably (see Okomato and Kimoto[2]) *trans*- and *cis*-2-methyldecahydroisoquinoline, 4% and 8%, respectively. The 5-amino-2-methyldecahydroisoquinoline isomeric mixture distils at 50–57° (0.2 mm). Exposure of this amine to air causes rapid formation of a solid carbonate.

***cis*-5,9,10-H- and *trans*-9,10-*trans*-5-H-5-Acetamido-2-methyldecahydroisoquinoline.**—Freshly distilled 5-amino-2-methyldecahydroisoquinoline (29.7 g) was dissolved in dried, distilled dimethylformamide (240 ml). To this solution, cooled to 0°, was added acetic anhydride (18.0 g) in benzene (75 ml) during 1.5 hr. The mixture was allowed to warm and stand at room temperature overnight. The benzene and dimethylformamide were removed at reduced pressure by rotary evaporation. The residue was dissolved in water (55 ml), cooled, and made basic (solution A). Scratching and stirring caused the insoluble viscous oil to crystallize. The crystalline product (**1**) was collected by filtration, washed with cold water, and allowed to dry over $CaCl_2$ in a vacuum desiccator (weight 16.0 g), mp 163–165°. When **1** was recrystallized from EtOH (30 ml) and H_2O (60 ml), and dried, 12.3 g of *cis*-5,9,10-H-5-acetamido-2-methyldecahydroisoquinoline (**1c**) was obtained, mp 168–169°. An analytical sample melted at 169–170°.

Anal. Calcd for $C_{12}H_{22}N_2O$: C, 68.52; H, 10.55; N, 13.32. Found: C, 68.69; H, 10.65; N, 13.00.

The basic filtrate (solution A) was extracted with eight 100-ml portions of ether. The ether solution was dried over Na_2SO_4 overnight. A light precipitate was decanted and collected by filtration to yield 1.0 g of II, mp 199.3–200.3°. The filtrate was concentrated to a residue of 9.4 g (II) which was recrystallized from EtAc–benzene several times to yield 1.0 g of product, mp 197.3–198.3°. The basic, aqueous solution A (after ether extraction) was then concentrated to a slightly tacky solid. This solid was extracted four times with EtAc to yield 4.7 g solid when dry. Two recrystallizations from EtAc–benzene afforded 2.5 g, white crystals of analytical *trans*-9,10-*trans*-5-H-5-acetamido-2-methyldecahydroisoquinoline (**2c**), mp 199.5–200.5°. Further work-up of the various mother liquors provided more **2c**.

Anal. Calcd for $C_{12}H_{22}N_2O$: C, 68.52; H, 10.55; N, 13.32. Found: C, 68.48; H, 10.50; N, 13.20.

Hydrolysis of *cis*-5,9,10-H-5-Acetamido-2-methyldecahydroisoquinoline to *cis*-5,9,10-H-5-Amino-2-methyldecahydroisoquinoline.—A solution of *cis*-5,9,10-H-5-acetamido-2-methyldecahydroisoquinoline (**1c**, 8.0 g), and concentrated H_2SO_4 (8 ml) in water (100 ml) was refluxed 20 hr. The acid solution was concentrated *in vacuo* to a small volume and made basic with NaOH pellets. The basic solution was extracted with ether. The ether solution was dried over K_2CO_3 and concentrated to yield 6.14 g of a straw-colored oil. The product was shown to be a single component by gas chromatography (column, 20 ft, 30% SE-30 on Chromosorb W) and corresponded in retention time to the larger peak of the gas chromatogram for the mixture produced by the hydrogenation of 5-nitro-2-methylisoquinolinium *p*-toluenesulfonate, *i.e.*, *cis*-5,9,10-H-5-amino-2-methyldecahydroisoquinoline (**1b**). A dipicrate of the amine melted at 237.8–238.8°.

Anal. Calcd for $C_{22}H_{26}N_8O_{14}$: C, 42.17; H, 4.18; N, 17.89. Found: C, 42.24; H, 4.30; N, 18.11.

Hydrolysis of *trans*-9,10-*trans*-5-H-5-Acetamido-2-methyldecahydroisoquinoline to *trans*-9,10-*trans*-5-H-5-Amino-2-methyldecahydroisoquinoline.—A solution of *trans*-9,10-*trans*-5-H-5-acetamido-2-methyldecahydroisoquinoline (**2c**, 8.7 g) and concentrated H_2SO_4 (22 ml) in water (200 ml) was refluxed for 144 hr. The solution was concentrated and made alkaline with NaOH pellets, extracted with ether, dried over K_2CO_3, and concentrated to yield 6.3 g of oily product. A vapor phase chromatogram showed a single component having the same retention time as the smaller peak for the chromatogram of the mixture produced from the

(7) W. G. Dauben, R. C. Tweit, and C. Mannerskantz, *J. Amer. Chem. Soc.*, **76**, 4420 (1954).

(8) W. Hückel and K. Heyder, *Chem. Ber.*, **96**, 220 (1963).

(9) The 5-nitroisoquinoline, mp 109.5–110.5° (from EtOH–H_2O), was prepared by the method of Claus and Hoffman [*J. Prakt. Chem.*, **47**, 252 (1893)] as modified by C. Lé Fevre and R. Lé Fevre [*J. Chem. Soc.*, 1475 (1935)]. Material from Aldrich Chemical Co., mp 106–109°, gave similar results.

hydrogenation of 5-nitro-2-methylisoquinolinium *p*-toluenesulfonate, *i.e.*, *trans*-9,10-*trans*-5-H-5-amino-2-methyldecahydroisoquinoline (**2b**). A dipicrate of the amine melted at 261.8–263.8°.

Anal. Calcd for $C_{22}H_{26}N_8O_{14}$: C, 42.17; H, 4.18; N, 17.89. Found: C, 42.23; H, 4.34; N, 17.90.

Deamination with Nitrous Acid[10] of *cis*-5,9,10-H-5-Amino-2-methyldecahydroisoquinoline to *cis*-5,9,10-H-5-Hydroxy-2-methyl decahydroisoquinoline.—To a solution of sodium nitrite (5.0 g) in water (4.0 ml) was added *cis*-5,9,10-H-5-amino-2-methyldecahydroisoquinoline (**1b**, 6.1 g) and acetic acid (8.0 g). The mixture was heated with stirring to 60° and acetic acid (0.87 g) in water (4 ml) was added over a period of 30 min. The mixture was heated with stirring for 13 hr at 55–65°. Then NaOH pellets (5.0 g) were added; the mixture was heated near reflux for 4 hr. More NaOH pellets were added, and the mixture was cooled and extracted with ether in a continuous extractor for 48 hr. The ether solution was dried over K_2CO_3 and concentrated to yield 5.5 g of viscous oil. Vapor phase chromatography (column, 20 ft, 30% SE-30 on Chromosorb W) of the crude oily product prior to distillation showed 2% olefins, 92% *cis*-5,9,10-H-5-hydroxy-2-methyldecahydroisoquinoline (**1a**), and 6% unidentified product. This oil crystallized on standing and was distilled to yield *cis*-5,9,10-H-5-hydroxy-2-methyldecahydroisoquinoline (**1a**, 4.4 g), mp 94–95°. Examination of the ir and nmr spectra of this alcohol showed them to be consistent with the proposed structure. An nmr ($CDCl_3$) peak appeared at 3.75 ppm (half-band width of 15 cps), >CH–OH.

Deamination with Nitrous Acid[10] of *trans*-9,10-*trans*-5-H-5-Amino-2-methyldecahydroisoquinoline to *trans*-9,10-*trans*-5-H-5-Hydroxy-2-methyldecahydroisoquinoline.—*trans*-9,10-*trans*-5-H-5-Amino-2-methyldecahydroisoquinoline (**2b**, 6 g) was deaminated in a procedure identical with that described above for the *cis* isomer. A viscous oil (5.8 g) was recovered from the continuous ether extraction and was shown by vapor phase chromatography to contain 87% *trans*-9,10-*trans*-5-H-5-hydroxy-2-methyldecahydroisoquinoline (**2a**), 7% olefins, and 6% unidentified product. Distillation of this material yielded 4.7 g of **2a**, bp 120–124° (0.3 mm). The ir and nmr spectra of this alcohol were consistent with the proposed structure. An nmr ($CDCl_3$) peak appeared at 3.75 ppm (half-band width of 16 cps), >CH–OH.

It was found that seeding of the above oil with a crystal of *trans*-9,10-*cis*-5-H-5-hydroxy-2-methyldecahydroisoquinoline[11] caused crystallization of 90 mg (2%) of this isomer, mp 131–132°. An nmr ($CDCl_3$) peak appeared at 3.8 ppm (half-band width of 6 cps), >CH–OH.

Registry No.—**1b**, 16336-19-9; dipicrate of **1b**, 16336-20-2; **1c**, 16336-21-3; **2b**, 16336-22-4; dipicrate of **2b**, 16336-23-5; **2c**, 16336-24-6.

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(10) W. Hückel and M. Hanack, *Angew. Chem. Intern. Ed. Engl.*, **6**, 534 (1967).

(11) Prepared from 5-hydroxy-2-methylisoquinolinium *p*-toluenesulfonate and isolated by the chromatographic procedure of Kimoto and Okamoto.[2]

Photoreactions. V. Mechanism of the Photorearrangement of Alkyl-*p*-benzoquinones[1]

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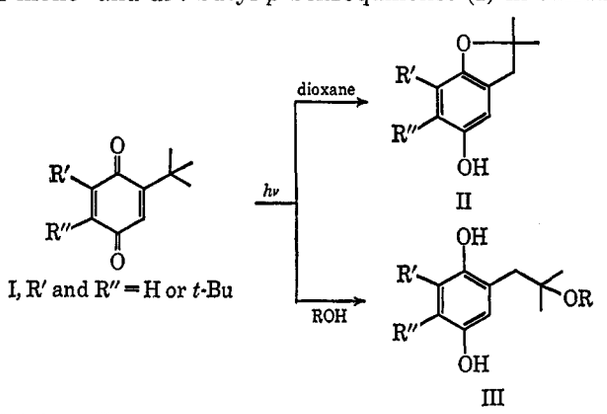
Photolysis of *p*-benzoquinones with various side chains have been studied in alcoholic solution. The identical ether was obtained by the photorearrangement of *t*-butyl- and isobutyl-*p*-benzoquinone. The rearranged side chain was the same from *n*-propyl- and isopropyl-substituted *p*-benzoquinones. Since light of wavelength longer than 400 mμ is capable of initiating the photolysis, it is assumed that the n → π* transition of the quinone system is involved. A spirocyclopropyl intermediate has been postulated to account for the observations on the photorearrangement of the side chain.

Previous investigations[1] in our laboratories have uncovered the photorearrangement of the side chain of mono- and di-*t*-butyl-*p*-benzoquinones (I) in various solvents. In nonalcoholic media, the *t*-butyl group undergoes rearrangement to generate the 2,2-dimethyl-5-hydroxycoumaran system (II), while in alcoholic solvents an analogous rearrangement leads to the formation of the 2-alkoxy-2-methyl-1-propyl side chain (III). We have now examined the effect of the side chain on the course of the photorearrangement and attempted to formulate a mechanism to account for the observations.



Results

The photolysis of dilute solutions of various alkyl-substituted *p*-benzoquinones (IV) was carried out under a sun lamp. For completeness of sequence, the following side chains were studied: methyl, ethyl, isopropyl, *n*-propyl, and isobutyl. The reaction mixtures were treated with alkaline dimethyl sulfate to convert the phenolic components into methyl ethers which were easily separated by gas chromatography. In general, spectral data (nmr, mass, ir, uv) were ade-

(1) For part IV, see C. M. Orlando, H. Mark, A. K. Bose, and M. S. Manhas, *J. Amer. Chem. Soc.*, **89**, 6527 (1967).

(2) (a) Kay-Fries Chemicals, Inc.; (b) General Electric Research and Development Center, Schenectady, N. Y. 12301; (c) Stevens Institute of Technology.