J = 7 Hz, ethoxy CH_3), 3.94 (q, 2 H, J = 7 Hz, ethoxy CH_2), 4.54 (s, 2 H, 6-CH_2), 6.03 (s, 1 H, 4-CH=), 6.85 (overlapped d, 2 H and 2 H, p-ethoxyphenyl protons), 7.18–7.84 ppm (m, 5 H, phenyl protons); uv λ_{max} (EtOH) 235 nm (ϵ 10,500), 290 (3550); mass spectrum m/e 352 (M^+), 310, 261, 242, 226, 219, 174, 150, 149, 148, 121 (base peak), 120, 93, 77.

Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.26; H, 5.79; N, 7.87.

1-(4-Methoxyphenyl)-2-phenyl-5-(4-toluenesulfonyloxy)-1,2,3,6-tetrahydropyridazin-3-one (8l). To a solution of **2l** in dry pyridine (1.2 g in 70 ml), TsCl (1.3 g) was added in small portions, and the mixture was stirred for 2 hr at room temperature. After evaporation of pyridine under reduced pressure, the resulting residue was extracted with benzene. The benzene solution was washed with 5% NaOH, 10% HCl, and water, successively, and dried over Na_2SO_4. After evaporation of benzene, the residual solid was dissolved in $CHCl_3$ and chromatographed over silica gel, affording enol tosylate **8l** (850 mg, 47%) as colorless crystals: mp 117°; ir ($CHCl_3$) 3000, 1660, 1640, 1600, 1510, 1500, 1387, 1360, 1248, 1192, 1185 cm^{-1}; nmr δ 2.44 (s, 3 H, tolyl CH_3), 3.77 (s, 3 H, $-OCH_3$), 4.50 (s, 2 H, 6-CH_2), 5.75 (s, 1 H, 4-CH=), 6.84 (overlapped d, 4 H, p-methoxyphenyl protons), 7.24 and 7.60 (AB q, 2 H and 2 H, J = 7 Hz, p-tosyl protons), 7.14–7.82 (m, 5 H, phenyl protons); uv λ_{max} (EtOH) 230 nm (ϵ 7100), 273 (3170); mass spectrum m/e 450 (M^+, base peak), 359, 328, 295, 225, 212, 162, 135, 120, 107, 91, 77.

Anal. Calcd for $C_{24}H_{22}N_2O_5S$: C, 63.99; H, 4.92; N, 6.22. Found: C, 64.00; H, 5.04; N, 5.97.

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Registry No.—**1a,** 103-33-3; **1b,** 584-90-7; **1c,** 588-04-5; **1d,** 501-60-0; **1e,** 7334-33-0; **1f,** 15426-14-9; **1g,** 1602-00-2; **1h,** 613-55-8; **1i,** 6319-23-9; **1j,** 501-58-6; **1k,** 588-52-3; **1l,** 2396-60-3; **1m,** 29418-43-7; **1n,** 52148-10-4; **1o,** 29418-44-8; **1p,** 52148-11-5; **1q,** 52148-12-6; **1r,** 40473-79-8; **1s,** 24948-93-4; **1t,** 29418-59-5; **1u,** 7466-38-8; **2a,** 52148-13-7; **2b,** 52148-14-8; **2c,** 52148-15-9; **2d,** 52148-16-0; **2e,** 52148-17-1; **2f,** 52148-18-2; **2g,** 52148-19-3; **2h,** 52148-20-6; **2i,** 52148-21-7; **2j,** 52148-22-8; **2k,** 52148-23-9; **2l,** 52148-24-0; **2m,** 52148-25-1; **2n,** 52148-26-2; **2o,** 52148-27-3; **2p,** 52148-28-4; **2q,** 52148-29-5; **2r,** 52148-30-8; **2s,** 52148-31-9; **2t,** 52148-32-0; **2u,** 52148-33-1; **3a,** 52148-34-2; **3a′,** 52148-35-3; **4,** 52148-36-4; **5l,** 52148-37-5; **6l,** 52148-38-6; **6o,** 52148-39-7; **6u,** 52148-40-0; **7l,** 52148-41-1; **7u,** 52148-42-2; **8l,** 52148-43-3; diketene, 674-82-8; hydrazobenzene, 122-66-7; ω-bromoacetoacetyl bromide, 52148-44-4.

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Synthesis and Stereochemistry of Some 8-Substituted 2-Methyldecahydroisoquinolines

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The synthesis and assignment of stereochemistry of three of the four possible diastereoisomers of the previously unreported 8-amino-2-methyldecahydroisoquinolines is reported. A one-step hydrogenolysis–catalytic hydrogenation of 5-bromo-8-nitro-2-methylisoquinolium tosylate was used to prepare the isomeric 8-amino-2-methyldecahydroisoquinolines. Separation of the diastereoisomers was achieved by the fractional crystallization of the corresponding acetamide derivatives and allowed the separation of the cis-8,9,10-H (30%, IIIa), trans-8,9,10-H (65%, IIIb), and cis-9,10,trans-8,9-H (1%, IIIc) isomers. Deamination with nitrous acid of the amines (obtained by hydrolysis of the acetamides) to the corresponding hydroxy compounds confirmed the equatorial stereochemistry of the 8 substituent in IIIb and IIIc. In the case of the amine obtained from IIIa, which possesses an intramolecular hydrogen bond and of necessity an axial substituent, high yields of the corresponding axial hydroxy compound were obtained on deamination. Owing to a conformational equilibrium this finding is not in conflict with the established high-yield conversions of equatorial amines to alcohols using nitrous acid. The isolation of alcohol IVc, as its methiodide derivative, completes the description of the four possible diastereoisomers of 8-hydroxy-2-methyldecahydroisoquinoline.

In a continuing study of the involvement of stereochemistry in the cardiovascular potencies of various derivatives of amino and hydroxy substituted decahydroisoquinolines[1] we report on the stereochemistry of 8-amino- and 8-hydroxy-2-methyldecahydroisoquinolines. Studies have been reported by Kimoto and Okamoto[2] on some 8-hydroxy-2-methyldecahydroisoquinolines; however, in comparing some of the melting point data with the present data, discrepancies are apparent. Elucidation of the conformation of the previously unreported 8-amino analogs is described.

The synthesis of 8-nitroisoquinoline (see Scheme I) was achieved by way of the bromination of isoquinoline using a swamping catalyst technique[3] to yield 5-bromoisoquinoline. Nitration using standard procedures gave good yields of the 5-bromo-8-nitroisoquinoline which was quaternized with methyl p-toluenesulfonate. The resulting salt (I) was then subjected to sequential reductions to produce the desired decahydroisoquinoline. The dehydrohalogenation of heterocycles is well documented[3] and using a base-supported palladium catalyst in addition to platinum oxide we

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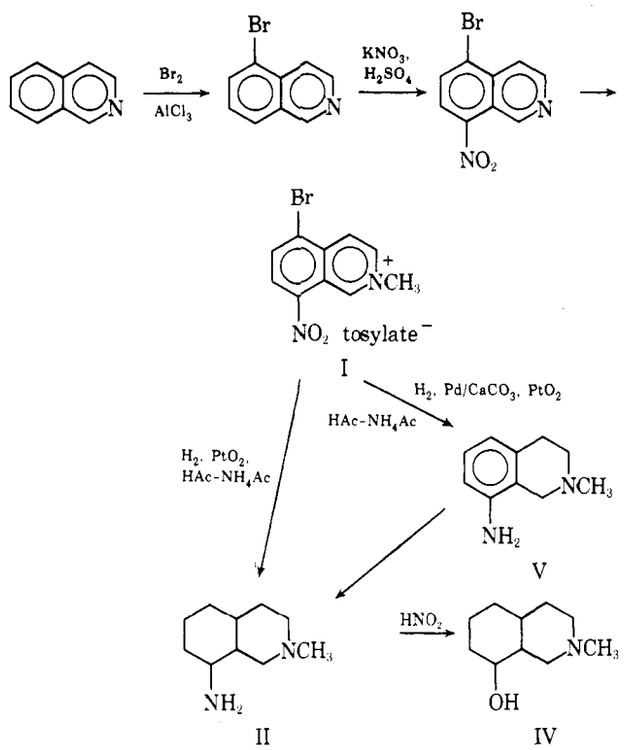
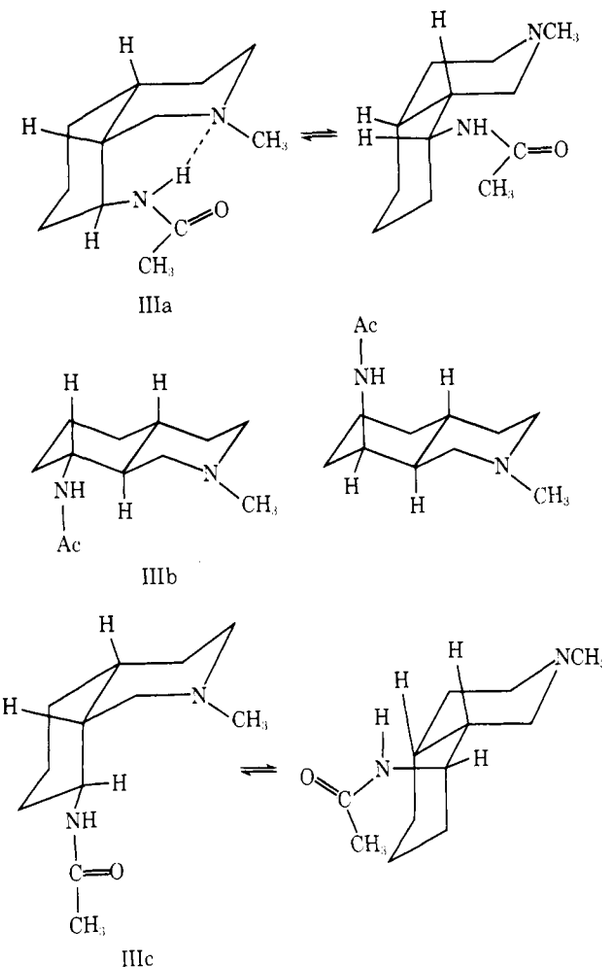
Scheme I
Synthesis of 8-Amino- and 8-Hydroxy-2-methyldecahydroisoquinoline



separation of isomers
via their acetamides (III)

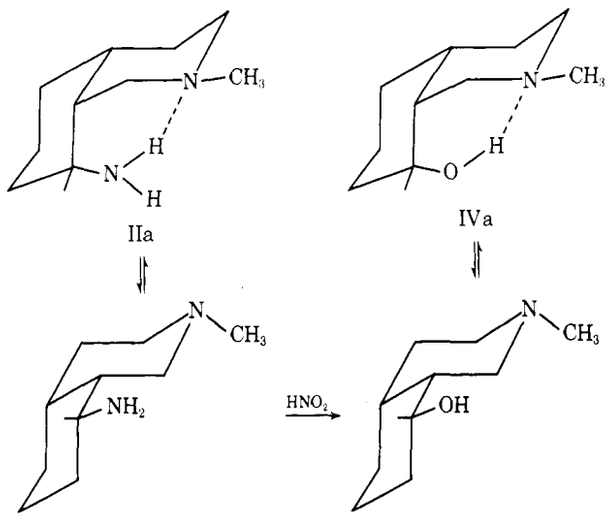
Chart I
Possible Diastereoisomers of 8-Acetamido-2-methyldecahydroisoquinolines



were able to produce 8-nitro-2-methyl-1,2,3,4-tetrahydroisoquinoline. While further reduction of the tetrahydro compound using a platinum oxide–acid catalyzed hydrogenation in glacial acetic acid[1a] gave the desired 8-amino-2-methyldecahydroisoquinoline, a one-step reduction from the completely unsaturated to the fully reduced system was sought. Low-pressure reduction (72 hr) of I using various catalysts yielded the desired 8-amino-2-methyldecahydroisoquinolines. Gas–liquid chromatography of the oily product indicated the production of the isomers in the ratio 65 (IIIb):30 (IIIa):1 (IIIc). Separation of the various isomers was achieved by the fractional recrystallization of the corresponding acetamides. The infrared spectra of the purified acetamides were most informative as to the stereochemistry of one of the separated isomers (IIIa). The presence of an –NH stretching absorption at 3200 cm^{-1} (CH_2Cl_2) which did not disappear on dilution indicated the presence of an intramolecular hydrogen bond.[4] Of the possible stereoisomers, only the cis-8,9,10-H isomer, having the acetamide grouping in the axial position, has the capability of forming such a bond (see Chart I). The equatorial nature of the 8 proton in IIIa (and thus an axial acetamide grouping) was obtained from its nmr spectrum. A narrow peak at δ 3.98 ($W_{1/2}$ = 14 Hz) established the equatorial nature of the 8 proton and the peak for the amide proton at δ 6.37 ($W_{1/2}$ = 75 Hz) indicated its participation in an intramolecular hydrogen bond. Hydrolysis of this acetamide with dilute acid yielded the corresponding amine, which on deamination with nitrous acid yielded the alcohol with retention of configuration in 85% yield. The high-yield production of alcohol in these deaminations occurs when the amine substituent is in an equatorial conformation.[5] We suggest that the high yields of the alcohol obtained with this axial amine are due to (a) nitrosation of the sterically more favored equatorial amine (in equilibrium with the axial amine) thus giving the equatorial alcohol following the decomposition of the intermediate diazonium compound; (b) hydrolysis of the conformationally favored equatorial diazonium salt to yield the equatorial alcohol. Conformational preference of the diazonium grouping for the equatorial position was suggested by examination of the nmr of the nonintramolecularly hydrogen bonded quaternary salt (methiodide) of IVa. The narrow peak ($W_{1/2}$ = 10 Hz) for the equatorial 8 proton in IVa was not present in the spectrum of the quaternary salt but was replaced by a broader peak (which overlapped other signals) indicating its axial position and thus the more favored equatorial position for the 8 substituent. Since the diazonium salt intermediate would likewise not possess an intramolecular hydrogen bond, the diazonium group would be expected to occupy an equatorial position. The conformational equilibrium of the equatorial alcohol formed would provide for the isolation of the axial alcohol (see Chart II). The stereochemical assignment of the hydroxy compound produced by this sequence is consistent with these proposals. The alcohol (IVa) isolated from this deamination was shown to be identical with that reported by Kimoto[2b] [with the exception that our methiodide had mp 238–239° (lit.[2b] mp 229–231°)]. The nmr and ir characteristics indicated that both the amine and alcohol possessed an intramolecular hydrogen bond between the amine or hydroxyl grouping and the hetero nitrogen, thus confirming the presence of an axially substituted grouping.

The second acetamide (IIIb) isolated during the fraction-

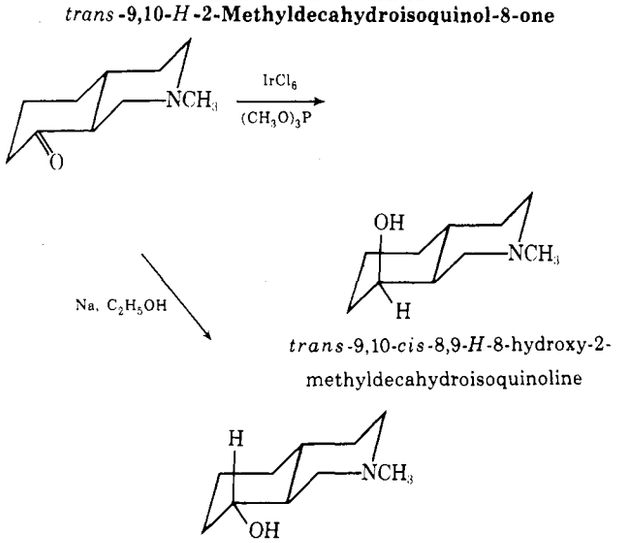
Chart II
Deamination of
cis-8,9,10-*H*-8-Amino-2-methyldecahydroisoquinoline



al crystallization required a more detailed study for its stereochemical elucidation. The equatorial conformation of the acetamide grouping was confirmed by the high yield of alcohol (IVb) following deamination of the corresponding solid amine (IIb). The infrared absorption of IVb at 1053 and 1013 cm^{-1} provided spectral evidence for the equatorial position of the hydroxyl grouping. Although the spectral data were similar to those reported for *trans*-8,9,10-H-8-hydroxy-2-methyldecahydroisoquinoline[2b] the melting point of the isolated compound and its derivatives (analytically pure) differed by as much as 46° with those reported; it was therefore necessary to confirm the ring junction stereochemistry of our isolated alcohol, and thus the acetamide and amine, by unambiguous chemical means.

The oxidation of alcohols adjacent to a ring junction leads exclusively to the production of a trans ring junction ketone.[6] Stereoselective reduction of the ketone (see Scheme II) yields the axial or equatorial alcohol as desired; by this means alcohols of known stereochemistry were synthesized for comparison with alcohol IVb. Alcohol IVb was oxidized by an Oppenauer procedure utilizing benzophenone and potassium *tert*-butoxide to yield *trans*-9,10-*H*-2-methyldecahydroisoquinol-8-one. Reduction of this ketone with sodium and alcohol yielded *trans*-8,9,10-*H*-8-hydroxy-2-methyldecahydroisoquinoline, which was shown to be identical with alcohol IVb. An alternate reduction of the ketone using chloroiridic acid and trimethyl phosphite yielded exclusively *trans*-9,10-*cis*-8,9-*H*-8-hydroxy-2-methyldecahydroisoquinoline comparable to the axial alcohol described by Kimoto and Okamoto.[2b]

Scheme II
Selective Reduction of
trans-9,10-*H*-2-Methyldecahydroisoquinol-8-one



The stereochemical characterization of the third acetamide, isolated in very small quantities, was made on the basis of its nmr spectrum. The wide $W_{1/2}$ (23 Hz) of the 8 proton (δ 4.38) indicated the presence of an equatorial acetamide grouping. Confirmation of the equatorial position of the substituent was obtained by hydrolysis of IIIc to its corresponding amine and subsequent deamination of the amine with nitrous acid. The alcohol obtained in high yield was converted to its methiodide derivative. Since one of the two possible equatorially substituted acetamides has been described (IIIb), and on the basis of our unambiguous synthesis of both trans-9,10-H isomers, with the limited quantities of material available our assignment for the cis ring junction stereochemistry, *i.e.*, *cis*-9,10,*trans*-8,9-*H*-8-acetamido-2-methyldecahydroisoquinoline, to IIIc would appear to be valid.

Experimental Section

Melting points were determined on a Büchi melting point apparatus and are uncorrected. Infrared (ir) spectra were obtained using either a Perkin-Elmer Model 137 Infracord spectrophotometer or a Beckman Model IR-33 grating infrared spectrophotometer. Nuclear magnetic resonance (nmr) spectra were recorded on either a Varian Associates A-60A, a Hitachi Perkin-Elmer Model R-24, or a Jeolco Model C-60-HL nmr spectrometer, using tetramethylsilane (TMS) as an internal standard. Deuterium oxide exchange was routinely performed on all compounds possessing labile hydrogens. Nmr signals are reported using current conventions: br = broad, s = singlet, d = doublet, t = triplet, q = quadruplet, and m = multiplet. Half-band widths ($W_{1/2}$) are in hertz. Vapor phase chromatography (vpc) was carried out on a Varian Aerograph Model A-700 using helium as carrier gas and a column (20 ft × 0.75 in.) packed with 30% SE-30 on Chromosorb W. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and Chemalytics, Inc., Tempe, Ariz. Analytical thin layer chromatography (tlc) was carried out on aluminum-supported, precoated tlc sheets of aluminum oxide (F-254, neutral Type E, layer thickness 0.20 mm) manufactured by E. Merck, Darmstadt, Germany. After development using $CHCl_3$–CH_3OH (45:4), the analytical spots were visualized by spraying with Dragendorf's reagent. For column chromatography, aluminum oxide (Matheson Coleman and Bell, activated alumina, chromatographic grade, 80–200 mesh) or (Fisher, adsorption alumina, A-540, 80–200 mesh) was used after activation by heating at 150° for 12 hr. The solvents used for development and elution of the compounds from the column (2 × 20 cm) were benzene, benzene–ether, ether, ether–chloroform, chloroform, and chloroform–methanol.

5-Bromoisoquinoline. The swamping catalyst procedure outlined by Gordon and Pearson[3] was used for the preparation of 5-bromoisoquinoline from isoquinoline (200 g, 1.55 mol), anhydrous $AlCl_3$ (450 g, 3.4 mol), and liquid bromine (150 g, 0.94 mol). Modification of the original procedure was made in the addition of the bromine. This involved the use of an addition funnel placed on top of a steam-heated condenser attached to the reaction flask containing the viscous, molten $AlCl_3$–isoquinoline complex. Utilizing this apparatus, the bromine was vaporized prior to contacting the vigorously stirred complex. Following the 5-hr addition of the bromine, the mixture was stirred for a further 2 hr at 75° and the product was worked up by the reported procedure. The fractional distillation of the crude product, bp 95–97° (0.1 mm), yielded a clear liquid which solidified. Recrystallization from pentane afforded *5-bromoisoquinoline* as white plates, 135 g (44%), mp 82–84° (lit.[3] mp 80–82°).

5-Bromo-8-nitro-2-methylisoquinolinium *p*-Toluenesulfonate (I). Nitration of 5-bromoisoquinoline according to the proce-

dure of Osborn, *et al.*,[6] gave a 93% yield of 5-bromo-8-nitroisoquinoline, mp 139–141° (lit.[3] mp 138–140°). Formation of the methyl *p*-toluenesulfonate salt was achieved by the treatment, with stirring, of the nitrobromo compound (315 g, 1.25 mol) dissolved in hot dimethylformamide (1200 ml) with 250 g (1.35 mol) of methyl *p*-toluenesulfonate for a period of 36 hr. After cooling in an ice bath, the reaction mixture was filtered, and the solid was washed with ether and acetone to yield I as a pale yellow solid, 435 g (80%), mp 252°.

Anal. Calcd for $C_{17}H_{15}BrN_2O_5S$: C, 46.48; H, 3.44; Br, 18.19; N, 6.38. Found: C, 46.63; H, 3.50; Br, 18.05; N, 6.34.

8-Amino-2-methyl-1,2,3,4-tetrahydroisoquinoline (V). A 25-g portion of salt I and an equal weight of ammonium acetate were dissolved in 200 ml of glacial acetic acid and hydrogenated at 40 psi for 12 hr over a mixed catalyst consisting of 8 g of palladium on $CaCO_3$ and 1 g of PtO_2. The exhausted catalyst was then filtered, and the filtrate was concentrated, made alkaline with NH_4OH, and extracted with ether. The dried ethereal extract was evaporated to yield a red oil which solidified on distillation and was recrystallized from ether-pentane to yield V as white needles in 50% yield, mp 62–63°.

Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 73.96; H, 8.82; N, 17.10.

8-Amino-2-methyldecahydroisoquinoline (II). Ammonium acetate (2.5 g) and I (25 g) were dissolved in glacial acetic acid (200 ml) and hydrogenated at 40 psi for 72 hr over either (a) PtO_2 (2 g), Pd/C (5 g) in the presence of KOH (5 g), or (b) PtO_2 (2 g) in the presence of KOH (5 g), or (c) PtO_2 (2 g) as catalyst. The exhausted catalyst was then filtered, and the filtrate was concentrated on a rotary evaporator and made alkaline with NH_4OH. The resulting solution was extracted with ether, and the ether solution was dried and evaporated to leave a pale yellow oil. Vpc examination of this oil indicated the presence of two major components, IIb (65%) and IIa (30%), subsequently shown to be the *trans*-8,9,10-*H*- and *cis*-8,9,10-*H*-8-amino-2-methyldecahydroisoquinolines, respectively. An indeterminate amount of a third isomer (IIc) (a small shoulder on the major peak) was subsequently shown to be the cis-9,10,trans-8,9-H isomer. Approximately 5% of the 2-methyldecahydroisoquinolines was also seen at shorter retention times than those of the desired products. Separation of the isomer mixture of II by distillation was not possible and instability of the purified mixture was noted in the absence of solvent. The purified isomer mixture was derivatized to the corresponding acetamides immediately following distillation.

***cis*-8,9,10-*H*- and *trans*-8,9,10-*H*-8-Acetamido-2-methyldecahydroisoquinoline (IIIa and IIIb).** The freshly distilled 8-amino-2-methyldecahydroisoquinoline mixture (41 g, 0.24 mol) was dissolved in dry dimethylformamide (375 ml), cooled to 10°, and stirred. Acetic anhydride (50 g, 0.49 mol) dissolved in dry benzene (100 ml) was added over a 15-min period. Following the addition, the mixture was allowed to warm to room temperature and stirred for 24 hr. The solvents were then removed by rotary evaporation and the residual oil was dissolved in water, made alkaline with NH_4OH, and extracted with ether. Removal of the solvent from the dried ethereal extract yielded the crude mixture of the diastereoisomers (34 g, 66%). Several fractional recrystallizations of the isomeric mixture (150 g) from ethyl acetate or petroleum ether (bp 30–60°)–ether afforded pure *trans*-8,9,10-*H*-8-acetamido-2-methyldecahydroisoquinoline (IIIb) as white, felted needles (35 g): mp 192.5–194°; ir ($CHCl_3$) 3440 (free N–H stretch), 3300 cm^{-1} (intermolecularly H-bonded N–H stretch); nmr ($CDCl_3$) δ 5.75 (br, 1, $W_{1/2}$ = 25 Hz, CONH), 3.68 (br, 1, $W_{1/2}$ = 23 Hz, CHNHAc), 2.27 (s, 3, NCH_3), and 1.98 ppm (s, 3, $COCH_3$).

Anal. Calcd for $C_{12}H_{22}N_2O$: C, 68.52; H, 10.55; N, 13.32. Found: C, 68.72; H, 10.26; N, 13.30.

The *cis*-8,9,10-H isomer (IIIa) was more soluble in the recrystallization solvent and was isolated as cuboid crystals by concentration of the mother liquors from which IIIb had been obtained. In some instances separation of IIIa, from the traces of IIIb still present, was achieved mechanically with tweezers. Recrystallization of IIIa from the same solvents as IIIb yielded pure *cis*-8,9,10-*H*-8-acetamido-2-methyldecahydroisoquinoline as cuboid crystals; mp 141–142°; ir ($CHCl_3$) 3440 (free N–H stretch), 3310 (intermolecularly H-bonded N–H stretch), and 3200 cm^{-1} (intramolecularly H-bonded N–H stretch, did not disappear on dilution); nmr ($CDCl_3$) δ 6.37 (br, 1, $W_{1/2}$ = 75 Hz, –NHAc), 3.98 (br, 1, $W_{1/2}$ = 14 Hz, –CHNHAc), 2.27 (s, 3, NCH_3), and 1.96 ppm (s, 3, $COCH_3$).

Anal. Calcd for $C_{12}H_{22}N_2O$: C, 68.52; H, 10.55; N, 13.32. Found: C, 68.79; H, 10.62; N, 13.58.

A third isomer (IIIc) was isolated by hand picking its leaflet clusters from the mixture obtained when the petroleum ether–ether solvent was allowed to slowly evaporate. Recrystallization from ethyl acetate yielded 35 mg of pure *cis*-9,10,*trans*-8,9-*H*-8-acetamido-2-methyldecahydroisoquinoline: mp 154–157°; ir ($CHCl_3$) 3415 (free N–H stretch) and 3320 cm^{-1} (intermolecularly H-bonded N–H stretch); nmr ($CDCl_3$) δ 5.57 (br, 1, $W_{1/2}$ = 25 Hz, –NHAc), 4.40 (br, 1, $W_{1/2}$ = 23 Hz, CHNHAc), 2.28 (s, 3, NCH_3), and 2.07 ppm (s, 3, $COCH_3$).

Anal. Calcd for $C_{12}H_{22}N_2O$: C, 68.52; H, 10.55; N, 13.32. Found: C, 68.57; H, 10.47; N, 13.14.

It should be noted that infrared dilution studies were carried out on all three isomers in dichloromethane solution. The peak at 3300–3320 cm^{-1} corresponding to the intermolecularly H-bonded NH stretching frequency disappeared on dilution from 0.15 to 0.03 *M* concentration. For compound IIIa, however, the absorption at 3200 cm^{-1} persisted throughout 0.15–0.01 *M* concentrations, indicative of an intramolecularly H-bonded N–H stretching frequency.[4]

Hydrolysis of *cis*-8,9,10-*H*-8-Acetamido-2-methyldecahydroisoquinoline (IIIa) to *cis*-8,9,10-*H*-8-Amino-2-methyldecahydroisoquinoline (IIa). A solution of IIIa (2.35 g, 0.011 mol) in 10% sulfuric acid (110 ml) was refluxed for 32 hr. The acidic solution, cooled in an ice bath, was made alkaline with concentrated sodium hydroxide solution and extracted with chloroform. The dried chloroform extract was evaporated on a rotary evaporator to yield *cis*-8,9,10-*H*-8-amino-2-methyldecahydroisoquinoline (IIa) as a straw-colored oil (1.86 g, 99%). The oil was quickly purged with nitrogen and stoppered to prevent formation of its solid carbonate which occurred when the amine was exposed to air. Attempts to crystallize the oil failed: ir ($CHCl_3$) 3375 (free N–H stretch), 3270 and 3160 (hydrogen-bonded N–H stretch), 1583 (N–H bending), and 1100 cm^{-1} (C–N); nmr ($CDCl_3$) δ 2.28 (s, 3, NCH_3) and 1.37 ppm (s, 2, NH_2). The dihydrobromide salt was prepared and recrystallized from acetonitrile–ethyl acetate, mp 297–300°.

Anal. Calcd for $C_{10}H_{22}Br_2N_2$: C, 36.38; H, 6.72; Br, 48.41; N, 8.49. Found: C, 36.25; H, 6.67; Br, 48.37; N, 8.52.

Hydrolysis of *trans*-8,9,10-*H*-8-Acetamido-2-methyldecahydroisoquinoline (IIIb) to *trans*-8,9,10-*H*-8-Amino-2-methyldecahydroisoquinoline (IIb). A solution of IIIb (8 g, 0.038 mol) dissolved in 15% sulfuric acid solution (100 ml) was refluxed for 72 hr. The acidic reaction solution, cooled in an ice bath, was made alkaline with sodium hydroxide solution and extracted with chloroform. The dried chloroform extract was concentrated, giving 6.35 g of a straw-colored oil (98% yield) which formed tan crystals on standing of the pure *trans*-8,9,10-*H*-8-amino-2-methyldecahydroisoquinoline (IIb): mp 44–47°; ir ($CHCl_3$) 3370 (free N–H stretch), 3280 and 3150 (hydrogen-bonded N–H stretch), 1575 (N–H bending), and 1100 cm^{-1} (C–N); nmr ($CDCl_3$) δ 2.30 (s, 3, NCH_3), and 1.21 ppm (s, 2, NH_2). The dihydrobromide salt was prepared and recrystallized from ethyl acetate–methanol–ether to give colorless, glassy crystals of *trans*-8,9,10-*H*-8-amino-2-methyldecahydroisoquinoline dihydrobromide, mp 256–258°.

Anal. Calcd for $C_{10}H_{22}Br_2N_2$: C, 36.38; H, 6.72; Br, 48.41; N, 8.49. Found: C, 36.24; H, 6.64; Br, 48.63; N, 8.30.

Deamination with Nitrous Acid of *cis*-8,9,10-*H*-8-Amino-2-methyldecahydroisoquinoline (IIa) to *cis*-8,9,10-*H*-8-Hydroxy-2-methyldecahydroisoquinoline (IVa). To a stirred solution of IIa (10 g, 0.06 mol) in glacial acetic acid (14.4 g, 0.24 mol) was added, dropwise, sodium nitrite (8.28 g, 0.12 mol) dissolved in water (65 ml).[7] This mixture was heated to 65°, and additional 2.88 g of acetic acid (20% excess in 20 ml of water) was added dropwise, and the resulting solution was heated for 3–4 hr. The reaction medium was made strongly alkaline with sodium hydroxide solution and refluxed for 2 hr. After cooling, the basic solution was extracted with chloroform. The chloroform extract was dried and concentrated, giving a viscous, straw-colored oil, which upon standing solidified to give 8.5 g of IVa, mp 68–75° (85% yield). Vpc indicated that the crude product contained 99% IVa and tlc showed one spot having an R_f value of 0.653. Recrystallization of the solid from petroleum ether (bp 30–60°) gave 7.6 g (76% yield) of pure *cis*-8,9,10-*H*-8-hydroxy-2-methyldecahydroisoquinoline (IVa) as colorless, glassy prisms: mp 78–81° (lit.[2] mp 78–80°); ir ($CHCl_3$) 3660 (free O–H stretch), 3170 (hydrogen-bonded O–H stretch), 1057, 1014 cm^{-1} (equatorial C–O); nmr ($CDCl_3$) δ 5.72 (br, 1, OH), 4.10 (br, 1, $W_{1/2}$ = 10 Hz, CHOH), and 2.25 ppm (s, 3, NCH_3). Two derivatives were prepared: the picrate, which was recrystallized from 95% ethanol, mp 183–184° (lit.[2a] mp 181–183°), and the methiodide, which was recrystallized from glyme–acetonitrile, mp 238–239° (lit.[2a] mp 229–231°).

Deamination with Nitrous Acid of *trans*-8,9,10-*H*-8-Amino-2-methyldecahydroisoquinoline (IIb) to *trans*-8,9,10-*H*-8-Hydroxy-2-methyldecahydroisoquinoline (IVb). *trans*-8,9,10-*H*-8-Amino-2-methyldecahydroisoquinoline (IIb, 6.2 g, 0.037 mol) was deaminated in a procedure identical with that described for the cis isomer. The viscous straw-colored oil (5.0 g) recovered from the chloroform extract was shown by vpc to contain 95.5% IVb and 4.5% olefins. Distillation of the oil *in vacuo* provided 3.41 g of *trans*-8,9,10-*H*-8-hydroxy-2-methyldecahydroisoquinoline (IVb), bp 92–96° (0.2 mm). Initial attempts to crystallize the oil failed; the hydrochloride salt was prepared and recrystallized from acetonitrile–ethyl acetate, giving 2.33 g (65%) of *trans*-8,9,10-*H*-8-hydroxy-2-methyldecahydroisoquinoline hydrochloride, mp 180–182°.

Anal. Calcd for $C_{10}H_{20}ClNO$: C, 58.38; H, 9.80; Cl, 17.23; N, 6.80. Found: C, 58.63; H, 10.01; Cl, 17.52; N, 6.71.

The hydrochloride salt was converted to the free base which, after standing overnight, crystallized to yield a tan, waxy solid, mp 50–53° (lit.[2] mp 84°). Attempts to recrystallize the material failed: ir ($CHCl_3$) 3610 (free O–H stretch), 3160 (hydrogen-bonded O–H stretch), and 1053 and 1013 cm^{-1} (equatorial C–O[2b,6]); nmr ($CDCl_3$) δ 4.05 (s, 1, OH) (**C**HOH was masked by other alkyl protons from δ 2.7 to 3.5 ppm) and 2.25 ppm (s, 3, NCH_3).

Two derivatives were prepared as follows.

A picrate was recrystallized from 1-propanol, mp 196–198° (lit.[2a] mp 147–150°).

Anal. Calcd for $C_{16}H_{22}N_4O_8$: C, 48.24; H, 5.57; N, 14.06. Found: C, 48.30; H, 5.53; N, 13.74.

A methiodide was recrystallized from ethyl acetate–acetonitrile, mp 216–218° (lit.[2a] mp 235°).

Anal. Calcd for $C_{11}H_{22}INO$: C, 42.46; H, 7.13; I, 40.78; N, 4.50. Found: C, 42.64; H, 7.26; I, 41.00; N, 4.29.

Oxidation of a Diastereoisomeric Mixture of 8-Hydroxy-2-methyldecahydroisoquinolines (IV) to *trans*-2-Methyldecahydroisoquinol-8-one. The alcohol mixture (IV, 0.75 g, 0.0044 mol) was dissolved in benzene and refluxed in a flask equipped with a Dean-Stark trap for 15–30 min. To this solution was added potassium *tert*-butoxide (1.25 g, 0.011 mol) and benzophenone (4.05 g, 0.0222 mol). The mixture was purged with dry nitrogen and refluxed for 6 hr with a continuous stream of dry nitrogen slowly passing through the reaction flask. After cooling, the reaction medium was extracted with 10% hydrochloric acid solution. The acidic extract was made alkaline by slowly adding it to a cooled, stirred ammonium hydroxide solution, and the resulting basic solution was extracted with ether on a continuous extractor for 6 hr. The ethereal extract was washed twice with a saturated aqueous sodium chloride solution, dried, and concentrated to yield an oil (0.501 g, 67%). A hydrobromide salt was prepared which was recrystallized from ethyl acetate–acetonitrile to give 0.629 g (57%) of *trans*-2-methyldecahydroisoquinol-8-one hydrobromide, mp 217–219°. A methiodide derivative was prepared by dissolving the ketone in anhydrous diethyl ether, adding an excess of methyl iodide, and boiling off the excess reagent and solvent. The residual methiodide was washed with diethyl ether and recrystallized from ethyl acetate–acetonitrile, giving white, felted needles, mp 291–294°. A subsequent recrystallization from acetone–acetonitrile gave very small, white, glassy crystals of the pure methiodide, mp 295–297° (lit.[2a] mp 288–290°).

Anal. Calcd for $C_{11}H_{20}INO$: C, 42.73; H, 6.52; I, 41.04; N, 4.53. Found: C, 43.11; H, 6.72; I, 41.32; N, 4.44.

Reduction[9] of *trans*-2-Methyldecahydroisoquinol-8-one to *trans*-9,10,*cis*-8,9-*H*-8-Hydroxy-2-methyldecahydroisoquinoline. To a solution of the catalyst, chloroiridic acid ($H_2IrCl_6 \cdot 2H_2O$, 0.0517 g, 0.12 mmol) in 0.2 ml of concentrated hydrochloric acid was added trimethyl phosphite (0.75 ml) and this solution was combined with a solution of the ketone (0.318 g, 1.9 mmol) dissolved in 2-propanol (10 ml). The mixture was refluxed for 72 hr followed by a removal of the 2-propanol by rotary evaporation. The remaining acidic solution was washed twice with ether and slowly added to cold ammonium hydroxide. The resulting alkaline solution was extracted with ether on a continuous extractor for 12 hr, dried, and concentrated, giving an oil which solidified to yield 0.316 g (98%), mp 102–113°. Analytical tlc of the crude product showed only one spot (R_f 0.56) indicating quantitative conversion of the trans ketone to the alcohol. The solid was recrystallized from petroleum ether (bp 30–60°) to give 0.225 g of pure *trans*-9,10,*cis*-8,9-*H*-8-hydroxy-2-methyldecahydroisoquinoline for a 73% overall yield; mp 114–115° (lit.[2a] mp 115°); ir ($CHCl_3$) 3615 (free O–H stretch), 3430, 3150 (hydrogen-bonded O–H stretch), and 992 cm^{-1} (axial C–O); nmr ($CDCl_3$) δ 2.84 (br, 1, CHOH), 3.85 (br, 1, $W_{1/2}$ = 8 Hz, CHOH), and 2.30 ppm (s, 3, NCH_3). Two derivatives were prepared: a picrate, which was recrystallized from absolute ethanol, mp 242–243° (lit.[2a] mp 235°), and a methiodide, which was recrystallized from ethyl acetate–acetonitrile, mp 194–196° (lit.[2a] mp 183–185°).

Reduction of *trans*-2-Methyldecahydroisoquinol-8-one to *trans*-8,9,10-*H*-8-Hydroxy-2-methyldecahydroisoquinoline.[10] Small portions of sodium metal (1.1 g) were added to a refluxing solution of the ketone (0.182 g, 1.08 mmol) in 30 ml of absolute ethanol. The solution was allowed to reflux for 10 hr, a further 0.5 g of sodium metal was then added, and refluxing was continued for an additional 1 hr. After allowing the reaction mixture to cool, water (2 ml) was cautiously added to ensure the destruction of residual sodium metal. The ethanol was removed on a rotary evaporator and the residue was dissolved in water, made strongly alkaline, and extracted with ether on a continuous extractor for 12 hr. The ethereal extract was dried and concentrated to yield 0.141 g (80%) of an orange-colored oil. The C–O stretching bands in the ir of this oil indicated a high percentage of the desired trans-equatorial alcohol. Analytical tlc showed one major spot (approximately 90%), R_f 0.520, representing the desired alcohol, and two minor spots (10% combined), consisting of unreacted ketone and the trans-axially substituted alcohol. The oil was chromatographed on alumina (10 g) and eluted with benzene, ether, and chloroform to yield 128 mg of pure *trans*-8,9,10-*H*-8-hydroxy-2-methyldecahydroisoquinoline (70% overall yield). A methiodide derivative was prepared (mp 215–218°) which, when mixed with the methiodide derived from the alcohol IVb, showed no melting point depression. The ir and nmr spectra of the alcohol prepared by the ketone reduction and the alcohol IVb were identical.

Hydrolysis of *cis*-9,10,*trans*-8,9-*H*-8-Acetamido-2-methyldecahydroisoquinoline (IIIc) and Subsequent Deamination with Nitrous Acid of the Corresponding Amine. *cis*-9,10,*trans*-8,9-*H*-8-Acetamido-2-methyldecahydroisoquinoline (IIIc, 20 mg) in 15% sulfuric acid (15 ml) was refluxed for 30 hr and the resulting amine was worked up in an identical manner with that described for the preparation of IIa from IIIa. The residual oil (~10 mg) was dissolved in glacial acetic acid (5 ml) and 5 ml of water was added. To this solution was added sodium nitrite (30 mg) dissolved in 15 ml of water and the resulting solution was heated to 60° for 1 hr. The solution was then made strongly alkaline with sodium hydroxide solution and refluxed for 2 hr. The product was obtained by extraction of the cooled solution with chloroform. The chloroform solution was dried over anhydrous sodium sulfate and the residue was refluxed with benzene using a Dean-Stark trap to ensure dryness. The crude oily residue (IVc) was dissolved in anhydrous ether (10 ml) and excess methyl iodide was added. The precipitated salt was recrystallized from methanol–ether to yield a very small quantity of rosette crystals of *cis*-9,10,*trans*-8,9-*H*-8-hydroxy-2-methyldecahydroisoquinoline methiodide, mp (hot-stage microscope) 237–241°.

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Registry No.—I, 52279-18-2; IIa, 52279-19-3; IIa dihydrobromide, 52341-52-3; IIb, 52341-53-4; IIb dihydrobromide, 52341-54-5; IIIa, 52279-20-6; IIIb, 52279-21-7; IIIc, 52279-22-8; IVa, 14788-35-3; IVb, 14788-37-5; IVb hydrochloride, 52279-23-9; IVb picrate, 52279-24-0; IVb methiodide, 14991-68-5; V, 14788-34-2; 5-bromoisoquinoline, 34784-04-8; *trans*-2-methyldecahydroisoquinol-8-one hydrobromide, 52279-25-1; *trans*-2-methyldecahydroisoquinol-8-one methiodide, 15778-55-9; *trans*-9,10,*cis*-8,9-*H*-8-hydroxy-2-methyldecahydroisoquinoline, 14788-36-4.

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Chemistry of α-Nitro Sulfones. IV.[1] Functionalization at the Activated Carbon

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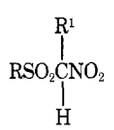
Condensation reactions of nitromethyl *p*-tolyl sulfone (1) with formaldehyde and benzenesulfinic acid are described. A proposed rationalization of the reaction involves the intermediacy of the vinyl sulfone **6**. Some other aldehydes than formaldehyde may be used as well. The product derived from acetaldehyde can be reduced by sodium borohydride to 1-nitro-1-tosylpropane (11). Primary and secondary α-nitro sulfones undergo Michael-type addition reactions to certain activated carbon–carbon double bonds.

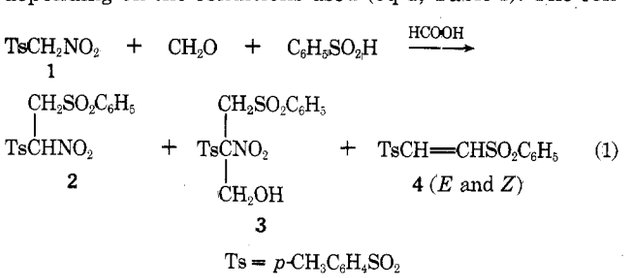
Electron-withdrawing substituents usually activate a neighboring C–H bond toward alkylation and condensation reactions.[2] However, several studies have demonstrated that the twofold activated C–H group in primary and secondary α-nitro sulfones (pK_a's of about 6 in 50% ethanol–water[3]) often is only reluctantly—or indeed not at all—functionalized by means of these types of reaction.[4,5] This is noteworthy since rather similar systems like α-nitro esters,[6] nitroacetonitrile,[7] bis(phenylsulfonyl)methane,[8] and bis(alkylsulfonyl)methanes[9] easily react with aldehydes to give alcohols, alkenes, or bisadducts; moreover, nitroalkanes can also condense with, for instance, *C*-nitroso compounds[10] and benzofuroxan.[11] With these results in mind and in continuation of our studies on α-nitro sulfones,[1,3,12] we have probed further into the propensity of α-nitro sulfones for functionalization at the activated carbon atom.



R^1 = H, alkyl, aryl

Results and Discussion

Under a variety of conditions and in the presence of either basic or acidic catalysts, nitromethyl *p*-tolyl sulfone (1) did not react with a series of aliphatic or aromatic aldehydes,[13] or with nitrosobenzene, *p*-dimethylaminonitrosobenzene, and benzofuroxan. However, when 1 was allowed to react with formaldehyde and benzenesulfinic acid in refluxing 90% aqueous formic acid, three types of condensation products (**2**, **3**, and **4**) could be isolated in yields depending on the conditions used (eq 1, Table I). The conversion of **1** into **2** is reminiscent of the condensation of carbon acids like indole or β-naphthol with formaldehyde and sulfinic acids.[14] Neither **2** nor **3** could be converted into **4** by refluxing in formic acid. Instead, starting material and partially esterified **3** were the only materials isolated. Surprisingly, an excess of benzenesulfinic acid effected the transformation of **3** into **4** in a yield of 31%. Since sulfinic acids are fairly strong reducing agents,[15] we presume that a reduction process induced by the sulfinic acid is part of the reaction.



Ts = *p*-$CH_3C_6H_4SO_2$

Table I
Condensation Products from 1 (Equation 1)

Formaldehyde, equiv[a]	Benzenesulfinic acid, equiv[a]	Reaction temp, °C	Reaction time, min	Yield, % product
1	1	100	13	31 (**2**), 6 (**3**)[b]
3	2	100	13	8 (**2**), 28 (**3**)
1	1	70	90	20 (**2**)[c]
3	2	50	180	93 (**3**)
3	1	50	180	89 (**3**)
3	2	100	180	42 (**4**)

[a] Relative to 1 equiv of **1**. [b] 44% recovery of **1**. [c] 60% recovery of **1**.

At the moment no clear-cut choice can be made between the several reaction pathways conceivable for the production of **2** and **3** from **1** (Scheme I). The intermediacy of hy-

Scheme I