Selective Hydrogenation of Quinoline and Its Homologs, Isoquinoline, and Phenyl-Substituted Pyridines in the Benzene Ring

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Hydrogenation of quinoline, its 2-, 3-, 6-, and 8-methyl and 2-isopropyl homologs, isoquinoline, acridine, benzo[*h*]quinoline, 2-phenylpyridine, 4-phenylpyridine, and 4-(3-phenylpropyl)pyridine over platinum oxide (and, in some instances, palladium or rhodium on charcoal) in strong acid (12 *N* HCl, 12 *N* H_2SO_4, CF_3COOH) leads to selective hydrogenation of the benzene ring. The fastest procedure is one employing PtO_2 in trifluoroacetic acid.

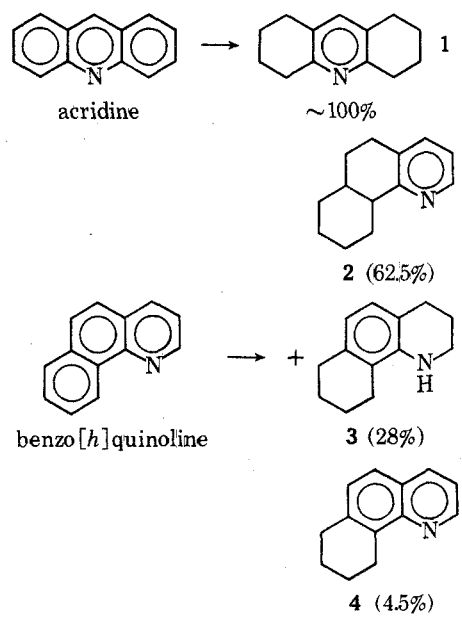
It is well documented[1-4] that catalytic hydrogenation of pyridines bearing phenyl substituents (either on or away from the pyridine rings) and of quinolines and isoquinolines and their homologs occurs preferentially in the pyridine ring. Thus hydrogenation of 4-benzylpyridine over rhodium on carbon gives 4-benzylpiperidine almost exclusively.[5,6] Hydrogenation of quinoline or isoquinoline over platinum oxide in acetic acid at room temperature and 50 psi initially gives the 1,2,3,4-tetrahydro products (benzpiperidines) in high yields.[8-10] Further reduction to the decahydro stage appears to be facilitated by the addition of mineral acid,[10] under which conditions the major product is the cis isomer[10,11] whereas in the absence of mineral acid the trans isomer is reported to predominate in the formation of decahydroquinoline.[6,10,11] *trans*-Decahydroquinoline is thus obtained in 62% yield by hydrogenation of quinoline over Raney Ni at 210° and 1000 psi[12] and isoquinoline is similarly hydrogenated to *trans*-decahydroisoquinoline in 80% yield over platinum.[13] A mixture of decahydroquinolines containing 90% of the trans isomer (along with tetrahydroquinoline and starting material) is reported[11] to be formed by hydrogenating quinoline acid oxalate in water at 40° and 30–45 psi over colloidal platinum; trans-rich decahydroquinoline mixtures also result[6,11] from similar hydrogenation of quinoline in acetic acid. In general, however, the synthesis of trans-fused decahydroquinolines and -isoquinolines is difficult.

Preparations of cyclohexylpyridines by catalytic hydrogenation do not appear to be on record and 5,6,7,8-tetrahydroquinolines[14] and -isoquinolines[10] were generally prepared by tedious, indirect methods, such as dehydrogenation of the corresponding decahydro compounds over hot platinum or palladium.[10,14] Only a few special cases of hydrogenation of quinolines to 5,6,7,8-tetrahydroquinolines have been reported;[16,17] these include the hydrogenation of certain alkylquinolines.[17] Bulky substituents in the 2, 3, and 4 positions evidently inhibit hydrogenation of the pyridine moiety and cause the reduction products to be mixtures of 5,6,7,8- and 1,2,3,4-tetrahydroquinolines.

It is clear that a method involving clean hydrogenation of the benzene ring in phenyl- and benzpyridines would be valuable not only in its own right, but also because reduction of 5,6,7,8-tetrahydroquinolines with sodium and ethanol[17,18] is a convenient route to the corresponding trans-decahydro compounds which constitute part of the carbon skeleton of many alkaloids. Such a method is reported here.

Booth and Bostock[19] recently hydrogenated quinoline to *cis*-decahydroquinoline with platinum in 12 *N* hydrochloric acid. Interruption of this very slow reduction when 2 mol of hydrogen had been adsorbed has now revealed that the major product (70%) at this stage is 5,6,7,8-tetrahydroquinoline. The optimized reduction procedure is described in the Experimental Section and the results for various substituted quinolines and isoquinolines are shown in Table I. Since reaction times were rather long (30–130 hr, the longer times applying to quinolines substituted in the benzene ring), other acids were substituted for HCl. Sulfuric acid (Table I) allowed reduction of quinoline to proceed in 4.5 hr but by far the best solvent proved to be trifluoroacetic acid, in which hydrogenation of the benzene ring was complete in 45–90 min (Table II). In this solvent, rhodium and palladium catalysts also yielded 5,6,7,8-tetrahydroquinoline from quinoline (Table II). Acridine was cleanly hydrogenated in both benzene rings, the pyridine ring being preserved; the same was true for benzo[*h*]quinoline, although the reduction proceeded less cleanly, the tetrasubstituted central benzene ring resisting hydrogenation (Scheme I). Both 2- and 4-phenylpyridine and 4-(3-phenylpropyl)pyridine were reduced in the benzene ring, the 2-substituted compound less cleanly than the 4-substituted ones (Table II).

Scheme I



Discussion

Hydrogenation of quinoline in neutral medium (absolute methanol) stops cleanly (97.5%) at the tetrahydro stage, 97% of the product being reduced in the pyridine and only 3% in the benzene ring (Table III, entry 1). It appears that the piperidine formed poisons the catalyst for further reduction.[8a,15,36] In acetic acid,[6,8,11] which prevents such poisoning by forming salts with the strongly basic benzpiperidine intermediates, reduction continues to the (predominantly trans) decahydro products;[6,11] this is true, contrary to an earlier report,[10] for isoquinoline also (Table III, item 4), though here the cis isomer predominates.

Table I
Selective Hydrogenation of Quinolines and Isoquinoline with PtO_2 in 12 *N* Hydrochloric and Sulfuric Acids at 50 psi and Room Temperature

Substance reduced (in HCl unless indicated)	Registry no.	Product composition[a] % 5,6,7,8-Tetrahydro product	% other products[a] (-quinolines)
Quinoline	91-22-5	70[b]	24 Decahydro[c] 6 $\Delta^{1,9}$-Octahydro[d]
Quinoline (H_2SO_4)		74	13 1,2,3,4-Tetrahydro[e] 6.5 $\Delta^{1,9}$-Octahydro 5.5 Decahydro[f]
Quinoline[g] (H_2SO_4)		58	42 1,2,3,4-Tetrahydro
Isoquinoline	119-65-3	95[h]	5, not isolated
2-Methylquinoline	91-63-4	95[i]	5, not isolated
2-Isopropylquinoline	17507-24-3	90[j]	3, overreduced, not isolated 7 Starting material
3-Methylquinoline	612-58-8	95[k]	5, not isolated
6-Methylquinoline	91-62-3	53[l]	24 1,2,3,4-Tetrahydro[m] 11.5 Decahydro[n] 8 Starting material 3.5 $\Delta^{1,9}$-Octahydro[o,p]
8-Methylquinoline	611-32-5	55[q]	22.5 1,2,3,4-Tetrahydro[r] 10 Starting material 6.5 Decahydro[n,o] 6 $\Delta^{1,9}$-Octahydro[o,s]

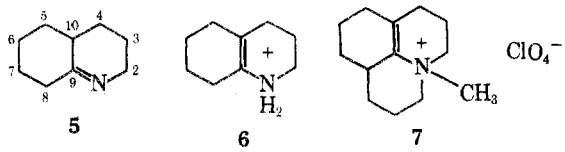
[a] Determined by VPC; see Experimental Section. [b] Picrate, mp 159–160° (lit.[20] mp 158–159°). [c] Mostly cis, by comparison with independently synthesized *trans*-[21] and *cis*-[19]decahydroquinoline. [d] Picrate, mp 136–137° (lit.[22] mp 136.5–137°). [e] Hydrochloride, mp 181° (lit.[23] mp 181°). [f] Cis and trans. [g] Catalyst 5% Pd/C. [h] Picrate, mp 143–144° (lit.[24] mp 144°). [i] Picrate, mp 158–159° (lit.[17b] mp 154°). [j] Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78. Found: C, 82.09; H, 9.75. Picrate, mp 142–143°. [k] Picrate, mp 182–183° (lit.[20] mp 182–183°). [l] Picrate, mp 161–162° (lit.[25] mp 159.5–160.5°). [m] Hydrochloride, mp 188–189° (lit.[26] mp 189°). [n] Mixture of isomers. [o] By comparison with independently synthesized compound(s), see ref 18b. [p] Picrate, mp 134–135°. [q] Picrate, mp 126–127° (lit.[25] mp 125–126°). [r] Hydrochloride, mp 218° dec (lit.[26] mp 214°). [s] Picrate, mp 151–152°.

A very different situation obtains when strong mineral acid (sulfuric, hydrochloric) is added to the acetic acid solution or when the hydrogenation is carried out in 12 *N* hydrochloric or sulfuric acid or in trifluoroacetic acid. The literature[8b,10] suggests that mineral acid facilitates reduction to the decahydro stage at least in the case of isoquinoline. However, when a large excess of acid is used, hydrogenation proceeds very slowly.[19] Indeed, it has been shown[37] that, whereas addition of small amounts of acid facilitates hydrogenation of pyridines, a large excess of acid slows it down. Of more interest, from the preparative point of view, is the fact that in strong acid the reduction proceeds via the 5,6,7,8-tetrahydroquinolines or -isoquinolines (benztetrahydro products) rather than via the 1,2,3,4-tetrahydro products mentioned above. Although the benztetrahydro products must have been intermediates in at least two previous reductions[10,19] in strong acid (cf. Table III, item 5), they have not heretofore been isolated except where reduction of the pyridine ring was impeded by alkyl substituents.[17] In the present work, we found (Table I) that the highest yields of 5,6,7,8-tetrahydroquinolines result when there is a methyl substituent in the pyridine ring, or a second fused benzene ring (as in acridine), lesser yields with no substituent, and the lowest yields when there is an alkyl substituent in the benzene ring, or a second benzene ring fused to it (as in benzo[*h*]quinoline).

The crucial factor in guiding the reaction toward hydrogenation of the benzene ring is the use of strong acid (compare Tables I and II with item 1 in Table III).[38] Under strongly acid conditions, not only quinoline and isoquinoline, but also acridine, benzo[*h*]quinoline, 2- and 4-phenylpyridine, and 4-(3-phenylpropyl)pyridine may be reduced in the benzene ring(s) in preference to the pyridine ring (Table II). It is tempting to propose, by way of explanation, that conversion to the salt impedes hydrogenation of the pyridine ring and thereby allows the normally slower hydrogenation of the benzene ring to occur preferentially. If this is so, it cannot be just a matter of placing a positive charge on the pyridine ring, however, since it is known[15,39,40] that *N*-alkylpyridinum salts are readily hydrogenated to N-substituted piperidines.

Of the three strong acids used in this work trifluoroacetic acid (Table II) is preferred because reduction times in this solvent are quite short.[41] In contrast, hydrochloric acid (Table I), perhaps by acting as a catalyst inhibitor, leads to very slow hydrogenation;[41] sulfuric acid (Table I) is intermediate.

Finally we note that $\Delta^{1,9}$-*octahydroquinolines* (**5**) frequently appear among the products of quinoline hydrogenation, in yields up to 11% (Tables I and II). While we have no definitive evidence as to whether these compounds are side products or intermediates in the hydrogenation, experiment 2 in Table III, in which $\Delta^{1,9}$-octahydroquinoline was obtained in 28% yield in the hydrogenation of 1,2,3,4-tetrahydroquinoline, raises the possibility that the Schiff base **5** arises from the enamine salt **6** derived from a $\Delta^{9,10}$-octahydroquinoline. The latter may logically be formed from either 1,2,3,4- or 5,6,7,8-tetrahydroquinoline if the sterically hindered 9,10 double bond escapes ultimate hydrogenation. Resistance of such a double bond to hydrogenation has been previously reported in the case of 1-methyl-Δ^5-tetrahydrojulolidinium perchlorate (**7**).[42] If this



5 **6** **7**

Table II
Hydrogenation of Quinolines, Isoquinoline, Quinoline Homologs, and Pyridines with Phenyl Substituents in Trifluoroacetic Acid at Room Temperature[a,b]

Substance reduced (catalyst[a])	Registry no.	Composition: % product[b] reduced in benzene ring(s)	Composition: % other products[b,c]
Quinoline		84	4.5 1,2,3,4-Tetrahydro 5 $\Delta^{1,9}$-Octahydro 3 Decahydro 3.5 Unidentified
Quinoline[d]		79.5	11.2 $\Delta^{1,9}$-Octahydro 7.3 Decahydro[e] 1.2 1,2,3,4-Tetrahydro
Quinoline (5% Rh/C)		69	15.6 1,2,3,4-Tetrahydro 9.2 Starting material 3.1 $\Delta^{1,9}$-Octahydro 2.3 Decahydro
Quinoline (5% Pd/C)		69	25 1,2,3,4-Tetrahydro 5.4 $\Delta^{1,9}$-Octahydro
Isoquinoline[f]		90.5	4 Decahydro[g] 4 Unidentified 1.5 1,2,3,4-Tetrahydro[h]
2-Methylquinoline		95	5, not isolated
2-Isopropylquinoline		95	5, not isolated
6-Methylquinoline		74	18.7 1,2,3,4-Tetrahydro 3.3 $\Delta^{1,9}$-Octahydro 2.1 Decahydro[i] 1.8 Starting material
8-Methylquinoline		55.8 (58)[j]	27.2 (12.4) 1,2,3,4-Tetrahydro 8.1 (21.6) $\Delta^{1,9}$-Octahydro 7.1 (0) Starting material 1.8 (5.7) Decahydro[i]
Acridine	260-94-6	100[k] (1)	None isolated
Benzo[*h*]quinoline	230-27-3	62.5 (42)[l,m] (2)	4.4 (33) 7,8,9,10-Tetrahydro (4)[n] 28 (25) 1,2,3,4,5,6,7,8-Octahydro (3)[o]
2-Phenylpyridine[p]	1008-89-5	49.8[q]	14.7 2-Cyclohexyl-3,4,5,6-tetrahydropyridine[r] 11.2 2-Cyclohexylpiperidine[s] 10.8 2-Phenylpiperidine[t] 13.5 Starting material
4-Phenylpyridine	939-23-1	87[u]	9 Overreduced, unidentified 4 Starting material
4-(3-Phenylpropyl)pyridine	2057-49-0	96[v]	4 Overreduced, unidentified

[a] Catalyst PtO_2, at 50 psi hydrogen, unless otherwise indicated. [b] Identification of products also listed in Table I is not indicated again. [c] Determined by VPC; see Experimental Section. [d] Reduction carried out at atmospheric pressure. Reaction time 8.5 hr. The material was deliberately slightly overreduced (uptake of more than 2 mol of hydrogen) to ascertain that all starting material had reacted. Starting material had to be purified by heating to reflux in ethanol over Raney Ni and distillation or else only 70% of theoretical amount of H_2 was taken up in 60 hr. [e] Cis:trans ratio 9:1. [f] Reduction carried out at atmospheric pressure. Reaction time 16 hr. Starting material was purified over Raney nickel. [g] Mixture of cis and trans. For identification see Table III, item 4. [h] Picrate, mp 194–195° (lit.[27] mp 194°). [i] Mixture of isomers; see footnote *o*, Table I. [j] Values in parentheses refer to a 75-min run, slightly overreduced. The unparenthesized figures refer to a 50-min run. [k] 1,2,3,4,5,6,7,8-Octahydroacridine, mp 69–71° (lit.[28] mp 69–71°). [l] The parenthesized figures refer to a 4-hr reaction time. The unparenthesized figures refer to an experiment with a greater than usual amount of catalyst, reaction time 1.5 hr. [m] 5,6,6a,7,8,9,10,10a-Octahydrobenzo[*h*]quinoline. Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15. Found: C, 83.20; H, 9.00. Picrate, mp 179–180°. [n] Picrate, mp 185–186° (lit.[29] mp 186°). [o] Picrate, mp 161–162° (lit.[30] mp 155–156°). A sample of the amine prepared according to this procedure[30] was not pure by VPC; ^1H NMR spectrum of the purified compound was identical with that of 3. [p] Reduction of amount of CF_3COOH by 25% led to consumption of only 80% starting material in 5.5 hr. [q] 2-Cyclohexylpyridine. Picrate, mp 111–112° (lit.[31] mp 128–129°, lit.[32] mp 104°; see Experimental Section). [r] Hydrochloride, mp 219–221° dec (lit.[33] mp 222–224°). [s] Hydrochloride, mp 255–256° (lit.[34] mp 251–252.5°). [t] Hydrate, mp 63° (lit.[7] mp 61–62°). [u] 4-Cyclohexylpyridine. Picrate, mp 154–155° (lit.[31] mp 154–155°). [v] 4(3-Cyclohexylpropyl)pyridine. Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41. Found: C, 82.51; H, 10.28. Picrate, mp 147–148°.

explanation is correct, the change from **6** to **5** (presumably in neutralization and work-up) must be essentially thermodynamically irreversible, since we were unable to regenerate **6** from **5** upon acidification (see Experimental Section). Alternatively, $\Delta^{1,9}$-octahydroquinoline salts may be formed as such in the reduction and resist further hydrogenation; indeed, when these Schiff bases are synthesized independently and hydrogenated in strong acid, reduction to the decahydro product is extremely slow (Table III, item 6).

Experimental Section

Melting points were determined on a Sargent Mel-Temp variable temperature heating block and are uncorrected. Analytical gas–liquid chromatography was carried out with a Hewlett-Pack-

Table III
Miscellaneous Reductions[a]

Item	Compd reduced	Conditions	% composition of products
1	Quinoline[b]	CH_3OH (anhydrous), 35 hr[c,d]	94.5 1,2,3,4-Tetrahydro 3 5,6,7,8-Tetrahydro 2.5 Decahydro (cis + trans)
2	1,2,3,4-Tetrahydroquinoline	12 *N* HCl, 75 hr	57.5 *cis*-Decahydro 14.5 *trans*-Decahydro 28 $\Delta^{1,9}$-Octahydro
3	Isoquinoline[e]	CH_3COOH, 1 atm, 4.5 hr[f]	61.9 1,2,3,4-Tetrahydro 20.8 *cis*-Decahydro[g] 7.7 *trans*-Decahydro[h] 5.8 5,6,7,8-Tetrahydro 3.8 Unidentified
4	Isoquinoline[e]	CH_3COOH, 1 atm, 35 hr[c]	62.5 *cis*-Decahydro[g,i] 33.2 *trans*-Decahydro[h,i] 4.3 Unidentified
5	Isoquinoline[e]	$CH_3COOH + H_2SO_4$,[j] 1 atm, 3 hr[f]	80 5,6,7,8-Tetrahydro 8.3 1,2,3,4-Tetrahydro 7.9 Starting material 2 Unidentified 1.8 Decahydro
6	8-Methyl-$\Delta^{1,9}$-octahydroquinoline	12 *N* HCl, ~70°, 48 hr[c]	71 Decahydro[k] 29 Starting material

[a] Over PtO_2, at 50 psi hydrogen, at room temperature unless otherwise indicated. [b] Conditions of ref 35. [c] Reduced until hydrogen uptake had practically ceased. [d] After 20 hr only 70% of starting material had reacted. [e] Conditions of ref 10. [f] Stopped after 2 mol of hydrogen had been absorbed. [g] Picrate, mp 150–151° (lit.[10] mp 150°). [h] Picrate, mp 177° (lit.[10] mp 177°). [i] Reference 10 reports reduction to stop at the 1,2,3,4-tetrahydro stage under similar conditions. Our starting material was purified by heating to reflux in ethanol over Raney Ni followed by distillation. [j] Initially precipitated isoquinolinium sulfate dissolved as hydrogenation proceeded. [k] Mixture of isomers; see footnote *o*, Table I.

ard 5750 research chromatograph, equipped with a thermal conductivity detector, on 0.125-in. columns. Columns used were a 12-ft, aluminum, 20% Carbowax 20M + 10% KOH on Chromosorb W, 80/100 mesh, and a 10-ft stainless steel 30% SE-30 on Chromosorb W, 60/80 mesh, at temperatures between 120 and 200°. A Varian Aerograph Series 2700 with 0.375-in. aluminum columns with matching phase on Chromosorb A were used for preparative VPC. NMR spectra were recorded on a Varian XL-100 equipped with Fourier transform for ^{13}C analysis, or on a Jeolco C60HL instrument. Microanalyses were carried out by Galbraith Laboratories, Inc.

Hydrogenations at 50 psi were carried out in a Parr low-pressure shaker type hydrogenation apparatus, in 500-ml glass bottles.[3] Atmospheric pressure hydrogenations were done in a sloping manifold hydrogenator,[3] with magnetic stirring.

Catalysts. Platinum oxide (83%), rhodium (5% on carbon), and palladium (5% on carbon) were purchased from Engelhard Industries, Inc.

Starting Materials. Quinoline, isoquinoline, 2-methylquinoline, acridine, benzo[*h*]quinoline, 4-phenylpyridine, and 4-(3-phenylpropyl)pyridine were purchased from various sources (Aldrich Chemical Co., Columbia Organic Chemicals Co., and Eastman Kodak). 6-Methylquinoline[43] and 8-methylquinoline[44] were prepared by the Skraup synthesis from *p*- and *o*-toluidine. 3-Methylquinoline[17b] was obtained by condensation of *o*-aminobenzaldehyde[45] with propionaldehyde. 2-Isopropylquinoline was first synthesized from 1-methylquinolinium iodide with isopropylmagnesium bromide and subsequent elimination of methane from the intermediate 1-methyl-2-isopropyl-1,2-dihydroquinoline,[46] but the alternative method,[47] reaction of 2-methylquinoline two times in succession with equimolar amounts of butyllithium and quenching with methyl iodide, was vastly superior (the intermediate 2-ethylquinoline was isolated and purified by distillation). 2-Phenylpyridine was made from phenyllithium and pyridine.[48] 1,2,3,4-Tetrahydroquinoline was obtained by hydrogenating quinoline in anhydrous methanol over PtO_2 (see Table III, item 1). $\Delta^{1,9}$-Octahydroquinoline was prepared by the method of Cohen and Witkop.[22] 8-Methyl-$\Delta^{1,9}$-octahydroquinoline was synthesized from the piperidine enamine of 2-methylcyclohexanone and 3-bromopropylamine hydrobromide as reported for the parent compound;[49] this synthesis will be described elsewhere.[18b]

Purification of Starting Materials. Commercially obtained products were dissolved in ethanol and heated to reflux over Raney nickel[19] for 12 hr. After filtering from the catalyst and evaporation of the solvent, the material was distilled and checked by gas chromatography. Occasionally reduction of the pyridine ring of the compounds took place in minor amounts; such by-products were separated by acetylation, and the pyridines and quinolines purified by distillation as described below. For hydrogenations at elevated pressure (50 psi) this purification normally proved unnecessary but prolonged hydrogenation times were required when unpurified amines were hydrogenated at atmospheric pressure (note Table II, footnote *d*). The purification was also necessary for 2-isopropylquinoline synthesized by the butyllithium–methyl iodide method (see above) or else hydrogenation at 50 psi was extremely slow.

Hydrogenations at 50 psi. Fifty millimoles of starting material was dissolved in a 500-ml Parr bottle in 40 ml of ice-cold acid (HCl, 12 *N*, or H_2SO_4, 12 *N*, or CF_3COOH), 750 mg of PtO_2 [or 3 g of Rh (5% on C) or 3 g of Pd (5% on C)] was added, the bottle was connected to the hydrogenator and the air was removed,[3] 50 psi pressure was applied, and the mixture was hydrogenated until the required amount of hydrogen had been consumed. The catalyst was then filtered from the solution through a glass fiber filter, and the solution was diluted with water. Catalysts could be reused without noticeable loss in activity (except with H_2SO_4 as a solvent; here occasionally the catalyst proved inactive upon reuse). The aqueous solution was chilled in ice, and was carefully made basic with strong NaOH. The products were extracted with either petroleum ether or ether, the organic solution was dried over KOH, and the solvent was distilled off. The remaining residue was purified by total distillation at reduced pressure (without fractionation) by means of a Kugelrohr unit, using bulb tubes equipped with ground glass joints. The distilled products were checked by VPC, using the columns described above. Compositions listed in Tables I–III were determined in this way.

Hydrogenations at Atmospheric Pressure. Starting material (50 mmol or the amount indicated in ref 10) was dissolved in 40 ml of CF_3COOH (or the solvent indicated in Table III) and added to 750 mg (or the amount indicated in ref 10) of PtO_2, which had been prereduced in 10 ml of CF_3COOH (or the solvent indicated in Table III). The mixture was hydrogenated with magnetic stirring under a slight positive pressure of the gas buret (filled with glycerol) until the theoretical amount of hydrogen had been consumed or

Table IV
^{13}C Shifts[a] of $\Delta^{1,9}$-Octahydroquinoline

	Carbon								
	2	3	4	5	6	7	8	9	10
$CDCl_3$	49.56	21.39	27.50	34.98	25.97	27.98	39.28	172.94	38.66
CF_3COOH	47.46	19.96	28.69	36.10	25.46	25.83	38.24	199.14	41.51

[a] In parts per million downfield from Me_4Si.

uptake had completely ceased. After the catalyst was filtered, the solution was worked up as described above.

Isolation of Pure Products. In a number of cases the products were separated by preparative gas chromatography and characterized by melting point of derivatives, ^1H NMR spectra, and (if necessary) elemental analysis. The isolation of 5,6,7,8-tetrahydroquinoline on a larger scale is described below.

Quinoline (6.45 g, 50 mmol) was dissolved in 40 ml of CF_3COOH, 750 mg of PtO_2 was added, and the mixture was hydrogenated at 50 psi in a Parr shaker. After 45 min, when the pressure had dropped 9.2 psi, the catalyst was filtered off and the solution was worked up as described above. The crude product (6.3 g) was stirred with 1.3 g of acetic anhydride (12.7 mmol) at 100° for 5 hr. At the end of that time the mixture was diluted with 100 ml of water, 15 ml of concentrated HCl was added, and the solution was extracted five times with ether. (From the ether extract the decahydro-, but not the octahydroquinoline, could be recovered by heating the amides with concentrated HCl and subsequently extracting the basified solution with petroleum ether.) The aqueous solution was chilled in ice, made carefully basic with a concentrated aqueous solution of NaOH, and extracted five times with petroleum ether. The organic extract was dried over KOH and the solvent distilled off. The residue was distilled in a Kugelrohr apparatus at 25 mm (air bath temperature 120°) to give 5.05 g (76%) of 5,6,7,8-tetrahydroquinoline. The product was pure by VPC.

In a similar way the other products with nonreduced pyridine ring were isolated preparatively. When small amounts of starting material were still present, they were separated by fractional distillation at reduced pressure.

$\Delta^{1,9}$-Octahydroquinoline. To determine the position of the double bond in octahydroquinoline and octahydroquinolinium trifluoroacetate, 300 mg of 5[22] was dissolved in 3 ml of $CDCl_3$ or CF_3COOH containing 2% Me_4Si and the ^{13}C NMR spectra were recorded (Table IV). Assignment of the signals of the nine carbon atoms was made by comparison with the spectra of the 8,8,10-trideuterio analog and a number of methyl homologs,[50] and by off-resonance decoupling.

The similarity of the two sets of shifts indicates that the protonated species produced from $\Delta^{1,9}$-octahydroquinoline does not have structure **6**, since there is only one olefinic carbon atom (9), and the signals of carbon atoms 8 and 10 are a triplet and a doublet in the off-resonance decoupled spectrum indicating their substitution with two protons and one proton, respectively.

2-Cyclohexylpyridine. The melting point of the picrate prepared from a gas chromatographically pure sample, 111–112°, did not agree with the literature data (lit.[31,32] mp 128–129°, 104°). Analysis of the picrate agreed with theory. Anal. Calcd for $C_{17}H_{18}N_4O_7$: C, 52.31; H, 4.65. Found: C, 52.47; H, 4.94.

Amine: $n^{25}D$ 1.5221 (lit.[31] $n^{20}D$ 1.5246; lit.[32] $n^{20}D$ 1.5295).

The 60-MHz ^1H NMR spectrum (10% in $CDCl_3$, Me_4Si) agreed only roughly with values reported in the literature[51] shown in parentheses (solvent not reported[51]): pyridine ring, δ 8.77 (d, 1 H, H_α) (8.51, d), 7.24 (m, 2 H, H_β) (7.06, m), 7.77 (m, 1 H, H_γ) (7.56, m); cyclohexane ring, 2.78 (broad m, 1 H, H_1) (2.40, m), 1.73 ppm (m, 10 H, H_{2-6}) (1.60, m).

^{13}C shifts (parts per million from Me_4Si, in $CDCl_3$, multiplicity in parentheses from off-resonance decoupled spectrum): pyridine ring, C_2 166.15 (s), $C_{3,5}$ 120.79[52] (d), C_4 136.07 (d), C_6 148.76 (d); cyclohexane ring, C_1 46.50 (d), $C_{2,6}$ 32.88[52] (t), $C_{3,5}$ 26.58[52] (t), C_4 26.07 (t).

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Registry No.—2-Isopropyl-5,6,7,8-tetrahydroquinoline, 55904-64-8; 2-isopropyl-5,6,7,8-tetrahydroquinoline picrate, 55904-65-9; 6-methyl-$\Delta^{1,9}$-octahydroquinoline picrate, 55904-66-0; 8-methyl-$\Delta^{1,9}$-octahydroquinoline picrate, 55904-67-1; 5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinoline, 55904-68-2; 5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinoline picrate, 55904-69-3; 4-(3-cyclohexylpropyl)pyridine, 55904-70-6; 4-(3-cyclohexylpropyl)pyridine picrate, 55904-71-7; 8-methyl-$\Delta^{1,9}$-octahydroquinoline, 52761-53-2; $\Delta^{1,9}$-octahydroquinoline, 1074-06-2; 2-cyclohexylpyridine, 15787-49-2; 2-cyclohexylpyridine picrate, 55904-72-8; 1,2,3,4-tetrahydroquinoline, 635-46-1.

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Reduction of 5,6,7,8-Tetrahydroquinolines and 2,3,4,5,6,7,8,10-Octahydroquinolines to *trans*-Decahydroquinolines†

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The reduction of the title compounds with sodium in ethanol gives largely (~90%) *trans*-decahydroquinolines. When alkyl substituents or fused rings are present in the starting materials, the decahydroquinoline juncture of the product is still largely trans, but two (or more) epimers at the point of alkyl substitution (or fused ring juncture) result; they are separated readily by preparative gas chromatography. Similar reduction of 5,6,7,8-tetrahydroisoquinoline gives mainly $\Delta^{9,10}$-octahydroisoquinoline (58%) with lesser amounts of *cis*- (20%) and *trans*-decahydroisoquinoline (22%). Reduction of 5,6,7,8-tetrahydroquinoline with sodium in ethanol-*O*-*d* surprisingly gives mainly 2,3,3,4,9,10-hexadeuterio-*trans*-decahydroquinoline with some deuteration also occurring at position 8. Evidently exchange at an intermediate reduction stage is involved. Similar reduction of pyridine gives 2,3,3,4,5,5,6-heptadeuteriopiperidine. Reduction of $\Delta^{1,9}$-octahydroquinolines with sodium in ethanol provides an alternative path for the synthesis of *trans*-decahydroquinolines, including compounds with methyl substituents at C-10. The synthesis of certain deuterated analogs is also described. The ^{1}H NMR spectra of the compounds synthesized (including the deuterated analogs) as well as of their *N*-methyl, *N*-ethyl, and *N*-isopropyl derivatives are described in some detail.

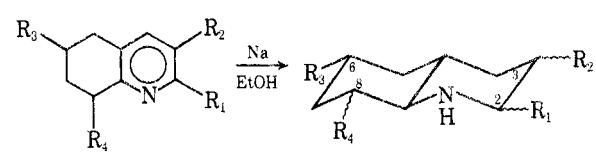
As explained in the accompanying paper,[1] there is a dearth of convenient known syntheses for the trans isomers of decahydroquinoline and decahyd oisoquinoline. Catalytic hydrogenation of quinolines and isoquinolines normally leads to the cis products, or at best (under special conditions) to mixtures in which the trans isomer may predominate. While the separation of *cis*- and *trans*-decahydroquinolines and decahydroisoquinolines by modern gas-chromatographic methods presents no insuperable difficulty, the problem is aggravated when there are alkyl substituents in the ring, in which case *four* diastereoisomers are formed: the α and β isomers[2] (referring to the stereochemical placement of the alkyl group) in both the cis and trans ring-fused series.

Chemical Reduction of 5,6,7,8-Tetrahydroquinolines. Having devised a convenient synthesis[1] of 5,6,7,8-tetrahydroquinolines and -isoquinoline by hydrogenation of the corresponding quinoline or isoquinoline over platinum oxide in strongly acidic medium, we decided to explore the sodium–ethanol[4,5] reduction of the benztetrahydro compounds as a means to obtaining the *trans*-decahydro compounds which we required in another investigation.[6] The results are summarized in Table I.

5,6,7,8-Tetrahydroquinoline (1) is reduced to *trans*-decahydroquinoline (90%) along with 10% of the cis isomer (Scheme I). In the case of the 2- (2), 3- (3), 6- (4), and 8-substituted (5) homologs, again the combined yield of the *trans*-decahydro product adds up to 90%, but in this case two diastereoisomers, α and β, result. Except in the case of the 6-methyl compound (9), where only the α (equatorial) isomer was isolated, the α and β isomers were cleanly separated by gas chromatography and identified by elemental

† This paper, and the preceding one, is dedicated by F.W.V. to Professor Dr. K. Kratzl on the occasion of his 60th birthday.

Scheme I



1	$R_1 = R_2 = R_3 = R_4 = H$	6	
2	$R_1 = CH_3$; $R_2 = R_3 = R_4 = H$	7	(α, β)
3	$R_2 = CH_3$; $R_1 = R_3 = R_4 = H$	8	(α, β)
4	$R_3 = CH_3$; $R_1 = R_2 = R_4 = H$	9	(α only)
5	$R_4 = CH_3$; $R_1 = R_2 = R_3 = H$	10	(α, β)

analysis, ^{1}H NMR (see below), and ^{13}C NMR[7] spectral study. In the tricyclic series, 1,2,3,4,5,6,7,8-octahydroacridine[1] (11) was reduced in high yield to *trans-syn-trans*-perhydroacridine (12, Scheme II).[8] The stereoisomeric mixture of 5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinolines (13) obtained by catalytic hydrogenation of the aromatic precursor[1] was reduced to a mixture of three perhydrobenzo[*h*]quinolines (14–16) in which the juncture of the piperidine to the adjacent cyclohexane ring was trans and the decalinoid ring fusion displayed the two possible cis junctures and one of the possible trans junctures (Scheme II).[8]

Unfortunately, 5,6,7,8-tetrahydroisoquinoline (17) is reduced in the main (58%) to the 1,2,3,4,5,6,7,8-octahydro compound[9] (18) with only minor amounts of *cis*- (20) and *trans*-decahydroisoquinoline (19) being formed (Scheme III). Apparently the sequence of reduction steps is such that the last of the three double bonds to be reduced ends up in the 9,10 position, where it is, of course, inert to further reduction.[10] A plausible though unproven sequence of events is suggested in Scheme IV. It should be noted that in the reduction of the tetrahydroquinoline analog (discussed below), even if a double bond remained in the 9,10