Selectivity of Hydrogenations. Part 3.[1] *N*-Methylquinolinium, *N*-Methylisoquinolinium, and 4-(3-Phenylpropyl)pyridinium Salts

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N-Methyl fluorosulphonates of quinoline, 8-methyl- and 8-t-butyl-quinoline, isoquinoline, and 4-(3-phenylpropyl)pyridine were hydrogenated by catalysis on platinum, in methanol or in trifluoroacetic acid. Hydrogenation in methanol gave *N*-methylpiperidine derivatives; in trifluoroacetic acid hydrogenation of the benzene rings gave *N*-methylpyridinium derivatives. Reaction mixtures were analyzed by ^{13}C n.m.r. spectroscopy and by isotachophoresis.

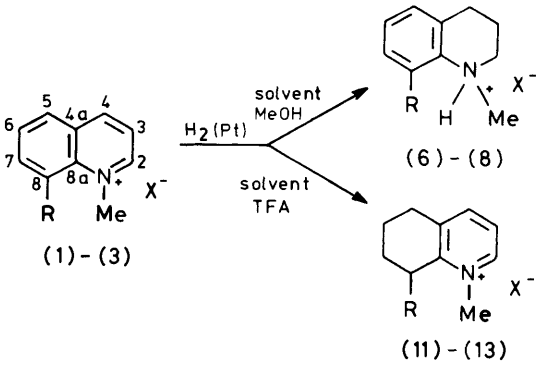
HYDROGENATION of benzene-condensed or phenyl-substituted pyridine usually occurs in the pyridine ring, and quaternization of the nitrogen facilitates this reaction, supposedly by prevention of the poisoning of the catalyst by the pyridine itself or by the resulting piperidine.[2] However, the use of increasing amounts of very strong acid eventually slows the rate of hydrogenation of the pyridine moiety [3] and at the same time activates the benzene ring towards hydrogenation, which leads to a preferential saturation of the carbocyclic portion of quinoline, isoquinoline, phenylpyridines, and related compounds in 12N HCl, 12N H_2SO_4, and CF_3CO_2H.[1a]

One possible reason for this change in hydrogenation selectivity was the complete conversion of the pyridine into its salt, and the higher stability of the latter against saturation. However, a number of examples in the literature [2,4] indicate that salt formation by alkylation of the pyridine ring has the opposite effect and that the *N*-alkylpyridinium salts are generally more easily hydrogenated to the corresponding piperidines than the parent bases. These hydrogenation reactions had been carried out in neutral or mildly acidic solution; it was therefore interesting to study the change, if any, in selectivity towards hydrogenation of salts changing the solution from neutral solvent (methanol) to strongly acidic solvent (trifluoroacetic acid).

RESULTS

From the compounds investigated earlier [1] five bases were used. Quinoline and isoquinoline were selected since they represent basic structures present in a large number of naturally occurring compounds; in addition, the non-heterocyclic component of isoquinoline has been reported [2] to be exceptionally difficult to saturate. 8-Methylquinoline has shown a much reduced selectivity towards hydrogenation in trifluoroacetic acid [1]; this was not likely to be for steric reasons, as demonstrated by comparison with 8-t-butylquinoline, which had an even higher specifity than the parent quinoline, and with the corresponding 6-substituted quinolines,[1b] which showed selectivities parallel to the 8-R-compounds. Finally, in 4-(3-phenylpropyl)pyridine the pyridine and benzene ring are separated by four single bonds and can be considered as independent rings; it seemed attractive to compare the high hydrogenation selectivity observed in the free base [1a] with the results obtained with the salt.

Quinoline was converted into its methiodide (1a),[5] which was hydrogenated on platinum at atmospheric pressure in anhydrous methanol to 1,2,3,4-tetrahydro-*N*-methylquinoline (6) in practically quantitative yield. In trifluoroacetic acid under otherwise identical conditions no hydrogen was taken up, apparently because of catalyst poisoning. The counterion of compound (1a) was consequently exchanged against $CF_3CO_2^-$, and the resulting salt (1b) was hydrogenated in trifluoroacetic acid (TFA). No measurable amounts of tertiary amine could be isolated after a hydrogen uptake of 2 mol mol^{-1}. The ^1H n.m.r. spectrum of the product indicated the exclusive formation of 5,6,7,8-tetrahydro-*N*-methylquinolinium trifluoroacetate (11b) (see Scheme 1).



(1), (6), (11): R = H
(2), (7), (12): R = Me
(3), (8), (13): R = Bu^t
a; X^- = I^-
b; X^- = $CF_3CO_2^-$
c; X^- = FSO_3^-

SCHEME 1

Since attempts to prepare the methiodides directly from the sterically hindered 8-substituted quinolines were unsuccessful, and ion exchange in the other cases gave only impure products; *N*-methylation was carried out with methyl fluorosulphonate, which even allowed the synthesis of *N*-methyl-8-t-butylquinolinium fluorosulphonate (3c). The fluorosulphonates could be hydrogenated both in methanol and trifluoroacetic acid at atmospheric pressure; only in case of the *N*-methylisoquinolinium fluorosulphonate did the speed of hydrogenation in MeOH have to be increased by a slightly elevated pressure.

Determination of structure and yield of the major and

minor hydrogenation products by separation was tedious because of their different character (quaternary salts and tertiary amines). Possible methods for their quantitative determination without preceding separation were ^{13}C n.m.r. spectroscopy and isotachophoresis.[6] After hydrogenation, the solvent was distilled off. For ^{13}C n.m.r. spectroscopy, the residue was taken up in TFA–D_2O (9 : 1), and the spectrum was recorded. Identification of the signals in the mixtures was achieved by comparison with the spectra of the pure compounds (6b)–(10b) (from their parent amines and TFA) and of compounds (11c)—(15c) (independently synthesized).

Hydrogenation [a] of the salts (1c)—(5c) in methanol or trifluoroacetic acid

Starting material	Solvent	Products [b] (%) Benzene-hydrogenation	Pyridine-hydrogenation	Others
(1c)	MeOH		(11) >95 [c,e]	
	TFA	(6) 70 [c,e]	(11) ≪5 [c,e]	(16) 30 [c,e]
(2c)	MeOH	(7) <10,[c] 2 [d]	(12) >90,[c] 98 [d]	
	TFA	(7) *ca.* 80,[c] 74 [d]	(12) *ca.* 20,[c] 26 [d]	
(3c)	MeOH		(13) >90,[c] 92 [d]	(3) 10,[c] 8 [d]
	TFA	(8) 86,[c] 86 [d]	(13) 14,[c] 14 [d]	
(4c)	MeOH [f]	(9) <10,[c] 4 [d]	(14) >90,[c] 96 [d]	
	TFA	(9) *ca.* 100,[c] 97 [d]		(4) 3 [d]
(5c)	MeOH		(15) >95,[c] 98 [g]	(17) <5,[c] 2 [g]
	TFA	(10) >80,[c] 92 [d]		(17) <20,[c] 8 [d]

[a] At atmospheric pressure unless indicated. For details see Experimental section. [b] Counterions for MeOH are FSO_3^- and for TFA are FSO_3^- plus $CF_3CO_2^-$. [c] Analysis by ^{13}C n.m.r. spectroscopy. [d] Analysis by isotachophoresis. [e] Isotachophoretic analysis in this case was unsuccessful because of detector problems. [f] Hydrogenation at 3 bar pressure in a Parr-hydrogenator. [g] Isotachophoresis did not distinguish between the compounds (15) and (17). The bases were freed from the salts and the composition was determined by gas chromatography (g.c.) (column 20% Carbowax 20M + 10% KOH on Chromosorb W).

For isotachophoresis, the samples were dissolved in MeOH–H_2O (1 : 1) and injected between the leading and terminating electrolyte. Comparison in this case was made with the free bases of compounds (6)—(10), and with compound (11c)—(15c).

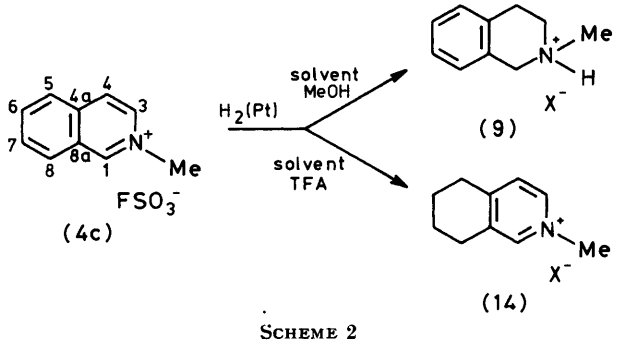
The results obtained by both methods are given in the Table. Limits of error in the ^{13}C n.m.r. spectral determinations, due to the S/N ratio obtained, and to possible differences in nuclear Overhauser enhancements were <10%, with 5% of a minor component easily detected. In the isotachophoretic determinations, error limits are ±1% for major (>85%) to 10—30% for minor (2—5%) products.

DISCUSSION

The results given in the Table and reference 1 show a surprising parallel between the hydrogenation of the pyridine bases and of their *N*-methyl quaternary salts in trifluoroacetic acid on the one hand, and in methanol on the other. In TFA, both for compound (1c) and for quinoline,[1] the 2,3,4,4a,5,6,7,8-octahydro-derivative was identified in the product mixture, which indicates that not only the pyridine ring, but also the imine double bond is stabilized against hydrogenation by the strong acid. In the hydrogenation of quinoline, 6% of the 1,2,3,4-tetrahydro-product were isolated;[1b] the *N*-methyl salts [both compounds (1b) and (1c)] gave no measurable amounts of product (6).

The hydrogenation of compound (2c) in TFA gave a noticeable proportion of pyridine-hydrogenated product; replacement of the 8-methyl- by the 8-t-butyl-group [compound (3c)] increased the benzene-hydrogenation. This is in excellent agreement with the results of the parent quinolines, where the proportion of benzene-hydrogenated product decreases from 80% for quinoline to 51% for 8-methylquinoline and increases again to 85% for 8-t-butylquinoline.[1b] In both compounds (4c) and in isoquinoline, formation of the pyridine-hydrogenated product was negligible (see Scheme 2). In *N*-methyl-4-(3-phenylpropyl)pyridinium-fluorosulphonate (5c), a palpable proportion (*ca.* 10%) of the product with both rings saturated was detected. Since no *N*-methyl-4-(3-phenylpropyl)piperidine was present in the mixture, this compound probably results from an eventual hydrogenation of the pyridine moiety of compound (10) in hydrogenation which was prolonged to ascertain the complete reaction of all starting material (see Scheme 3).

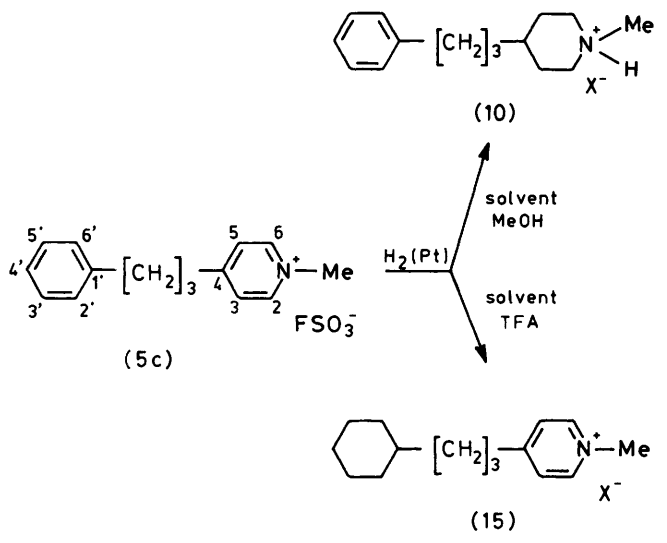
The situation is similar for the hydrogenations in methanol. As for the quinolines,[1b] the products were nearly pure pyridine-hydrogenated derivatives. The reaction is more facile with the salts than with the parent bases; hydrogen uptake in all cases except for salt (4c) readily took place at atmospheric pressure, whereas elevated pressure had to be used with the parent amines of the free bases (1)—(4), and no hydrogen at all was taken up by 4-(3-phenylpropyl)pyridine in MeOH.



SCHEME 2

Benzene- or pyridine-hydrogenated products can thus be prepared in good-to-satisfactory yields by selection of the acidity of the solvent, starting with the *N*-alkyl quaternary salts as with the parent bases. In addition to the practical use for synthetic applications, the results help to explain the solvent-dependence of the hydrogenation of

benzene-substituted and condensed pyridine. The introduction of the positive charge at the nitrogen is clearly not the deciding factor in both the stabilization of the heterocyclic and the activation of the carbocyclic ring for hydrogenation in strong acid, or else compounds (1)—(5) would give identical products in methanol and trifluoroacetic acid. Since the product distribution is very



b ; $X^- = CF_3CO_2^-$

c ; $X^- = FSO_3^-$

SCHEME 3

similar for the salts and the parent bases in each of the two solvents, the causes of the activation–de-activation are likely to be similar in the two classes of compounds. The nature of these causes remains uncertain, but the results obtained with compounds (1)—(5) do not contradict the hypothesis [16] of pyridine-ring stabilization by strong solvation, and benzene-ring activation by σ- or π-complexes in trifluoroacetic acid.

EXPERIMENTAL

^1H N.m.r. spectra were recorded on a Varian EM-360 spectrometer with internal-lock facility. Amines were dissolved in $CDCl_3$, salts in CF_3CO_2H with $SiMe_4$ (TMS) as internal reference and lock substance. ^{13}C N.m.r. spectra were recorded on a Bruker WM 250 spectrometer in the same solvents, but with 10% D_2O added to CF_3CO_2H to provide a lock signal. Direct inlet mass spectra were measured on a Varian CH-7 spectrometer (EI 70 eV; emission 1 000 μA; inlet temperature 80—180 °C). Melting points were determined on a Kofler hot-stage. Details for the preparation of the starting amines and the ^{13}C n.m.r. spectral data for the salts (6b)—(10b) are given in Supplementary Publication No. 23391 (11 pages).*

Preparation of Compounds (1)—(5) *and* (11)—(15).—*N*-Methylquinolinium iodide (1a) was prepared as reported.[5] *N*-Methylquinolinium trifluoroacetate (1b) was obtained by passing an aqueous solution of the iodide (1a) over a column filled with Lewatite (activated with 2M NaOH and washed until the washings were neutral), acidification of the resulting solution with CF_3CO_2H, and evaporation to dryness. The resulting oil crystallized; the impure product was used without purification.

The fluorosulphonates (1c)—(5c) and (11c)—(15c) were obtained by adding slightly less than the stoicheiometric amount of methyl fluorosulphonate in anhydrous benzene to the solution of the corresponding amine in anhydrous benzene. With the exception of compounds (3c), (12c), and (13c), essentially quantitative formation of the salt took place at room temperature. In the case of the fluorosulphonates (12c) and (13c) the benzene solutions were heated to reflux for 6 and 12 h, respectively. For the synthesis of compound (3c), 8-t-butylquinoline (0.02 mol) and 0.02 methyl fluorosulphonate (0.02 mol) were heated, with stirring, in a stoppered flask to 120 °C for 24 h. At intervals of 5 h the flask was cooled to below 90 °C and vented.

The resulting crystalline fluorosulphonates [with the exception of compound (15c), which melts at too low a temperature for recrystallization] were recrystallized from ethyl acetate–acetone (5 : 1). Elemental analysis of the salts was unsatisfactory, even after extensive drying, possibly because they are highly hygroscopic. Characterization was achieved by ^1H n.m.r. spectroscopy (and ^{13}C n.m.r. spectroscopy for the partly hydrogenated compounds), and by mass spectroscopy. In most mass spectra the cation of the quaternary ammonium salts could be detected as the peak of highest mass. Details of the spectra (^1H n.m.r. and mass) are given in the Supplementary publication for the following compounds: 1-methylquinolinium fluorosulphonate (1c), m.p. 198—199 °C; 1,8-dimethylquinolinium fluorosulphonate (2c), m.p. 255 °C; 1-methyl-8-t-butylquinolinium fluorosulphonate (3c), m.p. 130—133 °C; 2-methylisoquinolinium fluorosulphonate (4c), m.p. 158—159 °C; 1-methyl-4-(3-phenylpropyl)-pyridinium fluorosulphonate (5c), m.p. 108—110 °C; 5,6,7,8-tetrahydro-1-methylquinolinium fluorosulphonate (11c), m.p. 165.5—166.5 °C; 5,6,7,8-tetrahydro-1,8-dimethylquinolinium fluorosulphonate (12c), m.p. 102—104 °C; 5,6,7,8-tetrahydro-1-methyl-8-t-butylquinolinium fluorosulphonate (13c), m.p. 181—184 °C; 5,6,7,8-tetrahydro-2-methylisoquinolinium fluorosulphonate (14c), m.p. 105—106 °C; and 4-(3-cyclohexylpropyl)-1-methylpyridinium fluorosulphonate (15c), not crystalline at room temperature.

2,3,4,4a,5,6,7,8-*Octahydro*-1-*methylquinolinium Fluorosulphonate* (16c).—Compound (16c), needed for comparison in the hydrogenation of compound (1c) in CF_3CO_2H was prepared from 2,3,4,4a,5,6,7,8-octahydroquinoline [7] and methyl fluorosulphonate in a similar manner to compound (1c). The oil was repeatedly suspended in diethyl ether, the ether was siphoned off and the oil was dried in high vacuum (spectral details given in the Supplementary publication).

4-(3-*Cyclohexylpropyl*)-1-*methylpiperidinium Fluorosulphonate* (17c).—Compound (17c), formed by overhydrogenation of compound (5c), was prepared by adding a small amount of fluorosulphonic acid to the hydrogenation of compound (5c) in MeOH after 3 mol H_2 per mol compound (5c) had been consumed. An additional 3 mol H_2 per mol were taken up. The solution was filtered from the catalyst, the solvent was distilled off, and the residual oil was dried over KOH (spectral details given in the Supplementary publication). The base was freed from the salt and distilled to give 4-(3-cyclohexylpropyl)-1- methylpiperidine (spectral details given in the Supplementary publication), the *picrate*

* For details of the Supplementary publications Scheme, see Notice to Authors No. 7, *J. Chem. Soc., Perkin Trans. 1*, 1981, Index issue.

had m.p. 157—158 °C (Found: C, 55.85; H, 7.0. $C_{21}H_{32}N_4O_7$ requires C, 55.75; H, 7.15).

Hydrogenation Reactions.—Hydrogenation reactions were carried out at atmospheric pressure as described for the parent bases of compounds (1)—(3).[1b] Platinum oxide (400 mg) was prehydrogenated in TFA (20 ml) or MeOH (40 ml), respectively. Solutions of the starting material in TFA (10 ml) or MeOH (30 ml) were then added, and the mixture was stirred under hydrogen until uptake was complete. The solutions were filtered from the catalyst, the solvents were distilled off, and the composition of the residue was determined by ^{13}C n.m.r. spectroscopy or by isotachophoresis.

^{13}C *N.M.R. Spectra.*—Part of the residue was dissolved in 90% trifluoroacetic acid (TFA) + 10% D_2O, TMS was added, and the spectra were recorded. Assignment of peaks was accomplished by comparison with the spectra of pure samples. Ratios of components were calculated by comparing signal areas of corresponding C atoms to minimize effects of different T-1s, and nuclear Overhauser enhancements.

*Isotachophoresis.**—Isotachophoretic separations were carried out with two different instruments, provided with conductivity detector cells. One instrument, made from polytetrafluoroethylene, was similar to that described by Everaerts *et al.*[6] The other was a commercially available instrument (model TACHOPHOR, LKB, Bromma, Sweden), with electrolyte compartments made of TPX. Leading electrolyte was Na^+ (0.01 mol^{-1}), counter ion acetate, pH_{app} 5.50, with 0.05% poly(vinyl alcohol) as additive. Terminating electrolyte was 2-aminopropionic acid (0.01 mol^{-1}), counter ion acetate, pH_{app} 5.45, no additive. Solvent was water–MeOH (50%*v*/*v*).

* A detailed description of the isotachophoretic measurements is published elsewhere (ref. 8). The authors are grateful to Dr. E. Kenndler and Mr. E. Haidl, Institute for Analytical Chemistry, for the work carried out on the product mixtures.

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