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Precursors to Apomorphine and Morphinan Analogs. Studies on Catalytic Reduction of Quinoline and Isoquinoline*

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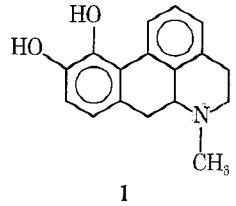
Hydrogenation of isoquinoline and quinoline over PtO_2 at atmospheric pressure in methanolic hydrochloric acid led predominantly to reduction of the benzene ring, whereas reaction of 5,6,7,8-tetrahydroisoquinoline with sodium–ethanol gave chiefly 1,2,3,4,5,6,7,8-octahydroisoquinoline. The experimental conditions established for the above reactions may be used in the synthesis of precursors of apomorphine and morphinan analogs from the readily synthesized derivatives of 1-benzylisoquinoline.

Apomorphine (1) has potentiated the therapeutic effects of levodopa (L-dopa, 3,4-dihydroxyphenylalanine) while diminishing some of its side effects in the treatment of Parkinsonism.[1] To separate synergistic from antagonistic effects we have been synthesizing analogs of **1**.[2] We report here findings obtained in exploring synthetic routes to new analogs.



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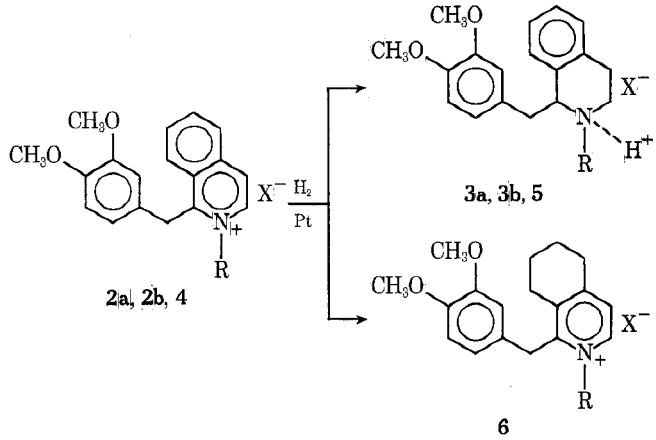
In the hydrogenation of 1-(3′,4′-dimethoxybenzyl)-2-methyl- (**2a**) and 1-(3′,4′-dimethoxybenzyl)-2-*n*-propylisoquinolinium iodide (**2b**) over PtO_2 at atmospheric pressure and room temperature, the pyridine ring was invariably reduced to piperidine to give **3a** and **3b** in yields of >90% (Scheme I). In contrast, under the same conditions, the hydrochloride of **4** yielded two products, 43–46% of 1-(3′,4′-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**5**) and 54–57% of 1-(3′,4′-dimethoxybenzyl)-5,6,7,8-tetrahydroisoquinoline (**6**) as the hydrochloride salts.

Until recently,[3] reports of hydrogenation of isoquinoline (**7**) and quinoline (**10**) derivatives always indicated a preferential, if not exclusive, reduction of the pyridine ring[4] depending on the experimental conditions used and the degree of ring substitution.[5] Therefore, 5,6,7,8-tetrahydroisoquinoline (**9**) and 5,6,7,8-tetrahydroquinoline (**12**) compounds have always been synthesized by multistep or indirect methods.[4a,6] It was also shown that **12** can be reduced with sodium–ethanol to the corresponding *trans*-decahydroquinoline.[3]

These observations suggested to us that the scope of synthesis of apomorphine analogs might be expanded to include derivatives of 1-benzyl-*trans*-decahydroisoquinolines obtained from their precursors, 1-benzyl-5,6,7,8-tetrahydroisoquinolines (**13**). These in turn may be reduced to 1-benzyl-1,2,3,4,5,6,7,8-octahydroisoquinolines, potential precursors in the synthesis of morphinans[7a,b] and apomorphine analogs.[7b]

To determine optimum mild hydrogenation conditions that may lead to the synthesis of derivatives of **13** in high yields, we chose to study the reduction of **7** and **10** in methanol, an effective solvent for precursors such as **4** with varying concentrations of HCl at room temperature and atmospheric pressure.

Scheme I



2a, R = CH_3; X = I
2b, R = $CH_2CH_2CH_3$; X = I
4, 5, 6, R = H; X = Cl

3a, R = CH_3; X = Cl
3b, R = $CH_2CH_2CH_3$; X = Cl

Results and Discussion

The structure of the two compounds, **5** and **6**, proposed is consistent with the elemental analysis, ^1H NMR spectra,

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Table I
Catalytic (PtO_2) Hydrogenation of Isoquinoline and Quinoline in Methanol-HCl

% products[a]	MeOH-HCl: MeOH	1.0 N	4.0 N
Substrate: Isoquinoline·HCl			
8	87	30	13
9	13	70	87
Reaction time, min	60	140	160
Substrate: Quinoline·HCl			
11	54	43	39
12	34	37	52
Decahydro- and octahydroquinoline	7	11	Trace
Reaction time, min	345	445	450

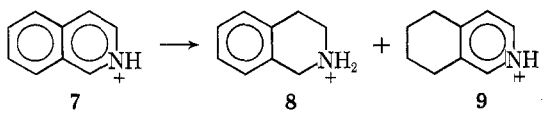
[a] Hydrogenation was carried out at room temperature and atmospheric pressure.

and TLC. In each case, TLC showed in more than one solvent system only one spot, which upon treatment with ninhydrin gave a yellow color for **5** (secondary amine)[8] and a negative reaction for **6**. The percent composition of **5** and **6** was determined in their crude yield by integration of their ^1H NMR spectra after proton bands were identified and assigned following separation and purification of **5** and **6** by successive crystallizations from absolute ethanol.

The two one-proton doublets at δ 7.60, 7.70 and 8.43, 8.53 (AB pattern, J = 5 Hz)[9a,b] were assigned respectively to H-4 and H-3 of **6**. A similar pattern was observed in the ^1H NMR spectrum of **9** (see Experimental Section). In both spectra, the doublet at the lower field was assigned to H-1.[9a] A multiplet at δ 6.90–7.25 in the spectrum of **5** represented the seven aromatic protons in this compound while the multiplet at δ 6.97–7.13 of **6** was due only to the three protons of the catechol.

To determine the percent composition of **5** and **6**, the two doublets assigned to H-3 and H-4 of **6** were integrated and the relative area for one proton was determined. From this, the relative area for three protons for **6** was derived and subtracted from the integrated area of the overlapping multiplets, δ 6.90–7.25. The difference obtained corresponded to the seven aromatic protons of **5**, from which the relative area for one proton was derived. Thus the ratio of the estimated areas associated with each proton of **5** and **6** permitted an approximate determination of the percent composition of each compound.

The two products of the hydrogenation of the hydrochloride of **7**, 1,2,3,4-tetrahydroisoquinoline (**8**) and **9** (Table I),



7 **8** **9**

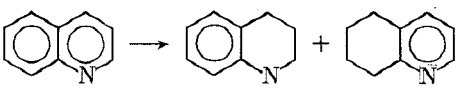
were identified by their ^1H NMR spectra, TLC, and melting points of their picrate and hydrochloride salts. The narrow band at δ 7.28 in the ^1H NMR spectrum of **8** was assigned to its aromatic protons while the AB quartet in the spectrum of **9** was assigned to H-3 and H-4. The band due to H-1 appeared coincidentally at δ 8.72. The clear separation of the aromatic band of **8** from that of **9** allowed a facile estimation of the percent composition of the two compounds by integration of their spectra.

In all the hydrogenations of the hydrochlorides of **10**, two major compounds were isolated: 1,2,3,4-tetrahydroquinoline (**11**) and **12**. Both these compounds were identified by

Table II
Reduction of Isoquinoline in Sodium-Ethanol

Compd	% composition	Retention time, min	Ninhydrin	Uv
14	22.4	14.2	Yellow	Negative
15	10.5	16.4	Purple	Negative
16	1.9	20.0	Negative	Positive
17	65.2	21.4	Yellow	Negative

the melting points of their picrate salts and their ^1H NMR spectra, and **11** also by the melting point of its hydrochloride salt. The ^1H NMR spectrum of **11** was shown to be identical with that of commercially available **11**. The two one-proton doublets of **10**, δ 8.78, 8.82 and 8.85, 8.88, were assigned to H-2[9b] and the multiplet at δ 7.14–8.01 to the remaining aromatic protons. The two two-proton multiplets, δ 6.88–7.03 and 6.28–6.57, were assigned to the aromatic protons of **11**.[10] In the spectrum of **12** the aromatic proton bands showed an ABX pattern almost identical with that of 2,3-lutidine[11] with analogous band assignments (see Experimental Section). The two doublets, δ 8.27, 8.30 and 8.35, 8.37, were assigned to H-2. Thus the nonoverlapping bands of H-2 of **10** and **12** and the multiplet at δ 6.28–6.66 of **11** were used to determine the composition of these three compounds as free bases in the hydrogenation mixtures. In addition to compounds **11** and **12**, TLC showed the presence in small amounts of two compounds which both failed to absorb in the uv but reacted positively with ninhydrin. The ^1H NMR spectra of the ether-extracted free bases from the hydrogenation mixtures showed a broad multiplet that began at δ 1.08 and overlapped with those of **11** and **12**

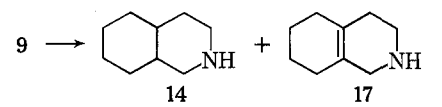


10 **11** **12**

above the aromatic region. Integration of the combined multiplets followed by subtraction of the areas ascribed to protons of **11** and **12**, derived from the integration of the bands discussed above, yielded the approximate percent composition of the two unknown compounds as decahydroquinoline.

After prolonged hydrogenation of **12** in 4 N HCl–methanol solution until only a trace of **12** remained, TLC revealed the same aforementioned two unknown compounds. One of the compounds was shown to be identical with a commercially available *trans*-decahydroquinoline. The ir spectrum of the above mixture showed a weak band at 1660 cm^{-1}, indicating the presence of a –C=C– stretching. Because the ^1H NMR spectrum of this mixture showed no olefinic proton band, such a double bond could exist only at the 9,10 position of the octahydroquinoline, since a positive reaction with ninhydrin ruled out the alternative 1,9 position.

Reduction of **9** with sodium–ethanol yielded four compounds as shown by TLC and preparative GC. Compounds



14 **17**

14 and **17** (Table II) were obtained in sufficient amount for extensive characterization. The spectra, physical properties, and the picrate and hydrochloride salts of **14** identified it as *trans*-decahydroisoquinoline (Table II).

The ^1H NMR spectrum of the major compound **17**, 65% of the total reaction mixture, showed no aromatic or olefinic protons and differed from that for *trans*- or *cis*-decahy-

droisoquinoline.[12] The ratio of the respective integrated areas under the broad multiplet, δ 1.33–2.00 and 2.60–3.47, was found to be 2.8. It showed a strong and sharp ir band at 1590 cm^{-1}. These findings along with the elemental analysis of its hydrochloride salt and comparison with known derivatives led us to postulate its structure as 1,2,3,4,5,6,7,8-octahydroisoquinoline. Because of inadequate amounts, **16** was characterized only by TLC. **15** was found by TLC to be unreacted **9**.

Conclusions

The results (Table I) are in general agreement with those of others[3] and show in addition that under the same experimental conditions (1) the ratios of **8** to **9** and of **11** to **12**, as well as the reaction times, increase with increasing HCl concentration; (2) satisfactory yields of **8** and **12** can be obtained at atmospheric pressure and in a relatively short time so that side reactions are minimized when sensitive functional groups are present.

Whereas others have shown that the predominant, if not exclusive, product of the sodium–ethanol reduction of **10** is *trans*-decahydroisoquinoline,[3] we have shown that under similar reaction conditions **9** yields predominantly **17** with **14** as a minor product. This is in accord with the finding that 1-(*p*-hydroxybenzyl)-5,6,7,8-tetrahydroisoquinoline and its methyl ether yield the corresponding octahydro compound when treated with sodium–isoamyl alcohol.[13] Further reduction of **17** to the *trans*-decahydroisoquinoline is possible under more strenuous hydrogenation conditions.[13]

In conclusion, the above results indicate that ring-substituted compounds of the type **16**, precursors to morphinan and apomorphine analogs,[7b,13] can be prepared directly from readily synthesized 1-benzylisoquinoline derivatives.

Experimental Section

Uncorrected melting points were determined on a capillary melting point apparatus. ^1H NMR spectra were obtained on a Varian T-60 NMR spectrometer at room temperature in $CDCl_3$ or DMSO-d_6 with Me_4Si used as an internal standard. Eastman Chromagram sheets (6060 silica gel with fluorescent indicator) were used for TLC. The following TLC solvent systems were used: 1-butanol–acetic acid–water, 4:1:1 (A), 9:1:2.5 (B); chloroform–MeOH–acetic acid, 17:2:1 (C); benzene–ethyl acetate, 4:1 (D); cyclohexane–ethyl acetate, 1:4 (E); benzene–MeOH, 4:1 (F). A preparative gas chromatograph, Perkin-Elmer F-21, with a flame ionization detector and a 15 ft × 8.0 mm column (20% Carbowax 20M + 4% KOH on Chromosorb W) was used for determining the percent composition and separating and identifying the products obtained from the sodium–EtOH reduction of **9**. Infrared spectra were obtained on a Perkin-Elmer 337 grating spectrometer. Elemental analyses were determined by Galbraith Laboratories, Inc., and Schwarzkopf Microanalytical Laboratories.

Materials. 3,4-Dimethoxybenzyl alcohol was obtained from International Chemical and Nuclear Corp.; K & K Laboratories; 3,4-dimethoxyphenylacetic acid, isoquinoline, 1,2,3,4-tetrahydroisoquinoline, and 1,2,3,4-tetrahydroquinoline were obtained from Aldrich Chemical Co.; *trans*-decahydroquinoline, 1-iodopropane, and MeI were obtained from Eastman Organic; picric acid was obtained from J. T. Baker Chemical Co.; PtO_2 (83.4%) was obtained from Engelhard Industries.

3,4-Dimethoxybenzyl Chloride (18). The method of synthesizing **18** was adapted from an early method.[14] HCl was bubbled through a solution of 3,4-dimethoxybenzyl alcohol (25.0 g, 0.149 mol) in absolute ether (80 ml) under anhydrous conditions and at ice–water temperature. After 35 min, the color of the ether solution changed to deep red. The ether solution was washed successively with water, saturated $NaHCO_3$ solution, and water to a pH of about 6.0. The ether layer was dried over anhydrous $MgSO_4$ and then filtered, and the ether was removed under reduced pressure. The residue, a colorless, viscous oil, slowly crystallized on standing, yielding 25.0 g (90%), mp 48–51° (lit. mp 50–50.5°,[15] 48°[14]).

1-Cyano-2-benzoyl-1,2-dihydroisoquinoline (Reissert's Compound). This compound was prepared as described in the literature.[16]

1-(3′,4′-Dimethoxybenzyl)isoquinoline Hydrochloride (4). The method of preparing **4** was essentially as reported elsewhere,[17] with the following modifications. After hydrolysis in CH_3OH–KOH and isolation of the crude free base, the base was extracted with ether (2 × 70 ml) and the extract was dried over anhydrous Na_2SO_4, filtered, and reduced in volume to 40 ml; then HCl-saturated ether was added. The precipitated HCl salt was filtered, triturated with ether repeatedly, and dried, 11.5 g (94%). This was recrystallized from EtOH–ethyl acetate, yielding 9.4 g (75%): mp 188–189.5°; ^1H NMR (DMSO-d_6) δ 3.63 (s, 3, $-OCH_3$), 3.73 (s, 3, $-OCH_3$), 4.92 (broad s, 2, $-CH_2-$), 6.69–8.30 [m, 3, $(MeO)_2C_6H_3-$], 7.64–8.75 (m, 6, isoquinoline H).

Anal. Calcd for $C_{18}H_{18}ClNO_2$: C, 68.46; H, 5.74; N, 4.44; Cl, 11.23. Found: C, 68.52; H, 5.74; N, 4.43; Cl, 11.33.

1-(3′,4′-Dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (5). **4** (3.86 g, 12.3 mmol) was hydrogenated at atmospheric pressure in MeOH (100 ml) over PtO_2 (0.60 g, 2.2 mmol). The reaction was completed 80 min later after the theoretical amount of H_2 (2 equiv) was absorbed. TLC (A, C) revealed two spots on visualization with uv, of which one yielded a yellow color when exposed to ninhydrin and the other reacted negatively. After removal of the catalyst, the solvent was evaporated under reduced pressure, yielding 3.7 g (94%) of a white, amorphous solid. Recrystallization from boiling EtOH (22 ml) yielded 3.1 g of colorless crystals, mp 194–197°. TLC again revealed the two spots upon visualization with uv and ninhydrin. Recrystallization was repeated in EtOH (30 ml) and allowed to proceed slowly overnight after seeding with crystals of **5** obtained previously. Colorless, heavy crystals were filtered off and washed with cold EtOH followed by ether, 0.97 g, mp 227–228°. TLC showed a single spot on visualization with uv and I_2 and yielded a yellow color when exposed to ninhydrin; ^1H NMR (DMSO-d_6) δ 2.97–3.50 [broad m, 6, $(MeO)_2PhCH_2-$, H-3, H-4], 3.77 [s, 6, $(-OCH_3)_2$], 4.60 (broad t, J = 5 Hz, H-1), 6.90–7.07 [broad, overlap, 3, $(MeO)_2C_6H_3-$], 7.25 (broad s, 4, H-4, H-5, H-6, H-7).

Anal. Calcd for $C_{18}H_{22}ClNO_2$: C, 67.59; H, 6.93; N, 4.38; Cl, 11.09. Found: C, 67.60; H, 6.88; N, 4.41; Cl, 11.06.

1-(3′,4′-Dimethoxybenzyl)-5,6,7,8-tetrahydroisoquinoline Hydrochloride (6). The mother liquor obtained after filtering off **5** was concentrated under reduced pressure to 20 ml and allowed to stand at room temperature. Colorless crystals were filtered off and washed with cold EtOH followed by ether, 1.30 g, mp 209–212°. Recrystallization from EtOH yielded 0.98 g: mp 211–212°; TLC (A, C) one spot (uv, I_2), negative to ninhydrin; ^1H NMR (DMSO-d_6) δ 1.53–2.0 (broad m, 4, H-6, H-7), 2.45–3.13 (broad m, 4, H-5, H-8), 3.72, 3.75 (2 s, 6, $-OCH_3$), 4.42 [s, 2, $(MeO)_2PhCH_2-$], 6.97–7.13 [broad m, 3, $(MeO)_2C_6H_3-$], 7.60, 7.70 (d, J = 5 Hz, 1, H-4), 8.43, 8.53 (d, J = 5 Hz, 1, H-3).

Anal. Calcd for $C_{18}H_{22}NO_2Cl$: C, 67.59; H, 6.93; N, 4.38; Cl, 11.09. Found: C, 67.60; H, 6.79; N, 4.28; Cl, 11.14.

1-(3′,4′-Dimethoxybenzyl)-2-methylisoquinolinium Iodide (2a). The free base of **2a** (6.88 g, 24.2 mmol) was dissolved in $MeNO_2$ (50 ml) and MeI (3.44 g, 242 mmol) was added. After 5 hr at room temperature copious long, yellow needles appeared. After 18 hr, only a trace of the starting material was evident by TLC (F). The addition of ethyl acetate (100 ml) completed the precipitation. The product was filtered off and recrystallized from absolute EtOH: 9.9 g (97%); mp 202–203° (lit.[17] mp 139–140°); ^1H NMR (DMSO-d_6) δ 3.72, 3.78 (s, 6, $-OCH_3$), 4.50 (s, 3, NCH_3), 5.15 [s, 2, $(MeO)_2C_6H_3CH_2-$], 6.31–7.17 [m, 3, $(MeO)_2C_6H_3-$], 7.96–9.0 (m, 6, isoquinoline H's).

Anal. Calcd for $C_{19}H_{20}INO_2$: C, 54.16; H, 4.79; I, 30.12; N, 3.33. Found: C, 54.19; H, 4.81; I, 30.05; N, 3.31.

1-(3′,4′-Dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (3a). **2a** (4.6 g, 98.6 mmol) was hydrogenated at atmospheric pressure in MeOH (120 ml) over PtO_2 (0.60 g, 22 mmol). After 0.5 hr, the theoretical amount of H_2 (2 equiv) was absorbed with a concomitant clumping of the catalyst signaling the end of the reaction. After removal of the catalyst by filtration and of the solvent under reduced pressure, the solid residue was dissolved in water (90 ml) and treated with excess $NaHCO_3$. The free base was extracted with ethyl acetate (2 × 50 ml), and the combined extracts were washed with water (30 ml), dried over anhydrous Na_2SO_4, and then filtered. The solvent was removed under reduced pressure, and the residue, a viscous oil, was dissolved in 40 ml of absolute ether to which another 40 ml of HCl-saturated ether was added. The HCl salt precipitate was isolated and washed with ether, 2.94 g (91%). The crude product was

recrystallized from absolute EtOH (45 ml), yielding colorless, stick-shaped crystals: 2.65 g (80%); mp 233–235° dec (lit.[17] mp 227–230°); ^{1}H NMR ($CDCl_3$) δ 2.92 (broad s, 3, NCH_3), 2.77–4.17 [broad m, H-3, H-4, and $(MeO)_2C_6H_3CH_2$–], 4.23–4.60 (m, 1, H-1), 3.77 (s, 3, $-OCH_3$), 3.87 (s, 3, $-OCH_3$), 6.4–6.8 (m, 4, H-5, H-6, H-7, H-8), 6.87–7.33 [m, 3, $(MeO)_2C_6H_3$–].

Anal. Calcd for $C_{19}H_{24}ClNO_2$: C, 68.35; H, 7.24; Cl, 10.62; N, 4.20. Found: C, 67.94; H, 7.25; Cl, 11.01; N, 4.25.

1-(3′,4′-Dimethoxybenzyl)-2-*n*-propylisoquinolinium Iodide (2b). The free base of 4 (0.93 g, 3.33 mmol) was treated at 90° with iodopropane (11.6 g, 70 mmol) in $MeNO_2$ (15 ml). Reaction was completed after 4–5 hr as shown by TLC (F). The product was precipitated by the addition of ether and allowed to stand overnight at 4°. The product was filtered and washed with ether, 1.45 g (91%), mp 205–206°. Recrystallization from absolute EtOH (35 ml) yielded 1.33 g (89%) of yellow, needle-shaped crystals: mp 211–212° dec; ^{1}H NMR ($CDCl_3$) δ 1.03 (t, 3, J = 7 Hz, CCH_3), 1.92 (m, 2, J = 7 Hz, $-CH_2Me$), 3.82 (s, 3, $-OCH_3$), 3.88 (s, 3, $-OCH_3$), 4.97 (t, 2, J = 7 Hz, $-CH_2CH_2CH_3$), 5.25 [s, 2, $(MeO)_2PhCH_2$–], 6.7–7.39 [m, 3, $(MeO)_2C_6H_3$–], 7.82–8.72 (m, 4, H-5, H-6, H-7, H-8), 8.47 (d, 1, J = 7 Hz, H-4), 9.23 (d, 1, J = 7 Hz, H-3).

Anal. Calcd for $C_{21}H_{24}INO_2$: C, 56.13; H, 5.38; I, 28.25; N, 3.12. Found: C, 56.21; H, 5.31; I, 28.38; N, 3.07.

1-(3′,4′-Dimethoxybenzyl)-2-*n*-propyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (3b). 2b (1.23 g, 2.74 mmol) was hydrogenated at atmospheric pressure in MeOH (35 ml) over PtO_2 (0.20 g, 0.73 mmol). In less than 0.5 hr, the theoretical amount of H_2 (2 equiv) was absorbed and clumping of the catalyst occurred. TLC (A) showed the presence of only one compound. The catalyst was removed by filtration and the solvent under reduced pressure. The yellow, amorphous solid residue was dissolved in MeOH (15 ml) and basified with 5% aqueous NaOH (45 ml). The free base was extracted with ether (3 × 40 ml), washed with water to a neutral pH, and then dried over anhydrous Na_2SO_4. The solution was filtered, and the light amber-colored oil remaining upon removal of the ether was converted to the HCl salt as described above, 0.77 g (77%), mp 201–203.5°. Recrystallization from a solution of MeOH (12 ml) and ether (20 ml) yielded a crystalline product: 0.60 g; mp 203–204°; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7 Hz, CCH_3), 1.93–2.27 (m, J = 6 Hz, 2, $-CH_2Me$), 2.75–4.05 (m, 9), 3.75 (s, 3, $-OCH_3$), 3.87 (s, 3, $-OCH_3$), 4.30 [t, J = 7 Hz, 2, $(CH_3O)_2PhCH_2$–], 6.37–7.38 (m, 7, aromatic H's).

Anal. Calcd for $C_{21}H_{28}ClNO_2$: C, 69.69; H, 7.80; Cl, 9.80; N, 3.87. Found: C, 69.67; H, 7.78; Cl, 9.82; N, 3.89.

Hydrogenation of Isoquinoline and Quinoline Hydrochlorides. General Procedure. The hydrogenation was carried out in absolute MeOH solution or MeOH solution of gaseous HCl with 0.25 M of substrate and a 10:1 ratio of substrate to PtO_2 at atmospheric pressure and room temperature with maximum agitation (magnetic stirrer) in a baffled hydrogenation flask. Reaction was discontinued when approximately 2 equiv of H_2 was absorbed. After removal of the catalyst by filtration, the solvent was removed under reduced pressure, and the residue salt was dried under high vacuum. The approximate percent composition of the crude products (as HCl salts of reduced **7** and free bases of **10**) was determined by integration of their ^{1}H NMR spectra. Free base components of these mixtures obtained by extraction with ether from basic aqueous solutions were separated by successive fractionation under reduced pressure followed by a final purification step in which the free bases were converted to picrate salts, recrystallized from absolute EtOH, and characterized by comparing their melting points with those in the literature (Table I). The picrates were then decomposed with aqueous 4 N HCl, and, after removal of the picric acid by ether extraction, the purified free bases were obtained by ether extraction from their basic solutions and converted to their hydrochloride salts. ^{1}H NMR spectra of these and of commercially available **8**, *trans*-, and a mixture of *cis*- and *trans*-decahydroquinolines were used for the assignment of bands in the spectra of their crude mixture. TLC (A, B, C, D, E) served to identify them further and to certify their purity. Melting points of picrates, °C (lit.): **8**, 199–201 (197–198,[18a] 202[18b]); **9**, 144–145 (142–144[19]); **11**, 142–143 (143[20]); **12**, 158–160 (157,[21] 158–159[6c]). Melting points of HCl salts, °C (lit.): **8**, 198–199 (195–197[18a]); **9**, 196–198 (196–197[18a]); **11**, 179–181 (179–180[20]).

^{1}H NMR Spectra (DMSO-d_6), δ: 8, 2.82–3.55 (symmetrical m, 4, H-3, H-4), 4.20 (s, 2, H-1), 7.28 (s, 4, aromatic H's); **9**, 1.66–1.90 (m, 4, H-6, H-7), 2.92–3.00 (two overlap broad s, 4, H-5, H-8), 7.84 (d, 1, J = 6 Hz, H-4), 8.68 (d, 1, J = 6 Hz, H-3), 8.72 (s, 1, H-1).

^{1}H NMR Spectra ($CDCl_3$), δ: 11, 1.89 (m, 2, H-3), 2.73 (t, 3, J = 6 Hz, H-2), 3.25 (t, 2, J = 6 Hz, H-4), 3.77 (broad s, 1, NH), 6.28–7.03 (m, 4, H-5, H-6, H-7, H-8); **12**, 1.70–1.93 (m, 4, H-6, H-7), 2.84 (m, 4, H-5, H-8), 6.85–7.07 (m, 1, H-3), 7.23–7.38 (m, 1, H-4), 8.32 (m, 1, H-2).

5,6,7,8-Tetrahydroisoquinoline (9). **7** (9.04 g, 0.07 mol) was hydrogenated over PtO_2 (1.99 g, 8.76 mmol) in 4 N HCl–MeOH (200 ml) at atmospheric pressure and room temperature. Reaction was discontinued after 2 equiv of H_2 was absorbed; the catalyst was filtered off and the solvent was removed under reduced pressure. The solid residue was dissolved in water (70 ml), basified with $NaHCO_3$, and extracted with ether (4 × 40 ml). The combined ether extracts were washed with water, dried over anhydrous $MgSO_4$, and then filtered. The solvent was removed under reduced pressure, and the oil residue was dried under vacuum to a constant weight, 7.2 g: TLC (A), one major spot (uv positive, ninhydrin negative), one trace spot (uv negative, ninhydrin yellow); ir 1600 cm^{-1} (–C=N–); ^{1}H NMR ($CDCl_3$) δ 1.45–2.05 (m, 4, H-6, H-7), 2.31–3.05 (m, 4, H-5, H-8), 6.93 (d, 1, J = 5 Hz, H-4), 8.24 (d, 1, J = 5 Hz, H-3), 8.20 (s, 1, H-1). **9** (7.0 g) was dissolved in absolute EtOH (15 ml) and picric acid–EtOH solution (300 ml, 4.4 g/100 ml) was added. The picrate salt, small yellow crystals, was filtered off and dried, 17.5 g (92%), mp 144–145°. The picrate salt was decomposed with aqueous 6 N HCl (100 ml), and the picric acid was removed by ether extraction. The aqueous layer was basified with excess $NaHCO_3$, and the free base **9** was extracted with ether, 6.3 g. TLC (A): one spot (uv positive, ninhydrin negative).

Reduction of 9 with Na–EtOH. 9 (3.0 g, 22.5 mmol) was dissolved in absolute EtOH (40 ml) and treated under anhydrous conditions while stirring with small pieces of freshly cut Na metal introduced over a period of about 1 hr. For the last 0.5 hr the reaction solution was heated to maintain a satisfactory rate of reaction. At the end of 1 hr, more EtOH (25 ml) was added, and the solution was refluxed for 0.5 hr to effect complete reaction of the metal. The solvent was removed under reduced pressure, and the white residue was dissolved in 200 ml of water and acidified with 6 N HCl to a pH of ca. 1.0; it was then extracted with ether (2 × 50 ml), which was discarded. The aqueous solution was basified with 50% aqueous NaOH to a pH of ca. 11, and the free amine was extracted with ether (4 × 40 ml). The ether extracts were combined and washed with water, and then the solvent was removed under reduced pressure after drying over $MgSO_4$. The colorless, oily residue was dried to a constant weight, 2.91 g (93%). TLC (A, C, E, F) revealed the presence of at least four compounds, two of which, including the major product, reacted with ninhydrin to yield a yellow color (secondary amine). One spot, a trace, reacted negatively to ninhydrin and, in contrast to the other three products, could be visualized under uv. The fourth spot, more than a trace, yielded a purple color with ninhydrin (primary amine). A preparative GC separation of the crude mixture yielded four peaks, well resolved and fairly symmetrical. The relative composition was estimated by dividing the area under each peak by the sum of the areas of all peaks. The area under each peak was estimated by multiplying the maximum height of the peak by the width at half the height. Two of the compounds, **14** and **17**, were collected in sufficient amount to permit the preparation of picrate and hydrochloride salts for melting points and, in the case of **17**, for ^{1}H NMR, ir, Bayers test, and elemental analysis. All isolated compounds were subjected to TLC analysis (A, C) and exposed to ninhydrin. In each case only one spot was shown.

Compound 14: mp of picrate 176–177° (lit.[12] mp 175–176°); mp of HCl salt 224–226° (lit.[22] mp 222–223°).

Compound 17: mp of picrate 176–178° (lit.[7a] mp 172°); mp of HCl salt 152–153° (lit.[7a] mp 150°); ^{1}H NMR ($CDCl_3$) δ 1.33–2.0 (m, 11, H-2, H-4, H-5, H-6, H-7, H-8), 2.60–3.47 (m, 4, H-1, H-3); ir 1590 cm^{-1} (s).

Anal. Calcd for $C_9H_{16}ClN$: C, 62.23; H, 9.29; Cl, 20.42; N, 8.07. Found: C, 62.28; H, 9.27; Cl, 20.49; N, 8.02.

Registry No.—2a, 50370-93-9; **2a** free base, 21965-92-4; **2b**, 54446-54-7; **3a**, 50370-94-0; **3b**, 54384-20-2; **4**, 51866-10-5; **5**, 3972-77-8; **6**, 54384-21-3; **7** HCl, 49563-76-0; **8**, 91-21-4; **9**, 36556-06-6; **10** HCl, 530-64-3; **11**, 635-46-1; **12**, 10500-57-9; **14**, 2744-09-4; **17**, 2721-62-2; **18**, 7306-46-9; 3,4-dimethoxybenzyl alcohol, 93-03-8; iodopropane, 107-08-4.

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Cycloaddition Reactions of Some 5-Substituted Isoquinolinium Salts[1]

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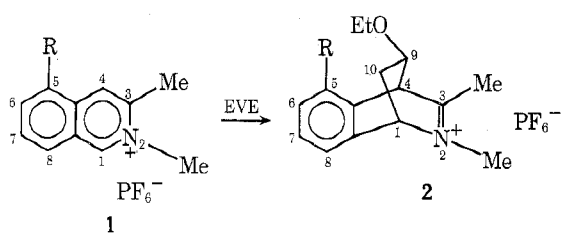
The reactivity of the 2,3-dimethylisoquinolinium nucleus (1) toward 1,4 cycloaddition with alkenes is greatly enhanced by the introduction of a nitro group at position 5, making possible new synthetic applications. The reactivity of the 2-methylisoquinolinium ion (15) is also enhanced by introduction of a nitro group into position 5, and the product (18) with cyclopentadiene is the first simple 1,4 adduct obtained from an isoquinolinium salt with no substituent at position 3.

The discovery that 2,3-disubstituted isoquinolinium salts (**1a**) would undergo cycloaddition reactions with alkyl vinyl ethers[2-4] and cyclopentadiene[4,5] offered the promise of easy access to a host of benzisoquinuclidine derivatives.



a, R = H
b, R = NO_2
c, R = NHCOMe

Unfortunately, the sluggishness of the cycloaddition at room temperature and the easy reversibility at higher temperatures have greatly limited the usefulness of the reaction. For example, 2,3-dimethyl-1,3-butadiene, which stands next below cyclopentadiene in reactivity toward the acridizinium ion,[6] does not react noticeably with **1a** in 3 months at room temperature.

In earlier work[7] it was shown that the introduction of the electron-withdrawing nitro group at position 9 of the acridizinium nucleus resulted in a 21-fold increase in the rate of cycloaddition toward styrene. This led us to examine the reactivity of 5-nitro-2,3-dimethylisoquinolinium ion (**1b**) toward activated alkenes. As measured by its reactivity with ethyl vinyl ether, the nitro derivative (**1b**) reacted approximately 120 times faster than the parent compound (**1a**). The magnitude of this rate enhancement raised the question whether the enhancement was entirely electronic in its origin or whether steric acceleration of cycloaddition[8] must play some part. A group at position 5 would tend to crowd the adjacent peri hydrogen, which is constrained further by the flanking methyl at position 3. Much of the resulting steric strain should be relieved during the cycloaddition, since the peri hydrogen moves out of plane. That some steric contribution is involved is suggested by the observation that the analog (**1c**) having an electron-releasing acetylamino group at position 5 is still twice as reactive as the parent compound (**1a**).

The 5-nitro-2,3-dimethylisoquinolinium ion (**1b**) reacts in good to excellent yield with a variety of the less reactive alkenes, including styrene, vinyl acetate, β-pinene, and norbornene (Table I). For none of the adducts was there any indication in the NMR spectrum of the presence of mixtures of regioisomers (always one set, rather than two, of bridgehead hydrogens). This is in conformity with all reported cycloadditions of unsymmetrical alkenes with quaternary aromatic salts.[9] Assignment of structure of the adducts has been made by analogy to the addition of unsymmetrical addends to the 2,3-dimethylisoquinolinium ion (**1a**) and to the acridizinium ion.[6] Direct assignment of the regiochemistry of the adducts on the basis of NMR evidence, following the method of Fields et al.,[6] was not possible. As usual, the quaternary nitrogen caused a characteristic deshielding of the adjacent bridgehead proton attached to C-1, but the nitro group at position 5 had a similar effect on the other bridgehead hydrogen at position 4, making the usual distinction between the bridgehead hydrogens on the basis of differences in chemical shift impossible.

At least four of the addends appeared to afford only a single geometrical isomer. Three of these, the ethyl vinyl ether (**2b**), the cyclopentadiene (**8**), and the norbornene (**12**) adducts, can definitely be assigned as syn (with respect to the phenylene ring). The first two of these (**2b** and **8**) had NMR spectra similar to those of the unnitrated prototype (e.g., **2a**) and in both of these cases, the structure of