Notes

Aporphines. 20.[1] Chemically Induced Fragmentation of Nitrobenzylisoquinolinium Salts

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The importance of 1-(2-nitrobenzyl)isoquinolines and their quaternary salts as key intermediates in the synthesis of aporphine alkaloids has been well documented in the recent literature.[2] Aporphine alkaloids can thus be conveniently prepared by the reduction of the isoquinolinium salts of 1-(*o*-nitrobenzyl)isoquinolinium salts and subsequent Pschorr cyclization.[3,4] In the course of the synthesis of such aporphines for biological evaluation, we have observed C-1 to C-α bond fission when certain 1-(2-nitrobenzyl)isoquinolinium salts (i.e., **1a**) were treated with excess potassium borohydride in refluxing ethanol.[5] In the limited number of 2-nitrobenzylisoquinolinium salts examined in these earlier experiments, we concluded that cleavage occurs when the nitro group is coplanar with the benzene ring and is able to stabilize the transition state for the nitrotoluene anion (i.e., **1a** and **1g**).[4,5] However, when the nitro group is sterically hindered and forced out of the plane of the benzene ring as in the case of **1e** and **1f** only reduction to the tetrahydrobenzylisoquinoline derivative takes place.[5] In an extension of these earlier studies several positional isomers of nitrobenzylisoquinolinium salts **1** were synthesized or were available in our laboratory and subjected to conditions known to lead to fragmentation. The quaternary salts **1** were prepared by refluxing the appropriate nitrobenzylisoquinoline[1] with either methyl iodide or 1-iodopropane and were then subjected to borohydride reduction as described in the Experimental Section.

Results and Discussion

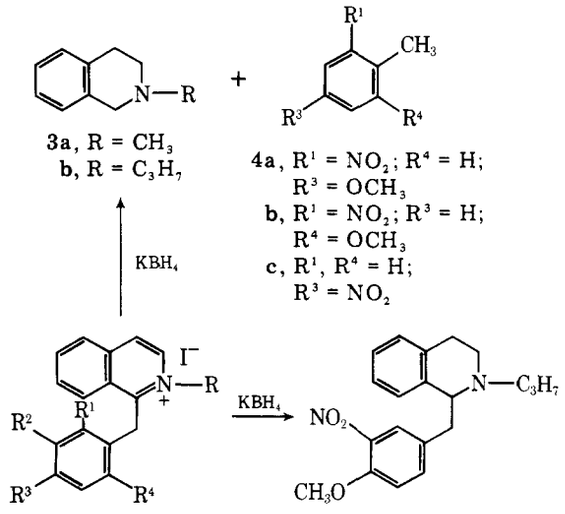
Refluxing **1a–c,g,h** in aqueous ethanol with an excess of the reducing agent leads to the isolation of the cleavage products *N*-propyl- and *N*-methyl-1,2,3,4-tetrahydroisoquinoline (**3a** and **b**) and the nitrotoluenes **4a–c** (Scheme I). Thus, as previously proposed,[5] in the absence of steric constraints the incipient negative charge of the benzyl anion is transmitted through the conjugated system to the nitro group, leading to scission of the carbon–carbon bond.

A similar case can be presented for the observed fragmentation of 1-(4-nitrobenzyl)isoquinoline methiodide (**1b**) to *N*-methyl-1,2,3,4-tetrahydroisoquinoline (**3a**) and 4-nitrotoluene (**4c**). Although the nitro group resides in the para position of the benzyl function, the substituent is still capable of accepting the electron pair.

In sharp contrast to these fragmentations is the reduction of 1-(4-methoxy-3-nitrobenzyl)isoquinoline propiodide (**1d**) to the corresponding benzyltetrahydroisoquinoline (**5**). Despite reaction conditions favoring cleavage, no scission of the exocyclic linkage was observed. The transition state cannot be stabilized by resonance, since the nitro group in the meta position is incapable of accepting the negative charge.

The failure to cleave under fragmentation conditions was in fact used to establish the structure of the product obtained from the reaction of 1-(4-methoxybenzyl)isoquinoline with nitric acid.[1] These results lend further support to the mechanism proposed[5] for such a carbon–carbon cleavage under these conditions. It is of interest to note that in the cleavage with KBH_4 as in the nitrobenzylisoquinolinium salts, the steric effects are reflected in electronic (resonance) phenomona as a function of the planarity of the nitro group and the benzene ring. However, in the case of the ionically induced MS fragmentations observed for the nitrobenzylisoquinolines discussed in the previous paper,[1] the steric effects in such fragmentations are reflected primarily in the case of elimination of the NO_2 or OCH_3 group.

Scheme I



1a, R = CH_3; R^1 = NO_2; R^2 = R^3 = R^4 = H **5**
b, R = CH_3; R^1 = R^2 = R^4 = H; R^3 = NO_2
c, R = C_3H_7; R^1 = NO_2; R^2, R^4 = H; R^3 = OCH_3
d, R = C_3H_7; R^1 = R^4 = H; R^2 = NO_2; R^3 = OCH_3
e, R = CH_3; R^1 = NO_2; R^2 = R^3 = OCH_3; R^4 = H
f, R = CH_3; R^1 = NO_2; R^2 = OCH_3; R^3 = R^4 = H
g, R = CH_3; R^1 = NO_2; R^2 = R^4 = H; R^3 = OCH_3
h, R = C_3H_7; R^1 = NO_2; R^2 = R^3 = H; R^4 = OCH_3

Experimental Section

Melting points were determined on a Thomas-Hoover (Unimelt) apparatus and are uncorrected. All microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. NMR spectra were recorded on a Varian T-60 spectrometer with Me_4Si as the internal standard.

1-(4-Nitrobenzyl)isoquinoline Methiodide (1b) A mixture of 1-(4-nitrobenzyl)isoquinoline[1] (0.12 g, 0.45 mmol) in 5 ml of methyl iodide was allowed to reflux for 4 h. After cooling in ice, the yellow crystals were collected, washed with ether, and dried to give 0.17 g (93%) of **1b**, mp 222–224 °C dec. The analytical sample was recrystallized from methanol. Anal. Calcd for $C_{17}H_{15}IN_2O_2$: C, 50.26; H, 3.72; N, 6.90. Found: C, 50.10; H, 3.87; N, 6.98.

1-(4-Methoxy-2-nitrobenzyl)isoquinoline Propiodide (1c). The preparation of this compound has been reported elsewhere.[4]

1-(4-Methoxy-3-nitrobenzyl)isoquinoline Propiodide (1d). A mixture of 1-(4-methoxy-3-nitrobenzyl)isoquinoline[1] (1.3 g, 4.4 mmol) in 15 ml of 1-iodopropane was allowed to reflux for 48 h. The yellow crystals were collected, washed with ether, and dried to give 1.73 g (85%) of **1d**, mp 217–218 °C dec. Recrystallization from methanol did not change the melting point. Anal. Calcd for $C_{20}H_{21}IN_2O_3$: C, 51.73; H, 4.56; N, 6.07. Found: C, 51.45; H, 4.56; N, 5.97.

In a similar manner as described for **1d** above, **1-(2-methoxy-6-nitrobenzyl)isoquinoline propiodide (1h)** was prepared, mp 214

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°C dec. Anal. Calcd for $C_{20}H_{21}IN_2O_3$: c, 51.74; H, 4.56; N, 6.03. Found: C, 51.66; H, 4.66; N, 6.03.

Potassium Borohydride Reductions. General Procedure. A stirred suspension of the quaternary salt (3 mmol) in a mixture of ethanol (24 ml) and water (11 ml) was heated to reflux. Potassium borohydride (36 mmol) was added in small aliquots over a period of 30 min. Refluxing was continued for 4.5 h and the mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, water (50 ml) was added to the residue, and extraction with ether (3 × 40 ml) followed. The combined organic layers were successively washed with 10% HCl (2 × 25 ml), water (25 ml), 10% NaOH (2 × 25 ml), and water (2 × 25 ml). After drying over Na_2SO_4 the solvent was removed in vacuo to give the toluene derivative (reduction and fragmentation). The combined acid layers were made basic by addition of solid potassium hydroxide under stirring and cooling in ice. Extraction with ether (2 × 25 ml) followed. The organic phases were washed with water and dried and the solvent was removed to yield the N-substituted 1,2,3,4-tetrahydroisoquinoline derivative (reduction and fragmentation), or the substituted 1-benzyl-1,2,3,4-tetrahydroisoquinoline (reduction only).

A. Reduction of 1-(4-Methoxy-2-nitrobenzyl)isoquinoline Propiodide (1c). Under identical conditions as described above 1.4 g (3 mmol) of **1c** was reduced to give 0.35 g (69%) of 4-methoxy-2-nitrotoluene (**4a**) and 0.46 g (87%) of 2-propyl-1,2,3,4-tetrahydroisoquinoline (**3b**) as an oil.

The hydrochloride of **3b** was formed and recrystallized from methanol–ether, mp 242 °C (lit.[6] mp 242 °C).

B. Reduction of 1-(2-Methoxy-6-nitrobenzyl)isoquinoline Propiodide (1h). Similarly reduced with 2.0 g (37 mmol) of potassium borohydride was 1.3 g (2.8 mmol) of **1h** to give 0.37 g (79%) of 2-methyl-3-nitroanisole (**4b**), mp 46–49 °C (lit.[7] mp 52 °C), and 0.41 g (84%) of **3b**, which was identified as described above.

C. Reduction of 1-(4-Methoxy-3-nitrobenzyl)isoquinoline Propiodide (1d). Only one product, 1-(4-methoxy-3-nitro)-2-propyl-1,2,3,4-tetrahydroisoquinoline (**5**), was obtained from the reduction of **1d** (2.8 mmol) with 2.0 g (37 mmol) of potassium borohydride. The reaction yielded 0.75 g (79%) of **5** as an oil.

A hydriodide of **5** was prepared, mp 184–185 °C. Recrystallization from absolute ethanol gave an analytical sample, mp 184 °C.

Anal. Calcd for $C_{20}H_{25}IN_2O_3$: C, 51.28; H, 5.38; N, 5.98. Found: C, 51.20; H, 5.45; N, 5.84.

D. Reduction of 1-(4-Nitrobenzyl)isoquinoline Methiodide (1b). Reaction of **1b** (1.3 g, 3.2 mmol) with 2.44 g (45 mmol) of potassium borohydride afforded 0.16 g (36%) of 4-nitrotoluene (**4c**), mp 49–51 °C (lit.[8] mp 54°C), and 0.4 g (85%) of 2-methyl-1,2,3,4-tetrahydroisoquinoline (**3a**), picrate mp 152–153 °C dec (lit.[5] mp 156 °C dec).

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Registry No.—**1b**, 60967-77-3; **1c**, 57559-56-5; **1d**, 60967-78-4; **1h**, 60967-79-5; **3a** picrate, 15032-31-2; **3b**, 57928-05-9; **3b** HCl, 57464-74-1; **4a**, 17484-36-5; **4b**, 4837-88-1; **4c**, 99-99-0; **5**, 60967-80-8; **5** HI, 60996-52-3; 1-(4-nitrobenzyl)isoquinoline, 21965-90-2; methyl iodide, 74-88-4; 1-(4-methoxy-3-nitrobenzyl)isoquinoline, 60967-81-9; 1-(2-methoxy-6-nitrobenzyl)isoquinoline, 60967-82-0; iodopropane, 107-08-4.

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Hydrogen Abstraction from Substituted Phenylacetonitriles[1]

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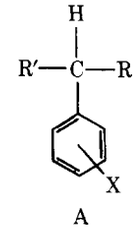
In the course of the development of linear free energy relationships, certain reaction types have required the introduction of new substituent parameters. Hammett's σ^- [3] and Brown's σ^+ [4] values recognize the possible extra stabilization shown by certain functional groups when charge is formed in direct conjugation with the ring. Reactions leading to the formation of benzylic radicals have long been correlated with σ^+ parameters.[5] It also seems likely that benzylic hydrogen abstraction by "nucleophilic radicals" may ultimately yield optimum correlation with σ^-.[6] The generally accepted view is that this would be indicative of charge separation in the transition state of the rate-determining step.[7]

Although there is substantially less documentation, it has been observed that some ring substituents show an enhanced ability to favor certain radical reactions. The copolymerization of substituted styrenes with maleic anhydride, for example, is generally favored by electron-donating groups in the former.[8] The *p*-CN compound, however, exhibits a reactivity which seems far greater than expected. This substituent may also behave anomalously in other systems. Pryor, Davis, and Gleaton have noted that both benzonitrile and nitrobenzene show enhanced reactivity in the para position during radical methylation.[9] This was attributed to an "extra resonance effect". Along these lines, a particularly striking result is the recent observation of Kaba and Ingold that tricyanomethyl radical is an extremely stable species.[10] This must be at least partially attributable to resonance effects and is somewhat surprising as most of the "persistent" carbon radicals studied by Ingold's group show much greater steric congestion at the radical site.[11]

Recently, one of us put forward an empirical approach for the evaluation of Hammett ρ values for benzylic hydrogen



A

abstraction from ring-substituted–α-substituted toluenes, A, by the trichloromethyl radical.[12] The essence of the argument is that for any single series of compounds, the sensitivity toward change of ring substituent would be a function of both the electronic and steric parameters associated with groups directly bonded to the reaction site. This may be expressed by eq 1, where the steric and electronic substituent parameters utilized refer to those for R and R′. Further studies with un-