N-benzylpyrrole, 2051-97-0; N-allylpyrrole, 7435-07-6; N-ethylindole, 10604-59-8; N-propylindole, 16885-94-2; N-isopropylindole, 16885-99-7; N-butylindole, 22014-99-9; N-benzylindole, 3377-71-7; N-allylindole, 16886-08-1; N-methylimidazole, 616-47-7; N-methylbenzimidazole, 1632-83-3; 1-methylbenzotriazole, 13351-73-0; N-methylcarbazole, 1484-12-4; methyl N-methylindole-3-acetate, 58665-00-2; ethyl bromide, 74-96-4; ethyl iodide, 75-03-6; n-propyl bromide, 106-94-5; n-propyl iodide, 107-08-4; isopropyl iodide, 75-30-9; n-butyl iodide, 542-69-8; tert-butyl bromide, 507-19-7; benzyl bromide, 100-39-0; allyl bromide, 106-95-6.

Comparative Study of Reactions of 2-Benzylisoquinolinium and 3,4-Dihydro-2-benzylisoquinolinium Salts with Carbon Disulfide in Two Base-Solvent Environments

James A. Duncan,*[1] Mark L. Bossé, and John M. Masnovi

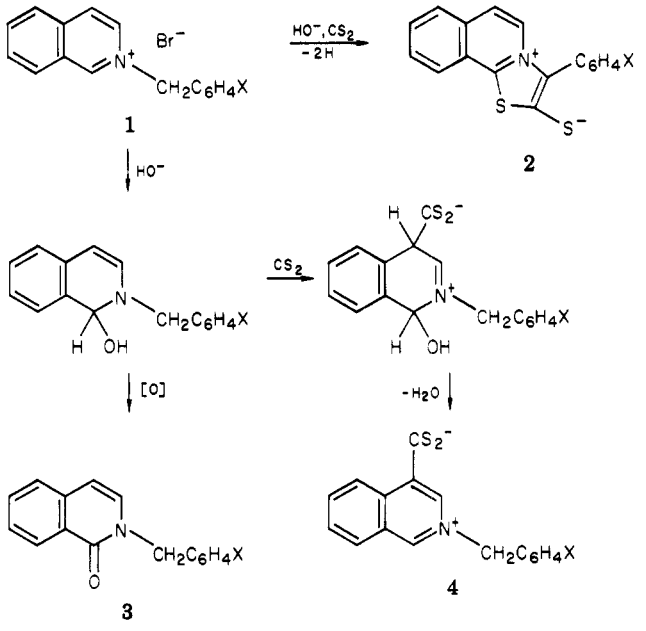
Departments of Chemistry, Lewis and Clark College, Portland, Oregon 97219, and University of Notre Dame, Notre Dame, Indiana 46556

Received December 27, 1979

3,4-Dihydro-2-(*p*-nitrobenzyl)isoquinolinium bromide (**9a**) reacts with carbon disulfide in both aqueous hydroxide–dioxane and triethylamine–pyridine to afford the expected 5,6-dihydro-3-(*p*-nitrophenyl)thiazolo[2,3-*a*]isoquinolinium-2-thiolate (**12**) and a new product identified as 1,2,3,4-tetrahydro-2-(*p*-nitrobenzyl)isoquinoline (**13a**). Deuterium-labeling studies reveal that **13a** is formed in a process by which adduct **12** is obtained from intermediate **11a**; a different pathway is followed in each base–solvent system. In contrast, 2-(*p*-nitrobenzyl)-isoquinolinium bromide (**1**, X = *p*-NO_2) gives only the thiolate product **2** (X = *p*-NO_2) in both base–solvent environments. Substrates **1** and **9a** undergo no hydrogen–deuterium exchange at C_α in either base–solvent system; only **1** sustains exchange at C_1 and then only in aqueous hydroxide–dioxane. The implications of these results concerning the mechanisms for the **1** to **2** and **9a** to **12** transformations are discussed. A convenient direct reduction of **9** with ammonium formate, initiated to confirm the structural assignment of **13**, is described.

We have reported[2,3] on the reaction of 2-benzylisoquinolinium bromides (**1**) with carbon disulfide in aqueous hydroxide–dioxane. In addition to 2-benzylisoquinolone side products (**3**), these reactions afforded 3-phenylthiazolo[2,3-*a*]isoquinolinium-2-thiolates[4] (**2**) and 2-benzylisoquinolinium-4-dithiocarboxylate adducts[5] (**4**) as the only isolable products[6] (Scheme I). By an isotopic dilution method, we estimated[3] the Hammett ρ value for the **1** → **2** conversion to be +2.3 and by deuterium-labeling experiments[2] on **1** (X = *p*-Br), determined that its most accessible conjugate base is **6** (X = *p*-Br) (Scheme II). These results raised logical questions about the accuracy of earlier mechanistic formulations[7,8] for this conversion that implicate the azomethine ylide 1,3-dipolar intermediate **5**, which through cycloaddition with carbon disulfide would produce **7** and then **2** by oxidation. We hypothesized an alternative scheme[3] leading to adduct **2** through **7** and involving nucleophilic attack on **1** by dithiocarbonate (or hydrogen dithiocarbonate) at C_1 to give intermediate **8**. The fate of the hydrogens lost in the alleged **7** → **2** conversion has not been determined.

Scheme I

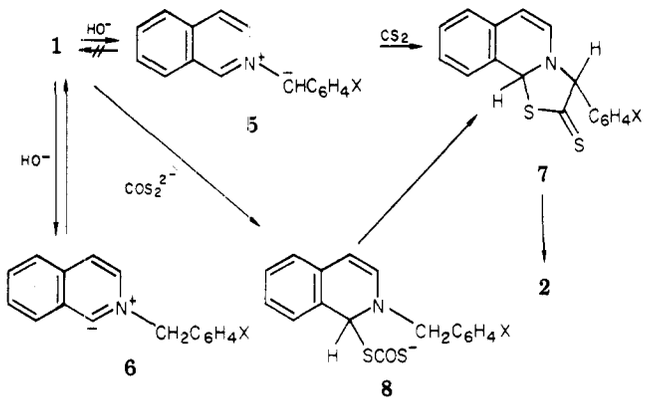


In earlier work, Huisgen[9] had reported, without experimental detail, the isolation of 5,6-dihydro-3-(*p*-nitrophenyl)thiazolo[2,3-*a*]isoquinolinium-2-thiolate (**12**) in 65% yield from a reaction that treated 3,4-dihydro-2-(*p*-nitrobenzyl)isoquinolinium bromide (**9a**) with carbon disulfide in triethylamine–pyridine (Scheme III). No other

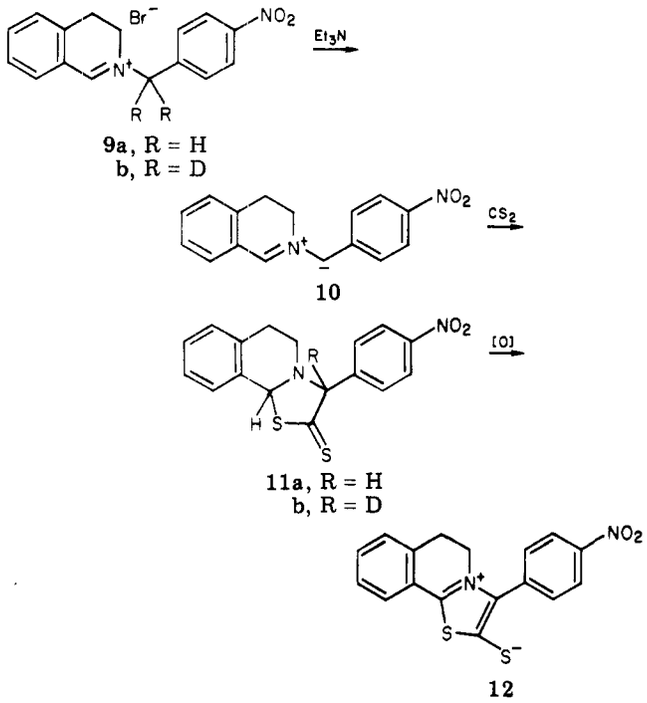
(1) To whom correspondence should be addressed at Lewis and Clark College.
(2) J. E. Baldwin and J. A. Duncan, *J. Org. Chem.*, **36**, 627 (1971).
(3) J. E. Baldwin and J. A. Duncan, *J. Org. Chem.*, **36**, 3156 (1971).
(4) X-ray data: M. G. Newton, M. C. McDaniel, J. E. Baldwin, and I. C. Paul, *J. Chem. Soc. B*, 1117 (1967).
(5) X-ray data: B. W. Matthews, P. M. Coleman, J. O. Selzer, L. H. Weaver, and J. A. Duncan, *Acta Crystallogr., Sect. B*, **B29**, 2939 (1973).
(6) All three products were always isolated when the substituent (X) was varied between *p*-CH_3O and *m*-CF_3 (11 cases); for X = *p*-CN, *m*-NO_2, and *p*-NO_2 only product **2** and the 2-benzylisoquinolinones were isolated.
(7) F. Kröhnke and H. H. Steuernagel, *Angew. Chem.*, **73**, 26 (1961); *Chem. Ber.*, **97**, 1118 (1964).
(8) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).
(9) R. Huisgen, R. Grashey, and E. Steingruber, *Tetrahedron Lett.*, 1441 (1963).

0022-3263/80/1945-3176$01.00/0

Scheme II



Scheme III



products were reported. It was proposed that through a mechanism similar to that suggested for 1 → 2, the 9a → 12 conversion involved intermediates 10 and 11a. It was also suggested that in the 11a → 12 conversion the hydrogen was transferred to excess carbon disulfide.[8]

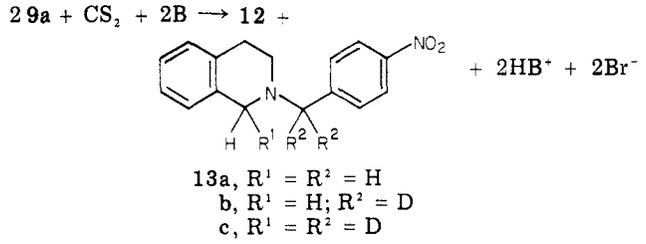
This article describes a detailed comparative study of the reactions of substrates 1 (X = p-NO_2) and 9 with carbon disulfide each in two different base–solvent environments: concentrated hydroxide–aqueous dioxane and triethylamine–pyridine.[10] Substrate 1 (X = p-NO_2) gives adduct 2, and substrate 8 gives adduct 12 in both environments.

Results and Discussion

(A). Reaction of 3,4-Dihydro-2-(p-nitrobenzyl)isoquinolinium Bromide (9a) with Carbon Disulfide in Hydroxide–Aqueous Dioxane and Triethylamine–Pyridine. In our hands, **9a** never gave more than a 45% yield of thiolate **12** in either base–solvent system. Instead it was always accompanied by approximately 1 molar equiv of 1,2,3,4-tetrahydro-2-(p-nitrobenzyl)isoquinoline (**13a**).

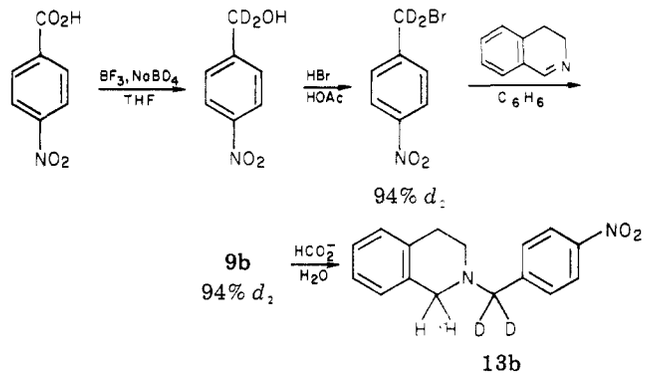
(10) Nitro-substituted cases were studied because of the inherent difficulty in preparing and purifying any other substituted 3,4-dihydro-2-benzylisoquinolinium bromide due to their hydroscopic and water-labile nature.

Scheme IV[a]



[a] B = Et_3N or ^-OH.

Scheme V



Scheme IV suggests the probable balanced equation for both cases. Overall yields varied from 80 to 90 percent of theoretical.

Amine **13a** is characterized by its ^1H NMR, IR, and high-resolution mass spectra and by elemental analysis. Furthermore, the spectra were identical with those of the product obtained in 94% yield by treatment of **9a** with ammonium formate. This reductive procedure is similar to the Leuckart–Wallach[11] reaction in which imines (Schiff bases), often generated in situ, are reduced via iminium ion intermediates,[12] usually with formic acid. To date, however, reductions of stable iminium compounds such as **8** have been performed only with metal hydrides or by catalytic hydrogenation.[13]

To help elucidate the mechanism of the alleged **9a** → **11a** → **12** conversions, presumably involving the concomitant formation of **13a**, we conducted a series of deuterium-labeling experiments. First, when **9a** was treated for 8 h with carbon disulfide in either concentrated sodium hydroxide-d–deuterium oxide–dioxane or triethylamine–pyridine–triethylamine hydrobromide-d, only deuterium free amine **13a** was isolated. This result effectively rules out a *reversibly* formed azomethine ylide 1,3-dipolar intermediate (**10**, Scheme III) for these reactions. Further confirmatory evidence was obtained in the deuterium oxide case; deuterium-free **9a** was reisolated in reactions both with and without carbon disulfide which were quenched after a short reaction time.

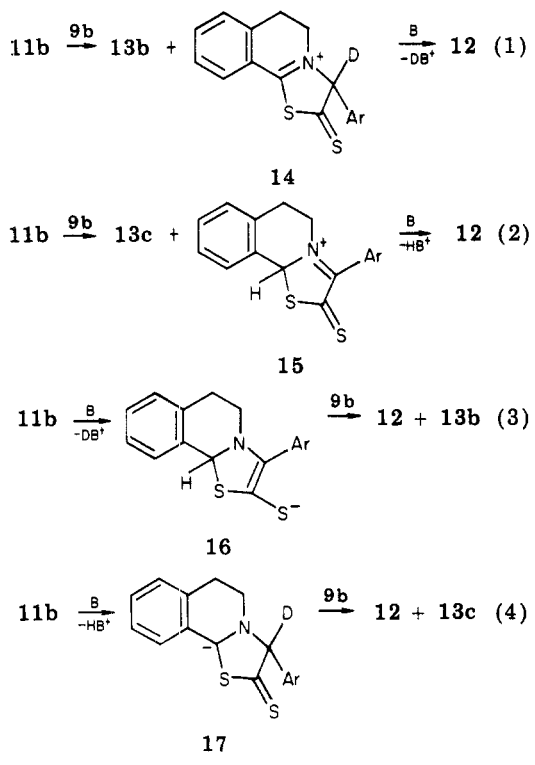
It also follows from these results that the corresponding reactions of the labeled salt 3,4-dihydro-2-(p-nitrobenzyl-α,α-d_2)isoquinolinium bromide (**9b**) would retain the α-deuterium atoms in the amine product **13**. Thus **9b** can be an effective mechanistic probe to both affirm the participation of **11** in these reactions and identify the steps involved in the **11** → **12** conversions in each case. The

(11) R. Leuckart, *Ber. Dtsch. Chem. Ges.*, **18**, 2341 (1885); O. Wallach, *Justus Liebigs Ann. Chem.*, **343**, 54 (1905); M. L. Moore, *Org. React.*, **5**, 301–330 (1949).

(12) A. Lukasiewicz, *Tetrahedron*, **19**, 1789 (1963).

(13) See, for example, N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, **77**, 439 (1955).

Scheme VI[a]



[a] Ar = p-$NO_2C_6H_4$ and B = Et_3N or ^-OH.

most convincing rationale for the formation of **13** is to view it as arising from the reduction of **9** by **11** or by one of its conjugate bases (**16** or **17**, Scheme VI); one or both of the five-membered-ring hydrogens of **11a** might participate in the hydride transfer process to give **13a**. To test for this, we prepared **9b** (see Scheme V and the Experimental Section) and determined the fate of its deuterium atoms in its reactions with carbon disulfide in both base–solvent systems. One possible product, amine **13b**,[14] was prepared for comparison from **9b** and ammonium formate (Scheme V).

The four possible a priori reaction sequences are given in Scheme VI (eq 1–4). When we treated **9b** with carbon disulfide in the hydroxide–aqueous dioxane environment, the labeled amine isolated had structure **13b**, i.e., no deuterium atoms at C_1. However, in triethylamine–pyridine we obtained **13c** instead.[15] Thus in the aqueous environment the reaction pathway may follow eq 1 and/or eq 3 which involve product **13b**. Similarly, in triethylamine–pyridine the pathway may be given by eq 2 and/or eq 4.

We suggest that the preferred pathway with triethylamine as the base is given by eq 2 and with hydroxide by eq 3, i.e., that reduction (hydride transfer) precedes proton transfer to triethylamine, but in the aqueous system proton transfer to hydroxide precedes reduction. First, if the processes in both base systems were to involve hydride transfer in the initial step, then it would be difficult to explain why they would not occur by the same pathway, i.e., both by eq 1 or both by eq 2, which they clearly do not as the deuterium-labeling results rule out eq 1 in triethylamine and eq 2 in hydroxide. Furthermore, the negatively charged conjugate bases **16** and **17**, implicated in eq 3 and 4, would be expected to be more effective hydride donors if they were to form under the reaction conditions. Hydroxide is apparently effective in converting **11b** into its most accessible conjugate base **16**, and eq 3 is followed. Equation 1, which would involve **11b** as a less effective hydride donor, does not appear to intervene since it seems (see below) that the more favored pathway involving **11b** in the initial step would be given by eq 2 not eq 1. Although the labeling results formally permit eq 4 with the weaker and bulkier triethylamine, it hardly seems likely that eq 3 should now be shunned as it must and eq 4, in which a less acidic proton would be removed to give **17**, followed instead. The pathway involving **11b** as the hydride donor (eq 2) is more likely since **16** must be an inaccessible conjugate base of **11b** with triethylamine. Finally, as only **13c** is formed in triethylamine–pyridine, eq 2 must be strictly followed in preference to eq 1. This could be because intermediate **15** might be more accessible than **14** due to the presence of an α,β-unsaturated thiocarbonyl moiety in the former.

(B). Reactions of 2-(p-Nitrobenzyl)isoquinolinium Bromide (1, X = p-NO_2) with Carbon Disulfide in Hydroxide–Aqueous Dioxane and Triethylamine–Pyridine. With carbon disulfide, 1 (X = p-NO_2) gave a 66% yield of adduct **2** (Scheme I) in hydroxide–aqueous dioxane[2,7] and a 92% yield in triethylamine–pyridine (Experimental Section). In the former case, 2-(p-nitrobenzyl)isoquinolinone (**3**, X = p-NO_2) is a side product, but in neither case were other products such as a reduction product of **1** detected. As expected, **1** could not be reduced by formate ion in the manner reported for the reduction of **9** to **13** (Scheme V), and the pathway for the **7** to **2** conversion (Scheme II) remains to be identified.

Deuterium-exchange experiments[2] involving reisolation procedures after a 4-min reaction time had already demonstrated that **1** (X = p-Br)[16] exchanges its C_1 hydrogen but not its C_α hydrogens for deuterium in sodium hydroxide-d–deuterium oxide–dioxane in the presence or absence of carbon disulfide. Furthermore, an α,α-d_2 moiety in **1** (X = p-Br) was retained in both products **3** and **4** obtained from an 8-h reaction in undeuterated media.[2] We have now established that **1** suffers no deuterium exchange at any location in triethylamine–pyridine. Deuterium-free **1** (X = p-NO_2) was reisolated from its reaction in triethylamine–pyridine containing 1 equiv of triethylamine hydrobromide-d after 4 min in the presence of carbon disulfide or for 8 h in its absence.

Comparison of Studies A and B. Given that **1** (X = p-Br; Scheme I) undergoes facile exchange at C_1, although not at C_α, in alkaline deuterium oxide–dioxane,[3,17] we were surprised to discover that deuterium-free amine **13a** was obtained from the dihydro salt **9a** and carbon disulfide under the same conditions, thus demonstrating that **9a** sustained no exchange at any location during the course of an 8-h reaction. Exchange at C_1 had been expected and at C_α considered a possibility, since it might be construed that ylide **10** (Scheme III) should be more accessible than **5** (Scheme II); electron delocalization in the 1,3-dipole moiety of **10** would not interfere, as it would in **5**, with a nitrogen-containing aromatic ring. From these deuteri-

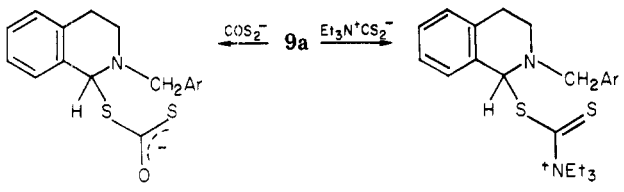
(14) The ^1H NMR spectrum in chloroform-d had resonances at δ 2.8 (m, 4 H), 3.6 (s, 1 H), 7.1 (m, 4 H), and 7.8 (AA'BB', 4 H). The singlet resonances at δ 3.6 and 3.7 which appear in the ^1H NMR spectrum of **13** (see Experimental Section) are thus assigned to the H_1 and H_α hydrogens, respectively; the H_α protons are deshielded relative to the H_1 protons as expected.

(15) These structural assignments were made by careful integration of the 60-MHz ^1H NMR spectra in chloroform-d. The deuterium content at C_1 in **13c** was determined to be 52 ± 2%.

(16) It appears that **1** (X = p-NO_2) behaves similarly; however, its reduced solubility relative to **1** (X = p-Br) in most solvents precluded its reisolation from this reaction mixture in a state pure enough to secure a definitive interpretation by ^1H NMR.

(17) C. J. Cooksey and M. D. Johnson, *J. Chem. Soc. B*, 1191 (1968); J. A. Zoltewicz and L. S. Helmick, *J. Am. Chem. Soc.*, **92**, 7547 (1970).

Scheme VII[a]



18 19

[a] Ar = p-$NO_2C_6H_4$.

um-labeling results together with those obtained with both substrates **1** (X = p-NO_2) and **9a** in triethylamine–pyridine–triethylamine hydrobromide-*d*, it must be concluded that neither 1,3-dipolar intermediate **5** nor **10** is readily accessible in either base–solvent environment. If **5** and or **10** are formed at all, they must be consumed rapidly as they do not revert back to **1** or **9a**, respectively. In this connection it is important to note that 67% of **1** (X = p-NO_2) was recovered after being treated for 8 h with triethylamine–pyridine, a time period which affords a quantitative yield of **2** when carbon disulfide is present. Furthermore, a ρ value of +2.3 would be required for the rate-limiting formation of **5**.[3]

Although early mechanistic formulations[18] for these reactions have accounted for the formation of **7** or **11a** in terms of a $_\pi4_s + _\pi2_s$ cycloaddition[19] between carbon disulfide and ylide **5** or **10**, an alternative scheme in the case of **1** in alkaline, aqueous dioxane has been hypothesized.[3] Although many descriptions are possible, given our recent results, we would like to suggest an extension of the scheme advanced for the **1** → **2** conversion[3] to cover both substrates in both base–solvent environments (see Scheme VII). If the dithiocarbonate ion, generated from hydroxide and carbon disulfide,[20] attacks **9a**, it would give **18** (cf. **8** in Scheme II) which through hydroxide attack or perhaps rearrangement of its hydrate[3] could sustain C–H_α bond cleavage with concomitant C–C bond formation, leading eventually to **11a** and finally to **12**. Carbon disulfide, which affords dithiocarbamic acids with primary and secondary amines,[21] should form $Et_3N^+CS_2^-$ with triethylamine. This inner salt may be sufficiently nucleophilic to attack **9a**, giving intermediate **19** which through attack by triethylamine could give **11a** in one step. In the same way, this scheme could account for the **1** → **7** conversion in triethylamine–pyridine.

Through deuterium-labeling studies the mechanisms for the **11a** → **12** part of the overall **9a** → **11a** → **12** reaction sequence (Schemes III and IV) in two base–solvent environments have been elucidated, and mechanistic possibilities for the **9a** → **11a** part as well as for the **1** → **7** part of the overall **1** → **7** → **2** sequence (Scheme II) in both environments have been explored. Still further work will be required in order to confirm a unified mechanistic scheme or, alternatively, logical separate schemes for these reactions.

Experimental Section

General Methods. All melting points were determined by using a Mel-Temp melting point apparatus and are uncorrected. Microanalyses were performed by R. Wielesek at the University of Oregon, Eugene, OR. Infrared spectra were measured with a Beckman IR-10 spectrophotometer. High-resolution mass spectra were recorded at 70 eV on either a CEC 21-110 or a Picker-Nuclear MC-902 mass spectrometer. ^1H nuclear magnetic resonance spectra were obtained on a Varian Associates Model A-60A or EM-360L spectrometer. All chemical shifts are reported in parts per million (δ) relative to internal tetramethylsilane. All integrations for the determination of the deuterium content of potentially labeled molecules were performed with the EM-360L spectrometer which has an integral reproducibility of 2%.

Solvents. Benzene was dried by distillation from lithium aluminum hydride and (diethyl) ether and tetrahydrofuran by distillation from calcium hydride. Pyridine was distilled from potassium hydroxide onto 4A molecular sieves. Chloroform was distilled prior to its use as a solvent for column chromatography.

3,4-Dihydroisoquinoline was prepared by the method of Schmitz[22] from isochroman through the intermediate *o*-(2-bromoethyl)benzaldehyde. The colorless product has a boiling point of 60 °C at 0.9 torr [lit.[22] bp 101–102 °C (11 torr)]. It slowly crystallized to a white solid, mp 42–45 °C (lit.[22] mp 33–36 °C). The ^1H NMR spectrum (CCl_4) had resonances at δ 2.6 (m, 2 H), 3.7 (td, 2 H), 6.9–7.4 (m, 4 H), and 8.2 (t, 1 H).

3,4-Dihydro-2-(*p*-nitrobenzyl)isoquinolinium Bromide[9] (9a). 3,4-Dihydroisoquinoline (5.00 g) in 50 mL of benzene and 8.26 g of α-bromo-*p*-nitrotoluene (Aldrich) in 100 mL of benzene were combined and heated with stirring for 20 min. After cooling, the mixture was filtered and the residue recrystallized from ethanol–ether, yielding 6.63 g (55%) of white solid, mp 196–199 °C. It had ^1H NMR (CF_3CO_2H) resonances at δ 3.4 (t, 3 H), 4.3 (t, 2 H), 5.5 (s, 2 H), 7.7 (m, 4 H), 8.1 (AA′BB′, 4 H), and 9.4 (s, 1 H). Anal. Calcd for $C_{16}H_{15}BrN_2O_2$: C, 55.35; H, 4.35; N, 8.07. Found: C, 55.57; H, 4.23; N, 8.26.

5,6-Dihydro-3-(*p*-nitrophenyl)thiazolo[2,3-*a*]isoquinolinium-2-thiolate (12). (A). From 3,4-Dihydro-2-(*p*-nitrobenzyl)isoquinolinium Bromide (9a) and Carbon Disulfide in Pyridine–Triethylamine.[2,9] A solution of 300 mg (0.87 mmol) of **9a** in 35 mL of dry pyridine was heated under a positive pressure of nitrogen to 70 °C, and to it with stirring were added by syringe through a septum 0.39 mL (480 mg, 6.3 mmol) of carbon disulfide (Baker) and 0.14 mL (94 mg, 0.94 mmol) of triethylamine. After a temperature of 74–77 °C was maintained for 8 h, most of the pyridine and triethylamine were distilled at 26–28 torr (maximum bath temperature of 50 °C). Three times chloroform was added and removed by evaporation at a water aspirator with heating in a water bath at approximately 50 °C to give a semisolid residue which was chromatographed in chloroform on a 12-mm-diameter column of 30 g of Woelm, neutral, activity grade II alumina. Two compounds were eluted. The first, a yellow oil (113 mg, 48%), was shown to be 1,2,3,4-tetrahydro-2-(*p*-nitrobenzyl)isoquinoline (**13a**) by comparison of its infrared and ^1H NMR spectra with those obtained for the product of formate reduction of **9a**. The thiolate **12** (123 mg, 42%) was the other compound eluted. It had a melting point of 288–290 °C after recrystallization from pyridine, and its ^1H NMR spectrum ($CDCl_3/CF_3CO_2H$) had resonances at δ 2.8 (t, 2 H), 3.8 (t, 2 H), 7.0 (m, 4 H), and 7.6 (AA′BB′, 4 H). The mass spectrum of this adduct had prominent peaks at m/e (proposed formula, relative intensity) 340 (M, 100), 339 (M – 1, 77), 294 (M – NO, 42), 293 (M – HONO, 62), 147 (*o*-$CH_2CHC_6H_4CS$, 20), and 121 (C_6H_5CS, 20).

(B). From 3,4-Dihydro-2-(*p*-nitrobenzyl)isoquinolinium Bromide (9a) and Carbon Disulfide in Dioxane–Deuterium Oxide–Sodium Hydroxide-*d*. A solution of 1.0 g of **9a** in 3 mL each of deuterium oxide and dioxane and 2 mL of carbon disulfide was heated to 52 °C with stirring. Approximately 3 mL of a solution prepared from 1.32 g of sodium hydroxide and deuterium oxide was added in one portion. The mixture was heated in a 72 °C bath for 8 h and after being cooled at 7 °C for 1 day was filtered to give 270 mg (26%) of red solid, mp 286–288 °C. In a run without deuterated reagents an analytical sample of the adduct **12** (mp 288–290 °C) was obtained after recrystallization from pyridine. Anal. Calcd for $C_{17}H_{12}N_2O_2S_2$: C, 59.98; H, 3.55;

(18) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565, 633 (1963).
(19) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).
(20) B. Philipp and H. Dantzenberg, *Z. Phys. Chem. (Leipzig)*, **231**, 270 (1966); H. H. Schmiedeknecht and W. Claus, *ibid.*, **240**, 411, 415 (1969).
(21) J. Kothari and M. M. Sharma, *Chem. Eng. Sci.*, **21**, 391 (1966); B. Phillipp and H. Dautzenberg, *Faserforsch. Textiltech.*, **19**, 23 (1968).
(22) E. Schmitz, *Chem. Ber.*, **41**, 1133 (1958).

N, 8.23. Found: C, 60.27; H, 3.21; N, 7.88. A mixture of the adducts (12) obtained in parts A and B above had a melting point of 288–290 °C.

The filtrate was partitioned between 10 mL of deuterium oxide and chloroform, and the dried chloroform extract ($CaCl_2$) was evaporated to afford a red oil. Chromatography of this oil in chloroform on 30 g of Woelm, neutral, activity grade II alumina afforded 130 mg (12%) of additional adduct and 330 mg (43%) of undeuterated 1,2,3,4-tetrahydro-2-(*p*-nitrobenzyl)isoquinoline (**13a**). The ^1H NMR spectrum ($CDCl_3$) was identical with the spectrum of the amine obtained by reduction of **9a**. Integration of the singlet methylene resonances at δ 3.6 and 3.7 with respect to the multiplet (for the other aliphatic protons) at δ 2.85 showed that the amine isolated above had no deuterium component.

In another run of the above reaction that was terminated by quenching in an ice bath after 4 min, **9a** was reisolated and shown by ^1H NMR (CF_3CO_2H) integration to have no deuterium component. When the carbon disulfide was omitted, the same result was obtained.

Reduction of 3,4-Dihydro-2-(*p*-nitrobenzyl)isoquinolinium Bromide (9a) with Ammonium Formate. A 250-mL flask was charged with 6.00 g of **9a**, 2.22 g of ammonium formate, and 120 mL of water, and the mixture was heated at reflux with stirring for 2 h. Most of the gas was evolved during the first few minutes. The resulting slightly basic solution was extracted twice with 100-mL portions of chloroform, and the combined extract was dried over magnesium sulfate and filtered. Evaporation of the chloroform afforded 4.35 g (94%) of yellow oil. This oil was identified as 1,2,3,4-tetrahydro-2-(*p*-nitrobenzyl)isoquinoline[23] (**13a**) by its ^1H NMR and mass spectra. The ^1H NMR spectrum ($CDCl_3$) had resonances at δ 2.8 (m, 4 H), 3.6 (s, 2 H), 3.7 (s, 2 H), 7.1 (m, 4 H), and 7.8 (AA'BB', 4 H). The high-resolution mass spectrum had its molecular ion peak at *m/e* 268.119 ($C_{16}H_{16}N_2O_2$; calcd *m/e* 268.121) and in addition exhibited prominent peaks at *m/e* 146 ($C_{10}H_{12}N$), 132 ($C_9H_{10}N$), and 104 (C_8H_8 or C_7H_6N). The IR spectrum (neat liquid) is as follows: $\bar{\nu}$ 3120, 3060, 3030, 2920, 2800, 2760, 1600, 1520, 1500, 1470, 1460, 1430, 1390, 1345, 1130, 1110, 1090, 1015, 930, 910, 850, 800, 730, 690, 640 cm^{-1}.

The hydrochloride was prepared from hydrogen chloride in toluene (Burdick and Jackson). An analytical sample (mp 237–242 °C dec) was obtained by recrystallization from dimethylformamide and washing the crystals with ether. Anal. Calcd for $C_{16}H_{17}ClN_2O_2$: C, 63.05; H, 5.62; N, 9.19. Found: C, 63.36; H, 5.50; N, 9.16.

The perchlorate salt was prepared from 70% perchloric acid in ethanol with azeotropic removal of water with toluene. An analytical sample (mp 178–181 °C dec) was obtained from acetone–ether by using decolorizing carbon. Anal. Calcd for $C_{16}H_{17}ClN_2O_2$: C, 52.11; H, 4.65; N, 7.60. Found: C, 52.08; H, 4.61; N, 7.60.

When 0.5 g of 2-(*p*-nitrobenzyl)isoquinolinium bromide (**1**, X = *p*-NO_2) was substituted for the 3,4-dihydro salt (**9a**) and the mixture heated at reflux for 2.5 h, only a quantitative recovery of starting material was secured upon workup, as determined from its ^1H NMR spectrum.

2-(*p*-Nitrobenzyl)isoquinolinium bromide[2] (**1**, X = *p*-NO_2) was prepared in 80–90% yield by heating equimolar amounts of freshly distilled isoquinoline and α-bromo-*p*-nitrotoluene (Aldrich, mp 98–100 °C) in dry benzene at reflux under a calcium sulfate drying tube for 3 h.

The precipitated salt was collected from the cooled reaction mixture and recrystallized from either 2-propanol or ethanol–ether; mp 206–207 °C.

3-(*p*-Nitrophenyl)thiazolo[2,3-*a*]isoquinolinium-2-thiolate (2, X = *p*-NO_2). In 60 mL of dry pyridine was suspended 2.00 g of 2-(*p*-nitrobenzyl)isoquinolinium bromide (**1**, X = *p*-NO_2) at 70 °C. About 10 g of carbon disulfide and 0.58 g of triethylamine were added, and the mixture was heated at 71–72 °C for 8.5 h whereupon the solvent was removed by evaporation. The dark red adduct was washed with water and dried to a constant weight of 1.75 g (92%). Recrystallization from pyridine and washing of the crystals with ethyl acetate gave a red-orange analytical sample, mp 311–312 °C (lit.[2] mp 300–302 °C). Anal. Calcd for $C_{17}H_{10}N_2O_2S_2$: C, 60.34; H, 2.98; N, 8.28. Found: C, 60.44; H, 2.89; N, 8.26.

***p*-Nitrobenzyl-α,α-d_2 Alcohol.**[24] A 100-mL reaction apparatus fitted with a condenser containing a calcium sulfate drying tube, a 25-mL addition funnel, and a thermometer was flame dried and flushed with dry nitrogen. Dry tetrahydrofuran (50 mL) and 0.85 g of sodium borohydride-d_4 (Stohler, 99%) were added, and the mixture was stirred under nitrogen as 3.86 g of 4-nitrobenzoic acid (Matheson Coleman and Bell) was added through a powder funnel at a rate which kept the foaming under control.

Following the addition, the thick mixture was heated at reflux, and a solution of 3.5 mL of boron trifluoride etherate [freshly distilled from CaH_2 at 48 °C (9.0 torr)] in 10 mL of dry tetrahydrofuran was added dropwise over a 10-min period with stirring. Heating at reflux was continued for 3 h, and then the mixture was stirred for 10 h at room temperature.

The white paste was poured onto 100 g of ice to which had been added 1 mL of concentrated hydrochloric acid. The solid residue was collected on a sintered-glass funnel and the filtrate extracted twice with 150-mL portions of ether. The solution of the solid residue in the combined extract was washed with 150 mL of ice-cold water and the separated ether layer dried over magnesium sulfate. Evaporation of the ether gave a yellow solid which was recrystallized from water to afford 2.17 g (62%) of near-white, dideuterated alcohol (mp 95–97 °C, after being dried at 45 °C over phosphorus pentoxide at 0.2 torr). The ^1H NMR spectrum ($CDCl_3$) had resonances only at δ 2.4 (s, 1 H) and 7.8 (AA'BB', 4 H).

α-Bromo-*p*-nitrotoluene-α,α-d_2. A 100-mL flask was charged with 2.12 g of crude *p*-nitrobenzyl-α,α-d_2 alcohol and 30 mL of glacial acetic acid and fitted with a gas capillary inlet tube, a condenser, and a stopper. Hydrogen bromide was admitted through the inlet tube at a moderate rate, and the excess neutralized with a sodium hydroxide trap connected to the condenser. The mixture was heated to reflux over 15-min, and the above conditions were maintained for 2 h and 15 min. After the mixture cooled, the solvent was removed from the resulting yellow solution in vacuo and the residue taken up in 150 mL of ether. The ether solution was washed with 150 mL of saturated sodium carbonate and the ether layer dried momentarily over sodium carbonate. Evaporation of the ether solution gave 2.3 g (77%) of near-white, dideuterated bromide, mp 97–100 °C (unlabeled α-bromo-*p*-nitrotoluene, lit.[25] mp 99–100 °C). The ^1H NMR spectrum ($CDCl_3$) had an AA'BB' pattern at δ 8.0 and was shown to be 94% dideuterated by integration.

3,4-Dihydro-2-(*p*-nitrobenzyl-α,α-d_2)isoquinolinium Bromide (9b). A flask fitted with a condenser and a calcium sulfate drying tube was flame dried and charged with 2.86 g of α-bromo-*p*-nitrotoluene-α,α-d_2, 1.72 g of 3,4-dihydroisoquinoline, and 50 mL of benzene. The solution was heated at reflux under a dry nitrogen atmosphere for 3 h. After cooling, the reaction mixture was filtered and the residue washed three times with 10-mL portions of cold benzene. After drying for 3 h at 56 °C and 1.0 torr, the near-white solid (mp 173–198 °C) was recrystallized from ethanol–ether. The crystals were crushed under ether and dried over phosphorus pentoxide at 100 °C and 1.0 torr for 4 h. This gave 3.85 g (84%) of white salt, mp 197–200 °C. The integrated ^1H NMR spectrum (CF_3CO_2H) of this labeled salt showed that it was 94% dideuterated.

Reduction of 3,4-Dihydro-2-(*p*-nitrobenzyl-α,α-d_2)isoquinolinium Bromide (9b) with Ammonium Formate. A 50-mL flask was charged with 0.75 g of **9b**, 0.30 g of ammonium formate, and 15 mL of water. The solution was heated at reflux for 1.5 h and then extracted twice with 15-mL portions of chloroform. After the solution was dried over magnesium sulfate, the chloroform was removed to give 0.53 g (91%) of yellow oil which was shown by its ^1H NMR spectrum ($CDCl_3$) to be 1,2,3,4-tetrahydro-2-(*p*-nitrobenzyl-α,α-d_2)isoquinoline (**13b**). Of the two singlets at δ 3.6 and 3.7, only the one at δ 3.6 was retained. The ratio of the area under the δ 3.6 resonance to that under the δ

(23) Compare with data for 2-benzyl-1,2,3,4-tetrahydro-7-nitroisoquinoline: A. McCoubrey and D. W. Mathieson, *J. Chem. Soc.*, 2851 (1951).

(24) Compare H. C. Brown and B. C. S. Rao, *J. Am. Chem. Soc.*, **82**, 681 (1960).

(25) J. F. Norris, M. Walt, and R. Thomas, *J. Am. Chem. Soc.*, **38**, 1077 (1916).

2.8 multiplet (for the four 3,4-dihydro protons) was 1:2.

Triethylamine Hydrobromide-*d*. A 20-mL sample of deuterium oxide was saturated with hydrogen bromide gas at room temperature and the flask connected to a gas trap submerged in a dry ice/2-propanol bath. The solution was gently heated with a Bunsen burner such that deuterium bromide–hydrogen bromide condensed in the trap. The trap was connected to a flask containing 30 mL of triethylamine in 100 mL of benzene, and the contents of the trap were carefully warmed to room temperature, providing a steady flow of gas into the solution which was stirred slowly. The gas flow was terminated after 33 min when the fumes were copiously evolved from the solution. Evaporation of the benzene afforded a white residue which was dissolved in 25 mL of deuteriuim oxide. A small amount (about 0.1 mL) of triethylamine was added and the solution heated for 30 min on a steam bath. Evaporation of the solvent and drying of the residue in a vacuum oven afforded nearly a quantitative yield of triethylamine-*d* (approximately 92% deuterated, by ^{1}H NMR), mp 251–254 °C (unlabeled hydrobromide, lit.[26] mp 253–254 °C).

3,4-Dihydro-2-(*p*-nitrobenzyl)isoquinolinium Bromide (9a) with Carbon Disulfide in Pyridine–Triethylamine–Triethylamine Hydrobromide-*d*. A solution of 2.00 g (5.76 mmol) of **9a**, 1.16 g (6.33 mmol) of triethylamine hydrobromide-*d*, 1.0 mL (6.4 mmol) of triethylamine (dried over KOH), and 3.3 mL (58 mmol) of carbon disulfide in 210 mL of dry pyridine was heated for 8 h at 70–80 °C. Removal of the solvents, treatment of the residue with chloroform, and chromatography on alumina as described above for the reaction omitting the hydrobromide-*d* afforded 663 mg (85%) of the amine. The integrated ^{1}H NMR spectrum ($CDCl_3$) of this sample showed that it was 1,2,3,4-tetrahydro-2-(*p*-nitrobenzyl)isoquinoline (**13a**) containing no deuterium at any location.

3,4-Dihydro-2-(*p*-nitrobenzyl-α,α-d_2)isoquinolinium Bromide (9b) with Carbon Disulfide. (A). Formation of 1,2,3,4-Tetrahydro-2-(*p*-nitrobenzyl-α,α-d_2)isoquinoline (13b) in Aqueous Dioxane–Sodium Hydroxide. A solution of 1.3 g of **9b** in 4 mL each of water and dioxane and 2.5 mL of carbon disulfide was heated to 52 °C with stirring. About 4 mL of 11 N aqueous sodium hydroxide was added, and the mixture was heated in a 72–78 °C bath for 8 h. After being cooled at 7 °C for 2 days, the mixture was diluted with 65 mL of water and extracted with 130 mL of chloroform. The red chloroform solution was washed twice with 80-mL portions of water and dried over calcium chloride.

The oil obtained upon evaporation of most of the solvent was chromatographed in chloroform on 32 g of Woelm, neutral, activity grade II alumina. A quantitative yield of amine was obtained as a yellow oil. The ^{1}H NMR spectrum ($CDCl_3$) was identical with the one obtained in the above procedure whereby **13b** was derived from **9b** and ammonium formate. The maximum amount of 1,2,3,4-tetrahydro-2-(*p*-nitrobenzyl-α,α-d_2)isoquinoline-1-*d* (**13c**) which might have been present due to the uncertainty in the NMR integration was 5%.

(26) "Dictionary of Organic Compounds", Vol. 5, Oxford University Press, New York, 1965, p 3126.

(B). Formation of 1,2,3,4-Tetrahydro-2-(*p*-nitrobenzyl-α,α-d_2)isoquinoline-1-*d* (13c) in Pyridine–Triethylamine. A solution of 300 mg of **9b** in 40 mL of dry pyridine was heated to 72 °C in a flame-dried flask under a nitrogen atmosphere. To the solution with stirring were added 0.13 mL of triethylamine (dried over KOH) and 0.15 mL of carbon disulfide by a syringe through a septum. After a temperature of 75–82 °C had been maintained for 8 h, most of the pyridine and triethylamine were removed at 15–20 torr (26–27 °C), and the residue was treated six times with 20-mL portions of chloroform, the solvent being removed each time in vacuo at less than 22 °C.

The residue was placed on a 20-mm-long column of 110 g of Woelm, neutral, activity grade II alumina and developed with chloroform. About 117 mg of the amine (72%) was isolated as a yellow oil. The ^{1}H NMR spectrum ($CDCl_3$) of this oil showed clearly that it was predominantly if not entirely 1,2,3,4-tetrahydro-2-(*p*-nitrobenzyl-α,α-d_2)isoquinoline-1-*d* (**13c**). Data obtained from 18 separate integrations on four separate spectra at different radio-frequency power settings indicated that the percent deuterium at the C_1 position was 52 ± 2%.

2-(*p*-Nitrobenzyl)isoquinolinium Bromide (1, X = *p*-NO_2) in Pyridine–Triethylamine–Triethylamine Hydrobromide-*d*. (A). In Carbon Disulfide. A solution of 2.00 g (5.79 mmol) of **1** (X = *p*-NO_2) and 1.06 g (5.79 mmol) of triethylamine hydrobromide-*d* in 200 mL of dry pyridine was heated to 72 °C, and 0.35 mL (5.79 mmol) of triethylamine (dried over KOH) and 0.29 mL (12 mmol) of carbon disulfide were added with a syringe. After 4.0 min at 72 °C, the solvents were immediately removed in vacuo. Three times 20-mL portions of chloroform were added and evaporated, and the residue was treated with 200 mL of water. The aqueous mixture was filtered, the water removed in vacuo, and the residue dried for 24 h at 0.5 torr over phosphorus pentoxide at 100 °C. The residue (0.90 g, 45%) was shown by ^{1}H NMR (CF_3CO_2H) to be deuterium-free recovered starting material (1, X = *p*-NO_2).

(B). In the Absence of Carbon Disulfide. The reaction was carried out in the same manner and in the exact proportions of reagents as the above reaction; however, the carbon disulfide was omitted, and the reaction was continued for 8 h. A similar workup afforded 1.24 g (62%) of recovered **1** (X = *p*-NO_2) which was shown by ^{1}H NMR (CF_3CO_2H) to have no deuterium component.

Acknowledgment. We are grateful for the financial support provided by the Research Corp. We also thank the Olin Foundation for their generous contribution of a Varian Associates EM-360L nuclear magnetic resonance spectrometer, as part of a major capital gift to Lewis and Clark College.

Registry No. **1** (X = *p*-NO_2), 16726-82-2; **2** (X = *p*-NO_2), 50979-43-6; **9a**, 73908-56-2; **9b**, 73908-57-3; **12**, 73908-58-4; **13a**, 70638-30-1; **13a** hydrochloride, 73908-59-5; **13a** perchlorate, 73908-60-8; **13b**, 73908-61-9; **13c**, 73908-62-0; 3,4-dihydroisoquinoline, 3230-65-7; α-bromo-*p*-nitrotoluene, 100-11-8; carbon sulfide, 75-15-0; *p*-nitrobenzyl-α,α-d_2 alcohol, 73908-63-1; 4-nitrobenzoic acid, 62-23-7; α-bromo-*p*-nitrotoluene-α,α-d_2, 73908-64-2; triethylamine hydrobromide-*d*, 73908-65-3.