N-Benzylisoquinolinium 4-Dithiocarboxylate Adducts from *N*-Benzylisoquinolinium Halides and Carbon Disulfide[1]

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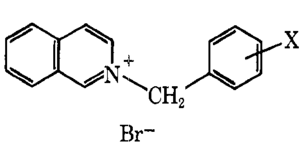
N-Benzylisoquinolinium halides, when combined with carbon disulfide in alkaline aqueous dioxane, give both the mesoionic cycloadducts first described by Kröhnke and Steuernagel[3] and products identified as *N*-benzylisoquinolinium 4-dithiocarboxylates. The derivation of this structural assignment through physical methods and deuterium-labeling experiments and a plausible rationale for the formation of these novel adducts are presented.

Mesoionic adducts derived from *N*-benzylisoquinolinium bromides (**1**) and carbon disulfide in alkaline aqueous dioxane are 3-phenylthiazolo[2,3-*a*]isoquinolinium-2-thione betaines (**2**).[3-5]



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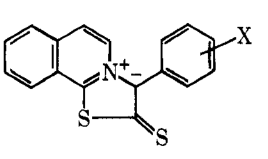

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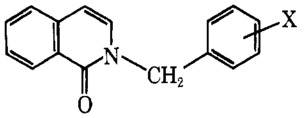
It was observed[3] that the isolated yields of the betaine **2** increased as the substituent became more electronegative; from **1** (4′-X = Cl, CH=CH$_2$, CN, NO$_2$) the yields of the corresponding adducts **2** were 20, 34, 40, and 66% of theory. In the chlorobenzyl case, an anticipated[6] side product, *N*-(4-chlorobenzyl)isoquinolone (**3**), was obtained in low yield.[3]



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In the course of studies directed toward reducing the mechanistic ambiguities associated with this cycloaddition process, we prepared and subjected a series of substituted benzylisoquinolinium salts to the reaction conditions. Eleven representatives of a new class of adducts were obtained. This manuscript describes the structural elucidation of these hitherto unexamined products.

Results

An *N*-benzylisoquinolinium halide, carbon disulfide, and aqueous alkaline dioxane react to give the corresponding mesoionic adduct **2**, *N*-benzylisoquinolone (**3**), and a third major product having a molecular formula relative to the isoquinolinium starting material corresponding to loss of hydrogen halide and gain of carbon disulfide.

The new adducts had prominent mass spectrometric fragmentation ions at *m/e* 172 ($C_{10}H_6NS$), 128 (C_9H_6N), M − 76 (loss of carbon disulfide), and at values corresponding to substituted tropylium ions (*e.g.*, 169 and 171 from the 4-bromobenzyl product). The elemental compositions for these fragments were confirmed by high resolution data. The mass spectrum of the adduct derived from *N*-(4-bromobenzyl-α-d_2)isoquinolinium bromide contained the intense tropylium ion peaks at *m/e* 171 and 173 and molecular ions at 375 and 377, thus demonstrating complete retention of the deuterium labels.

The ultraviolet spectra of the new adducts typically exhibited λ_{max} 236 nm (log ϵ 4.5) and 335 (4.0) in ethanol, values in close agreement with those appropriate for *N*-benzylisoquinolinium systems[7] (Figure 1).

The mass and ultraviolet spectra thus provide sound grounds for assigning the new adducts as *N*-benzylisoquinolinium dithiocarboxylates.

The correct position of the dithiocarboxylate group on the isoquinolinium nucleus was uncovered through deuterium-labeling experiments.

1-Deuterio-, 4-deuterio-, and 8-deuterioisoquinolinium salts in the 4-bromobenzyl series were synthesized and converted to products. Mass spectrometric analyses (Table I) of the new adducts indicated that most of the 1-deuterium label was lost during the process; all of the 4-deuterium label was eliminated; none of the 8-deuterium tag was removed.

TABLE I

DEUTERIUM ANALYSES IN ISOQUINOLINES AND DITHIOCARBOXYLATE ADDUCTS

Label in isoquinoline	% of d_1 in isoquinoline[a]	% of d_1 in derived adduct **4** (X = 4′-Br)[a]
1	93[b]	1.4
4	96.4	0.3
8	50.2	52.0

[a] Except as noted, by mass spectrometry. [b] By nmr.

Exchange experiments were used to learn when exchange at C_1 occurred: in alkaline deuterium oxide–dioxane, the salt **1** (X = 4′-Br) incorporated 86% of one deuterium atom at C_1 in 4 min; the 1-deuterio salt (**1**, X = 4′-Br, H_1 = D) in aqueous alkaline dioxane–carbon disulfide incorporated 60% of one hydrogen at C_1 in 4 min; and the unlabeled adduct, resubmitted to deuterated media under the reaction conditions for 9.5 hr, gave no detectable d_1 component in the reisolated product. Thus the exchange at C_1 is a reaction of the *N*-benzylisoquinolinium salt, and the dithiocarboxylate

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(2) National Institute of General Medical Sciences Predoctoral Fellow, 1969–present.

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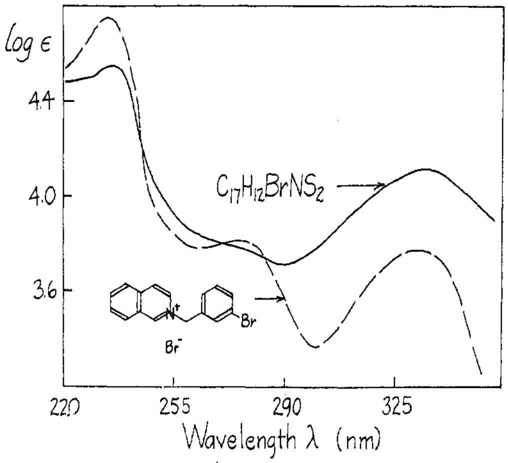
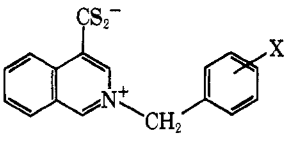


Figure 1.—Ultraviolet absorption spectra in ethanol for *N*-(3-bromobenzyl)isoquinolinium bromide (- - -) and the derived $C_{17}H_{12}BrNS_2$ adduct (——).

group in the new class of adducts must be located at C_4. The structure is thus assigned as **4**.



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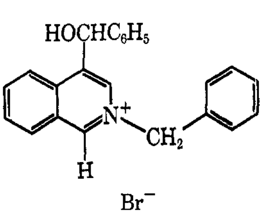
The nmr spectra of these adducts provide valuable confirmatory evidence. In trifluoroacetic acid, the unsubstituted adduct (**4**, X = H) has absorptions at δ 6.0 (s, 2), 7.6 (s, 5), 8.4 (m, 5), and 9.7 (s, 1). Similar spectra were obtained in hexafluoroacetone. Interpretation of these data in terms of structure **4** follows at once from literature precedent for isoquinolines[8,9] and for the very similar isoquinolinium salt **5**,[10-13] which in trifluoroacetic acid has corresponding absorptions at 6.0 (s, 2), 7.50 (s, 5), 8.2 (m, 4), 8.87 (s, 1), and 9.68 (s, 1), assigned respectively to the methylene, phenyl, $H_{5,6,7,8}$, H_3, and H_1.



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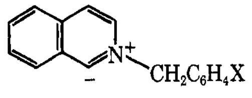
A still more conclusive conformation has been secured through an X-ray single-crystal structure determination on **4** (X = 4′-Br).[14]

Discussion

A reaction scheme in conformity with the labeling results given above may be easily constructed. The most accessible conjugate base of the *N*-benzylisoquinolinium salt is not **7** but rather **6**, produced through abstraction of H_1; the pseudobase **8** of the isoquinolinium salt behaves as an enamine sufficiently reactive to attack carbon disulfide nucleophilically. Base-catalyzed 1,4 elimination of water from the 1,4-dihydroisoquinolinium intermediate so produced (**9**) gives the isolable adduct **4**.



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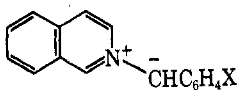

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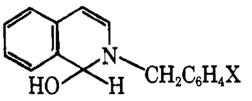

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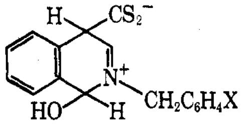

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The apparent discrepancy between the labeling results, which provide no basis for postulating reversible formation of the 1,3-dipolar intermediate **7**, and the obtention of mesoionic compounds **1**, which can be most promptly rationalized[15,16] in terms of cycloadditions between **7** and carbon disulfide, followed by an oxidation, will be considered in another context.[17]

Experimental Section

Except when noted otherwise, nmr spectra were determined at 60 MHz as solutions in $CDCl_3$ using a Varian spectrometer; mass spectrometric data were obtained at the Battelle Memorial Institute High Resolution Mass Spectrometry Center, Columbus, Ohio, and by Mrs. Mary Mitchell on a CEC 21-110 at the University of Oregon; elemental analyses were done by J. Nemeth and associates, Urbana, Ill., and by Chemalytics, Tempe, Ariz.; melting points were determined on a "Kofler" micro hot state.

4-Chlorobenzyl Bromide.—A 500-ml three-necked flask fitted with a thermometer and gas inlet and outlet tubes was charged with 14.9 g of 4-chlorobenzyl alcohol (Aldrich) in 300 ml of benzene. Hydrogen bromide was bubbled into the cooled solution. The reaction temperature rose to 11°, and, when it subsequently fell to 5°, the addition was terminated. Sodium sulfate was added, the mixture was stirred overnight, and, upon filtration and concentration, a white solid was obtained. Recrystallization of this solid from petroleum ether (bp 30–60°) gave 16.8 g (78%) of 4-chlorobenzyl bromide, mp 50–52° (lit.[18] mp 51°). This lachrymator had nmr singlets at δ 4.39 (2) and 7.25 (4).

Through similar reactions, **4-methoxybenzyl bromide** [bp 94° (1 mm), lit.[19] bp 128–129° (16 mm)], which was promptly combined with isoquinoline, and **3-methoxybenzyl bromide** [bp 75° (1 mm), lit.[19] bp 127° (16 mm)] were prepared from the corresponding alcohols. The other substituted benzyl bromides utilized were commercially available. All were lachrymatory.

***N*-Benzylisoquinolinium bromides** (**1**) were prepared in 74–98% yields by heating solutions of a benzyl bromide and isoquinoline in benzene at reflux from 9 to 14 hr and then collecting the precipitated salt from the cooled reaction mixture. Samples for elemental analysis (Table II) were recrystallized at least twice from methanol–ethyl acetate.

***N*-(3-Trifluoromethylbenzyl)isoquinolinium chloride**, mp 215°, from the reaction of 8.3 g of isoquinoline and 12.5 g of 3-trifluoromethylbenzyl chloride in 150 ml of toluene at reflux for 24 hr, was obtained in 31% yield (6.49 g).

Reaction of *N*-(3-Methylbenzyl)isoquinolinium Bromide with Carbon Disulfide in Alkaline Aqueous Dioxane.—A 500-ml three-necked flask, containing 9.12 g (0.029 mol) of *N*-(3-methylbenzyl)isoquinolinium bromide, 30 ml of water, 30 ml of dioxane,

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TABLE II

N-BENZYLISOQUINOLINIUM BROMIDES[a] 1

Benzyl substituent	Molecular formula	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Nmr data, δ, ppm
H	$C_{16}H_{14}BrN$	157–158	64.01	4.70	4.67	63.61	4.65	4.38	6.40 (s, 2), 7.0–8.5 (m, 9), 8.84 (AB, 2), 11.04 (s, 1)
3-CH_3	$C_{17}H_{16}BrN$	156–158	64.97	5.13	4.46	64.70	5.33	4.25	2.26 (s, 3), 6.50 (s, 2), 7.0–8.6 (m, 8), 8.94 (AB, 2), 11.26 (s, 1)
4-CH_3O	$C_{17}H_{16}BrNO$	235–236	61.83	4.88	4.24	62.15	4.67	4.03	
3-NO_2	$C_{16}H_{13}BrN_2O_2$	228–229	55.66	3.80	8.12	55.66	3.76	7.88	6.34 (s, 2), 7.6–9.2 (m, 10), 10.66 (s, 1)[b]
3-Br	$C_{16}H_{13}Br_2N$	210–211	50.68	3.46	3.69	50.62	3.28	3.68	6.16 (s, 2), 7.2–8.7 (m, 8), 8.84 (AB, 2), 10.56 (s, 1)[b]
4-Br	$C_{16}H_{13}Br_2N$	161–162	50.68	3.46	3.69	50.76	3.71	3.85	6.58 (s, 2), 7.2–8.5 (m, 8), 8.96 (AB, 2), 11.32 (s, 1)

[a] Other *N*-benzylisoquinolinium bromides prepared and utilized synthetically: 4-CH_3 (mp 79–81°), 3-F (155°), 4-CN (193–194°), 3-CH_3O (172–173°), 4-NO_2 (206–207°), 3-Cl (164°), and 4-Cl (100–124°). [b] In DMSO-d_6.

TABLE III

ANALYTICAL DATA FOR *N*-BENZYLISOQUINOLINIUM 4-DITHIOCARBOXYLATE ADDUCTS 4

Benzyl substituent	Molecular formula	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H	$C_{17}H_{13}NS_2$	209–210	69.12	4.44	4.74	69.23	4.33	4.47
4-CH_3	$C_{18}H_{15}NS_2$	198–201	69.86	4.89	4.53	69.58	4.82	4.79
4-CH_3O	$C_{18}H_{15}NOS_2$	191–193	66.43	4.64	4.30	66.64	4.76	4.11
3-F	$C_{17}H_{12}FNS_2$	204–205	65.15	3.86	4.47	64.98	3.55	4.68
3-Cl	$C_{17}H_{12}ClNS_2$	210–213	61.90	37.6	4.25	62.04	4.09	4.38
3-Br	$C_{17}H_{12}BrNS_2$	207–208	54.55	3.23	3.74	54.32	3.22	3.82

and 20 ml of carbon disulfide was heated to 52°. Over a 3-min period, 30 ml of 11 *N* sodium hydroxide was added to the vigorously stirred mixture, which was then brought to and maintained at about 72° for 8 hr. After 2 hr at room temperature with stirring and 4 days at −20° without, the mixture was filtered. The solid collected was washed with three 30-ml portions of warm water and dried; 3.0 g of dark solid was obtained.

The filtrate was extracted with chloroform; the chloroform solution was washed twice with 0.1 *N* hydrochloric acid and once with water, dried over calcium carbonate, filtered, and concentrated, leaving a thick black oil. Chromatography of this dark oil and the 3.0 g of dark solid obtained above on 250 g of neutral Woelm II alumina with chloroform gave a sequence of 20-ml automatically collected fractions.

The early fractions contained *N*-(3-methylbenzyl)isoquinolone (**3**, X = 3′-CH_3): nmr δ 2.2 (s, 3), 5.1 (s, 2), 7 (q, 2), 7–8 (m, 7), and 8.4 (m, 1).

The middle fractions contained the 3-tolyl mesoionic adduct **2** (X = 3′-CH_3): mp 201–204° (176 mg after recrystallization from chloroform); nmr δ 2.36 (s, 3), 7–8 (m, 10).

When concentration of the oil prior to chromatography was incomplete, and dioxane remained in the residue, the isoquinolone and mesoionic adducts were separated only after a second chromatographic development on 50 g of alumina.

The sand and alumina on the top of the column were extracted with hot *N,N*-dimethylformamide, and the extract was concentrated to give 0.56 g of red solid, mp 191–194°. Recrystallization from DMF–acetonitrile gave 327 mg of an analytically pure $C_{18}H_{15}NS_2$ sample (**4**, X = 3′-CH_3), mp 195–197°.

Molecular formulas for this and other isoquinolinium dithiocarboxylate adducts prepared and isolated through similar procedures were secured through elemental analysis (Table III) and/or high resolution mass spectrometric determinations of *m/e* values for molecular ions (Table IV). These adducts had very strong infrared bands at 1040 cm^{-1} (KBr).

The dithiocarboxylate adducts were obtained in yields ranging from 16.5% for the 4-CH_3O compound to only 2.9% for the 3-CF_3 case. No adducts in this class were isolated from reaction mixtures derived from the two nitrobenzyl- and the cyanobenzylisoquinolinium salts.

Molecular formulas for the mesoionic adducts obtained in these reactions were confirmed by elemental analyses (Table V) and/or high resolution mass spectrometry (Table VI). The yields of these adducts ranged from 2.1% for the 4-CH_3O derivative to 52.2% for the 4-CN analog.

4-Bromobenzyl-α-d_2 Alcohol.—A 100-ml three-necked flask fitted with a 50-ml dropping funnel, condenser, and drying tube was flushed with nitrogen and charged with 0.50 g (11.9 mmol) of lithium aluminum deuteride (Stohler) and 25 ml of anhydrous ether. A solution of methyl 4-bromobenzoate (2.80 g, 13 mmol) in 17 ml of ether was added to the funnel. The ester was added dropwise over 15 min to the stirred reaction mixture heated to reflux. After another 1 hr at reflux, the reaction mixture was cooled, decomposed through the cautious addition of 0.5 ml of water, 0.5 ml of 15% sodium hydroxide, and an additional 1.5 ml of water, and filtered. The solid was washed several times with ether. The total filtrate was dried over magnesium sulfate, filtered, and concentrated to afford 2.29 g (93%) of light yellow solid, mp 76–78° (lit.[20] mp 76–76.5°). The nmr showed δ 2.65 (s, 1) and 7.33 (AA′BB′, 4).

TABLE IV

HIGH RESOLUTION MASS SPECTROMETRIC MOLECULAR IONS FOR *N*-BENZYLISOQUINOLINIUM 4-DITHIOCARBOXYLATE ADDUCTS 4

Benzyl sub-stituent	Molecular formula	Mp, °C	*m/e* Calcd	*m/e* Found	Error (×10^3)
H	$C_{17}H_{13}NS_2$	209–210	295.0489	295.0504	1.5
3-CH_3	$C_{18}H_{15}NS_2$	198–199	309.0646	309.0644	0.2
4-CH_3		198–201		309.0645	0.1
3-CH_3O	$C_{18}H_{15}NOS_2$	215–218	325.0595	325.0552	4.3
4-CH_3O		191–193		325.0613	1.8
3-^{35}Cl	$C_{17}H_{12}ClNS_2$	210–213	329.0100	329.0133	3.3
4-^{35}Cl		208–209		329.0116	1.6
3-CF_3	$C_{18}H_{12}F_3NS_2$	135–155	363.0363	363.0372	0.9
3-^{79}Br	$C_{17}H_{12}BrNS_2$	207–208	372.9595	372.9609[a]	1.4
4-^{79}Br		206–207		372.9709	11.4
3-^{81}Br			374.9574	374.9599[a]	2.5
4-^{81}Br				374.9633	5.9

[a] Purdue University Mass Spectrometry Center data.

4-Bromobenzyl-α-d_2 Bromide.—Treating 4-bromobenzyl-α-d_2 alcohol (1.74 g) with hydrogen bromide by the procedure detailed above gave 1.98 g (86%) of light yellow crystals, mp 50–59° (lit.[21] mp 63°). The nmr spectrum showed only the AA′BB′ pattern at δ 7.42.

***N*-(4-Bromobenzyl-α-d_2)isoquinolinium Bromide.**—A solution of 1.73 g of 4-bromobenzyl-α-d_2 bromide and 0.89 g of isoquinoline in 30 ml of benzene was heated at reflux for 7.5 hr with stirring. The reaction mixture was cooled to give 1.9 g of a colorless solid. The mother liquor, after an additional 22 hr at reflux, gave an additional 0.3 g of solid when cooled. The two crops of salt, mp 115–145°, showed no benzylic proton absorption in the nmr.

1-Cyano-2-benzoyl-1,2-dihydroisoquinoline[22] was prepared

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TABLE V

ANALYTICAL DATA FOR MESOIONIC ADDUCTS **2**

Phenyl substituent	Molecular formula	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
3-F	$C_{17}H_{10}FNS_2$	213–215	65.57	3.24	4.50	65.32	3.05	4.82
4-Cl	$C_{17}H_{10}ClNS_2$	288–291	62.28	3.07	4.27	62.53	2.92	4.41
4-Br[a]	$C_{17}H_{10}BrNS_2$	299–300	54.84	2.71	3.76	55.03	2.68	3.56
3-NO_2[b]	$C_{17}H_{10}N_2O_2S_2$	279–287	60.34	2.98	8.28	60.54	2.88	8.00

[a] *Anal.* Calcd: S, 17.22; Br, 21.46. Found: S, 17.52; Br, 21.80. [b] *Anal.* Calcd: S, 18.95. Found: S, 18.74.

TABLE VI

HIGH RESOLUTION MASS SPECTROMETRIC MOLECULAR IONS FOR MESOIONIC ADDUCTS **2**

Phenyl substituent	Molecular formula	Mp, °C	m/e Calcd	m/e Found	Error (×10³)
H	$C_{17}H_{11}NS_2$	223–225	293.0333	293.0303	3.0
3-CH_3	$C_{18}H_{13}NS_2$	203–206	307.0489	307.0474	2.5
4-CH_3		267–269		307.0489	
4-CN	$C_{18}H_{10}N_2S_2$	335–337	318.0285	318.0267	1.8
3-CH_3O	$C_{18}H_{13}NOS_2$	170–172	323.0405	323.0417	1.2
4-CH_3O		255–257		323.0403	0.2
3-^{35}Cl	$C_{17}H_{10}ClNS_2$	206–207	326.9943	326.9982	3.9
4-^{35}Cl		288–291		326.9959	1.6
3-NO_2	$C_{17}H_{10}N_2O_2S_2$	279–287	338.0184	338.0153	3.1
4-NO_2		300–302		338.0159	2.5
3-CF_3	$C_{18}H_{10}F_2NS_2$	218–219	361.0207	361.0194	1.3
3-^{79}Br	$C_{17}H_{10}BrNS_2$	229–230	370.9438	370.9442	0.4
4-^{79}Br		299–300		370.9463[a]	2.5

[a] Purdue University Mass Spectrometry Center data.

from 8.6 g of isoquinoline and benzoyl chloride in aqueous sodium cyanide. The crude product (8.8 g, 51%, mp 123–127°) was recrystallized from 95% ethanol to obtain 4.68 g of nearly colorless crystals, mp 125–127° (lit.[22] mp 124–126°). The nmr in $CDCl_3$ had δ 6.4 (AB, 2), 6.6 (s, 1), and 7.2–7.8 (m, 9).

1-Deuterioisoquinoline.[23]—A mixture of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline (4.3 g), tetrahydrofuran (10 ml), and deuterium oxide (10 ml) was stirred and heated at reflux for 6 hr. The cooled reaction mixture was extracted with three 20-ml portions of ether, and the ethereal solution was washed with water, dried over magnesium sulfate, filtered, concentrated, and distilled. The colorless product, bp 48° (0.3 mm), 1.57 g (73% yield), which froze readily just below room temperature, was 93% d_1 according to nmr analysis.

***N*-(4-Bromobenzyl)-1-deuterioisoquinolinium Bromide.**—A mixture of 1-deuterioisoquinoline (1.57 g, 93% d_1), a slight excess of α,4-dibromotoluene (3.15 g, Aldrich Chemical), and 60 ml of benzene was stirred at reflux for 19 hr and then cooled overnight at 5°. The colorless salt was collected and dried 7 hr over phosphorus pentoxide (0.5 mm); it had mp 126–143° and the expected nmr spectrum.

4-Deuterioisoquinoline.[24]—A solution of 4-bromoisoquinoline (2.50 g, Aldrich) in 35.2 ml of 2 *N* deuteriosulfuric acid and 1.84 g of zinc dust were stirred and heated to reflux for 2 hr. The cooled reaction mixture was filtered and the filtrate was made just basic with about 7 ml of 11 *N* sodium hydroxide. Steam distillation and the normal work-up gave 988 mg (63%) of crude product; distillation gave 817 mg of colorless 4-deuterioisoquinoline: bp 97° (13 mm); mp 25°, containing less than 3% of the starting material. The nmr spectrum of the neat product [δ 7.2–8.0 (m, 4), 8.84 (s, 1), and 9.52 (s, 1)] indicated at least 90% d_1 material and 96.4% d_1 by mass spectrometry.

***N*-(4-Bromobenzyl)-4-deuteriosoquinolinium bromide,** from 1.52 g of α-4-dibromotoluene and 790 mg of 4-deuterioisoquinoline, had mp 105–145° (2.07 g, 89%).

2-Deuteriobenzonitrile.[25]—In a 200-ml three-necked flask, 2-bromobenzonitrile (Aldrich, carcinogen), 37.2 g of zinc dust, 38.8 ml of deuterium oxide, and 17.6 g of acetic anhydride were vigorously stirred and heated to reflux for 21 hr. The cooled reaction mixture was extracted with four 20-ml portions of benzene, which were combined, washed several times with aqueous sodium bicarbonate, washed once with water, dried over magnesium sulfate, filtered, and concentrated. Distillation afforded 3.04 g (49%) of 2-deuteriobenzonitrile, bp 59° (5 mm).

2-Deuteriobenzylamine.[26]—A 200-ml three-necked flask fitted with an overhead stirrer, a reflux condenser and drying tube, and a 50-ml addition funnel was charged with 1.11 g of lithium aluminum hydride and 50 ml of anhydrous ether. To this stirred mixture heated to reflux was added a solution of 2-deuteriobenzonitrile (3.04 g) in 30 ml of ether over a 25-min period. After another hour at reflux the reaction mixture was cooled; 5.6 ml of water was added slowly to the stirred mixture, followed by 72 ml of 20% aqueous potassium sodium tartrate. The milky aqueous suspension separated; it was separated from the ether layer and was extracted twice with 25-ml portions of ether. The ethereal solutions were combined, dried over magnesium sulfate, filtered, concentrated, and distilled. The 2-deuteriobenzylamine obtained [1.41 g, 45% yield; bp 40° (2.2 mm)] had nmr absorptions (neat) at δ 1.40 (s, 2), 3.65 (s, 2), and 7.21 (broad s, 4).

Schiff's Base from 2-Deuteriobenzylamine and Glyoxal Semidiethyl Acetal.[27]—2-Deuteriobenzylamine (1.05 g) and glyoxal semidiethyl acetal[28] (1.35 g, partially polymerized according to the nmr spectrum) were combined and warmed on a steam bath 1 hr. The cooled reaction mixture was dissolved in ether, and the ethereal solution was dried, filtered, concentrated, and distilled to give 0.34 g of pale yellow product, bp 123° (5 mm).

8-Deuterioisoquinoline.[27]—To 0.5 ml of cooled, concentrated sulfuric acid was added 0.337 g of the Schiff's base derived from 2-deuteriobenzylamine and glyoxal semidiethyl acetal. The resulting tan solution was added dropwise in 5 min with stirring to 1 ml of sulfuric acid held at 160°. The reaction mixture was cooled, slowly made alkaline with 11 *N* sodium hydroxide, and steam distilled. The distillate was extracted with ether (three 6-ml portions). The ethereal material was dried, filtered, and concentrated to give 70 mg (36%) of 8-deuterioisoquinoline, 50% d_1, according to the mass spectrum (Table I).

***N*-(4-Bromobenzyl)-8-deuterioisoquinolinium Bromide.**—A solution of 70 mg of 8-deuterioisoquinoline, 50% d_1, and 227 mg of α-4-dibromotoluene in 10 ml of benzene was heated at reflux for 14.5 hr. After the usual work-up, the salt obtained (208 mg) had mp 105–143°.

***N*-(4-Bromobenzyl)isoquinolinium Bromide Exchange Reactions. A. In Alkaline Deuterium Oxide–Dioxane.**—Unlabeled isoquinolinium bromide (2.0 g) and 5.5 ml each of deuterium oxide and dioxane were heated to 72°, and 5.5 ml of approximately 11 *N* sodium deuterioxide (from 2.5 g of sodium hydroxide and deuterium oxide) was added in one portion. After 4 min at 72°, the reaction mixture was cooled in an ice bath with stirring, neutralized at temperatures below 20° with a solution of about 5 g of hydrogen bromide in 2.7 ml of deuterium oxide, and finally diluted with 75 ml each of water and chloroform. Concentration of the organic phase gave a residue from which the isoquinolinium bromide was isolated from sodium bromide and organic impurities by sequential extractions and concentrations with warm water and chloroform. The 100-MHz nmr spectrum of the recovered starting material (410 mg) was integrated and found to contain only 14% of hydrogen at the C_1 position.

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(23) Compare V. Boekelheide and J. Weinstock, *J. Amer. Chem. Soc.*, **74**, 660 (1952); A. Albert and G. Catterall, *J. Chem. Soc. C*, 1533 (1967).

(24) Compare B. Bak, L. Hansen, and J. Rastrap-Andersen, *J. Chem. Phys.*, **22**, 2013 (1954); A. Murray, III, and D. L. Williams, "Organic Synthesis with Isotopes," Interscience, New York, N. Y., 1958, p 1384.

(25) B. Bak and J. T. Nielsen, *Z. Elektrochem.*, **64**, 560 (1960).

(26) R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, **70**, 3738 (1948).

(27) E. Schlitter and J. Müller, *Helv. Chem. Acta*, **31**, 914 (1948).

(28) A. Wohl and C. Newberg, *Ber.*, **33**, 3099 (1900); E. J. Witzemann, W. L. Evans, H. Hass, and E. F. Schroeder, "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 307.

In a trial run omitting deuterated reagents, the material from the chloroform extract which failed to dissolve in warm water was thoroughly dried and shown by nmr spectroscopy to be mostly *N*-(4-bromobenzyl)isoquinolone (1.29 g, 78%).

B. 1-Deuterio Salt in Aqueous Alkaline Dioxane–Carbon Disulfide.—A stirred mixture of *N*-(4-bromobenzyl)-1-deuterioisoquinolinium bromide (93% d_1), 5.5 ml of water, 5.5 ml of dioxane, and 3.7 ml of carbon disulfide was heated to 72°, and 5.5 ml of 11 *N* sodium hydroxide was added in one portion. After 4 min, the reaction mixture was quenched in an ice bath with stirring, made just acidic at temperatures below 16° with concentrated sulfuric acid, and diluted with water (100 ml) and chloroform (50 ml). The aqueous layer was concentrated, the remaining water was removed with benzene as the azeotrope, and the dry salts obtained were extracted with chloroform. The isoquinolinium salt obtained from the chloroform extract (357 mg) had 60% hydrogen at C_1, according to nmr analysis.

Reactions of Deuterium Labeled *N*-(4-Bromobenzyl)isoquinolinium Bromides with Carbon Disulfide in Alkaline Aqueous Dioxane. A. *N*-(4-Bromobenzyl-α-d_2)isoquinolinium Bromide.—A 100-ml three-necked flask was charged with 2.00 g of this isoquinolinium salt, 5.5 ml of water, 5.5 ml of purified dioxane, and 3.7 ml of carbon disulfide. The mixture was stirred mechanically, heated, and diluted with 5.5 ml of 11 *N* sodium hydroxide; the red mixture obtained was stirred at 72° for 8 hr, cooled to room temperature with stirring, stored at −15° for 2 days, and filtered on a sintered glass funnel. The crude products were washed on the funnel with three 6-ml portions of warm water and dried in the air. The red solid obtained (1.07 g) was chromatographed in the usual way on 50 g of neutral Woelm II alumina. The yellow band was isolated and concentrated to give *N*-(4-bromo-α-d_2-benzyl)isoquinolone. No benzyl hydrogens were detected by nmr analysis. The dark material at the top of the column was extracted with hot *N*,*N*-dimethylformamide; concentration of the extract gave a dark red solid, mp 197–201°. Recrystallization of the solid from DMF–acetonitrile gave 100 mg of adduct, mp 202°, having a mass spectrum indicative of the α-d_2-benzyl moiety.

B. *N*-(4-Bromobenzyl)-1-deuterioisoquinolinium Bromide.—Following the given reaction procedure, 2.0 g of the isoquinolinium salt gave rise to 1.04 g of red solid. A slurry of the solid in chloroform was delivered to the top of a column of alumina, which was eluted with more chloroform. The residue in the sand at the top of the column was extracted with hot DMF. The red solid isolated, mp 190–260°, was extracted in a Soxhlet with chloroform for 23 hr. The residue in the thimble, 83 mg, mp 200–202°, was recrystallized to give a sample for mass spectrometric analysis, 52 mg of bright red crystals, mp 202–204°. Most, but not all, of the deuterium in the starting material had been lost (Table I).

C. *N*-(4-Bromobenzyl)-8-deuterioisoquinolinium Bromide.—The reaction of 208 mg of the isoquinolinium bromide was carried through in the normal manner. The crude product was extracted in a micro Soxhlet with 10 ml of chloroform for 16 hr. The residue from the thimble, 10.4 mg, mp 200°, was analyzed mass spectrometrically; the adduct retained the deuterium present in the starting material (Table I).

D. *N*-(4-Bromobenzyl)-4-deuterioisoquinolinium Bromide.—The crude product from 1.0 g of the isoquinolinium salt, amounting to 312 mg, was continuously extracted with chloroform for 22.5 hr. The residue was thoroughly dried; it had mp 198–205° and a mass spectrum showing no deuterium label (Table I).

Attempted Exchange in *N*-(4-Bromobenzyl)isoquinolinium 4-Dithiocarboxylate Adduct.—To 50 mg of the $C_{17}H_{12}BrNS_{12}$ adduct was added 5.5 ml each of deuterium oxide, dioxane, and 11 *N* sodium deuterioxide, and 3.7 ml of carbon disulfide. The stirred mixture was heated at 72° for 9.5 hr, cooled, and filtered to give 37 mg of starting material. Recrystallization from DMF–acetonitrile gave red crystals, mp 202–204°, having no deuterium incorporation detectable by mass spectrometric analysis.

Registry No.—1 H, 23277-04-5; 1 3-CH_3, 27415-57-2; 1 4-CH_3O, 27415-58-3; 1 3-NO_2, 27410-57-7; 1 3-Br, 27410-58-8; 1 4-Br, 27371-56-8; 2 3-F, 27371-57-9; 2 4-Cl, 27371-58-0; 2 4-Br, 27371-59-1; 2 H, 27371-60-4; 2 3-CH_3, 27371-61-5; 2 4-CH_3, 27371-62-6; 2 4-CN, 27410-59-9; 2 3-CH_3O, 27410-60-2; 2 4-CH_3O, 27410-61-3; 2 3-^{35}Cl, 27410-62-4; 2 3-NO_2, 27410-63-5; 2 4-NO_2, 27410-64-6; 2 3-CF_3, 27410-65-7; 2 3-^{79}Br, 27410-66-8; 2 4-^{79}Br, 27410-67-9; 4 3-F, 27410-68-0; 4 3-Cl, 27410-69-1; 4 3-Br, 27410-70-4; 4 H, 27371-63-7; 4 3-CH_3, 27371-64-8; 4 4-CH_3, 27410-71-5; 4 3-CH_3O, 27410-72-6; 4 4-CH_3O, 27410-73-7; 4 4-^{35}Cl, 27410-74-8; 4 3-CF_3, 27410-75-9; 4 3-^{79}Br, 27410-76-0; 4 4-^{79}Br, 27410-77-1; 4 3-^{81}Br, 27371-65-9; 4 4-^{81}Br, 27410-78-2; *N*-(4-bromobenzyl-α-d_2)isoquinolinium bromide, 27410-79-3; *N*-(4-bromobenzyl)-1-deuterioisoquinolinium bromide, 27410-80-6; *N*-(4-bromobenzyl)-4-deuterioisoquinolinium bromide, 27410-81-7; *N*-(4-bromobenzyl)-8-deuterioisoquinolinium bromide, 27410-82-8; carbon disulfide, 75-15-0.

Synthesis of Fluoroarenes by Photolysis of Aryldiazonium Salts in the Solid State[1a]

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Photolysis of crystalline aryldiazonium fluoroborates and fluorophosphates gives the corresponding fluoroarenes. In some cases yields are much better than those obtained by pyrolysis.

The photochemistry of aryldiazonium salts in the solid state seems to have been ignored except for one study[2] of gas evolution from slurries in which the organic products were not identified. As the first step in a mechanistic study of this phenomenon, the principal products formed upon irradiation of crystalline films of a number of aryldiazonium salts have been determined.

In the photolysis of diazonium tetrafluoroborates and hexafluorophosphates, the corresponding fluoroarenes were usually the only volatile product as in pyrolysis. In some cases the yields of fluoroarenes were higher than those obtained by pyrolysis of these salts (the Balz–Schiemann reaction), which remains the most generally used means of introducing a fluorine substituent into an aromatic ring.[3] The Balz–Schiemann reaction fails

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[1] (a) Part of this work has been described by R. C. P. and A. D. in U. S. Patent 3,481,850 (1969); (b) Fellow of the Cancer Association of Greater New Orleans, Inc., summer 1966; (c) National Science Foundation Undergraduate Research Participant; (d) taken in part from the B.S. Thesis of J. P. Mykytka, Loyola University, New Orleans, 1968.

[2] G. Gavlin, "Increased Light-Sensitivity of a Diazotype Substance," Report of Armour Project No. 90-595C, Armour Research Institute, Department of Army Project, 3-99-04-052.

[3] K. O. Christe and A. E. Pavlath, *J. Org. Chem.*, **30**, 3170 (1965).