TABLE I

REACTION OF HALO AROMATIC COMPOUNDS WITH ALKALI AMIDES IN DIMETHYLAMINE

Halo aromatic, GC_6H_4X			Salt, NaCHRCN	N,N-Dimethylarylamines			Arylated salt		
					Isomer ratio[a]			Isomer ratio[a]	
G	X	Base	R	Yield, %	o:m	m:p	Yield, %	o:m	m:p
H	Br	$NaNH_2$		91					
H	Br	KNH_2		93					
H	Cl	KNH_2		87					
H	Cl	$NaNH_2$		5					
H	Cl	$NaNH_2$	H	78			11		
H	Cl	$NaNH_2$	C_6H_5	68			8		
o-CH_3	Cl	KNH_2		90	53:47				
o-CH_3	Cl	$NaNH_2$		5	53:47				
o-CH_3	Cl	$NaNH_2$	H	62	53:47		17	50:50	
o-CH_3	Cl	$NaNH_2$	C_6H_5	67	53:47		14	50:50	
p-CH_3	Cl	KNH_2		90		50:50			
p-CH_3	Cl	$NaNH_2$	H	64		50:50	18		50:50

[a] Isomer ratios were determined by vpc analysis.

Experimental Section[4]

Chemicals.—All starting halo aromatic compounds and potassium were obtained from J. T. Baker Chemical Co. and were of the highest purity grade available. Sodamide was obtained from Fisher Chemical Co. and was used as received. Anhydrous dimethylamine was obtained from Matheson Co. and was distilled directly into the reaction flask through an anhydrous potassium hydroxide filled drying tube. All inorganic salts were thoroughly dried under vacuum at 110° for 24 hr and then stored in a drybox until use. All weighing procedures of the salts were also carried out in the drybox.

General Procedure for the Aryne Reaction.—In a typical experiment, the organic salt was prepared by adding 0.2 mol of the approximate nitrile to a stirred suspension of 0.4 mol of sodamide or potassium amide (prepared by the action of 0.4 g-atom of potassium in 200 ml of ammonia in the presence of 0.01 g of ferric nitrate, followed by removal of ammonia) in 500 ml of anhydrous dimethylamine. The inorganic salt (0.05 mol) was added directly to a stirred suspension of the base in 500 ml of anhydrous dimethylamine. After 30 min, the appropriate halo aromatic compound was added over a period of 5 min and the resulting mixture was allowed to stand for an additional 3 hr. At this time, the mixture was quenched by the addition of 0.45 mol of ammonium chloride and the solvent was removed by heating with a steam bath. The residue was washed out of the flask first with 150 ml of water and then with 100 ml of ether. The combined mixture was filtered, acidified with 50 ml of 6 *N* hydrochloric acid and was extracted with several portions of ether to remove the arylated acetonitrile and starting halo-aromatic compound. The acidic aqueous layer was made basic by the addition of sodium hydroxide (pH 14) and then was extracted with several portions of ether in order to remove the arylated amines. The combined acidic and basic ether extracts were dried (sodium sulfate), concentrated, and distilled in order to determine the percentage yields of each product.

Authentic Compounds.—N,N-Dimethylaniline was purchased from Aldrich Chemical Co. N,N-Dimethyl-*o*-toluidine, bp 98–99° (17 mm) [lit.[5] bp 98.5–99° (17 mm)], and N,N-dimethyl-*m*-toluidine, bp 207–208° (atm) [lit.[5] bp 206–207° (atm)], were prepared by the method of Hünig.[5] Phenylacetonitrile was purchased from Eastman Kodak Co. Diphenylacetonitrile, mp 73–74° (lit.[6] mp 73.5–74.5), was prepared by the method of Leake,[7] whereas *o*-methylphenylacetonitrile, bp 244° (atm) [lit.[8] bp 244° (atm)], *m*-methylphenylacetonitrile, bp 116° (8.5 mm) [lit.[8] bp 133° (15 mm)], and *p*-methylphenylacetonitrile, bp 122° (13 mm) [lit.[9] bp 122 (13 mm)], were prepared by the method of Titley.[8]

Registry No.—Bromobenzene, 108-86-1; chlorobenzene, 108-90-7; *o*-chlorotoluene, 95-49-8; *p*-chlorotoluene, 106-43-4; $NaNH_2$, 24781-98-4; KNH_2, 24781-99-5; acetonitrile (sodium salt), 14904-37-1; phenylacetonitrile (sodium salt), 14904-38-2.

(4) All melting points are uncorrected. The quantitative determinations were performed on a MicroTek Instrument Model GC 1600 using helium as the carrier gas at a flow rate of 45 ml/min and inlet and detector temperatures at 300°. A 5 ft × 1/8 in. i.d. column packed with 3% SE-30 (silicone rubber) on Chromosorb W, acid washed, mesh 80–100, was used to analyze the nitriles whereas the amines were analyzed using a 10 ft × 1/8 in. i.d. column packed with 5% Carbowax 20M (polyethylene oxide) on Chromosorb W, acid washed, 60–80 mesh. The peak areas were measured by a Ball-Disc integrator, an integral part of the Sargent recorder Model SR. The chromatographic bands were identified by comparing their retention times with those of authentic samples. Percentages of each compound were calculated from the areas of the bands. These areas were assumed to be equal to the peak height times the width at one-half peak height. Molar response ratios were determined and the observed areas were corrected as necessary.

(5) S. Hünig, *Chem. Ber.*, **85**, 1056 (1952).

(6) F. W. Bergstrom and R. Agostinho, *J. Amer. Chem. Soc.*, **67**, 2152 (1945).

(7) W. W. Leake, Ph.D. Thesis, University of Pittsburgh, 1958, p 130.

(8) A. F. Titley, *J. Chem. Soc.*, 515 (1926).

(9) H. Pupe and F. V. Wiederkehr, *Helv. Chim. Acta*, **7**, 654 (1924).

Quinazolines and 1,4-Benzodiazepines. XLV.[1a] 1,4-Benzodiazepines from 4-Isoquinolones

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In connection with our interest in examining new possibilities for the synthesis of 1,4-benzodiazepine derivatives,[1b] we have examined the ring expansion of some substituted 2,3-dihydro-4(1H)-isoquinolones.

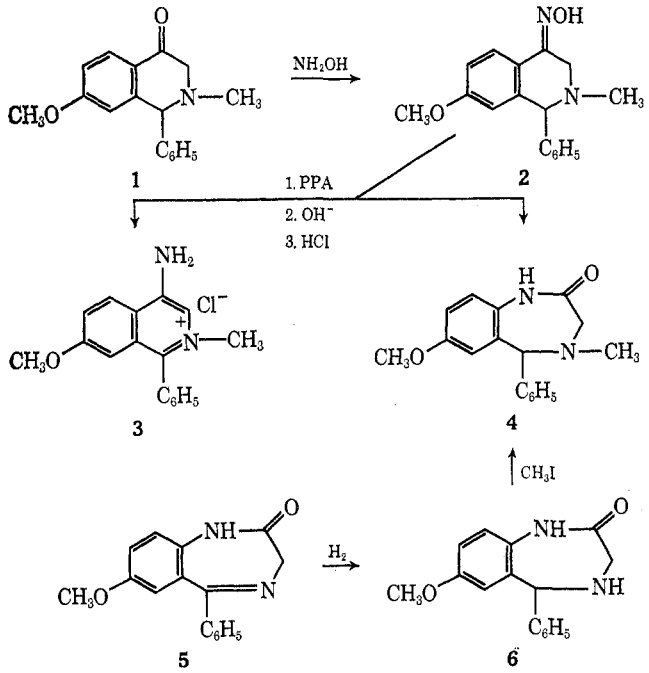
In our initial experiments (Scheme I) we prepared the oxime **2** from the known isoquinolone **1**[2] and examined the products obtained by treating this with polyphosphoric acid. In addition to the expected Beckmann rearrangement product, the benzodiazepinone **4**, we also obtained the isoquinolinium salt **3**. In fact, **3** was the major product found in the reaction mixture and was obviously the result of a Schroeter type of dehydration reaction.[3] A possible mechanism for the

(1) (a) Paper XLIV: R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.*, **34**, 649 (1969). (b) See G. A. Archer and L. H. Sternbach, *Chem. Rev.*, **68**, 747 (1968), and references cited therein.

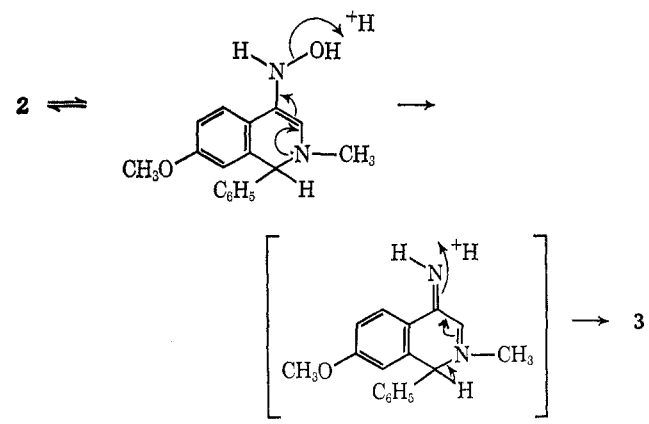
(2) G. Grethe, H. Lee, M. Uskokovic, and A. Brossi, *J. Org. Chem.*, **33**, 491 (1968).

(3) G. Schroeter, *Ber.*, **63**, 1308 (1930).

SCHEME I



dehydration of **2** which involves the tautomeric hydroxylamine is shown below.



The structure of **4** was confirmed by reducing the known 2,3-dihydrobenzodiazepinone,[4] **5**, to the corresponding tetrahydro derivative **6** and then selectively alkylating this product[5] to give an authentic sample of **4**.

Treatment of either of the quaternary salts **7** or **8** with phenyllithium[6] or with phenylmagnesium bromide led to the new isoquinolone **9a**[7] (Scheme II). Oximation of **9a** and the known **9b**[2] led to the oximes **10a** and **10b**, respectively. Polyphosphoric acid treatment of these oximes under the conditions used for compound **2** again afforded as the major products, the dehydration compounds **12a** and **12b**. The quaternary compound **7** was prepared by Grethe and coworkers by mercuric acetate oxidation of the corresponding dihydroquinolone.[8] We found that the yield in this reaction could be increased from the 37% reported, to approximately 90% by using chloranil as the oxidant.

The best yields of 1,4-benzodiazepin-2-ones were obtained by using Schmidt rearrangement conditions. Thus the ketones **9a**, **9b**, and **15** (prepared by catalytic debenzylation of **9a**) gave excellent yields of the corresponding benzodiazepines **11a**, **11b**, and **14**, respectively. The structures were ascertained for **11a** and **14** by a direct comparison with authentic samples. The known **14**[5] was treated with benzyl chloride to afford the 4-benzyl derivative **11a**. The structure of **11b** was ascertained by a comparison of its spectral properties with other tetrahydrobenzodiazepin-2-ones.[5]

The structures of the Schroeter rearranged products **3**, **12a**, and **12b**, was shown for **12b**, which on catalytic hydrogenation gave compound **13**. This compound was also obtained by hydrogenation of the oxime **10b**. When palladium was used as the catalyst, this reduction could be stopped after debenzylation when the intermediate reduction product **16** was isolated. This could also be prepared directly from the ketone **15** by oximation with hydroxylamine. As with the other oximes, dehydration was preferred over rearrangement, and with polyphosphoric acid the 4-aminoisoquinoline **18** was formed.

As expected the ketone **15** was unstable as the free base, and on exposure to air was slowly oxidized to the 4-hydroxyisoquinoline, compound **17**. This conversion was more rapidly effected by refluxing in solution with chloranil.

An additional example of a Beckmann rearrangement under reducing conditions[9] was observed when the oxime **10b** was treated with $LiAlH_4$ in refluxing tetrahydrofuran. The major product isolated was the tetrahydro-1,4-benzodiazepine, compound **19**. The structure of this compound was confirmed by an alternate preparation from **11b** by $LiAlH_4$ reduction.

Experimental Section[10]

1,2,3,4-Tetrahydro-7-methoxy-2-methyl-1-phenyl-4-isoquinolone Oxime (2).—A mixture of 1.0 g of 1,2,3,4-tetrahydro-7-methoxy-2-methyl-1-phenyl-4-isoquinolone,[2] 1.0 g of hydroxylamine hydrochloride, 2.0 g of hydrated sodium acetate, 10 ml of water, and 20 ml of ethanol was heated under reflux for 0.5 hr. The mixture was cooled and filtered. The precipitate was recrystallized from a mixture of dioxane and water to give 797 mg (86%) of the pure oxime, mp 211–214°.

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.59; H, 6.58; N, 9.38.

4-Amino-7-methoxy-2-methyl-1-phenylisoquinolinium Chloride (3).—A mixture of 0.9 g of **2** and 10 g of polyphosphoric acid was heated to 125–130° for 10 min and then poured into ice. The mixture was made basic with ammonium hydroxide and extracted with dichloromethane.[11] The aqueous solution was next acidified with concentrated hydrochloric acid and the resulting precipitate was obtained by filtration. The salt was recrystallized from a

(4) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).

(5) R. I. Fryer, B. Brust, J. Earley, and L. H. Sternbach, *J. Med. Chem.*, **7**, 386 (1964).

(6) See W. J. Gensler, "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1960, p 475.

(7) First prepared in these laboratories by Dr. G. Grethe.

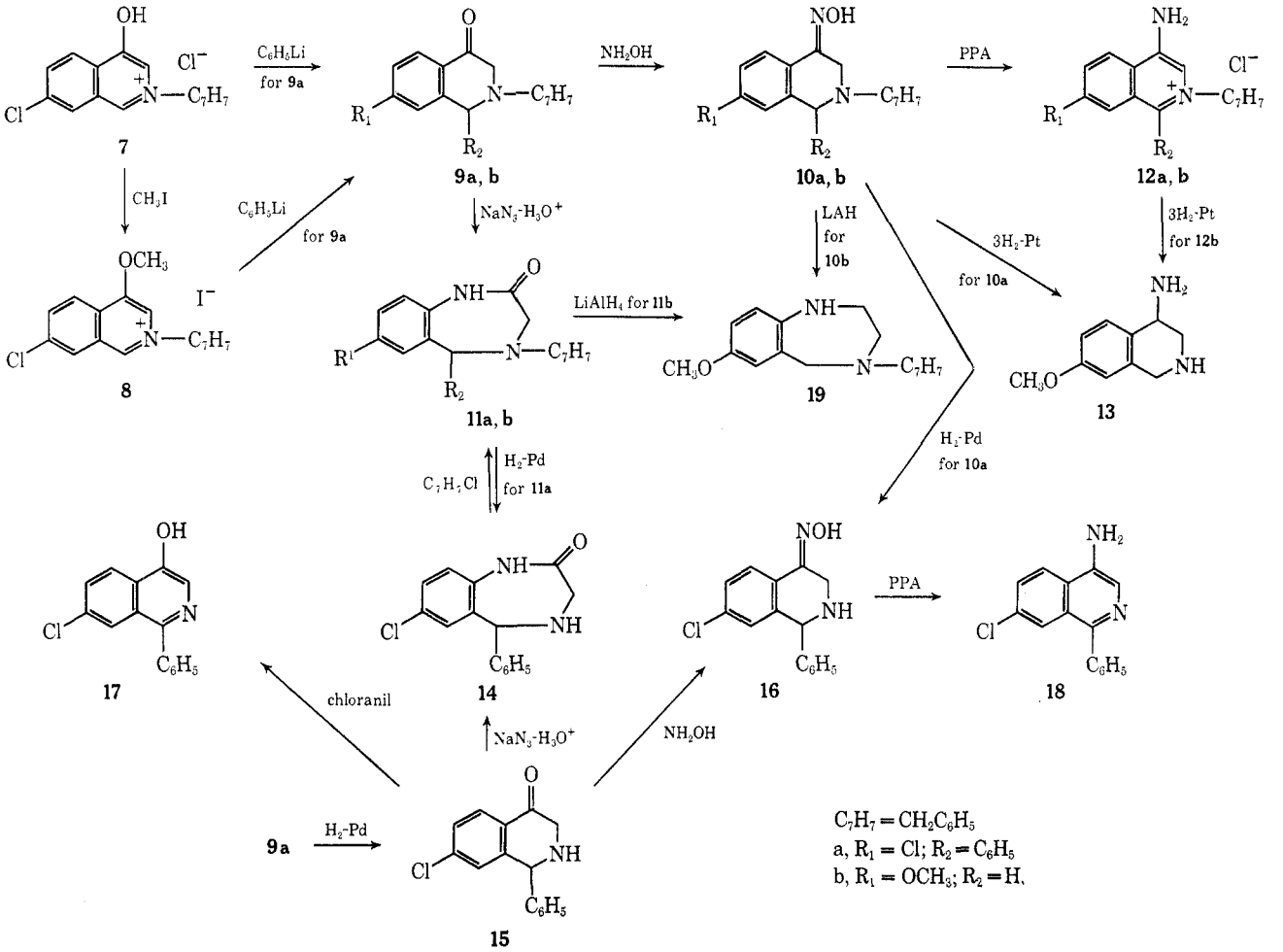
(8) G. Grethe, H. L. Lee, M. Uskokovic, and A. Brossi, *J. Org. Chem.*, **33**, 494 (1968).

(9) Acetophenone oximes have been rearranged and reduced under similar conditions. See E. Larson, *Svensk. Kem. Tidskr.*, **61**, 242 (1949), and *Chem. Abstr.*, **44**, 1898 (1950); and R. E. Lyle and H. J. Troscianiec, *J. Org. Chem.*, **20**, 1757 (1955).

(10) All melting points were determined microscopically on a hot stage and are corrected. The uv spectra were determined in 2-propanol on a Cary Model 14 spectrophotometer, nmr spectra with a Varian A-60 instrument, and ir spectra on a Beckman IR-9 spectrophotometer. All spectra were compared in order to confirm or exclude the expected changes.

(11) The dichloromethane layers contain all of the benzodiazepinone **4**.

SCHEME II



methanol–ether mixture to give 0.4 g of **3** as yellow rods, mp 211–213°.

Anal. Calcd for $C_{17}H_{17}ClN_2O$: C, 67.88; H, 5.70; N, 9.31. Found: C, 68.01; H, 5.93; N, 9.41.

7-Methoxy-4-methyl-5-phenyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (4). A. From 2.—A mixture of 500 mg of the oxime **2** and 10 g of polyphosphoric acid was slowly heated to 130° and maintained at this temperature ±5° for 10 min. The reaction mixture was then treated with 300 g of ice, made basic with ammonium hydroxide, and filtered. The precipitate was dissolved in a small amount of dioxane and filtered through 5 g of neutral activated alumina. Solvent was removed under reduced pressure. The residual oil (300 mg) was next dissolved in 50 ml of dichloromethane which was then extracted with 3 *N* hydrochloric acid (three 25-ml portions). The acid extracts were combined, made basic (ammonium hydroxide), and extracted with dichloromethane (three 20-ml portions). The dichloromethane layers were combined, washed with water (two 10-ml portions), dried (anhydrous sodium sulfate), filtered, and evaporated to give 200 mg of crystalline product. Recrystallization from dichloromethane gave 100 mg of the pure benzodiazepinone, mp and mmp (with an authentic sample prepared as in B) 214–215°.

B. From 6.—A solution of 3 g of **6** in 25 ml of N,N-dimethylformamide was treated with 5 g of methyl iodide. The solution was stirred at 45° for 6 hr and allowed to stand at room temperature for 12 hr when 400 ml of water was added. The aqueous mixture was extracted with three 100-ml portions of dichloromethane, which were then combined, washed with water, dried over anhydrous sodium sulfate, and evaporated. The mixture was recrystallized from dichloromethane to give 1.3 g (39%) of **4** as white prisms, mp 214–215°.

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.33; H, 6.43. Found: C, 72.53; H, 6.49.

7-Methoxy-5-phenyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (6).—A mixture of 6.4 g (0.0242 mol) of 7-methoxy-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one (**5**),[4] 2 g of platinum oxide, 100 ml of acetic acid, and 100 ml of water was hydrogenated at room temperature and under atmospheric pressure until hydrogen uptake ceased. The mixture was filtered and the filtrate was adjusted to pH 8 with sodium hydroxide solution. This was then extracted with three 100-ml portions of methylene chloride. The organic layers were combined, washed with water, dried over sodium sulfate, and evaporated. The residue was recrystallized from a mixture of acetone and hexane to give 5.65 g (87.5%) of **6** as white prisms, mp 150–153°.

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01. Found: C, 71.71; H, 6.06.

2-Benzyl-7-chloro-4-hydroxyisoquinolinium Chloride (7).[8]—A solution of 79.5 g (0.258 mol) of 2-benzyl-7-chloro-2,3-dihydro-4-(1H)-isoquinolone hydrochloride[8] and 128 g (0.523 mol) of chloranil in 2.4 l. of glacial acetic acid was refluxed and stirred for 4 hr. The solvent was evaporated and the residue was washed several times with hot benzene. The crystalline solid was suspended in 500 ml of warm ethanol, 150 ml of saturated methanolic hydrogen chloride was added, and the mixture was stirred for 10 min. Cooling and filtration afforded 71.8 g (91%) of **7** as white prisms, mp 284–286° dec.

2-Benzyl-4-methoxy-7-chloroisoquinolinium Iodide (8).—A mixture of 6.12 g (20 mmol) of **7**, 18 ml of methyl iodide, 5.68 g of potassium carbonate, and 80 ml of dry acetone was refluxed and stirred for 3.5 hr. A bright yellow precipitate formed within 30 min. The solid material was collected and the filtrate was evaporated to a yellow-orange solid, which after washing with hot benzene was recrystallized from a mixture of chloroform and ether to give 2 g of **8** as yellow prisms: mp 182–184°; nmr ($CDCl_3$) δ 4.34 (s, 3, OCH_3), 6.42 (s, 2, CH_2), 8.95, 10.48 (AB, 2, J = 1 Hz, H-1, H-3).

Anal. Calcd for $C_{17}H_{15}ClNO$: C, 49.60; H, 3.67; N, 3.40. Found: C, 49.56; H, 3.75; N, 3.42.

The original precipitate was extracted with hot methanol which was then evaporated. The residue was recrystallized from

a mixture of chloroform and ether to give 6.4 g of **8** as a tan solid. This material was used without further purification for the preparation of **9a**.

2-Benzyl-7-chloro-1,2-dihydro-1-phenyl-4(3H)-1-isoquinolone (9a). A. From 7.—Compound **7** (15.2 g, 49.7 mmol) was added in small portions to 75 ml of an ice-cold 2 *N* solution of phenyllithium in benzene–ether which was kept under nitrogen. The reaction mixture was allowed to warm to room temperature and after stirring for 1 hr 10 ml of methanol was added cautiously. The thick slurry was poured into 500 ml of ether and the mixture was stirred for several minutes. The insoluble material was filtered. To the filtrate was added 10 ml of 10 *N* hydrochloric acid in methanol. The precipitated salt was collected, washed with ether, dissolved in methylene chloride, and extracted twice with sodium bicarbonate solution. The organic phase was dried over anhydrous sodium sulfate and evaporated. The residue was crystallized from a mixture of methanol and ether to give 5 g of **9a** as white prisms, mp 115–123°. Recrystallization from methanol and ether yielded 3.9 g (22.5%) of pure material: mp 119.5–121°; ir ($CHCl_3$) 1685 cm^{-1} (C=O); uv max (2-propanol) 255–256 mμ (ε 16,400), sh 290 (2400); nmr ($CDCl_3$) δ 3.25, 3.58 (AB, 2, J_{gem} = 17.5 Hz, CH_2CO), 3.52, 3.73 (AB, 2, J_{gem} = 13.5 Hz, $NCH_2C_6H_5$) 4.92 (s, 1, CH).

B. From Compound 8.—Compound **8** (6 g, 14.6 mmol) was added in small portions to 20 ml of an ice-cold 2.28 *N* solution of phenyllithium in benzene–ether which was kept under nitrogen. The reaction mixture was allowed to warm to room temperature and after 7 hr of stirring 6 ml of methanol was added cautiously to destroy excess reagent. The thick brown slurry was poured into 300 ml of ether and the insoluble material was filtered off. The filtrate was evaporated and the residue was refluxed for 2 hr in 75 ml of 28% HBr in glacial acetic acid. The solvent was removed under reduced pressure and the oily residue was washed several times with ether and benzene. The product was then dissolved in methylene chloride and extracted with dilute sodium hydroxide solution. The organic phase was dried over anhydrous sodium sulfate and evaporated. Crystallization from methanol–ether gave 1.05 g (20.7%) of **9a**, mp 119–121°.

2-Benzyl-1,2-dihydro-7-chloro-1-phenyl-4(3H)-isoquinolone Oxime (10a).—A solution of 0.5 g of **9a** in 2 ml of ethanol was treated with 0.5 g of hydroxylamine hydrochloride, 1 g of sodium acetate, and 10 ml of water. The solution was heated under reflux for 0.5 hr and then cooled in an ice bath. The precipitated product was removed by filtration and recrystallized from a mixture of ether and petroleum ether, bp 30–60°, to give 350 mg (67%) of **10a** as pale yellow rods, mp 152–155°.

Anal. Calcd for $C_{22}H_{19}ClN_2O$: C, 72.82; H, 5.28. Found: C, 72.94; H, 5.50.

2-Benzyl-1,2-dihydro-7-methoxy-4(3H)-isoquinolone Oxime (10b).—A mixture of 10.0 g of 2-benzyl-1,2-dihydro-7-methoxy-4(3H)-isoquinolone,[2] 10.0 g of hydroxylamine hydrochloride, 20.0 g of sodium acetate hydrate, 100 ml of water, and 200 ml of ethanol was heated under reflux for 0.5 hr. The mixture was cooled and filtered to give 8.9 g (83.5%) of the oxime, mp 189–192°. Recrystallization from an aqueous dioxane solution gave the pure oxime, mp 192–194°.

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43. Found: C, 72.53; H, 6.37.

4-Benzyl-7-chloro-1,3,4,5-tetrahydro-5-phenyl-2H-1,4-benzodiazepin-2-one (11a). A. From 9a.—A solution of 0.3 g (0.864 mmol) of **9a** in 20 ml of chloroform was treated at 0° with 1.2 ml of concentrated sulfuric acid. The reaction mixture (<10°) was next treated portionwise (30 min) with 0.141 g (2.17 mmol) of sodium azide and was then heated to 50° for 90 min. The mixture was cooled in an ice bath, 3 g of potassium carbonate was added, and the mixture was then made basic with a 50% aqueous solution of potassium hydroxide. The precipitate was removed by filtration and the filtrates were separated and extracted with two 10-ml portions of chloroform. The combined chloroform layers were washed with 20 ml of saturated brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was recrystallized twice from a mixture of dichloromethane, ether, and petroleum ether to give 0.17 g (55%) of **11a** as white rods, mp 197–204°.

Anal. Calcd for $C_{22}H_{19}ClN_2O$: C, 72.82; H, 5.28. Found: C, 72.83; H, 5.53.

B. From 14.—A mixture of 50 g of **14**[5] and 21 ml of benzyl chloride in 250 ml of N,N-dimethylformamide was heated overnight at 60°. The precipitate was filtered and partitioned between dichloromethane and dilute ammonium hydroxide. The organic layer was separated, washed, dried, and evaporated. The residue was recrystallized from a mixture of ethanol and chloroform to give 10.5 g of **14** as white rods, mp and mmp (with a sample prepared as in A) 197–204°. The original filtrates were treated with ether when the hydrochloride of the starting material (**14**) precipitated. The solution was filtered, poured into 1 l. of water, made basic with ammonium hydroxide, and again filtered. The precipitate was dissolved in dichloromethane which was washed, dried, and evaporated. The residue was recrystallized from a mixture of ethanol and chloroform to give an additional 22.6 g of product, mp 197–204°.

4-Benzyl-7-methoxy-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (11b).—A solution of 2.0 g (7.35 mmol) of 2-benzyl-2,3-dihydro-7-methoxy-4(1H)-isoquinolinone (**9b**)[2] in 40 ml of chloroform was cooled to 0° and 8 ml of concentrated sulfuric acid was added dropwise with stirring. The reaction mixture was treated with 1.2 g (18.4 mmol) of sodium azide over a 1-hr period, keeping the temperature below 10°, and was then stirred at 50° for 90 min. The mixture was cooled in an ice bath (<30°) while 5 g of potassium carbonate was added, followed by 20 ml of a 50% aqueous solution of potassium hydroxide. The solution was filtered, and the filtrates were extracted with two 10-ml portions of chloroform. The combined organic layers were washed with 30 ml of saturated brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was crystallized from methanol and then recrystallized from a mixture of dichloromethane and petroleum ether, bp 30–60°, to give 1.7 g (81%) of **11b** as white rods, mp 145–148°.

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.40; H, 6.46; N, 9.88.

4-Amino-2-benzyl-7-chloro-1-phenylisoquinolinium Chloride (12a).—A mixture of 0.9 g of **10a** and 10 g of polyphosphoric acid was heated to 125–135° for 15 min. The mixture was cooled, made basic with ammonium hydroxide, and extracted with chloroform. The chloroform layer was washed with brine, dried over sodium sulfate, and evaporated to dryness. The residual oil was treated with 3 *N* HCl and was allowed to stand until the product crystallized. The quaternary salt obtained by filtration was dissolved in dichloromethane, which was dried over sodium sulfate, filtered, and evaporated. Recrystallization of the residue from a mixture of methanol and ether gave 0.7 g (74%) of **12a** as pale yellow rods, mp 213–215°.

Anal. Calcd for $C_{22}H_{18}Cl_2N_2$: C, 69.30; H, 4.76; N, 7.35. Found: C, 69.12; H, 4.88; N, 7.29.

4-Amino-2-benzyl-7-methoxyisoquinolinium Chloride (12b).—A mixture of 10 g of **10b** and 45 ml of polyphosphoric acid was heated at 130° for 15 min with stirring. The mixture was cooled, poured into ice, and made basic with ammonium hydroxide. The basic solution was filtered and the filtrate was first extracted with dichloromethane and then acidified with concentrated hydrochloric acid. The quaternary was salted out with sodium chloride. Filtration gave 9 g of **12b** as yellow rods. Recrystallization from water gave the analytical sample, mp 128–130°.

Anal. Calcd for $C_{17}H_{17}ClN_2O$: C, 67.88; H, 5.70; N, 9.31; Cl, 11.79. Found: C, 67.86; H, 5.94; N, 8.94; Cl, 11.76.

4-Amino-1,2,3,4-tetrahydro-7-methoxyisoquinoline Dihydrochloride (13). A. From 10b.—A mixture of 2 g of **10b**, 25 ml of glacial acetic acid, 5 ml of water, and 0.2 g of platinum oxide was hydrogenated at room temperature and atmospheric pressure until hydrogen uptake ceased. The catalyst was removed by filtration and the filtrates were made basic with sodium hydroxide. The basic solution was extracted with three 100-ml portions of dichloromethane which were then combined, washed with saturated brine, dried over sodium sulfate, and evaporated to dryness. The residue was dissolved in ether and treated with an excess of ethanolic hydrogen chloride solution. The precipitate was recrystallized from a mixture of methanol and ether to give **13** as white prisms, mp 248–255°.

Anal. Calcd for $C_{10}H_{14}N_2O \cdot 2HCl$: C, 47.82; H, 6.42; N, 11.15. Found: C, 47.71; H, 6.51; N, 11.42.

B. From 12b.—A mixture of 1.5 g of **12b**, 25 ml of acetic acid, 5 ml of water, and 0.25 g of platinium oxide was hydrogenated at room temperature and atmospheric pressure until hydrogen uptake ceased. The product was obtained as described in A to give the dihydrochloride as white prisms, mp and mmp 248–255°.

7-Chloro-1,3,4,5-tetrahydro-5-phenyl-2H-1,4-benzodiazepin-2-one (14). A. From 11a.—A solution of 1 g (2.75 mmol) of **11a** in 40 ml of glacial acetic acid, 10 ml of concentrated hydrochloric acid, and 40 ml of water was treated with 0.2 g of

a 10% palladium-on-charcoal catalyst. Hydrogenation at atmospheric pressure was stopped when 80 ml of hydrogen had been adsorbed, and the reaction mixture was filtered through Celite and made basic with ammonium hydroxide. The solution was extracted with 100 ml of dichloromethane which was washed with 50 ml of saturated brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was recrystallized from a mixture of dichloromethane and hexane to give 0.5 g (67%) of **14** as white prisms, mp and mmp (with an authentic sample[5]) 183–185°.

B. From 15.—A suspension of 200 mg (0.68 mmol) of **15** in 30 ml of chloroform was cooled in an ice bath to 0–3°. While stirring, 4 ml of concentrated sulfuric acid was added, followed by the portionwise addition of 1.0 g of sodium azide (addition time 1 hr, temperature 10°). The reaction mixture was then heated to 50° for 1.5 hr, cooled, poured over ice, and neutralized with solid potassium carbonate. After adding 2 ml of 50% KOH, the solids were removed by filtration and washed with dichloromethane. The organic layer of the filtrates was separated and the aqueous phase was twice extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and evaporated to a crystalline solid, which after washing with a mixture of ether and petroleum ether yielded 0.90 g (48.4%) of product as white prisms, mp 174–178°. Recrystallization from a mixture of dichloromethane, ether, and petroleum ether gave the pure product, mp and mmp (with an authentic sample[5]) 180–183°.

7-Chloro-2,3-dihydro-1-phenyl-4(1H)-isoquinolone Hydrochloride (15).—A solution of 1 g (2.88 mmol) of **9a** in 75 ml of glacial acetic acid was treated with 0.1 ml of concentrated hydrochloric acid, 5 ml of water, and 200 mg of a 10% palladium-on-carbon catalyst. The reaction mixture was hydrogenated at atmospheric pressure and room temperature until the uptake of hydrogen slowed down considerably (total uptake 160 ml). Solids were removed by filtration over Celite. The Celite was washed with dichloromethane and the filtrates were combined. After removal of the solvent, the residue was treated with 2 ml of 10 *N* hydrogen chloride in methanol which was then evaporated to a solid residue. The crude product was washed with acetonitrile to give 450 mg (53.2%) of **15**·HCl as a white crystalline material, mp 233–235°. Recrystallization from a mixture of acetonitrile and ether afforded an analytical sample: mp 235° dec; ir (KBr) 1715 cm^{-1} (C=O); uv max (2-propanol) 210 mμ (ε 24,200), 256–257 (12,720), sh 285 (2100), sh 297 (1650).

Anal. Calcd for $C_{15}H_{12}ClNO \cdot HCl$: C, 61.24; H, 4.45; N, 4.76. Found: C, 61.15; H, 4.53; N, 4.74.

1-Phenyl-7-chloro-2,3-dihydro-4(1H)-isoquinolone Oxime (16).

A. From 15.—A mixture of 1.16 g (3.33 mmol) of **9a**, 40 ml of glacial acetic acid, 1 ml of concentrated hydrochloric acid, 10 ml of water, and 0.3 g of 10% palladium on carbon was hydrogenated and worked up in the same way as described for the preparation of **15**. The crude product was partially dissolved in 50 ml of ethanol and refluxed under nitrogen for 2 hr together with a mixture of 3.5 g of hydroxylamine hydrochloride, 4.5 g of sodium acetate, and 4.5 g of sodium bicarbonate. The solid precipitate which formed was filtered after cooling, washed well with water, dissolved in ether, and dried over anhydrous sodium sulfate. The solvent was removed and the remaining residue was triturated with ether–hexane. Filtration afforded 500 mg (55%) of crude **16** as white prisms, mp 162–172°. Recrystallization of a sample from ether–hexane gave analytically pure **16**: mp 168–171°; ir (KBr) 3270 (N–OH), 2800 cm^{-1} (broad, OH); uv max (2-propanol) 263 mμ (ε 16,000), infl 293 (2800), sh 304 (1600); nmr (DMSO) δ 3.76 (s, 2, CH_2), 5.00 (s, 1, CH), 11.08 (br, 1, NOH).

Anal. Calcd for $C_{15}H_{13}ClN_2O$: C, 66.06; H, 4.80; N, 10.27. Found: C, 66.01; H, 4.81; N, 10.22.

B. From 10a.—A mixture of 363 mg (1 mmol) of **10a**, 50 ml of acetic acid, 0.1 ml of concentrated hydrochloric acid, and 0.2 g of 10% palladium on carbon was hydrogenated and worked up in the same manner already described. The crude residue obtained after removal of the reaction solvents and the washings was taken up in methylene chloride and extracted with a solution of saturated sodium bicarbonate in water. The organic phase was dried over anhydrous sodium sulfate and evaporated to a crystalline solid which, after treatment with ether–petroleum ether, yielded 150 mg (55%) of **16**, mp and mmp (with a sample prepared as in A) 168–171°.

1-Phenyl-4-hydroxy-7-chloroisoquinoline (17).—A mixture of 8.7 g (25 mmol) of **9a**, 250 ml of glacial acetic acid, 10 ml of concentrated hydrochloric acid, 5 ml of water, and 750 mg of 10% palladium on carbon was hydrogenated as previously described to give **15**, and the mixture was then filtered over Celite. The filtrate (225 ml) corresponding to 21.2 mmol of starting material was refluxed and stirred for 1.5 hr with 6.1 g (25 mmol) of chloranil. After removal of the solvent, the residue was washed several times with warm benzene, suspended in dilute ammonium hydroxide, and stirred for several minutes. The solid was then filtered, washed with water, ether, and hot benzene and finally recrystallized from a mixture of methanol and methylene chloride to give 2.4 g (44%) of pure **17** as white prisms: mp 270–274°; ir (KBr) broad OH centered at 2500 cm^{-1}; uv max (2-propanol); 215 mμ (ε 44,600), 259 (26,100), 309 (7200), 342–345 (7250); nmr (DMSO) δ 7.40–8.40 (9 aromatic H).

Anal. Calcd for $C_{15}H_{10}ClNO$: C, 70.46; H, 3.94; N, 5.48. Found: C, 70.62; H, 4.03; N, 5.41.

1-Phenyl-7-chloro-4-aminoisoquinoline (18).—A mixture of 100 mg (0.37 mmol) of **16** and 4.5 g of polyphosphoric acid was heated for 12 min at 120–130° with occasional stirring. The reaction mixture was cooled and poured onto ice. The solution was basified with ammonium hydroxide. The precipitated solid was collected and washed repeatedly with water to give 100 mg of crude **18**, mp 142–146°. This was recrystallized from ether and petroleum ether to give 55 mg (58%) of analytically pure **18** as white prisms: mp 143–145.5°; ir (KBr) 3450, 3320 (NH_2) broad 3140, 1650 cm^{-1}; uv max (2-propanol) 213–214 mμ (ε 43,250), 263–266 (16,600), infl 330 (6600), 362–364 (8000); nmr ($CDCl_3$) δ 4.17 (s, 2, NH_2), 7.30–8.20 (9 aromatic H).

Anal. Calcd for $C_{15}H_{11}ClN_2$: C, 70.73; H, 4.35; N, 11.00. Found: C, 70.76; H, 4.29; N, 10.96.

4-Amino-2-benzyl-1,2,3,4-tetrahydro-7-methoxyisoquinoline (19). **A. From 10b.**—A mixture of 3 g (0.01 mol) of **10b**, 0.8 g (0.21 mol) of lithium aluminum hydride, and 75 ml of dry tetrahydrofuran was stirred and heated under reflux for 6 hr. The mixture was cooled and 1 ml of water was added, followed by the addition of enough saturated potassium bicarbonate solution required to coagulate the solids. The solution was filtered and the filtrates were extracted with dichloromethane which were then washed with water, dried over sodium sulfate, and evaporated. The residual oil was dissolved in benzene and chromatographed over Florisil using benzene and ether as eluents. The benzene fractions were discarded. The ether fractions gave, on evaporation, 1 g (35%) of a colorless oil which was crystallized from a mixture of ether and petroleum ether, bp 30–60°, to give pure **19** as white prisms, mp 43–49°.

Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44. Found: C, 76.21; H, 7.17; N, 10.19.

B. From Compound 11b.—A mixture of 0.5 g of **11b**, 0.176 g of lithium aluminum hydride, and 50 ml of dry tetrahydrofuran was heated under reflux for 10 hr. The mixture was cooled and excess reagent was decomposed with water. Saturated potassium bicarbonate solution was added as in A and the solution was filtered and evaporated. The residue was dissolved in ether and the product was extracted into 0.5 *N* hydrochloric acid. The acid layer was made basic and was extracted with dichloromethane. The organic layers were dried and evaporated, and the residual oil was chromatographed over Florisil as above to give 50 mg of **19** as white prisms, mp and mmp 43–49°.

Registry No.—**2**, 24781-76-8; **3**, 24781-77-9; **4**, 24781-78-0; **6**, 24781-79-1; **7**, 15365-49-8; **8**, 24781-81-5; **9a**, 24781-82-6; **10a**, 24781-83-7; **10b**, 24781-84-8; **11a**, 24781-85-9; **11b**, 24781-86-0; **12a**, 24781-87-1; **12b**, 24781-88-2; **13**, 24781-89-3; **14**, 1824-69-7; **15**, 24781-91-7; **16**, 24781-92-8; **17**, 24781-93-9; **18**, 24781-94-0; **19**, 24781-95-1.

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