Bimolecular Reduction of Isoquinoline. Epimeric 1,1′,2,2′,3,3′,4,4′-Octahydro-1,1′-biisoquinolines and Derivatives

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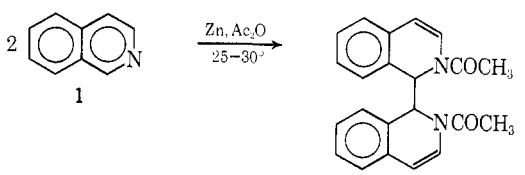
Bimolecular reduction of isoquinoline with zinc–acetic anhydride led to a 1:1 mixture of epimeric 2,2′-diacetyl-1,1′,2,2′-tetrahydro-1,1′-biisoquinolines, **2a,b** (54–58% total yield). Hydrogenation of **2a,b** with rhodium–charcoal catalyst in acetic acid gave, with retention of stereochemistry, epimeric 2,2′-diacetyl-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinolines, **3a,b** (98% yield); these were hydrolyzed with aqueous hydrobromic acid–acetic acid to the corresponding 1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline bishydrobromide salts, **4a,b**, which were converted to the title diamines, **5a,b**, on neutralization. Hydrolysis of *dl*-diamide **3a** in refluxing concentrated hydrobromic acid produced *dl*-8-methyl-5,6,7,9,10,11,15b,15c-octahydrodiisoquino[2,1-*c*:1′,2′-*e*]imidazolinium bromide, **7a**; hydrolysis of *meso*-diamide **3b** under the same conditions gave only bishydrobromide, **4b**. Imidazolinium bromide **7a** is stable in refluxing aqueous hydrobromic acid–acetic acid; in refluxing aqueous ethanolic sodium hydroxide it forms *dl*-2-acetyl-1,1′,2,2′,3,3′,4,4′-*octahydro*-1,1′-*biisoquinoline* (**6a**). Reaction of diamines **5a,b** with formaldehyde led to epimeric 5,6,7,9,10,11,15b,15c-octahydro-8H-diisoquino[2,1-*c*:1′,2′-*e*]-imidazoles, **8a,b**; the stereochemistry of these compounds was established by interpretation of their nmr spectra. Hydrogenation of 1,1′-biisoquinoline bishydrochloride with platinum in ethanol led to *meso*-diamine, **5b**, exclusively. 1,1′-Biisoquinoline was produced by dehydrogenation of diamines **5a,b** with palladium–charcoal catalyst in refluxing *p*-cymene (65–70% yield). Hydrogenation of 1,1′-biisoquinoline with rhodium–charcoal catalyst in acetic acid gave 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-biisoquinoline (**13**). Reaction of diamides **2a,b** with N-bromosuccinimide in acetic acid led to epimeric 2,2′-diacetyl-1,1′-dibromo-1,1′,2,2′-tetrahydro-1,1′-biisoquinolines, **18a,b**; in refluxing aqueous ethanolic sodium hydroxide, **18a,b** produce nearly equal amounts of isoquinoline and 1-bromoisoquinoline.

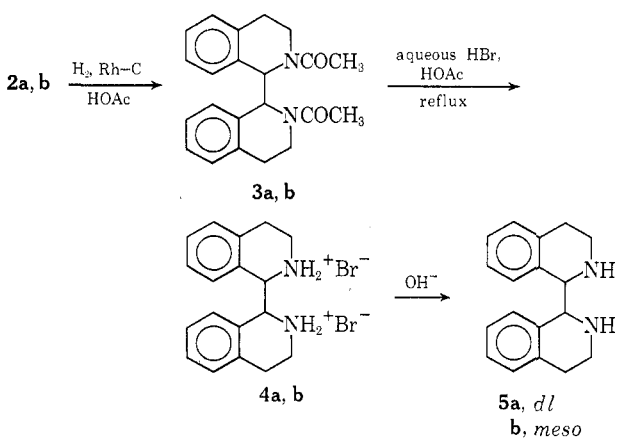
Bimolecular reduction of isoquinoline (**1**) under conditions of the Dimroth reaction (zinc–acetic anhydride)[1] has provided a convenient entry into the unsubstituted 1,1′-biisoquinoline ring system. Employing an improved procedure which had been applied to pyridine,[2] isoquinoline gave epimeric 2,2′-diacetyl-1,1′,2,2′-tetrahydro-1,1′-biisoquinolines (**2a,b**) in



1 → **2a**, *dl*; **b**, *meso*

54–58% total yield (*ca.* 1:1 ratio). In a previous study of the reaction with isoquinoline, Elliott and McGriff obtained epimer **2a** only (18% yield).[3] The very low solubility of **2b** in various solvents, relative to that of **2a**, facilitates separation of the epimer mixture. Stereochemistry of these compounds has been established.

2,2′-Diacetyl-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline epimers **3a,b** were obtained in 98% yield by



2a,b → **3a,b** → **4a,b** → **5a**, *dl*; **b**, *meso*

hydrogenation of the corresponding tetrahydro compounds **2a,b** with rhodium–charcoal catalyst in acetic acid solvent. Stereochemistry is retained in the reduction.

Amides **3a,b** are quite resistant to hydrolysis by acids and bases. Hydrolysis to the 1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline bishydrobromide salts, **4a,b**, was effected in aqueous hydrobromic acid–acetic acid (48-hr reflux; 70–80% yield). The free diamines, **5a,b** were liberated quantitatively from their salts in aqueous methanolic sodium hydroxide–tetrahydrofuran solution.

Hydrolysis of diamides **3a,b** was incomplete in refluxing concentrated hydrobromic acid containing no added acetic acid. The two epimers behaved differently. *dl* epimer **3a** produced *dl*-8-methyl-5,6,7,9,-10,11,15b,15c-octahydrodiisoquino[2,1-*c*:1′,2′-*e*]imidazolinium bromide (**7a**). The *meso* epimer (**3b**) was hydrolyzed to diamine bishydrobromide salt **4b**.

Imidazolinium salt **7a** was hydrolyzed readily in refluxing aqueous ethanolic sodium hydroxide to produce monoamide **6a**; like diamides **3a,b**, amide **6a** is rather resistant to alkaline hydrolysis. Monoamide **6a** in refluxing concentrated hydrobromic acid regenerated **7a**, and in aqueous hydrobromic–acetic acid formed bishydrobromide salt **4a**. Monoamide **6a** is clearly an intermediate in these transformations originating from diamide **3a**; it reacted with acetic anhydride to regenerate **3a**. Salts of 1,2-diamine monoamides form imidazolinium salts on heating.[4]

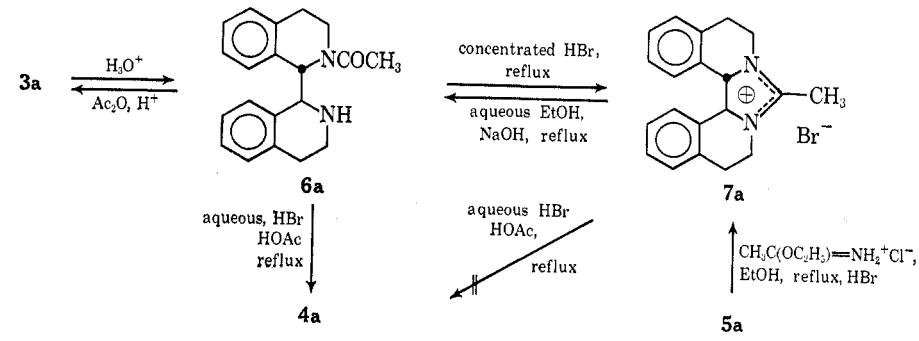
Hydrolysis of imidazolinium salt **7a** to bishydrobromide salt **4a** could *not* be effected in refluxing aqueous hydrobromic acid–acetic acid (48 hr). In view of the

(1) (a) O. Dimroth and R. Heene, *Chem. Ber.*, **54**, 2934 (1921); (b) O. Dimroth and F. Frister, *ibid.*, **55**, 1223 (1922).

(2) The product, 1,1′-diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine, is obtained in 45–47% yield. (a) A. T. Nielsen, D. W. Moore, G. M. Muha, and K. H. Berry, *J. Org. Chem.*, **29**, 2175 (1964). (b) A. T. Nielsen, D. W. Moore, J. H. Mazur, and K. H. Berry, *ibid.*, **29**, 2898 (1964).

(3) I. W. Elliott, Jr., and R. B. McGriff *J. Org. Chem.*, **22**, 514 (1957).

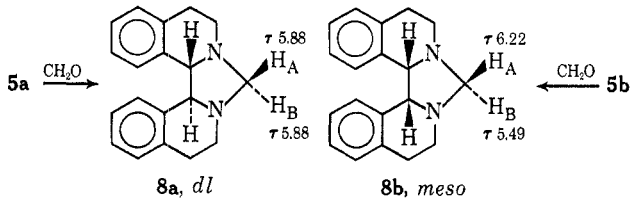
(4) E. Waldmann and A. Chwala, *Chem. Ber.*, **74**, 1763 (1941).



ease of formation of salt **4a** from monoamide **6a** in this medium, this finding indicates the rate of the **6a** → **4a** transformation to be very fast, relative to formation of imidazolinium salt **7a**, in this more dilute acid medium. The more strongly acidic concentrated hydrobromic acid favors the dehydration reaction involved in the **6a** hydrobromide → **7a** transformation over the **6a** → **4a** hydrolysis. Rehydration of **7a** to form **6a** evidently does not occur in dilute acid.

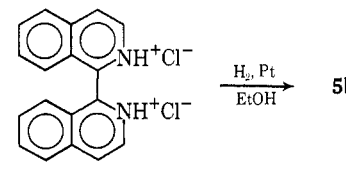
The structure and stereochemistry of imidazolinium salt **7a** was affirmed by an alternate synthesis. Reaction of *dl*-diamine **5a** with ethyl acetimidate hydrochloride in refluxing ethanol[5] led to the imidazolinium chloride salt (**7a**, Br = Cl), which could be converted to **7a** by treatment with excess hydrobromic acid. No imidazolinium salt could be prepared by reaction of *meso*-diamine **5b** with ethyl acetimidate hydrochloride, nor from *meso*-diamide **3b** in strongly acidic medium.

Ring closure to the more flexible imidazolidine ring could be realized with both diamine epimers, **5a,b**. Reaction with formaldehyde in dioxane at 90° led to the epimeric 5,6,7,9,10,11,15b,15c-octahydro-8H-diisoquino[2,1-*c*:1′,2′-*e*]imidazoles: 100% yield of **8a** from **5a**; 62% yield of **8b** from **5b**.



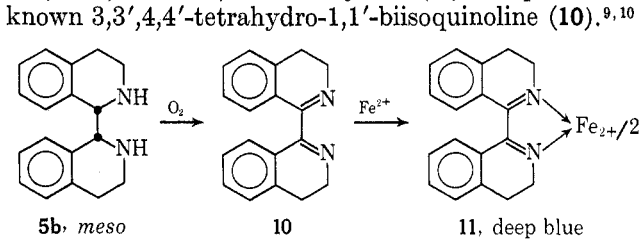
The stereochemistry of imidazolidines **8a,b** is apparent from an examination of their nmr spectra. The signals exhibited by the C-8 methylene bridge hydrogens ($H_{A,B}$) of the imidazolidine ring establish the stereochemistry. In the *dl* epimer this signal is a single line at τ 5.88, since H_A and H_B are in a similar environment with respect to the lone-pair electrons of the adjacent nitrogens and the imidazolidine ring hydrogens at C-15b and C-15c, which appear as a singlet at τ 6.03. In the *meso* epimer **8b** the $H_{A,B}$ signals are split and appear as an AB quartet centered at τ 5.86 with bands at τ 6.22 and 5.49 (J = 7.7 Hz) assigned as shown in the formula. The imidazolidine ring hydrogens in **8b** appear as a single line at τ 5.32. The remainder of the spectrum in both epimers is similar and reveals aryl protons (8) at τ 2.6–3.3 and piperidine ring protons (8) at τ 6.7–7.5. Published investigations on the stereochemistry of *meso*- and *dl*-perhydropyrido[1.2-*c*:2′,1′-*e*]imidazoles,[6] and 15b,15c-dimethyl derivatives of **8a,b**,[7] reveal similar nmr spectra.

Diamine epimer **5b** was synthesized by an alternate route—hydrogenation of 1,1′-biisoquinoline dihydrochloride (**9**) in ethanol with platinum catalyst. Neither

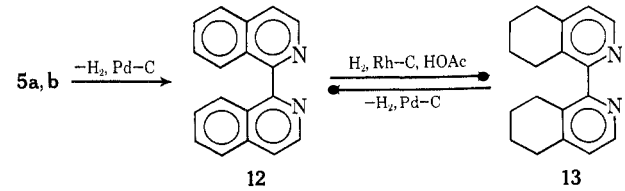


epimer **5a** nor any crystalline product other than **5b** was isolated as a product of this reduction. Methoxy derivatives of 1,1′-biisoquinoline hydrochloride have been hydrogenated under similar conditions to produce a single epimer of methoxy derivatives of **5** (stereochemistry unknown).[8]

Dimer epimer **5b** was found to decompose slowly to an oily yellow material when stored in air at room temperature for several weeks; the *dl*-diamine **5a** showed no evidence of decomposition when stored under these conditions. The decomposition reaction is evidently complex. Partially decomposed samples show ultraviolet absorption bands characteristic of isoquinoline and biisoquinoline (λ_{max}^{EtOH} 323 nm). They also react with ferrous salts to produce an intense blue color (λ_{max}^{EtOH} 550, 635, 656 nm) shown by iron(II) complex **11** of known 3,3′,4,4′-tetrahydro-1,1′-biisoquinoline (**10**).[9,10]



Diamines **5a,b** were each readily dehydrogenated to 1,1′-biisoquinoline (**12**) by palladium–charcoal catalyst in boiling *p*-cymene (65–70% yield).



(5) C. Djerassi and C. R. Scholz, *J. Amer. Chem. Soc.*, **69**, 1688 (1947).

(6) P. J. Chivers, T. A. Crabb, and R. O. Williams, *Tetrahedron*, **24**, 6625 (1968); **25**, 2921 (1969).

(7) P. Cerutti and H. Schmid, *Helv. Chim Acta*, **47**, 203 (1964).

(8) I. Matsuo and T. Takahashi, Japanese Patent 16551 (1965); *Chem. Abstr.*, **63**, 18,053 (1965).

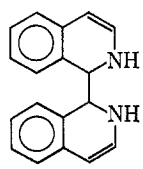
(9) R. A. Henry and C. Heller, forthcoming publication, this laboratory.

(10) I. Matsuo, T. Takahashi, and S. Ohki, *Yakugaku Zasshi*, **83**, 518 (1963); *Chem. Abstr.*, **59**, 7483 (1963).

Hydrogenation of 1,1′-biisoquinoline (**12**) in acetic acid with rhodium–charcoal catalyst produced neither diamine **5a** nor **5b**. Prolonged reaction (80–90 hr) at 25° resulted in hydrogenation of the carbocyclic rings, with formation of 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-biisoquinoline (**13**) as the sole crystalline product (*ca.* 34% yield).

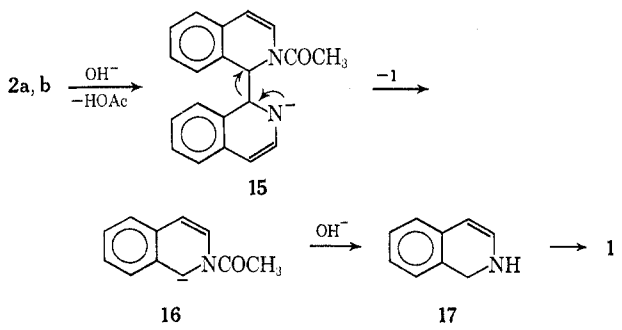
The structure of **13** follows from its nmr spectrum which shows the bipyridine ring protons as an AB quartet, with the C-3,3′ proton signal centered at τ 1.66 and the C-4,4′ signal at 3.03 (J = 6 Hz); the 6,6′,7,7′-ethylene protons (8) appear at 8.0–8.5 as a multiplet, the C-5,5′ methylene protons (4) as a multiplet centered at 7.55, and the C-8,8′ protons (4) as a multiplet centered at 7.22. The ultraviolet spectrum of **13** is equivalent to two independently absorbing alkyl-substituted pyridine rings rather than a coplanar 2,2′-bipyridine, owing to the noncoplanarity of the isoquinoline rings: λ_{max} 272 nm (ϵ_{max} 6200).[11] Dehydrogenation of **13** by heating with palladium–charcoal catalyst in boiling *p*-cymene led to 1,1′-biisoquinoline.

The 1,1′,2,2′-tetrahydro-1,1′-biisoquinoline epimers, **14a,b**, parents to diamides **2a,b**, could not be isolated. Diamides **2a,b** are converted principally to isoquinoline by acid or basic hydrolysis, and are rather resistant to acid hydrolysis.[3] Traces of 1,1′-biisoquinoline have been obtained by acid hydrolysis of **2a**.[3]



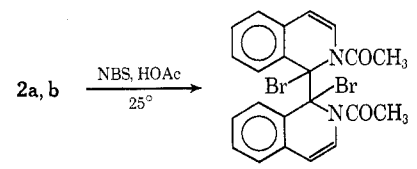
14a, b

Reaction of diamides **2a,b** with refluxing aqueous ethanolic sodium hydroxide (16 hr) produced isoquinoline in nearly quantitative yield. This facile base-catalyzed cleavage contrasts with the behavior of the corresponding octahydrodiamides, **3a,b**, and monoamide **6a**, which are quite stable under the same conditions. The results suggest ease of 1,1′-carbon-bond cleavage in the amide anion intermediate (**15**), leading to isoquinoline and anion intermediate **16**. Hydrolysis of protonated **16** (known, relatively stable 1-acetyl-1,2-dihydroisoquinoline)[12] leads to 1,2-dihydroisoquinoline, **17**. Unpolymerized, neat 1,2-dihydroisoquinoline is reported to disproportionate very rapidly to isoquinoline and 1,2,3,4-tetrahydroisoquinoline,[12] and oxygen oxidation of the latter provides 1,2-dihydroisoquinoline.[13] Thus 1,2-dihydroisoquinoline can be completely consumed in formation of isoquinoline.



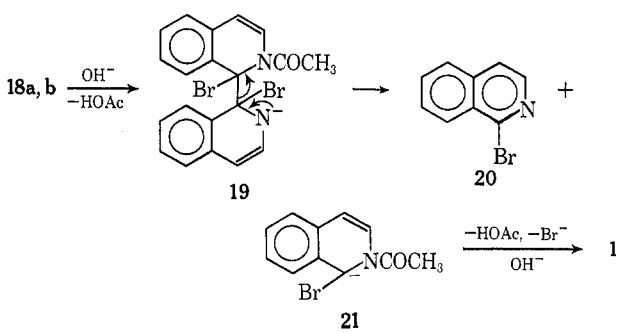
15 **16** **17**

Reaction of diamides **2a,b** with N-bromosuccinimide in acetic acid led to 2,2′-diacetyl-1,1′-dibromo-1,1′,2,2′-tetrahydro-1,1′-biisoquinolines (**18a,b**). Exclusive formation of a single epimer, in nearly quantitative yield, is observed in each case, probably with retention of stereochemistry (*e.g.*, *dl*-**2a** → *dl*-**18a**). A highly reactive radical intermediate would be involved in a stereoselective process.[14,15]



18a, b

Hydrolysis of both dibromo compounds (**18a,b**) in refluxing aqueous ethanolic sodium hydroxide led to a mixture of 1-bromoisoquinoline (**20**) and isoquinoline (**1**) in nearly equal amounts. Supposing an initial amide hydrolysis, amide ion intermediate **19** would cleave to (or a synchronous process would lead to) 1-bromoisoquinoline (**20**) and anion intermediate **21**. Hydrolysis of protonated **21** (2-acetyl-1-bromo-1,2-dihydroisoquinoline) would result in elimination of bromide ion with formation of isoquinoline.



19 **20** **21**

Experimental Section

Melting points were determined on a Kofler block and are corrected. Ultraviolet spectra were determined on a Cary Model 11 spectrophotometer in 95% ethanol, infrared spectra on a Perkin-Elmer Model 137 spectrophotometer, and nmr spectra on a Varian A-60 spectrometer. Mass spectra were determined on a Hitachi Model RMU-6E, 80 eV. Magnesium sulfate was employed as drying agent. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

***dl*-2,2′-Diacetyl-1,1′,2,2′-tetrahydro-1,1′-biisoquinoline (2a).**—Isoquinoline (270 g of 95% assay, mp 18–20°, 2.0 mol) was dissolved in 1500 ml of acetic anhydride. While stirring vigorously, maintaining a nitrogen atmosphere, zinc dust (300 g of CP, 99% assay) was added in small portions at regular intervals during 3 hr keeping the temperature of the reaction mixture at 30–35° by external ice bath cooling. Stirring was continued at 25–30° for 15 hr (nitrogen atmosphere). The pale yellow mixture was then poured into a large stainless steel beaker containing 4 l. of water and 4 l. of ice cubes. After a period of 7 hr most of the liquid was removed by decantation. The remaining material was filtered and the collected solid washed several times with

(11) Alkyl-substituted 2,2,-bipyridine derivatives not substituted in the 6 position have intense bands between 280 and 290 nm (ϵ_{max} 12,000–17,000): W. H. F. Sasse and C. P. Whittle, *J. Chem. Soc.*, 1347 (1961). Alkylpyridines have relatively weak bands near 270 nm (ϵ_{max} 2000–3000): C. T. Kyte, G. H. Jeffery, and A. I. Vogel, *ibid.*, 4454 (1960).

(12) W. P. Neumann, *Justus Liebigs Ann. Chem.*, **618**, 90 (1958).

(13) W. Bartok and H. Pobiner, *J. Org. Chem.*, **30**, 274 (1965).

(14) F. R. Jensen, L. H. Gale, and J. E. Rodgers, *J. Amer. Chem. Soc.*, **90**, 5793 (1968).

(15) C. W. Jefford and E. H. Yen, *Tetrahedron Lett.*, 4477 (1966).

water. The orange-yellow, granular solid was digested with 1300 ml of boiling methanol for 2 hr, filtered hot, and the solid washed with 500 ml of methanol. The filtrate was concentrated to a volume of *ca.* 500 ml and chilled at 0°; the crystals were collected and washed with ice-cold methanol to yield 82 g (24%) of **2a**, mp 185–196°. Recrystallization from methanol gave 64 g of large, colorless, chunky prisms, mp 194–195°, which changed to needles near the melting point and melted at 205–208°, lit.[3] mp 193–194°. Parallel runs gave 24–26% yields of high purity, uncrystallized **2a**. When the temperature during the addition was maintained above 30–35° (up to 60°), yields of **2a** decreased slightly and yields of **2b** increased; total yields remained approximately the same (54–58%). Spectra of **2a**: λ_{max} (EtOH) 207 nm (ϵ 27,000), 228 (28,100), 306 (14,500); lit.[3] 229 nm (15,800), 205 (10,200); ν_{KBr} 1670 cm^{-1} (C=O), 1620 (C=C); nmr ($CDCl_3$) τ 2.4–2.7 (m, 4, aryl), 2.8–3.2 (m, 4, aryl), 3.97 (s, 2, CH at C-1,1′), AB quartet at 3.60, 3.85 (J = 8 Hz, 4, CH=CH at C-3,3′,4,4′) 7.78 (s, 6, CH_3CO).

Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13; mol wt, 344.4. Found: C, 76.87; H, 5.87; N, 8.27; mol wt, 333 (osmometry).

A 1.0-g sample of **2a**, 2.5 g of sodium hydroxide, 3 ml of water, and 15 ml of ethanol were heated on the steam bath for 16 hr. The solution was concentrated under reduced pressure and the residue extracted with methylene chloride. The dried extracts were concentrated to dryness to yield 0.77 g of a mobile oil, soluble in heptane, having the odor of isoquinoline; its infrared spectrum (film) was practically identical with that of isoquinoline (theoretical yield, 0.75 g).

***meso*-2,2′-Diacetyl-1,1′,2,2′-tetrahydro-1,1′-biisoquinoline (2b).**—The dried residue remaining after extraction with hot methanol in the preparation of **2a** described above is a mixture containing principally zinc and rather pure **2b** (white crystals, mp 250–251°). It was extracted continuously with 1200 ml of methylene chloride in a Soxhlet apparatus for 30 hr, leaving 184 g of zinc and depositing from solution 79.7 g of white, crystalline **2b**, mp 255–257°; concentration of the filtrate to dryness, followed by washing of the residue with water and ethanol, gave 23.6 g more of **2b**, mp 250–251°; total yield of **2b** was 103.3 g (30%); in parallel runs the yield was 28–32%. The compound is quite insoluble in all organic solvents tested. Recrystallization from boiling acetic acid (2% solution) yields rectangular prisms: mp 257–260°; λ_{max} (EtOH) 207 nm (ϵ 23,900), 241 (26,800), 315 (12,200); ν_{KBr} 1660 cm^{-1} (C=O), 1620 (C=C).

Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.49; H, 6.01; N, 7.98.

A 3.44-g (0.01 mol) sample of **2b** and 25 ml each of concentrated hydrobromic acid, acetic acid and water were heated under reflux for 63 hr. The clear, pale yellow solution was concentrated in vacuum to remove solvents. One-half of the residue was dissolved in 10 ml of hot absolute ethanol and diluted with 100 ml of ether; an oil precipitated which failed to crystallize. One-half of the residue was dissolved in water (10 ml) and treated with saturated potassium carbonate solution to liberate an oil which was extracted with methylene chloride. Concentration of the extracts in vacuum gave 1.26 g of a viscous, dark red oil, not completely soluble in heptane, which had a strong odor of isoquinoline and an infrared spectrum similar to that of isoquinoline (C=O bands absent). Attempted crystallization of the oil from heptane–benzene gave a gum.

***dl*-2,2′-Diacetyl-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline (3a).**—*dl*-2,2′-Diacetyl-1,1′,2,2′-tetrahydro-1,1′-biisoquinoline (**2a**, 50.0 g), 200 ml of acetic acid, and 15.0 g of 5% rhodium–charcoal catalyst were shaken with hydrogen (25–55 psi) in a Parr apparatus at 25° until hydrogen uptake ceased (86 hr) and 2 mol equiv of hydrogen was absorbed. The mixture was filtered through a Büchner funnel and the catalyst extracted three times with hot acetic acid. The extracts and the filtrate were concentrated to dryness and the residue was triturated with water, filtered, and washed with water to yield 49.4 g (98%) of diamide **3a**, mp 204–210°. Recrystallization from benzene gave chunky white prisms: mp 211–213°; ν (KBr) 1645 cm^{-1} (C=O); nmr ($CDCl_3$) τ 2.7–3.5 (m, 6, aryl), 4.03 (d, 2, J = 8 Hz, CH at C-8,8′), 4.53 (s, 2, CH at C-1,1′), 6.0–7.5 (m, 8, CH_2CH_2 at C-3,3′,4,4′), 7.92 (s, 6, CH_3CO). Substitution of platinum oxide or palladium–charcoal catalysts for the rhodium–charcoal failed to hydrogenate **2a** which was recovered.

Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04; mol wt, 348.43. Found: C, 76.05; H, 7.07; N, 7.98; mol wt, 332 (osmometry).

A solution of **3a** (0.50 g) and 1.0 g of sodium hydroxide in 10 ml of 50% aqueous ethanol was heated under reflux for 16 hr. The pale yellow solution was concentrated to dryness and the residue diluted with water to precipitate 0.49 g of recovered **3a**, mp 190–210°.

A solution of **3a** (0.50 g) in 5 ml of concentrated hydrobromic acid was heated on the steam bath (90°) for 18.5 hr. The solution was concentrated to dryness and the residue diluted with water to precipitate 0.47 g of recovered **3a**, mp 210–212°; when this was mixed with **3a** the melting point was not depressed.

***meso*-2,2′-Diacetyl-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline (3b).**—*meso*-2,2′-Diacetyl-1,1′,2,2′-tetrahydro-1,1′-biisoquinoline (**2b**, 50.0 g), 230 ml of acetic acid, and 15.0 g of 5% rhodium–charcoal catalyst were shaken with hydrogen as in the preparation of **3a**, above; 2 mol equiv of hydrogen were absorbed in 76 hr, after which time hydrogen uptake ceased. The insoluble product mixed with catalyst was filtered and extracted continuously with methylene chloride in a Soxhlet apparatus for 40 hr. The extract was concentrated to dryness and the residue triturated with water, filtered, and washed with water to yield 49.5 g (98%) of diamide **3b**, mp 231–233°. Recrystallization from benzene gave flat square prisms: mp 231–232°; ν (KBr) 1640 cm^{-1} (C=O). The nmr spectrum ($CDCl_3$) at *ca.* 30° revealed two acetyl and C-1,1′ proton signals due to the presence of two conformers (A, *ca.* 67% and B, *ca.* 33%); τ 2.3–3.6 (m, 8, aryl), 3.92 (s, CH at C-1,1′ of B), 4.08, 4.63 (AB quartet, J = 5 Hz, CH at C-1,1′ of A), 6.0–7.5 (m, 8, CH_2CH_2 at C-3,3′,4,4′), 7.90 (s, CH_3CO of A), 8.20 (s, CH_3CO of B).[16] In DMSO-d_6 the nmr spectrum at 40° is very similar to that in $CDCl_3$, but at 120° there resulted a collapse of the methyl signals to a single line; also, the signals for the C-1,1′ protons coalesce to a single broad signal.

Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04; mol wt, 348.43. Found: C, 76.16; H, 6.84; N, 8.02; mol wt, 351 (osmometry).

***dl*-1,1′,2,2′,3,3′,4,4′-Octahydro-1,1′-biisoquinoline Bishydrobromide (4a).**—A mixture of *dl*-2,2′-diacetyl-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline, **3a**, (34.8 g, 0.1 mol) and 250 ml each of concentrated hydrobromic acid, acetic acid, and water was heated under reflux for 48 hr. The clear, pale yellow solution was concentrated to dryness under reduced pressure. The residue was triturated with water, filtered, and washed with water to yield 32.2 g (75.5%) of salt **4a**, small prisms, mp 280–285°. Recrystallization from 0.8 *N* aqueous hydrobromic acid gave large chunky prisms: mp 290–292°; nmr (D_2O) τ 2.3–2.9 (m, 8, aryl), 4.18 (d, J = 1 Hz, CH at C-1,1′), 5.8–6.8 (m, 8, CH_2CH_2 at C-3,3′,4,4′). Parallel runs gave **4a** in 75–79% yield.

Anal. Calcd for $C_{18}H_{22}Br_2N_2$: C, 50.73; H, 5.20; N, 6.57; Br, 37.50. Found: C, 50.77; H, 5.17; N, 6.58; Br, 37.50.

***meso*-1,1′,2,2′,3,3′,4,4′-Octahydro-1,1′-biisoquinoline Bishydrobromide (4b).**—The procedure employed above with the *dl* isomer **3a** was applied to *dl*-2,2′-diacetyl-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline, **3b** (34.8 g, 0.1 mol), to yield 30.3 g (71%) of salt **4b** as chunky prisms, mp 264–269°. Parallel runs gave **4b** in 71–80% yield.

Anal. Calcd for $C_{18}H_{22}Br_2N_2$: C, 50.73; H, 5.20; N, 6.57; Br, 37.50. Found: C, 50.93; H, 4.93; Br, 37.57.

***dl*-1,1′,2,2′,3,3′,4,4′-Octahydro-1,1′-biisoquinoline (5a).**—A 30.0-g sample of the *dl* bishydrobromide salt **4a** was dissolved in a solution of 100 ml each of 10% aqueous sodium hydroxide, methanol, and tetrahydrofuran by shaking at 25°. The clear solution was concentrated under reduced pressure on the steam bath to a volume of *ca.* 50 ml. The residue was filtered and the solid washed with water to yield 18.6 g (100%) of diamine **5a**, mp 134–138°. Recrystallization from 4:1 ethanol–water gave chunky prisms: 15.6 g; mp 135–137.5°; λ_{max} (EtOH), 259 nm (ϵ 955), 266.5 (1100), 273.5 (1100); nmr ($CDCl_3$) τ 2.5–3.0 (m, 8, aryl), 5.32 (s, 2, CH at C-1,1′), 6.6–7.7 (m, 8, CH_2CH_2 at C-3,3′4,4′), 8.27 (s, 2, NH).

Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60; mol wt, 264.36. Found: C, 81.78; H, 7.68; N, 10.53; mol wt 262 (osmometry).

The **dinitrate** salt was prepared in hot 10% aqueous nitric acid and recrystallized from 10% nitric acid: mp 235–236° with decomposition.

(16) The reported nmr spectra of 1-substituted 2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines indicate the presence of two conformers due to restricted acetyl group rotation: D. R. Dalton, K. C. Ramey, H. J. Gisler, Jr., L. J. Lendvay, and A. Abraham, *J. Amer. Chem. Soc.*, **91**, 6367 (1969).

Anal. Calcd for $C_{18}H_{22}N_4O_6$: C, 55.38; H, 5.68; N, 14.35. Found: C, 55.25; H, 5.79; N, 14.19.

meso-**1,1′,2,2′,3,3′,4,4′-Octahydro-1,1′-biisoquinoline (5b). Method A. From Bishydrobromide Salt 4b.**—The procedure employed in the preparation of *dl*-diamine **5a** from hydrobromide salt **4a** was used with *meso*-bishydrobromide salt **4b** to yield *meso*-diamine **5b**, 100% yield, mp 82–86°. Recrystallization from heptane gave white prisms: mp 86–88°; λ_{max} (EtOH) 267 nm (ϵ 920), 275 (895); nmr ($CDCl_3$) τ 2.7–3.3 (m, 8, aryl), 5.40 (s, 2, CH at C-1,1′), 6.5–7.5 (m, 8, CH_2CH_2 at C-3,3′,4,4′), 8.08 (s, 2, NH).

Method B. Hydrogenation of 1,1′-Biisoquinoline Hydrochloride.—A solution of 1.00 g of 1,1′-biisoquinoline in 100 ml of 95% ethanol containing 2 ml of concentrated hydrochloric acid was shaken with hydrogen in a Parr apparatus (50 psi, 25°) until 4 mol equiv of hydrogen was absorbed (5.5 hr). The catalyst was filtered and the filtrate concentrated to near dryness. The residue was treated with 20 ml each of 10% aqueous sodium hydroxide solution, ethanol and tetrahydrofuran; the resulting clear solution was concentrated to dryness and the residue extracted four times with ether. The dried ether extracts were combined and concentrated to yield 0.94 g of a viscous, pale yellow oil; crystallization from heptane gave 0.34 g of crystals, mp 60–85°; recrystallization from heptane gave diamine **5b** as prisms, mp 85–88°.

Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60; mol wt, 264.36. Found: C, 81.96; H, 7.63; N, 10.44; mol wt, 268 (osmometry).

The **dinitrate** salt was prepared in hot 10% aqueous nitric acid and recrystallized from water, mp 228–229°, with decomposition and previous softening.

Anal. Calcd for $C_{18}H_{22}N_4O_6$: C, 55.38; H, 5.68; N, 14.35. Found: C, 55.77; H, 5.70; N, 14.19.

Diamines **5a** and **5b** react with group VIII metal chlorides to produce colors in aqueous ethanol as follows: nickel(II), greenish; cobalt(II), pink; iridium(IV), yellow-orange; iron(III), yellow; iron(II) with **5a**, yellow-orange. Ferrous chloride with **5b** gave a slight greenish color which after *ca.* 24 hr became deep blue; longer standing intensified the blue color which is produced within 1–2 hr by bubbling air through the solution, or by heating on the steam bath. With **5a** no blue color is produced under these conditions; **5a** could not be made to react with ferrous salts to produce a blue color under any conditions tested.

Samples of pure, white, crystalline *meso*-diamine **5b** on standing at room temperature became yellow after a few days. After several weeks the samples became oily with an odor of isoquinoline. For example, a sample stored *ca.* 1 month had its melting point lowered to 82–86° and its ultraviolet spectrum had changed—λ_{max} (EtOH), 259 nm (ϵ 1350), 267 (1470), 275 (1320), 290–310 sh (320), 323 (240). In contrast to pure **5b** it immediately gave a deep inky blue color with ferrous chloride; λ_{max} (aqueous EtOH) 550, 635 (most intense), 656, 658 nm. 3,3′,-4,4′-Tetrahydro-1,1′-biisoquinoline (**10**) was found to give the same blue color and absorption maxima with ferrous chloride. Diamine **10**[9] has λ_{max} (EtOH) 258 nm (ϵ 15,400), but no strong bands near 323 nm. 1,1′-Biisoquinoline has λ_{max} (EtOH) 274 nm (ϵ 8500), 286 (7900), 312 (7400), 324 (10,700); it produces a pink color with aqueous ethanolic ferrous chloride. Isoquinoline has λ_{max} (EtOH) 260 nm (ϵ 3700), 267 (3700), 271 (3700), 308 (2500), 320 (2700)[17]; it produces a yellow color with ferrous chloride.

dl-**8-Methyl-5,6,7,9,10,11,15b,15c-octahydrodiisoquino[2,1-*c*:1′,2′-*e*]imidazolinium Bromide (7a). Procedure A. Hydrolysis of 3a.**—*dl*-2,2′-Diacetyl-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline, **3a** (0.50 g), in 10 ml of concentrated hydrobromic acid was heated under reflux for 26 hr. The solution was concentrated to dryness and the residue diluted with water to precipitate 0.13 g (26%) of recovered **2a**, mp 212–218°. The filtrate was concentrated to dryness and the residue triturated with 2-propanol to yield 0.26 g (49%) of crude imidazolinium salt **7a**, mp 270–280°; recrystallization by dissolving in ethanol and precipitating with ether gave small, flat, square prisms, 0.17 g, mp 280–285°.

The above procedure applied to *meso* epimer **3b** (0.5 g) (49-hr reflux) gave 0.10 g (20%) of recovered **3b**, mp 230°, and 0.28 g (47%) of bishydrobromide salt **4b**, mp 265–268°, as the only crystalline product. Shorter reaction periods gave larger amounts of recovered reactant **3b** and less **4b**.

Procedure B.—A solution of *dl*-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline (**5a**, 1.0 g) and ethyl acetimidate hydrochloride (0.54 g) in 10 ml of absolute ethanol was heated under reflux for 9 hr.[5,18] The solution was cooled and the filtrate diluted with 300 ml of ether and let stand overnight. White crystals separated, 1.0 g, mp 230–260°, believed to be *dl*-8-methyl-5,6,7,9,10,11,15b,15c-octahydrodiisoquino[2,1-*c*:1′,2′-*e*]imidazolinium chloride complexed with acetic acid:[19] ν (KBr) 1680 cm^{-1} (C=O, acetate), 1605 (C=N$^+$); nmr (D_2O) 7.47 (s, $CH_3C{=}N^+$), 7.58 (s, CH_3CO_2H). In a parallel 2.0-g run employing a 22-hr reflux period there was obtained 2.3 g of this crude chloride salt, mp 230–275°. Attempts to obtain the pure chloride salt free of acetic acid by crystallization from various solvents were unsuccessful. The crude material (1.0 g) was dissolved in 20 ml of concentrated hydrobromic acid and concentrated to dryness in vacuum. Crystallization of the residue from water gave 0.88 g (63%) of hydrated bromide salt **7a**, mp 280–283°, with prior melting at 110–115° and loss of solvent. The hydrated material was dissolved in ethanol and precipitated with ether to give small prisms of anhydrous **7a**: mp 275–280°, with previous softening; ν (KBr) 1610 cm^{-1} (C=N$^+$), 1570 (C=C); nmr (D_2O) τ 2.45 (m, 8, aryl), 4.55 (s, 2, CH at 15b, 15c), 6.02 (m, 4, CH_2 at C-3,3′), 6.80 (m, 4, CH_2 at C-4,4′), 7.47 (s, 3, CH_3), sodium 3-trimethylsilylpropanesulfonate internal standard.

Anal. Calcd for $C_{18}H_{21}BrN_2$: C, 65.05; H, 5.73; Br, 21.64; N, 7.59. Found: C, 64.90; H, 5.71; Br, 21.74; N, 7.48.

A 0.10-g sample of imidazolinium bromide salt **7a** in a solution of 5 ml each of concentrated hydrobromic acid, acetic acid, and water was heated under reflux for 48 hr. Concentration to near dryness and dilution of the residue with 1 *N* hydrobromic acid gave, in successive crops, 0.09 g of recovered **7a** hydrate, mp 280–283° after prior melting at 110° and resolidifying; infrared spectrum was identical with that of **7a** hydrate.

dl-**2-Acetyl-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biisoquinoline (6a).**—A solution of *dl*-8-methyl-5,6,7,9,10,11,15b,15c-octahydrodiisoquino[2,1-*c*:1′,2′-*e*]imidazolinium bromide (**7a**, 0.20 g) in a solution of 5 ml each of ethanol and 10% aqueous sodium hydroxide was heated under reflux for 18.5 hr. The solution was concentrated to a volume of 3 ml and chilled at 0° to precipitate 0.13 g of crystals, mp 121–135°. Recrystallization from benzene gave small flat prisms, mp 143–144°, with a change near 135° to chunky prisms. The imidazolinium chloride salt described above may also be employed in this preparation (99% yield of **6a**).

Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.34; H, 7.14; N, 8.99.

A solution of 7.1 mg of monoamide **6a** in 1 ml of acetic anhydride containing 1 drop of sulfuric acid was warmed on the steam bath for 40 min. Water (15 ml) was added and the mixture chilled to 0° and subsequently filtered to yield 5.6 mg of *dl*-bisamide **3a**, mp 212–213° (mixture melting point with authentic **3a** undepressed).

A solution of 0.20 g of **6a** in 4.0 ml of concentrated hydrobromic acid was heated under reflux for 26.5 hr. Concentration to dryness gave crystals which were triturated with 25 ml of ether and filtered to yield 0.22 g of imidazolinium salt **7a**, mp 250–270°; recrystallization from ethanol–ether gave a sample, mp 275–285°; infrared spectrum identical with that of an authentic sample of **7a**.

A solution of 0.20 g of **6a** in 1.3 ml each of concentrated hydrobromic acid, water, and acetic acid was heated under reflux for 48 hr. Concentration to near dryness, followed by dilution with 5 ml of water and chilling to 0°, gave 0.17 g of bishydrobromide salt **4a**, mp 294–298° (mixture melting point with authentic sample undepressed).

dl-**5,6,7,9,10,11,15b,15c-Octahydro-8H-diisoquino[2,1-*c*:1′,2′-*e*]imidazole (8a).**—A solution of diamine **5a** (0.52 g, 0.002 mol) and 0.15 ml of 37% formalin in 5 ml of dioxane was heated on the steam bath for 2.7 hr and kept at 25° for 15 hr. Concentration of the solution to dryness gave 0.55 g (100%) of crude **8a**, mp 110–125°. Recrystallization from dilute ethanol gave 0.39 g (72%) of **8a**, colorless prisms, mp 125–128°.

(17) J. M. Hearn, R. A. Morton, and J. C. E. Simpson, *J. Chem. Soc.*, 3318 (1951).

(18) S. M. McElvain and J. W. Nelson, *J. Amer. Chem. Soc.*, **64**, 1825 (1942).

(19) Many substituted 2-imidazolines form stable complexes with acetic acid: J. L. Riebsomer, *J. Amer. Chem. Soc.*, **70**, 1629 (1948).

Anal. Calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14; mol wt, 276.37. Found: C, 82.71; H, 7.20; N, 10.03; mol wt, 280 (osmometry).

meso-**5,6,7,9,10,11,15b,15c-Octahydro-8H-diisoquino[2,1-*c*:1′,2′-*e*]imidazole (8b).**—The procedure employed with diamine **5a** was used with 0.52 g of diamine **5b** to yield an oil which was extracted with hot heptane. Chilling the extracts gave 0.30 g (55%) of **8b**, mp 90–93; concentration of the filtrate gave an additional 0.04 g, mp 80–90° (62% total). Recrystallization of the first crop from heptane gave prisms, mp 90–92°.

Anal. Calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14; mol wt, 276.37. Found: C, 82.86; H, 7.37; N, 10.02; mol wt, 280 (osmometry).

1,1′-Biisoquinoline (12).—*dl*-1,1′,2,2′,3,3′,4,4′-Octahydro-1,1′-biisoquinoline, **5a** (1.0 g), in 25 ml of *p*-cymene was heated under reflux with 0.3 g of 10% palladium–charcoal for 27 hr; a stream of nitrogen was passed over the surface of the liquid during the heating. The catalyst was filtered and extracted several times with hot *p*-cymene. The filtrate and extracts were combined and concentrated to dryness under reduced pressure and the crystalline residue triturated with heptane; after the mixture chilled at −15° for several hours the mixture was filtered to yield 0.70 g (72%) of crystalline 1,1′-biisoquinoline, mp 155–163°. Recrystallization from benzene–heptane gave large, chunky prisms, 0.56 g, mp 167–168°, lit.[20] mp 162–163°; on admixture with an authentic sample the melting point was not depressed (infrared spectrum identical). Parallel runs gave 65–70% yields of 1,1′-biisoquinoline. Best yields were obtained with 10% palladium–charcoal catalyst of high activity and recrystallized, high purity diamine.

meso-1,1′,2,2′,3,3′,4,4′-Octahydro-1,1′-biisoquinoline (**5b**) was employed in the above procedure to provide 1,1′-biisoquinoline in 66% yield, mp 158–166° before recrystallization.

5,5′,6,6′,7,7′,8,8′-Octahydro-1,1′-biisoquinoline (13).—1,1′-Biisoquinoline (2.56 g, 0.01 mol) dissolved in 100 ml of acetic acid was shaken with 1.0 g of 5% rhodium–charcoal catalyst and hydrogen (50 psi, 25°) in a Parr apparatus for 80 hr; approximately 2 mol equiv of hydrogen was absorbed. The catalyst was filtered and washed with acetic acid, and the filtrate concentrated to near dryness *in vacuo*. The residue was treated with 20 ml of 10% aqueous sodium hydroxide, 10 ml of ethanol, and 10 ml of tetrahydrofuran. The clear solution was concentrated to dryness and the residue extracted with methylene chloride; the dried extracts were concentrated to yield 2.45 g of dark oil. Extraction of the oil with hot heptane and treatment with Darco-G 60 decolorizing carbon, followed by concentration and chilling at −15°, gave 1.35 g of white crystals, mp 93–120°, a mixture of **13** (*ca.* $^2/_3$; 34% yield) and 1,1′-biisoquinoline (*ca.* $^1/_3$) which could not be separated completely by fractional crystallization from heptane. The mixture was separated by preparative scale tlc on silica gel (Mallinckrodt Silicar 7GF) with ether developer; the fast-moving component was pure 1,1′-biisoquinoline, mp 162–163°, identified by mixture melting point and infrared spectrum. The slower moving component was **13** containing some 1,1′-biisoquinoline which was very difficult to remove completely. Column chromatography on basic alumina (elution with heptane) gave a sample (fast-moving component) which was recrystallized from heptane, mp 135–139°.

Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60; mol wt, 264.36. Found: C, 81.74; H, 7.34; N, 10.61; mol wt, 264 (mass spectrometry).

A 0.29-g sample of **13**, 0.15 g of 10% palladium–charcoal and 50 ml of *p*-cymene were heated under reflux in a nitrogen atmosphere for 29 hr. Filtration of the catalyst, followed by concentration of the filtrate to dryness, gave an oil which was triturated with heptane to yield 0.24 g of crystals, mp 143–154°; recrystallization from benzene–heptane gave chunky prisms of 1,1′-biisoquinoline, mp 156–163°, identified by mixture melting point and infrared spectrum.

dl-**2,2′-Diacetyl-1,1′-dibromo-1,1′,2,2′-tetrahydro-1,1′-biisoquinoline (18a).**[21]—A mixture of 1.2 g of *dl*-diamide **2a** and 25 ml of acetic acid was treated with 1.3 g of N-bromosuccinimide. Complete solution of the reactants was rapidly obtained, accompanied by a small temperature rise. After 24 hr at room temperature, the solution was diluted with 50 ml of water; the white precipitate was filtered and washed well with water; 1.7 g (97%), mp 192–195°, was obtained. Recrystallization from benzene gave felted needles, mp 212–214°.

Anal. Calcd for $C_{22}H_{18}Br_2N_2O_2$: Br, 31.83; N, 5.58; mol wt, 502. Found: Br, 31.95; N, 5.56; mol wt, 526 (osmometry).

meso-**2,2′-Diacetyl-1,1′-dibromo-1,1′2,2′-tetrahydro-1,1′-biisoquinoline (18b).**[21]—The procedure employed in the preparation of **18a** gave with *meso*-diamide **2b** an 84% yield of **18b**, fine white powder, mp 231–232° after recrystallization from benzene.

Anal. Calcd for $C_{22}H_{18}Br_2N_2O_2$: Br, 31.83; N, 5.58. Found: Br, 32.08; N, 5.50.

Hydrolysis of 18a and 18b.[21]—*dl*-Dibromo compound **18a** (0.7 g) was heated under reflux with a solution of 0.3 g of sodium hydroxide in 20 ml of 50% aqueous ethanol. The cooled solution was diluted with 12 ml of water and extracted with three small portions of ether; evaporation of the extracts gave 0.43 g of oil containing two components which were easily separated by glc (10 ft × $^1/_4$ in. column of 20% SE-52 on Chromosorb W; 190°). Isoquinoline (*ca.* 55% yield) came off the column first: retention time the same as isoquinoline; *m/e* (parent) 129; calcd for C_9H_7N, 129.15. The second component (*ca.* 40% yield) showed parent *m/e* values of 207 and 209 of nearly equal intensity; calcd for C_9H_6BrN, 208.06; mp 41–41.5°, lit.[22] mp 41.5–42.3° for 1-bromoisoquinoline.

Hydrolysis of the *meso* isomer **18b**, under conditions comparable with those employed with **18a**, occurred more slowly; a reaction time of 11 hr was required to effect complete solution. The yield of liquid product from 1.4 g of **18b** was 0.89 g (*ca.* 95% total yield of approximately equal amounts of isoquinoline and 1-bromoisoquinoline, based on glc analysis).

Registry No.—**2a**, 25080-52-8; **2b**, 25055-08-7; **3a**, 25055-09-8; **3b**, 25062-09-3; **4a**, 25062-12-8; **4b**, 25062-13-9; **5a**, 25062-14-0; dinitrate salt of **5a**, 25062-15-1; **5b**, 25062-16-2; dinitrate salt of **5b**, 25062-17-3; **6a**, 25062-18-4; **7a**, 25062-19-5; **8a**, 25080-54-0; **8b**, 25080-55-1; **13**, 25056-48-8; **18a**, 25062-20-8; **18b**, 25062-21-9.

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(20) F. H. Case, *J. Org. Chem.*, **17**, 471 (1952).

(21) The author is indebted to Dr. R. A. Henry for these experimental results.

(22) H. E. Jansen and J. P. Wibaut, *Recl. Trav. Chim., Pays-Bas*, **56**, 699 (1937).