Hydrosulfite Reduction of *N*-Nitroso-1,2,3,4-tetrahydroisoquinolines and Oxidation of *N*-Amino-1,2,3,4-tetrahydroisoquinolines (1)

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Received September 2, 1982

The sodium hydrosulfite reduction of *N*-nitroso-1,2,3,4-tetrahydroisoquinoline (**5**) does not result in the loss of nitrogen and leads to the corresponding hydrazine **6** which upon oxidation with mercuric oxide in ethanol at 62° gives the hexahydrotetrazine **7** in 39% yield. Treatment of the *N*-tosyl derivative of **6** with base affords **7** in nearly quanitative yield. Oxidation of **6** in 1-butanol at 95° results in the formation of a complex product mixture from which only one component, 1,1'-azobis-3,4-dihydroisoquinoline (**8**) could be isolated. Surprisingly the sodium hydrosulfite reduction of 2-nitroso-3-phenyl-1,2,3,4-tetrahydroisoquinoline (**15**) also failed to proceed with loss of nitrogen and yields the corresponding hydrazine **16**. However, **16** was cleanly oxidized by mercuric oxide in ethanol at 62° with concurrent elimination of nitrogen to afford 2-phenylindane in 75% yield. Possible rationalizations for these results are presented.

J. Heterocyclic Chem., **20**, 121 (1983).

Introduction.

N-Nitrenes have been postulated as intermediates of the oxidation of hydrazines and of the "abnormal" reduction of *N*-nitrosamines (3). Although the reactions are far from being well understood, it has been suggested that the presumed *N*-nitrenes can undergo a variety of subsequent transformations such as the *diazene-hydrazone* rearrangement, addition to unsaturated systems, insertion and extrusion of nitrogen (Fig 1). This last path most often predominates when both substituents can cleave as stable radicals.

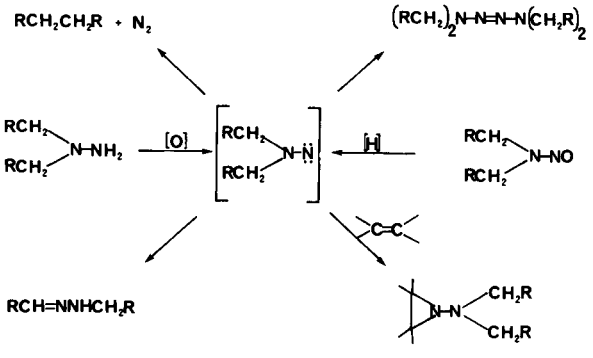
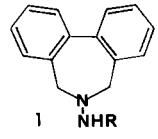


FIGURE 1

Although a considerable amount of work has been carried out on the oxidation of acyclic and cyclic hydrazines (4) much less is known about systems incorporating hydrazines fused to benzene rings. Carpino (5) found that treatment of 1-*p*-toluenesulfonamido-2,7-dihydro-3,4,5,7-dibenzazepine (**1b**) with aqueous base gave a 95% yield of 9,10-dihydrophenanthrene. Oxidation of *N*-aminodihydroisoindole (**2a**) with mercuric oxide in methylene chloride or the alkaline degradation of the corresponding *p*-toluenesulfonylhydrazide **2b** gave the dimer of *o*-quinodimethane (6). With mercuric oxide, *trans*-1,3-diphenyl-2-aminodihydroisoindole (**3a**) afforded a good yield of *trans*-1,2-diphenylbenzocyclobutene while oxidation with manganese dioxide of the *cis*-isomer of **3a** gave a fair yield of *cis*-1,2-diphenylbenzocyclobutene.



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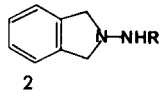

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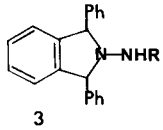

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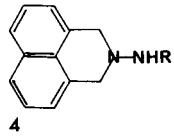

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Baker, McOmie and Preston (7) found that base-catalyzed decomposition of *N*-*p*-toluenesulfonamidodihydroisoindole (**3b**) gave a mixture of benzocyclobutene, *o*-xylene and 1,2,5,6-dibenzocyclooctadiene. They also observed that treatment of 1,3-diphenyl-2-aminodihydroisoindole (**3a**) with tosyl chloride in pyridine resulted in spontaneous

decomposition to a mixture of 1,2-diphenylbenzocyclobutene and 9,10-dihydro-9-phenylanthracene. These products were postulated to arise by radical reaction of an intermediate *o*-quinodimethane.

In contrast 2-amino-2,3-dihydro-1*H*-benz[*de*]isoquinoline (**4a**) did not yield the expected acenaphthene (8). Instead, mercuric oxide oxidation gave a low yield of the tetrazene while alkaline degradation of the corresponding *p*-toluenesulfonyl derivative (**4b**) afforded an unidentified product, isomeric with the tetrazene.

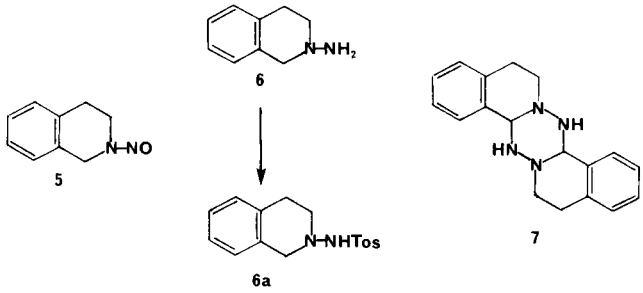
In an effort to better understand the factors affecting nitrogen elimination by the sodium hydrosulfite reduction of nitrosamines and to extend the study of the oxidation of hydrazines, the preparation of 2-nitroso-1,2,3,4-tetrahydroisoquinoline (**5**), of 2-nitroso-3-phenyl-1,2,3,4-tetrahydroisoquinoline (**10**) and of the corresponding hydrazines was undertaken.

Results and Discussion.

1. 1,2,3,4-Tetrahydroisoquinolines.

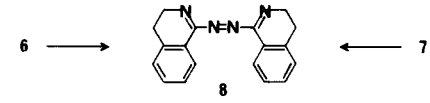
2-Nitroso-1,2,3,4-tetrahydroisoquinoline (**5**) was obtained by treatment of 1,2,3,4-tetrahydroisoquinoline with sodium nitrite and dilute hydrochloric acid at 75° (9). Treatment of **5** with sodium hydrosulfite in aqueous base under the usual conditions (10) did not lead to nitrogen evolution. Instead the corresponding hydrazine **6** (12) isolated as its hydrochloride salt, was formed in 54% yield; it was identical to the product obtained by the lithium aluminum hydride reduction of the nitrosamine (69% yield). It was previously reported (11) that the sodium hydrosulfite reduction of 1-nitroso-2-phenylpiperidine also gave the hydrazine instead of leading to nitrogen evolution. This suggested that both α-carbon atoms must be activated for nitrogen evolution to occur during the sodium hydrosulfite reduction. The free hydrazine proved to be quite sensitive to air oxidation. Since upon exposure to air at room temperature, the initially clear, oily, hydrazine rapidly became cloudy with formation of a precipitate, the hydrazine was isolated and stored as the hydrochloride salt.

Oxidation of **6** with yellow mercuric oxide in ethanol at 58° gave **7** (39%) (13) thus confirming the previous results of Höft and Reiche (12). No gas evolution was observed.



Treatment of 2-*p*-toluenesulfonamido-1,2,3,4-tetrahydroisoquinoline (**6a**) with hot aqueous base afforded hexahydrotetrazine **7** in essentially quantitative yield.

When the merccuric oxide oxidation of 2-amino-1,2,3,4-tetrahydroisoquinoline (**6**) was carried out in 1-butanol at 95°, a complex reaction occurred and a small amount of nitrogen (25%) was evolved. Vapor phase chromatography of the crude oxidation product showed only the presence of 1-butanol; no indane or other relatively volatile material was detected. The complex nature of the reaction mixture (at least ten spots by tlc) precluded the isolation of but one component, identified as 1,1′-azobis-3,4-dihydroisoquinoline (**8**), in 46% yield (spectrophotometric assay of the crude reaction mixture). The same product was formed in 66% yield by treatment of **7** with mercuric oxide in 1-butanol at 100°.



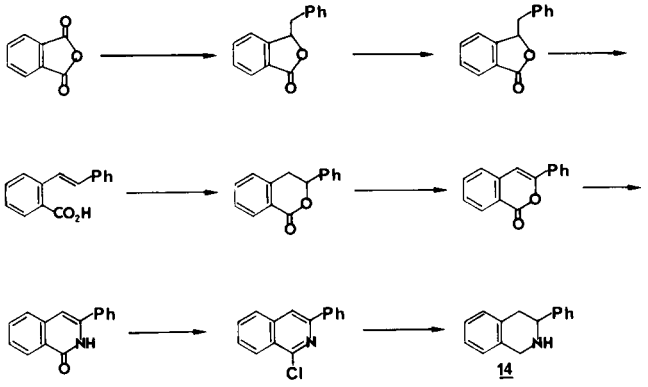
The structural assignment for **8** rests mainly on spectroscopic evidence. Elemental analysis suggested an empirical formula of $C_9H_8N_2$ while a molecular weight determination indicated the dimeric nature of the product thus requiring an empirical formula of $C_{18}H_{16}N_4$. The infrared spectrum of **8** was consistent with the assigned structure, showing only aromatic, aliphatic and olefinic absorptions at 3050 and 2900 cm^{-1} and a triplet at 1620, 1600 and 1575 cm^{-1}. A triplet between 1650 and 1550 cm^{-1} is reported by Battersby, Davidson and Harper to be characteristic of 3,4-dihydroisoquinolines (14). The ultraviolet spectrum (methanol) showed a weak band at 374 mμ (log ϵ 2.56) and an intense band at 263 mμ (log ϵ 4.51) with a shoulder at 303.5 mμ (log ϵ 3.66). The low intensity band at 374 mμ is undoubtedly due to the azo group (15a), while the band at 263 mμ is probably due to the 3,4-dihydroisoquinoline structure. 3,4-Dihydroisoquinolines are reported to display bands around 231, 270 and 310 mμ in ethanol (15b). The nmr spectrum of **8** showed a pair of triplets at δ 3.05 and 3.66 (J = 5.5 Hz) due to the hydrogens at positions 3 and 4, and two complex bands at δ 7.28 (aromatic hydrogens). The peak at δ 8.05 is due to the hydrogen at position 8 and is shifted downfield from the normal aromatic region by the adjacent azo group. The lack of any absorption ascribable to a hydrogen at position 1 indicates that the two 3,4-dihydroisoquinoline groups are joined at the 1 position. Although the oxidation of **6** with sodium bromate at 0° was too complex to be studied in detail, ~80% of nitrogen was evolved. A Beilstein test on the crude tarry residue suggested that brominated products had been formed and only the presence of **8** could be inferred from the tlc of the crude reaction mixture.

2. 3-Phenyl-1,2,3,4-tetrahydroisoquinolines.

The classical Bischler-Napieralski and Pictet-Spengler routes to 1,2,3,4-tetrahydroisoquinolines give poor yields

or fail altogether unless the aromatic ring is activated. As an example, Day and Ramanathan (16) reported the failure of *N*-benzoyl- and *N*-acetyl-α,β-diphenylethylamine to cyclize with phosphorus oxychloride. A British patent (17) had reported the aluminum chloride-catalyzed cyclization of α-phenylphenethyl isocyanate to give 3-phenyl-3,4-dihydroisocarbostyryl but this result could not be duplicated. Berti prepared 4-phenylisoquinoline from 3-methyl-3-phenylphthalide; however, the same series of reactions using benzalphthalide or stilbene-2-carboxylic acid failed to give the desired 3-phenylisoquinoline (18). 3-Phenyl-1,2,-3,4-tetrahydroisoquinoline (**14**) was prepared by a modification of the original route of Gabriel (Scheme 1) (19).

The reactions, as far as 3-phenyl-3,4-dihydroisocoumarin, followed well-known procedures and proceeded as expected. Introduction of the double bond in 3,4-dihydroisocoumarins by bromination-dehydrobromination has now been reported as a general method by Bose and Chaudhury (20). However, in the present case, the resulting 3-phenylisocoumarin proved resistant to the removal of



SCHEME 1

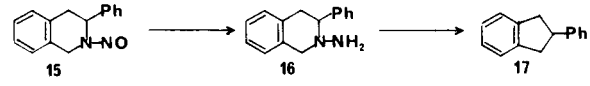
bromine-containing impurities. Various attempts to remove bromine by chemical means, such as zinc-acetic acid, sodium iodide-triethylamine-methyl ethyl ketone, *etc.*, failed. Apparently the intermediate 4-bromo-3-phenyl-3,4-dihydroisocoumarin is unstable and readily loses hydrogen bromide; copious quantities of hydrogen bromide were evolved during the *N*-bromosuccinimide bromination. The resulting 3-phenylisocoumarin was brominated to 3,4-dibromo-3-phenyl-3,4-dihydroisocoumarin; dehydrobromination of the latter compound gave 4-bromo-3-phenylisocoumarin which is resistant to further debromination. However, when the crude 3-phenylisocoumarin was treated with ammonia in ethanol at 100°, the resulting 3-phenylisocarbostyryl was easily purified by recrystallization.

Since attempted reduction of 3-phenylisocarbostyryl proved difficult under a variety of conditions (20), the compound was converted to its 1-chloro derivative by the method of Gabriel (19); reduction of the 1-chloro derivative with amalgamated zinc and hydrochloric acid gave a good yield of 3-phenyl-1,2,3,4-tetrahydroisoquinoline (**14**). The use of ammonia instead of sodium hydroxide in the workup prevented precipitation of zinc salts and the product was obtained free of metallic contamination.

2-Nitroso-3-phenyl-1,2,3,4-tetrahydroisoquinoline (**15**) was obtained in 77% yield by treatment of **14** with sodium nitrite and acetic acid at 73°. When **15** was treated with alkaline sodium hydrosulfite, reduction to the corresponding hydrazine **16** occurred. This constitutes an unexpected failure of a *doubly* activated *N*-nitroso compound to extrude nitrogen under these conditions. It should be recalled that both 2-nitroso-1,2,3,4-tetrahydroisoquinoline and 1-nitroso-2-phenylpiperidine also failed to eliminate nitrogen on treatment with alkaline sodium hydrosulfite. Apparently, reductive nitrogen elimination is much more sensitive to structural parameters than is oxidative nitrogen elimination from the corresponding hydrazine.

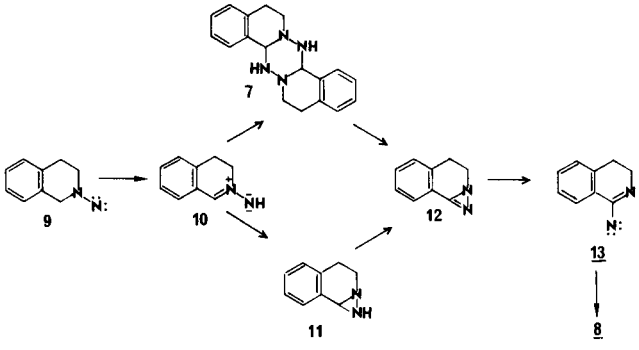
A second unanticipated result was obtained when a large scale hydrosulfite reduction was attempted. In this run, the product consisted of approximately a 1:1 mixture of the desired hydrazine and 3-phenyl-1,2,3,4-tetrahydroisoquinoline. Even though the reductive cleavage of nitrosoamines is well known, sodium hydrosulfite was thought to be relatively free from this side-reaction; only *N*-nitrosodiphenylamine was reductively cleaved to diphenylamine (22). Although 2-amino-3-phenyl-1,2,3,4-tetrahydroisoquinoline did not appear to be air sensitive, it was nonetheless stored as its hydrochloride salt and the free base regenerated just before use.

When 2-amino-3-phenyl-1,2,3,4-tetrahydroisoquinoline (**16**) was treated with yellow mercuric oxide in ethanol at 62°, 83% of the theoretical amount of nitrogen was collected. Chromatography of the crude product on alumina with hexane gave a 75% yield of 2-phenylindane (**17**), which was identical to an authentic sample. The nmr and ultraviolet spectra of the crude product before chromatography did not show any evidence of olefinic material. Indeed, the nmr spectrum showed only minor contamination of the 2-phenylindane. Authentic 2-phenylindane was prepared by the route of Datta and Bardhan (23a), after the cyclization of 2-benzoylphenethyl alcohol, prepared by an improved procedure, failed to give the desired 2-phenylindanone (2-phenylindenone?).



The Carpino reaction of *N*-tosylamino-1,2,3,4-tetrahydroisoquinoline (**6a**) and the mercuric oxide oxidation of *N*-amino-1,2,3,4-tetrahydroisoquinoline (**6**) may be rationalized by consideration of the possible modes of reac-

tion of the purative *N*-nitrene intermediate generated. It would appear that the formation of the hexahydrotetrazine **7** from the oxidation of **6** in ethanol and the Carpino reaction of **6a**, may be understood in terms of the dimerization of the dipolar tautomer **10** (3a). This dimerization, first reported by Schmitz (13) was also observed by Höft and Rieche (12), upon oxidation of **6** with a variety of oxidizing agents. The formation of **7** in this type of reaction has been adequately discussed previously and will not be dealt with further. On the other hand, the structure of the azo imine **8** suggests the imino nitrene (**13**) as its precursor. The data of Lemal *et al.* (24) ruled out diaziridines, *e.g.* **11**, as precursors of the hydrazones under the Carpino reaction conditions. It is nonetheless possible that subsequent oxidation of **11**, resulting from cyclization of **10** would yield the anti-aromatic 1-H diazirine (*e.g.* **12**). The ring opening of such diazirines to the imino nitrenes has been previously postulated (25).



It is also conceivable that the hexahydrotetrazine **7**, by a mechanism which is far from obvious, is the precursor of **8** since we have found that it is oxidized to **8** in 1-butanol at 100°. This result is to be compared with the observation of Lemal and Rave (26), who obtained the tetrahydro- and dihydro-1,2,4,5-tetrazines upon oxidation with mercuric oxide. The difference may be due to the fact that our oxidation was carried out in 1-butanol at 100° and perhaps **7** reverted to **10** under these conditions (27).

N-Nitrene intermediates may appear to be a convenient and coherent theme to rationalize many diverse reactions; however, the present data coupled with those obtained in these and other laboratories underscore the need for caution as the fate and indeed the very formation of the *N*-nitrenes may depend not only on the reaction parameters but also on the means of generation. It has been generally assumed that, if nitrogen elimination leads to stabilized fragments, fragmentation will be favored. While the oxidation of the **16** *does* lead to nitrogen extrusion, the dithionite reduction of the structurally related *N*-nitrosamine **15** clearly indicated that the possibility of generating stabilized radicals from the *N*-nitrene does not always result in the loss of nitrogen.

EXPERIMENTAL

All melting points were determined in open capillaries with total immersion thermometers. Infrared spectra were recorded on a Perkin-Elmer model 137 Infracord and the ultraviolet spectra were recorded on a Cary model 11 spectrophotometer. The nmr spectra were determined by Dr. B. Arison of the Merck Sharp and Dohme Research Laboratories on a Varian Associates A-60 spectrometer with tetramethylsilane as an internal standard. Molecular weights were determined on a Merchrolab model 301 vapor pressure manometer. Thin layer chromatogaphy (tlc) was carried out on 2 × 8 inch glass plates coated with alumina according to the Stahl method. Microanalyses were performed by Mr. R. N. Boos and associates of the Merck Sharp and Dohme Research Laboratories.

2-Nitroso-1,2,3,4-tetrahydroisoquinoline (**5**).

To a solution of 50.0 g (0.376 mole) of 1,2,3,4-tetrahydroisoquinoline in 31.4 ml (0.380 mole) of concentrated hydrochloric acid and 150 ml of water heated to 75°, was added dropwise over a period of 2 hours a solution of 26.7 g (0.380 mole) of sodium nitrite in 75 ml of water. After being stirred at 75° for an additional 2 hours, the reaction mixture was extracted four times with ether. The combined ethereal extracts were washed with water, dried over anhydrous potassium carbonate and evaporated *in vacuo*. After two recrystallizations of the yellow residue from Skelly B, there was obtained 32.9 g (54%) of 2-nitroso-1,2,3,4-tetrahydroisoquinoline, mp 52-54.5°, lit (9b) mp 51-53°. An analytical sample prepared by recrystallization from Skelly B melted at 50.5-52.5°; uv (methanol) λ max 223 mμ (log ε 3.98) and 347 mμ (log ε 1.98). Its infrared spectrum (chloroform) exhibited strong absorption at 1360 cm^{-1} (N-NO) (28).

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.28. Found: C, 66.73; H, 5.96; N, 17.35.

2-Amino-1,2,3,4-tetrahydroisoquinoline (**6**).

a) Lithium Aluminum Hydride Reduction.

A slurry of 11.2 g (0.286 mole) of lithium aluminum hydride in 300 ml of dry ether was heated at reflux for 1 hour and then cooled in an ice bath. To the cold slurry was added a solution of 32.6 g (0.200 mole) of 2-nitroso-1,2,3,4-tetrahydroisoquinoline in 100 ml of dry ether over a 1.5 hours period. The reaction mixture was stirred in an ice bath for 1 hour and then at room temperature for an additional hour. Since there was still evidence of reaction, the mixture was then heated at reflux for 1 hour before being quenched. After the dropwise addition of 50 ml of water to the cooled mixture, the precipitated salts were removed and washed with ether. The combined filtrate from washings after separation from any aqueous layer was dried over magnesium sulfate and gaseous hydrogen chloride introduced with cooling until no further precipitate formed. The white granular precipitate was collected and dried to give 16.3 g (44%) of crude 2-amino-1,2,3,4-tetrahydroisoquinoline hydrochloride, mp 189.5-192.5° dec. One recrystallization from 2:1 2-propanol-methanol gave 12.8 g of product, mp 194-196° dec. An analytical sample prepared by two recrystallizations from 2-propanol had a melting point of 199.5-202°, lit (12), mp 206-207°. Its ultraviolet spectrum exhibited (methanol): λ max 272 mμ (log ε 2.50) and 264 mμ (log ε 2.50) and its infrared spectrum (nujol) had bands at 3130 and 3230 cm^{-1} (-NH), and 2500 and 2620 cm^{-1} (≡NH^+).

Anal. Calcd. for $C_9H_{13}ClN_2$: C, 58.53; H, 7.10; N, 15.16. Found: C, 58.55; H, 7.00; N, 14.75.

A solution of 0.50 g (2.71 mmoles) of 2-amino-1,2,3,4-tetrahydroisoquinoline, 1.90 g (12.6 mmoles) of *p*-nitrobenzaldehyde and 1.00 g of anhydrous potassium acetate in 20 ml of absolute ethanol was heated at reflux for 15 minutes. After removal of the solvent *in vacuo* the residue was dissolved in ether and the ethereal solution washed successively with a 5% sodium bisulfite solution, water and saturated sodium chloride solution. The ethereal layer was then dried over magnesium sulfate, the ether removed *in vacuo* and the residue recrystallized from ethanol. The resulting yellow 2-(*p*-nitrobenzylidenamino)-1,2,3,4-tetrahydroisoquinoline weighed 0.65 g (73%), mp 116.5-117.5°, lit (12) mp 116-117°.

The benzal derivative was prepared in the same manner from 0.50 g of

2-amino-1,2,3,4-tetrahydroisoquinoline to give 0.71 g of crude product. Recrystallization from 30-60° petroleum ether gave 0.46 g (73%) of 2-benzylidenamino-1,2,3,4-tetrahydroisoquinoline, mp 65-66.5°.

b. Sodium Hydrosulfite Reduction.

The 2-nitroso-1,2,3,4-tetrahydroisoquinoline (2.44 g, 15.0 mmoles) was dissolved in 100 ml of a 1:1 ethanol-aqueous 20% sodium hydroxide solution in a 250 ml three-neck flask equipped with a stirrer, a solids addition tube (29), and a reflux condenser. The condenser was fitted with a tube leading to a 1 ℓ graduate cylinder which was filled with water and inverted in a beaker of water. After the sodium hydrosulfite (5.22 g, 30.0 mmoles) was placed in the solids addition tube, the reaction flask was placed in an oil bath heated at 62° and flushed with nitrogen for 0.5 hour. The system was then sealed and the sodium hydrosulfite added to the reaction mixture all at once. After having been stirred at 62° for 4 hours (less than 10 ml of gas was collected), the reaction mixture was cooled to room temperature and diluted with 100 ml of saturated sodium chloride solution. This solution was then extracted with two 100 ml portions and with two 50 ml portions of ether, and the combined extracts were washed once with water and then with a saturated sodium chloride solution. Gaseous hydrogen chloride was bubbled into the cooled solution, previously dried over magnesium sulfate, until no more precipitate formed. This gave 1.49 g (54%) of 2-amino-1,2,3,4-tetrahydroisoquinoline hydrochloride, mp 195.5-196.5°. Its infrared spectrum was identical to that of the lithium aluminum hydride reduction product.

Oxidation of 2-Amino-1,2,3,4-tetrahydroisoquinoline.

a) Mercuric Oxide at 58°.

A 250 ml three-neck flask equipped with a stirrer, an addition funnel and a water cooled condenser, was placed in an oil bath held at 58° and the condenser was connected to a gas buret. Yellow mercuric oxide (10.83 g, 50.0 mmoles) and 50 ml of ethanol were placed in the reaction flask and 2.80 g (18.9 mmoles) of 2-amino-1,2,3,4-tetrahydroisoquinoline (generated from the hydrochloride salt immediately before use) dissolved in 50 ml of ethanol was placed in the addition funnel. The apparatus was then flushed with nitrogen for 0.5 hour and sealed. After the hydrazine solution had been added to the mercuric oxide over a 35 minute period, the reaction mixture was stirred at 58° for 2 hours. The reaction mixture was cooled, the solid material was filtered, and the filtrate concentrated *in vacuo*. The resulting red oil weighed 1.38 g (49% recovery) and from its infrared spectrum (chloroform), appeared to be recovered starting material. The ultraviolet spectra in methanol and 0.1 *N* hydrochloric acid solution were also the same as corresponding spectra of the starting hydrazine.

The precipitate (from above) was extracted twice with 100 ml and four times with 50 ml of hot chlorobenzene and the extracts concentrated to a small volume *in vacuo*. This gave 1.09 g (39.5%) of tan 5,6,8,8a,13,13a,-16,16a-octahydro-*s*-tetrazine[6,1-*a*:3,4-*a*']diisoquinoline, (7, "hexahydrotetrazine") mp 242.5-243.5° dec. Recrystallization from 50 parts of chlorobenzene gave pure hexahydrotetrazine, mp 234-235° dec, lit mp 246-247° dec.

Anal. Calcd. for $C_{18}H_{20}N_4$: C, 73.92; H, 6.90; N, 19.16. Found: C, 73.80; H, 6.65; N, 19.11.

The picrate, prepared by refluxing the hexahydrotetrazine with alcoholic picric acid for 15 minutes was recrystallized from water to give yellow needles, mp 189-190° dec, lit (13a) mp 186-189° dec.

The nmr spectrum of the hexahydrotetrazine (as a 6% solution in dilute deuteriosulfuric acid) showed peaks (relative to external benzene at δ 6.50) at δ 3.23 (triplet, J = 7.2 Hz), 4.14 (triplet, J = 7.2 Hz), 7.55 (multiplet), and 8.51 (singlet).

b) Mercuric Oxide at 95°.

The oxidation was carried out in the same manner as the run at 58° except that the oil bath was held at 95° and 1-butanol was used as the solvent. 2-Amino-1,2,3,4-tetrahydroisoquinoline (3.31 g, 22.4 mmoles) in 90 ml of 1-butanol was added over a 1 hour period to 10.83 g (50.0 mmoles) of yellow mercuric oxide and 50 ml of 1-butanol. The reaction mixture was than allowed to stir at 95° for an additional 1.15 hours. By this time gas evolution had ceased and 163 ml of gas was collected over water at 26.5° and 762 mm pressure (25% of theory). The reaction mixture was then filtered to remove mercury salts and globules of mercury and the precipitate washed with 1-butanol. A total of 160 ml of clear red filtrate was obtained. A sample of this was diluted 1,000 fold with 1-butanol and the ultraviolet spectrum determined, λ max (1-butanol): 285 mμ (d = 0.620), infl 270 mμ d = 0.957), 264.5 mμ (d = 1.39), and infl mμ (d = 1.025). The peak at 264.5 mμ corresponds to 1.48 g or 46% of 1,1'-azobis-3,4-dihydroisoquinoline (**8**). The solvent was removed by vacuum distillation to leave a dark reddish brown oil. Vapor phase chromatography (2.5 meter column packed with 20% DC 200 on Chromosorb W, column temperature 120°, 60 ml/minute helium flow, Burrell Kromatog) indicated that the distillate contained only 1-butanol. Thin layer chromatography (alumina, benzene) of the distillation residue indicated that it contained at least ten components. The distillation residue was dissolved in chloroform washed with dilute hydrochloric acid, and the solvent removed *in vacuo*. The residual oil was dissolved in ether and the ether-insoluble portions was removed. The dried filtrate was evaporated *in vacuo* and gave 2.09 g of a red oil which was shown by tlc (alumina, benzene) to contain five components with one of them making up the bulk of the material. The partially purified material was chromatographed (100 g of Merck alumina for chromatography, eluting with five portions of 10-60° petroleum ether containing 0, 1, 2, 5, 10, 25, 50 and 100% benzene). The fractions eluted with benzene were combined and the solvent removed *in vacuo* to give 0.43 g of reddish needles shown by tlc to contain one major and one minor spot. After five recrystallizations from *n*-hexane, 97.3 mg of 1,1'-azobis-3,4-dihydroisoquinoline (**8**) was obtained as orange prisms, mp 150.5-151.5°. Its ultraviolet spectrum showed λ max (methanol): 374 mμ (log ε 2.56), infl 303.5 mμ (log ε 3.66), and 263 mμ (log ε 4.51); and also λ max (0.1*H* hydrochloric acid): infl 324.5 mμ (log ε 3.86), infl 307 mμ (log ε 4.05), 297 mμ (log ε 4.04). The infrared spectrum (chloroform) showed absorptions at 3050 cm^{-1}, 2900 cm^{-1}, 1600 cm^{-1}, and 1575 cm^{-1}. The molecular weight in chloroform was 929 (theory 288). The nmr spectrum (deuteriochloroform) exhibited multiplets at δ 8.05 and 7.28, a triplet at δ 3.66 (J = 5.5 Hz) and a triplet at δ 6.95 (J = 5.5 Hz).

Anal. Calcd. for $C_{18}H_{16}N_4$: C, 75.13; H, 5.59; N, 19.43. Found: C, 75.15; H, 5.55; N, 19.75.

2-*p*-Toluenesulfonamido-1,2,3,4-tetrahydroisoquinoline (**6a**).

A mixture of 1.85 g (10.0 mmoles) of 2-amino-1,2,3,4-tetrahydroisoquinoline hydrochloride, 2.81 ml (20.2 mmoles) of triethylamine, 1.91 g (10.0 mmoles) of *p*-toleuenesulfonyl chloride and 10 ml of dimethylformamide was stirred in an ice bath for 0.5 hour. The reaction mixture was then diluted with 100 ml of water to give an oil which slowly crystallized. The solid was collected and dissolved in 20 ml of hot acetone, and this solution slowly diluted with 50 ml of water. The crude product, 2.53 g, mp 122-124° dec, was crystallized once from acetone-water, then twice from benzene to give 1.51 g (50%) of pure 2-*p*-toluenesulfonamido-1,2,3,4-tetrahydroisoquinoline, mp 125-127° dec. The ultraviolet spectrum exhibited λ max (methanol 272 mμ (log ε 2.97), 263 mμ (log ε 3.06), infl 255 mμ (log ε 3.08), and infl 255 mμ (log ε 4.10). The infrared spectrum (chloroform) showed absorption at 3250 cm^{-1}, (-NH), and strong absorption at 1330 cm^{-1} and 1160 cm^{-1} (-SO_2-).

Anal. Calcd. for $C_{16}H_{18}N_2O_2S$: C, 63.54; H, 6.00; S, 10.60. Found: C, 63.21; H, 5.84; S, 10.51.

Reaction of 2-*p*-Toluenesulfonamido-1,2,3,4-tetrahydroisoquinoline with Base.

A slurry of 1.00 g (3.31 mmoles) of 2-*p*-toluenesulfonamido-1,2,3,4-tetrahydroisoquinoline in 5 ml of 20% aqueous sodium hydroxide was heated for 2 hours at 80-90°. During the reaction, the slurry changed in appearance but never cleared up. After dilution with 10 ml of water, the precipitate was collected, washed with water, and dried in vacuum. The yield of 5,6,8,8a,13,14,16a-ocathdyro-*s*-tetrazine[6,1-*a*:3,4-*a*']diisoquinoline (hexahydrotetrazine) was 0.49 g (99%), mp 222-229° dec, mixed mp with hexahydrotetrazine (prepared by mercuric oxide oxidation at 58°) 228-230°. The mp varies with the rate of heating; a sample melted at

241-243° dec, when heated at about 6°/minute the infrared spectrum (nujol) was identical with that of the product obtained from the mercuric oxide oxidation of the corresponding hydrazine at 58°.

The filtrate was acidified with hydrochloric acid and extracted with ether. After being washed with water and a saturated sodium chloride solution, the ethereal extract was dried over magnesium sulfate. Removal of the ether in vacuum gave 0.40 g (77%) of *p*-toluenesulfinic acid, mp 86.5-88.5°.

Reaction of 5,6,7,8a,13,14,16,16a-Octahydro-*s*-tetrazine[6,1-*a*:3,4-*a*']diisoquinoline (**7**) with Mercuric Oxide.

A mixture of 150 mg (0.695 mole) of yellow mercuric oxide, 100 mg (0.343 mmole) of hexahydrotetrazine, and 2 ml of 1-butanol was heated under nitrogen at 100° for 2 hours. During this time the mercuric oxide became brown and globules of mercury were visible. The reaction mixture was filtered and the filtrate evaporated to dryness in vacuum to give 80.0 mg of a red oil. A tlc (alumina, benzene) showed a major spot corresponding to compound **8**, a less intense spot at the origin and two minor spots just ahead of the azobis spot of **8**. The infrared spectrum (chloroform) was consistent with compound **8** and the ultraviolet spectrum showed λ max (methanol): 262.5 mμ (E% 905) corresponding to 81% of **8** or 66% of theory. Three recrystallizations from hexane gave 12.7 mg of orange needles, mp 147-150°. The infrared spectrum (chloroform) was identical to that of 1,1'-azobis-3,4-dihydroisoquinoline obtained above.

3-Phenylisocoumarin.

To a 2 ℓ three-neck flask equipped with a stirrer and a reflux condenser protected by a drying tube was added 100 g (0.448 mole) of 3,4-dihydro-3-phenylisocoumarin, 95.6 g (0.548 mole) of *N*-bromosuccinimide, 1.00 g (0.004 mole) of benzoyl peroxide and 1 ℓ of carbon tetrachloride. The mixture was then rapidly heated to reflux whereupon a vigorous reaction occurred with the evolution of copious quantities of hydrogen bromide. An ice bath was used to moderate the reaction during the first few minutes. After the vigorous reaction had subsided, the mixture was heated at reflux for 2 hours at which time the color had faded from red to light yellow and the evolution of hydrogen bromide had diminished. Succinimide was removed by filtration and the filtrate was concentrated in vacuum to remove carbon tetrachloride. To the residual oil dissolved in 1 ℓ of ethanol, was added 50 g of sodium acetate and the mixture heated at reflux for 2 hours. The ethanol was then removed in vacuum, the residue partitioned between 500 ml of water and 500 ml of benzene, and the layers separated. The aqueous phase was extracted twice with 200 ml of benzene, the combined organic phase was washed twice with 200 ml of a saturated sodium chloride solution and dried over magnesium sulfate. Removal of the solvent in vacuum gave 113 g of crude product which gave a strong Beilstein test. A sodium iodide in acetone test gave a light yellow color.

The crude product, combined with 139 g of the crude material for a second run (prepared from 123 g of 3,4-dihydro-3-phenylisocoumarin) was recrystallized from 95% ethanol to give 142 g of impure 3-phenylisocoumarin, mp 73-84°, lit (30) 90-91°. A Beilstein test was strongly positive while a sodium iodide in acetone test was negative. A tlc (alumina, benzene) showed one major spot and one small, slightly more mobile spot. All attempts at purification failed.

3-Phenylisocarbostyryl.

Crude 3-phenylisocoumarin (50.0 g, 0.225 mole, mp 73-84°) and 500 ml of ethanol saturated with ammonia (150 g) were heated at 100° for 4 hours. After removal of the solvent in vacuum, the residue was recrystallized from ethanol to give 36.7 g (73%) of tan needles, mp 200-203°; tlc (alumina, chloroform) was single spot.

A sample was recrystallized from ethanol to give pure 3-phenylisocarbostyryl, mp 201-202.5°, lit (31) 194-195°.

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.39; H, 5.01; N, 6.33. Found: C, 81.22; H, 4.75; N, 6.15.

1-Chloro-3-phenylisoquinoline.

A mixture of 60.0 g (0.271 mole) of 3-phenylisocarbostyryl and 120 g of phosphorus oxychloride was heated at reflux for 0.5 hour. After cooling in an ice bath, the reaction mixture was quenched by the cautious addition of 60 ml of ethanol followed by 300 ml of water. The resulting precipitate was filtered, washed with water, and crystallized from ethanol (charcoal) to give 54.2 g (84%) of grey needles, mp 76-78°. Recrystallization from ethanol (charcoal) gave 40.4 g of 1-chloro-3-phenylisoquinoline, mp 76.5-78°. A tlc (alumina, hexane) showed only a single spot.

Anal. Calcd. for $C_{15}H_{10}ClN$: Cl, 14.79. Found: Cl, 14.94.

3-Phenyl-1,2,3,4-tetrahydroisoquinoline (**14**).

In a 2 ℓ three-neck flask equipped with a stirrer, a condenser and a dropping funnel was placed 37.1 g (0.154 mole) of 1-chloro-3-phenylisoquinoline, 240 g of amalgamated zinc dust [amalgamated by the method of Marvel and Caesar (32)] and 600 ml of ethanol. The mixture was heated to reflux and 40 ml of concentrated hydrochloric acid was added over a 0.75 hour period. Reflux was continued for three days with 20 ml portions of concentrated hydrochloric acid being added on the second and third days. The reaction mixture was then decanted from unreacted zinc and the bulk of the solvent removed in vacuum. The residue was cooled in an ice bath and 500 ml of concentrated ammonium hydroxide was slowly added. The oil which separated, was extracted into ether and the extract was washed successively with dilute ammonium hydroxide, water and a saturated sodium chloride solution. After being dried over magnesium sulfate, the solvent was removed in vacuum to give 32.7 g of 3-phenyl-1,2,3,4-tetrahydroisoquinoline, mp 40-46°, lit (19) 45-48°.

The free base was slurried with ether and 6 g of gaseous hydrogen chloride introduced with cooling. This gave 34.8 g (92%) of 3-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride, mp 250-254°.

Anal. Calcd. for $C_{15}H_{16}ClN$: N, 5.70; Cl, 14.46. Found: N, 5.55; Cl, 14.17.

2-Nitroso-3-phenyl-1,2,3,4-tetrahydroisoquinoline (**15**).

A solution of 8.00 g (32.5 mmoles) of 3-phenyl-1,2,3,4-tetrahydroisoquinoline in 40 ml of water and 4 ml of acetic acid was heated at 75° while a solution of 2.35 g (34.1 mmoles) of sodium nitrite in 10 ml of water was added over a 1 hour period. After an additional 2 hours at 75°, the reaction mixture was extracted with chloroform. The chloroform extract was washed with water and a saturated sodium chloride solution and dried over magnesium sulfate. Removal of the solvent in vacuum gave a tan solid which was recrystallized from benzene-hexane to give 5.95 g (77%) of 2-nitroso-3-phenyl-1,2,3,4-tetrahydroisoquinoline, mp 135-137°. The ultraviolet spectrum showed λ max (methanol): 235 mμ (log ε 3.94) and the infrared spectrum (chloroform) showed strong absorption at 1350 cm^{-1} (N-N=O).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.63; H, 5.93; N, 11.76. Found: C, 75.60; H, 5.63; N, 11.54.

2-Amino-3-phenyl-1,2,3,4-tetrahydroisoquinoline (**16**).

A slurry of 5.00 g (21.0 mmoles) of 2-nitroso-3-phenyl-1,2,3,4-tetrahydroisoquinoline in 125 ml of ethanol and 125 ml of 20% aqueous sodium hydroxide solution was heated to 50°. The system was flushed with nitrogen and 8.02 g (46.0 mmoles) of sodium hydrosulfite was added. After heating at 50° for 5 hours, the reaction mixture was diluted with an equal volume of a saturated sodium chloride solution and extracted with ether. The ethereal extract was washed with a saturated sodium chloride solution and dried over magnesium sulfate. Then 2.6 ml of 10*N* hydrogen chloride in ethanol was added and the crude product collected by filtration to give 3.10 g (56%), mp 177-183° dec. A tlc (alumina, 1:1 benzene-chloroform) indicated that the product contained one major spot and a trace spot with mobility corresponding to the starting *N*-nitroso compound, while the mother liquor showed a trace spot of product, a major spot corresponding to the starting *N*-nitroso compound and a medium intensity spot at the solvent front. Two recrystallizations from ethanol-ether gave 1.63 g of pure 2-amino-3-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride, mp 220.5° dec, very dependent on the rate of heating,

about 3°/minute. The ultraviolet spectrum showed λ max (methanol): 272 mμ (log ε 2.60), 264 mμ (log ε 2.74), and 252 mμ (log ε 2.64).

Anal. Calcd. for $C_{15}H_{17}ClN_2$: C, 69.07; H, 6.57; N, 10.74. Found: C, 69.00; H, 6.47; N, 11.01.

A sample of the hydrochloride was converted to the free base to give 2-amino-3-phenyl-1,2,3,4-tetrahydroisoquinoline, mp 119.5-121°.

A *p*-nitrobenzal derivative was prepared by refluxing a mixture of 0.50 g (1.91 mmoles) of 2-amino-1-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride, 2.00 g (13.3 mmoles) of *p*-nitrobenzldehyde, and 1.00 g of sodium acetate in 20 ml of ethanol to give 0.42 g (62%) of bright orange needles, mp 137-140°. The infrared spectrum (chloroform) showed absorption at 1540 cm^{-1} (C=N), and 1510 and 1330 cm^{-1} (s) (NO_2).

Anal. Calcd. for $C_{22}H_{29}N_3O_2$: N, 11.75. Found: N, 12.05.

A second sodium hydrosulfite reduction was made starting with 25.00 g (0.105 mole) of 2-nitroso-3-phenyl-1,2,3,4-tetrahydroisoquinoline. The reduction was carried out as before except that the temperature was 54° and the reaction time was 4 hours. The yield of crude hydrochloride salt was 16.7 g (61%) mp 197-208°. Two recrystallizations from ethanol-ether gave 11.3 g of material melting at 204-213° dec. A tlc (alumina, 1:1 benzene-chloroform) showed two spots of approximately equal intensity with mobilities corrsponding to 3-phenyl-1,2,3,4-tetrahydroisoquinoline and 2-amino-3-phenyl-1,2,3,4-tetrahydroisoquinoline.

Mercuric Oxide Oxidation of 2-Amino-3-phenyl-1,2,3,4-tetrahydroisoquinoline.

A slurry of 0.815 g (13.76 mmoles) of yellow mercuric oxide in 10 ml of absolute ethanol in a 50 ml three-neck flask fitted with a stirrer, an addition funnel, and a reflux condenser was heated to 62° in a constant temperature oil bath. In the addition funnel was placed a solution of 0.385 g (1.71 mmoles) of 2-amino-3-phenyl-1,2,3,4-tetahydroisoquinoline in 20 ml absolute ethanol and the apparatus was flushed with nitrogen for 0.5 hour. The nitrogen inlet was then removed and the condenser connected to a water filled gas buret. After addition of the hydrazine solution over a 15 minute period, the reaction mixture was allowed to stir at 62° for an additional 4.25 hours. By this time gas evolution had ceased and a total of 35.67 ml (83% of theory) at 25.5° and 765 mm pressure being collected. After filtration of the grey inorganics, the ethanol was removed in vacuum (water pump, 40°) to leave a light red oil weighing 0.460 g. A tlc (silica gel, hexane) showed one major spot corresponding to 2-phenylindane and three minor, more polar spots, while a second tlc (alumina, 1:1 benzene-chloroform) indicated that the polar spots were neither 2-amino-3-phenyl-1,2,3,4-tetarhydroisoquinoline nor 3-phenyl-1,2,3,4-tetrahydroisoquinoline but were more mobile. The nmr spectrum (15% in deuteriochloroform) showed peaks attributable to 2-phenylindane (estimated to make up 80-90% of the total), a weak peak at δ 0.25 (probably due to silicone oil used to lubricate the stirrer shaft), a very weak hump δ 1.28 and a weak shoulder on the low field side of the aromatic band.

The crude product was chromatographed on 30 g of Merck acid-washed alumina and eluted with hexane. The first fraction was discarded; the next seven fractions were combined and the hexane removed *in vacuo* (4 mm Hg, bath temperature slowly increased to 90°) to give 0.250 g (75%) of an oil which was distilled through a 10 cm Vigreux column to yield pure 2-phenylindane bp 136-138°/2.2 mm Hg, n_D^{25} 1.5906, lit (23b) n_D^{25} 1.5910. Its infrared spectrum was identical to that of authentic 2-phenylindane while a tlc (silica gel, hexane) showed a single spot with the same mobility as 2-phenylindane. The nmr spectrum (10% in deuteriochloroform) exhted a complex band at δ 3.25 due to the four hydrogens at positions 1 and 3, a complex band at δ 3.65 due to the single hydogen at position 2, and a doublet at δ 7.25 due to the aromatic hydrogens.

2-Benzoylphenethyl Alcohol.

A mixture of 3.90 g (19.9 mmoles) of desoxybenzoin, 0.65 g (21.6 mmoles) of paraformaldehyde, 0.20 g (1.45 mmoles) of anhydrous potassium carbonate and 10 ml of dimethylformamide was stirred at room temperature overnight. The reaction mixture was then poured into 100 ml of water, acidified with concentrated hydrochloric acid, and the resulting oil was extracted into benzene. The extract was washed with water, then with a saturated sodium chloride solution and dried over magnesium sulfate. Removal of the solvent *in vacuo* gave 4.19 g (96%) of crude product, mp 60-70°. One recrystallization from benzene-hexane gave 3.39 g of pure 2-benzoylphenethyl alcohol, mp 70.5-74.5°; Plattner *et al.* (23b) reported a bp 123°/0.1 mm. The ultraviolet spectrum showed λ max (methanol): infl 269 mμ (log ε 3.32) and 246.5 mμ (log ε 408). The infrared spectrum (chloroform) showed absorption at 3650 cm^{-1} (OH) and strong absorption at 1680 cm^{-1} (C=O). The nmr spectum (10% in deuteriochloroform) showed a broad singlet at δ 3.20 (OH), a pair of quartets at δ 3.82 and δ 4.28 (nonequivaent protons adjacent to the OH), a quartet centered at δ 4.80 (benzylic proton), a complex band at δ 7.35 (aromatic protons), and a complex band at δ 7.93 (aromatic protons *ortho* to the carbonyl).

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