Synthesis of Isoquinolines. III. A New Synthesis of 1,2,3,4-Tetrahydroisoquinolines[1]

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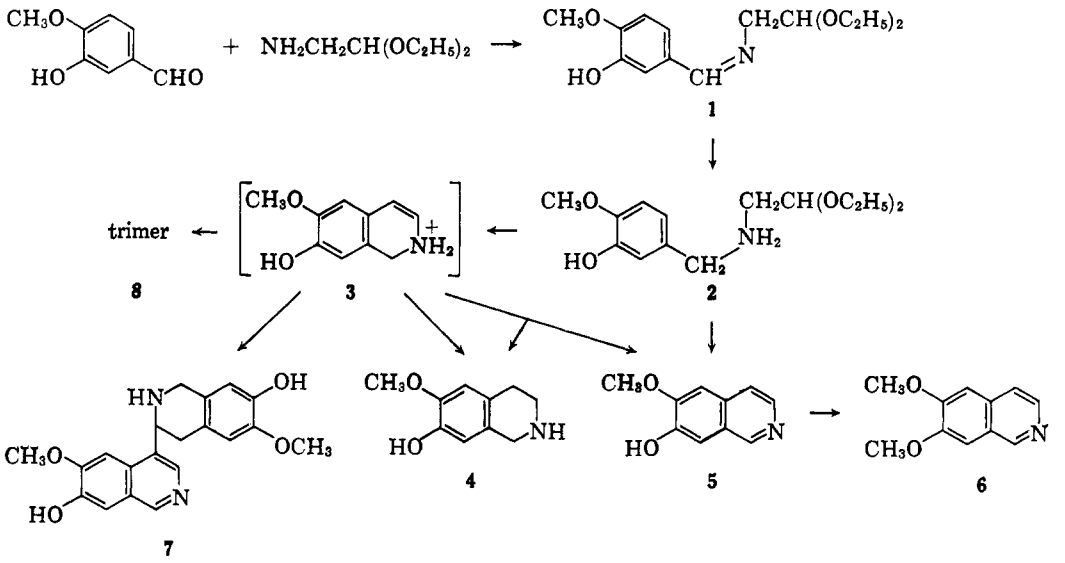
A new synthesis of 1,2,3,4-tetrahydroisoquinolines has been elaborated. It is based upon the reductive cyclization of N-benzylaminoacetaldehydes and is similar to the Fischer modification of the Pomeranz–Fritsch synthesis. The reactions of N-benzylaminoacetaldehydes with dilute acid were studied.

The initial goal of this research was to synthesize 7-hydroxy-6-methoxyisoquinoline (**5**) for use in a program of isoquinoline alkaloid synthesis. During the course of the work, **5** was produced, but, more importantly, a new synthesis of 1,2,3,4-tetrahydroisoquinolines was discovered. The new synthesis is characterized by high yields and experimental simplicity.

The most attractive route to **5** involved a Pomeranz–Fritsch[3–5] synthesis from isovanillin. Accordingly, **1** was prepared and treated with sulfuric acid under a variety of conditions. Tars were the only products. The most common variation of the Pomeranz–Fritsch synthesis (the Fischer variation[5,6]) would involve treatment of the N-benzylaminoacetaldehyde diethyl acetal (**2**) with fuming sulfuric acid. Catalytic reduction of **1** to **2** proceeded satisfactorily and treatment of **2** with acid yielded **5** in 12% yield. Compound **5** was crystalline and was characterized as a picrate and a styphnate. Its structure was confirmed by methylation to the known compound **6**.[7]



Next, the cyclization of **2** was attempted under mild conditions.[8] Hopefully, the 1,2-dihydroisoquinoline **3** would be sufficiently stable[9] to isolate and aromatize to **5**. Such was not the case, but treatment of **2** with 6 *N* hydrochloric acid did lead to a host of compounds.

Two monomeric products, **5** and **4**,[10] were isolated in yields of 6 and 2%, respectively. Compound **4** was converted to **5** by aromatization. The Fischer variation has been assumed[5] to involve fuming sulfuric acid as both a cyclization reagent and an oxidizing agent. The presence of **4** and **5** in the reaction mixture with dilute hydrochloric acid suggests that a disproportionation is taking place, as suggested by Hückel and Graner.[11]

A dimeric compound precipitated as the hydrochloride when the reaction mixture (**2** and 6 *N* hydrochloric acid) was allowed to stand several days. Basification of the hydrochloride yielded a compound which was crystalline, not particularly stable, and insoluble in almost any solvent except dimethyl sulfoxide. Methylation and acetylation of the compound gave inseparable mixtures, and no chemical means were found to prove the structure. Fortunately, the n.m.r. spectrum was unique and allowed the postulation of structure **7**. Compound **7** would result from an acid-catalyzed aldol condensation of **3**[12] followed by aroma-

(1) (a) Paper II: J. M. Bobbitt, K. L. Khanna, and J. M. Kiely, *Chem. Ind.* (London), 1950 (1964). (b) This work was supported in part by Grant CA-3905 from the National Cancer Institute of the National Institutes of Health.

(2) Abstracted in part from the M.S. Thesis of J. M. K., The University of Connecticut, 1964.

(3) C. Pomeranz, *Monatsh. Chem.*, **14**, 116 (1893); **15**, 299 (1894).

(4) P. Fritsch, *Ann.*, **286**, 1 (1895).

(5) W. J. Gensler, *Org. Reactions*, **6**, 192 (1951).

(6) (a) E. Fischer, *Ber.*, **26**, 764 (1893); (b) R. H. F. Manske and M. Kulka, *Can. J. Res.*, **27B**, 161 (1949).

(7) (a) L. Rügheimer and P. Schön, *Ber.*, **42**, 2374 (1909); (b) E. Späth and N. Polgar, *Monatsh. Chem.*, **51**, 190 (1929); (c) R. Forsyth, C. Kelly, and F. Pyman, *J. Chem. Soc.*, **127**, 1659 (1925).

(8) This was suggested to us by Professor C. K. Bradsher of Duke University.

(9) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 960 (1949); L. M. Jackman and D. I. Packham, *Chem. Ind.* (London), 360 (1955).

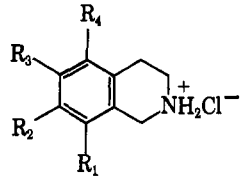
(10) (a) This compound has been reported,[b] but there is a considerable discrepancy in the melting points reported and those in this paper, see Table I. (b) M. Onda, M. Kawanishi, and M. Sasamoto, *J. Pharm. Soc. Japan*, **76**, 409 (1956); *Chem. Abstr.*, **50**, 13930 (1956).

(11) W. Hückel and G. Graner, *Ber.*, **90**, 2017 (1957).

(12) (a) R. W. Layer, *Chem. Rev.*, **63**, 498 (1963); (b) R. Grewe, W. Krueger, and F. Vangermain, *Ber.*, **97**, 119 (1964).

TABLE I

SYNTHESIS OF 1,2,3,4-TETRAHYDROISOQUINOLINE HYDROCHLORIDES



Compd.	R_1	R_2	R_3	R_4	Yield,[a] %	M.p., °C.	Calcd., % C	H	N	Cl	Found, % C	H	N	Cl
14	H	OH	OCH_3	H	67	256–258[b]	55.67	6.54	6.50	16.46	55.53	6.79	6.51	16.81
15	H	OCH_3	OH	H	71	260–263[c]	55.67	6.54	6.50	16.46	55.23	6.45	6.53	16.62
16	OH	OCH_3	H	H	75	282–283	55.67	6.54	6.50	16.46	55.54	6.63	6.56	16.50
17	H	OCH_3	OCH_3	OCH_3	78	268–269	55.48	6.98	5.39	13.68	55.88	6.94	5.22	13.89
18	H	OCH_3	OCH_3	H	68	251–252[d]	57.50	7.02	6.09	15.45	57.61	7.14	6.31	15.99
19	H	OCH_3	H	H	58	233–234[e]	60.13	7.07	7.01	17.77	60.07	7.25	7.15	18.15

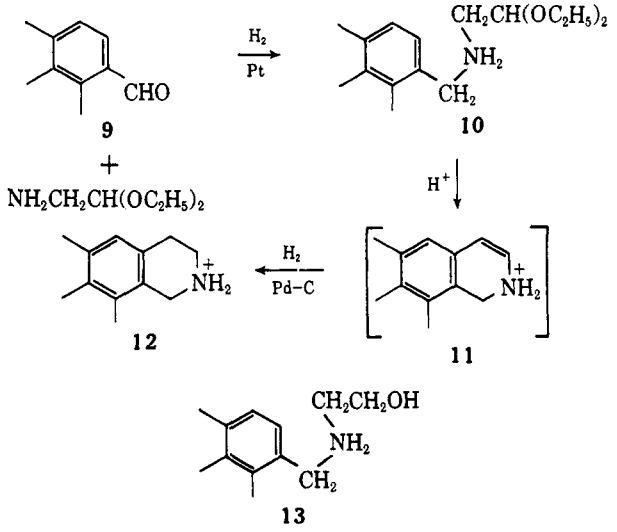
[a] Yields are based on starting aldehydes. [b] Lit.[10b] m.p. 248°. [c] D. Beke and C. Szantay [*Acta Chim. Acad. Sci. Hung.*, **14**, 325 (1958)] reported m.p. 247–249°. [d] J. S. Buck [*J. Am. Chem. Soc.*, **56**, 1769 (1934)] reported m.p. 253°. [e] Lit.[4] m.p. 228–229°.

tization (by disproportionation). The spectrum taken in dimethyl sulfoxide had six singlets corresponding to the six aromatic protons at τ 1.10, 1.58, 2.44, 2.67, 3.32, and 3.44. The peak at τ 1.58 can be assigned to one of the protons α to the aromatic nitrogen.[13] The two methoxyl group peaks occur at τ 6.05 and 6.27.[14] The peak at τ 6.05 has a shoulder at 6.00 which corresponds to two protons. This may be the ring methylene protons adjacent to the nitrogen. There are two split peaks accounting for three protons in the spectrum, a triplet at τ 5.45 and a doublet at 7.06. These have identical splitting constants (J = 8 c.p.s.). The CH_2CH ring group would be expected to give this splitting combination. Finally, the hydroxylic protons occur around τ 4.9.

The last product was isolated by column chromatography of the product mixture obtained by basification and extraction of the reaction mixture. It was a crystalline compound whose elemental analysis corresponded to either **3** or **7**, but which was completely insoluble in all available organic solvents. It may well be a trimer (**8**) corresponding to the trimer isolated by Hückel and Graner[11] from 1,2-dihydroisoquinoline.

If it is assumed that compound **3** is formed first and has a reasonable lifetime in the reaction mixture, it would appear that cyclization in the presence of appropriate reducing conditions would give **4** in reasonable yield. In fact, treatment of **2** with 6 N hydrochloric acid in a hydrogenation apparatus in the presence of hydrogen and palladium on carbon yielded **4** as its crystalline hydrochloride in good yield. The aromatization of **4** to **5** in 63% yield finally realized the basic intent of the work.

It appeared that the reductive cyclization of **2** to **4** might well serve as a new synthetic method for the preparation of 1,2,3,4-tetrahydroisoquinolines. This could be visualized as **9** → **10** → **11** → **12**. Quelet, Vinot, and their co-workers[15] explored extensively the reaction of derivatives of **10** with boron trifluoride. The products were 4-ethoxy-1,2,3,4-tetrahydroisoquinolines which could easily be transformed to the aromatic isoquinolines by dehydrogenation (loss of ethanol and hydrogen). The reactions, however, gave reasonable yields only when the isoquinoline obtained was unsubstituted in the benzene ring or when it had a 6-substituent. The presence of oxygen functions in the benzene ring markedly decreased the yields.[15b]



Attempts were subsequently made to convert the aldehydes mentioned in Table I to 1,2,3,4-tetrahydroisoquinolines. The aldehydes were combined with a molar amount of aminoacetaldehyde diethyl acetal and reduced, in ethanol at room temperature and pressure, over a platinum oxide catalyst. The mixtures were filtered, evaporated to dryness, and, without isolation, taken up in 6 N hydrochloric acid. The acid solutions were washed with ether, allowed to stand overnight, and reduced, again at room temperature and pressure, over a palladium-on-carbon catalyst. The filtered solutions were evaporated under vacuum and addition of alcohol precipitated the 1,2,3,4-tetrahydroisoquinoline hydrochlorides (Table I). In most cases, the bases were liberated from their hydrochloride salts and characterized as such. In all cases, picrates were prepared. These are given in Table II.

There was no evidence of any *ortho* ring closure in the compounds where such could occur. In particular, the n.m.r. spectra of 6-hydroxy-7-methoxy- and

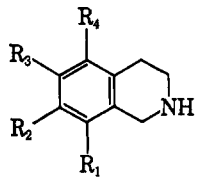
(13) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press Ltd., London, 1959, p. 64.

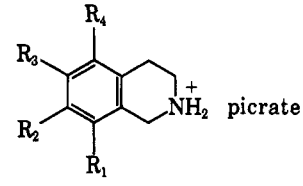
(14) Reference 13, p. 55.

(15) (a) R. Quelet and N. Vinot, *Compt. rend.*, **244**, 909 (1957); (b) N. Vinot and R. Quelet, *ibid.*, **246**, 1712 (1958); *Bull. soc. chim. France*, 1164 (1959); (c) N. Vinot, *Ann. chim.* (Paris), [13], **3**, 461 (1958); *Bull. soc. chim. France*, 617 (1960).

TABLE II

1,2,3,4-TETRAHYDROISOQUINOLINES AND THEIR PICRATES





Compd.	M.p., °C.	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	M.p., °C.	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
14	216–217[a]	67.02	7.31	7.82	67.39	7.51	7.48	221–223	47.06	3.95	13.72	47.13	3.91	13.71
15	230–233	67.02	7.31	7.82	66.98	7.42	7.88	238–240	47.06	3.95	13.72	47.25	3.78	14.00
16	*b*							204–206	47.06	3.95	13.72	47.28	4.01	13.78
17	71–72	64.55	7.67	6.27	64.20	7.53	6.10	175–177	47.79	4.46	12.38	47.47	4.43	12.06
18	84–85	68.37	7.82	7.25	68.67	7.60	7.17	203–205	48.35	4.30	13.27	48.61	4.21	13.28
19	*b*							215–216	48.98	4.11	14.28	49.21	4.06	14.46

[a] Lit.[4] m.p. 197–199°. [b] These free bases were fairly unstable liquids and were not characterized.

7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinolines showed the two aromatic protons as uncoupled single peaks (at about τ 3.3 and 3.4). When the acid reaction mixture was not allowed to stand overnight before reduction, the yields were lower owing to the formation of compounds of type **13**. Compound **13** itself was isolated from the reaction of vanillin after a short-term reaction. It was prepared as confirmation from vanillin and ethanolamine. This appears to be the major side reaction. Various other acid concentrations (3 and 9 *N*) as well as several time intervals for the acid reaction were investigated. In each case yields were lower.

Several compounds were investigated which gave unsatisfactory results. Three halogen compounds, 3-chlorobenzaldehyde, 4-chlorobenzaldehyde, and 4-bromobenzaldehyde were studied. In each of these, the first hydrogenation step appeared to be at fault (much over-reduction) and no products could be isolated. The reactions with 4-methoxybenzaldehyde, 2,4-dimethoxybenzaldehyde, and 3-methylbenzaldehyde yielded products whose analysis agreed best with structures similar to **13**. In summary, it appears that an oxygen must be in the position *para* to the point of ring closure.

Experimental[16]

N-(3-Hydroxy-4-methoxy)benzylaminoacetal (2).—3-Hydroxy-4-methoxybenzaldehyde (11.5 g.) and aminoacetaldehyde diethyl acetal (11.4 g.) were placed in a 500-ml., round-bottom flask and 300 ml. of benzene was added. The mixture was heated under reflux until separation of water in a Dean–Stark apparatus was complete. The benzene was evaporated and 190 ml. of absolute ethanol was added. The compound was hydrogenated in a Parr low-pressure hydrogenation apparatus under an initial pressure of 50 p.s.i. Raney nickel W-5 (about 3 g.) was used as a catalyst. After the theoretical amount of hydrogen was absorbed (about 3 hr.), the catalyst was removed by filtration and solvent was evaporated. Crystals formed. The compound was recrystallized from a mixture of benzene and hexane. The melting point of the pure compound (14.3 g.) was 59.5–61°.

Anal. Calcd. for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.38; H, 8.27; N, 5.08.

6-Methoxy-7-hydroxyisoquinoline (5).—Compound **2** (5 g.) was dissolved in 100 ml. of concentrated sulfuric acid. The solution was heated to 120° for 1 hr. After it had cooled to room temperature, it was poured into ice–water. The solution was made alkaline with ammonia and then extracted continuously with ether for 12 hr. The ether was evaporated, and the residue was taken up in chloroform. Filtration of the solution followed by evaporation of the solvent yielded 0.6 g. of the crude isoquinoline which was sublimed at 140° and 1.01 mm. The compound was recrystallized from a benzene–ethanol solution. The yield of pure 6-methoxy-7-hydroxyisoquinoline was 0.4 g. (12%). The compound melted at 182–183°.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.78; H, 5.14; N, 7.78.

The **picrate** was prepared by mixing equal volumes of saturated ethanolic solutions of picric acid and **5**. The pure picrate was recrystallized from 95% ethanol and melted at 252–254°.

Anal. Calcd. for $C_{16}H_{12}N_4O_9$: C, 45.53; H, 2.99; N, 13.86. Found: C, 47.45; H, 3.02; N, 14.03.

The **styphnate** was prepared in a manner similar to that of a picrate. The melting point of the pure styphnate recrystallized from 95% ethanol was 249–250°.

Anal. Calcd. for $C_{16}H_{12}N_4O_{10}$: C, 45.72; H, 2.88; N, 13.33. Found: C, 45.61; H, 3.25; N, 13.33.

Methylation of 6-Methoxy-7-hydroxyisoquinoline.—An ethereal solution of diazomethane (5 g.) was prepared from N,N'-dinitroso-N,N'-dimethylterephthalamide[17] according to the manufacturer's directions. The ethereal solution (about 200 ml.) was added to 100 mg. of the isoquinoline dissolved in 50 ml. of methanol. The mixture was allowed to stand overnight in an ice bath. Thin layer chromatography using 9:1 benzene–ethanol as developer showed one spot.

The **picrate** of 6,7-dimethoxyisoquinoline was prepared by addition of a saturated ethanolic picric acid solution to one-half of the isoquinoline solution. The melting point of the pure picrate recrystallized from ethanol was 223–225° (lit. m.p. 218–220°[7a,b] and 225–226°[7a,b]).

The **methiodide** of 6,7-dimethoxyisoquinoline was prepared in benzene from the second half of the solution. The crystalline derivative precipitated and was recrystallized from absolute ethanol. After prolonged drying over phosphorus pentoxide the pale buff crystals melted at 253–254° (lit.[7c] m.p. *ca.* 256° dec.).

Acid Cyclization of N-(3-Hydroxy-4-methoxy)benzylaminoacetal (2). A. Monomeric Products.—The reduced Schiff base (1.566 g.) was dissolved in 60 ml. of 6 *N* hydrochloric acid, and the solution was allowed to stand for 1 hr. and 20 min. at room temperature. The solution was made alkaline with ammonium hydroxide and then was extracted in a liquid–liquid extractor with chloroform. Evaporation of the chloroform left 1.223 g. of solid material. Of this 1.129 g. was sublimed in a vacuum sublimation (at 0.1 mm.) over a range of 150–185°. The material collected was chromatographed on preparative thin layers using methanol as developer. Three zones were separated. Two of these were crystallized. The top zone yielded 60 mg. (6%) of 6-methoxy-7-hydroxyisoquinoline (**5**). The bot-

(16) All melting points were taken on a Kofler micro hot-stage apparatus and were corrected. The n.m.r. spectra were taken on a Varian Associates A-60 instrument. The microanalyses were performed by H. Fröhofer of the Organic Chemistry Institute of the University of Zürich, Switzerland. Thin layer chromatography was done on silica gel G (Brinkmann, New York) layers, 250 μ thick. Preparative thin layer chromatography was done on silica gel G layers 1 mm. thick prepared with a Stahl-Desaga apparatus (Brinkmann, New York).

(17) Du Pont product EXR-101.

tom zone yielded 23 mg. (2%) of 6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (**4**). The tetrahydroisoquinoline was recrystallized from absolute ethanol. It melted at 216–217°.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.39; H, 7.51; N, 7.48.

The middle zone did not yield sufficient material for further work.

Acid Cyclization of 2. B. Isolation of Isoquinoline Dimer (7).—Compound **2** (2.062 g.) was dissolved in 75 ml. of 6 *N* hydrochloric acid. The solution was allowed to stand at room temperature. After several days, yellow crystals precipitated. These were removed by filtration, and new crops were collected periodically until precipitation ceased. A total of 385 mg. (24%) was collected. The hydrochloride was recrystallized from water containing a small amount of hydrochloric acid. The analytical sample melted at 272–274°.

Anal. Calcd. for $C_{20}H_{22}Cl_2N_2O_4$: C, 56.47; H, 5.18; Cl, 16.70; N, 6.59. Found: C, 56.00; H, 5.56; Cl, 16.48; N, 6.80.

The **picrate** was prepared in hot water–ethanol and melted at 238–241°. Attempted recrystallization from several solvents lowered the melting point. The analytical sample was not recrystallized.

Anal. Calcd. for $C_{32}H_{26}N_8O_{18}$: C, 47.41; H, 3.21; N, 13.83. Found: C, 47.56; H, 3.51; N, 13.69.

The free base **7** was prepared from the hydrochloride. The hydrochloride was dissolved in hot water and enough ammonium hydroxide was added to make the solution alkaline. This solution was continuously extracted with chloroform in a liquid–liquid extractor. Evaporation of solvent left a partially crystalline yellow solid which was appreciably soluble only in dimethylformamide and dimethyl sulfoxide. A sample for analysis was recrystallized from a large volume of 95% ethanol. The melting point was 233–235°. The compound was not very stable and could not be recrystallized more than once.

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95; OCH_3, 17.61. Found: C, 67.40; H, 5.91; N, 7.60; OCH_3, 17.43.

Acid Cyclization of 2. C. Isolation of Trimeric Compound (8).—The acid reaction was carried out as described in A on 4.2 g. of **2**. The chloroform extract (3.73 g. dry weight) was chromatographed on a column of silica gel 36 cm. × 3.5 cm. The column was eluted with a benzene–ether mixture (1:2 v./v.) followed by benzene–ether–methanol (1:1:1). Finally, pure methanol was passed through the column. A white crystalline solid was found in 84 fractions. This solid melted at 268–270° with some decomposition beginning at 243°. It was insoluble in all available organic solvents. The analytical sample was not recrystallized. This may be the trimer **8**.[11] The monomeric compounds were present on the column but were not isolated.

Anal. Calcd. for $C_{30}H_{33}N_3O_6$: C, 67.78; H, 6.26; N, 7.90. Found: C, 66.64; H, 6.36; N, 7.82.

Aromatization of 6-Methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (4).—The tetrahydroisoquinoline (185 mg.) was placed in a flask with 200 mg. of 10% palladium on charcoal. The mixture was refluxed in 18 ml. of *p*-cymene with magnetic stirring for 1 hr. The catalyst was removed by filtration and the solution was allowed to stand overnight. Crystals of 6-methoxy-7-hydroxyisoquinoline precipitated (90 mg.). The charcoal was treated with several portions of hot benzene and 24 mg. (total 114 mg., 63%) more of isoquinoline was collected. The compound was identical in every respect with **5** as characterized above.

1,2,3,4-Tetrahydroisoquinolines. General Procedure.—A mixture of aromatic aldehyde (0.02 mole) and aminoacetaldehyde diethyl acetal (0.02 mole) in 80 ml. of absolute ethanol was added to 0.2 g. of platinum oxide which had been prereduced under 20 ml. of the same solvent. The mixture was reduced at room temperature and pressure until hydrogenation ceased (about 4–6 hr.). The catalyst was removed by filtration and the solvent was evaporated under vacuum. The residue was taken up in 100 ml. of 6 *N* hydrochloric acid, washed with 50 ml. of ether, and allowed to stand for about 15 hr. Two grams of 5% palladium on carbon was added and the solution was reduced at room temperature and pressure until hydrogenation ceased (about 6–9 hr.). The catalyst was removed by filtration and the solvent and acid were removed on a rotary vacuum evaporator.[18] Ethanol (two 20-ml. portions) was added to the residue and evaporated. A third portion was added to facilitate removal of the product from the flask.

The products crystallized either during the second hydrogenation (8-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride), during the final evaporation, or upon addition of ethanol to the residue after evaporation. When the product crystallized with the catalyst during hydrogenation, it was removed by washing with warm water. The washings were added to the catalyst filtrate and concentrated as usual.

In each case, the product was removed by filtration and washed with a small amount of cold ethanol, dried, and weighed. The analytical samples were recrystallized from ethanol.

The **free bases** were prepared by basification of aqueous solutions with ammonium hydroxide. The solutions were extracted with chloroform; the solvent was evaporated and the analytical samples were crystallized from ethanol. The yields on a 1-g. scale were 80–90%.

The **picrates** were prepared by mixing ethanolic solutions of the hydrochlorides with saturated solutions of picric acid in benzene. The picrates crystallized and were recrystallized for analysis from ethanol.

Isolation and Synthesis of N-(4-Hydroxy-3-methoxybenzyl)-ethanolamine (13).—The reaction with vanillin was carried out as described above except that the acid cyclization reaction mixture was reduced immediately rather than after 15 hr. After the product filtration (2.1 g., 49%) the filtrate was concentrated almost to dryness. A second compound precipitated (1.1 g., 23%) which was recrystallized several times from ethanol to give pure **13** hydrochloride, m.p. 146–149°.

Anal. Calcd. for $C_{10}H_{15}NO_3 \cdot HCl$: C, 51.39; H, 6.90; Cl, 15.21; N, 6.02. Found: C, 51.34; H, 6.71; Cl, 15.40; N, 6.22.

A compound identical in every respect with this one was prepared in 83% yield by reduction of a mixture of equimolar amounts of vanillin and ethanolamine over a platinum catalyst.

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(18) This evaporation is somewhat easier if a flask containing a 10–20% solution of sodium hydroxide is in the vacuum system.