Anal. Calcd for $C_{16}H_{14}Cl_3NS$: C, 53.57; H, 2.93; Cl, 29.65; N, 3.91; S, 8.94; mol wt, 358.71. Found: C, 53.51; H, 3.92; Cl, 29.60; N, 3.70; S, 8.92; mol wt, 370.

Registry No.—**6** (R = H; X = tosyl), 16622-37-0; **6** (R = H; X = I), 16622-21-2; **6** (R = CH_3; X = I), 16622-22-3; **6** (R = $CH_2C_6H_4NO_2$; X = Br), 16622-23-4; **6** (R = H; X = Cl), 16622-24-5; **6** (R = C_6H_5; X = tosyl), 16622-25-6; **6** (R = C_6H_5; X = I), 16622-26-7; **7** (R = H), 16622-27-8; **7** [R = $C_6H_3(NO_2)_2$], 16622-28-9; **7** (R = C_6H_5), 16622-29-0; **8a**, 16622-30-3; **8b**, 16622-31-4; **8c**, 16622-32-5; **8a**, 16638-70-3; **9**, 16622-33-6; **10** (R = H), 16622-34-7; **10** (R = C_6H_5), 16622-35-8; 2-diphenylmethylbenzothiazole, 16622-36-9.

Acknowledgment.—Thanks are extended to Dr. A. J. Speziale for many helpful discussions and to Mr. F. B. Clark for technical assistance.

Synthesis of 11H-Indeno[1,2-c]isoquinoline Compounds Related to Chelerythrine

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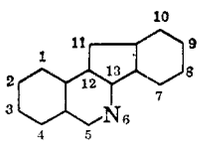
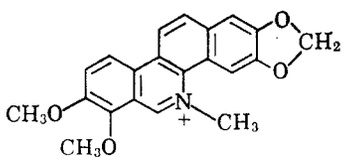
Reactions leading to the 11H-indeno[1,2-c]isoquinoline nucleus are described. 7,8-Dimethoxyisoquinoline was obtained by an acid-catalyzed cyclization of 2,3-dimethoxybenzylaminoacetal to 4-hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline followed by dehydration and dehydrogenation. Reductive condensation of the methiodide of 7,8-dimethoxyisoquinoline with benzaldehyde gave 2-methyl-4-benzyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline in low yield. The Bobbitt process, by which a benzylaminoacetal is condensed with an aromatic aldehyde, was employed effectively in producing several 4-benzylisoquinolines. Reduction of the corresponding methiodides with lithium aluminum hydride gave 1,2-dihydroisoquinolines, which cyclized under the proper acid conditions to give tetrahydro-11H-indeno[1,2-c]isoquinolines. Dehydrogenation with iodine completed the synthesis. In this way, 3,4-dimethoxy-6-methyl-8,9-methylenedioxy-11H-indeno[1,2-c]isoquinolinium iodide and 3,4,8,9-tetramethoxy-6-methyl-11H-indeno[1,2-c]isoquinolinium iodide—both related to chelerythrine—were prepared.

The authors wish to report a new synthesis for the little known 11H-indeno[1,2-*c*]isoquinoline system **1**.[1,2] The general purpose was to open a convenient way to compounds of this class; the particular purpose was to synthesize structural variations of the Sanguinaria alkaloids,[3] *e.g.*, chelerythrine (**2**).



1



chelerytarine (**2**)

The plan of synthesis required 4-benzylisoquinolines (specifically **9**) as key intermediates. Such compounds should be accessible by reductively condensing an isoquinoline methiodide (specifically **7**) with an aromatic aldehyde.[4] The resulting 4-benzyltetrahydroisoquinoline products **8** could then be dehydrogenated to produce **9**. For the compounds of interest, this approach required 7,8-dimethoxyisoquinoline (**6**), which was prepared in two ways, both making use of 2,3-dimethoxybenzylaminoacetal (**3**) as the starting material. Treatment of acetal **3** with hydrochloric acid in the presence of hydrogen and a catalyst[5] gave tetrahydroisoquinoline (**5**). Treatment of acetal **3** with hydrochloric acid in the absence of hydrogen and catalyst gave 4-hydroxytetrahydroisoquinoline (**4**).[6] Structure **4** for the hydroxy compound is consistent with its nmr spectrum. Thus, the ratio of methoxy protons to aromatic protons is 6:2 as required, and the two-proton multiplet at 2.98 ppm corresponds to the methylene group at position 3. Formation of a dibenzoyl derivative of compound **4** is also consistent with its assigned structure. Catalytic dehydrogenation converted both tetrahydroisoquinolines **4** and **5** into the same compound, the fully aromatic 7,8-dimethoxyisoquinoline (**6**).[7] The isoquinoline preparation *via* hydroxy compound **4** gave good yields (*ca.* 60%) and was simpler to carry out than the alternate preparation involving **5**. Both methods were far superior to the Pomeranz–Fritsch synthesis.[8] (See Scheme I.)

Attachment of a 4-benzyl group[4] was tried with benzaldehyde itself as the aromatic aldehyde. When a mixture of methiodide **7** and benzaldehyde was exposed to hydrogenation conditions in acid solution, the expected product, 2-methyl-4-benzyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**8**, $R_1 = R_2 = H$), was obtained. However the low yield was discouraging and,

(1) The name and numbering follow the recommendations of "The Ring Index" [L. T. Capell and D. F. Walker, Jr., 2nd Suppl. to 2nd ed, American Chemical Society, Washington, D. C., 1964, p 189] in ring number 10815.

(2) Only three references could be found, *i.e.*, J. N. Chatterjea and H. Mukherjee, *J. Indian Chem. Soc.*, **37**, 379 (1960); S. Wawzonek, J. K. Stowell, and R. E. Karll, *J. Org. Chem.*, **31**, 1004 (1966); S. F. Dyke and D. W. Brown, *Tetrahedron*, **24**, 1455 (1968).

(3) R. H. F. Manske and H. L. Holmes, "The Alkaloids," Academic Press Inc., New York, N. Y., Vol. IV, 1954; p 253; Vol. VII, 1960, p 430.

(4) Method of R. Grewe, W. Krüger, and E. Vangermain, *Chem. Ber.*, **97**, 119 (1964).

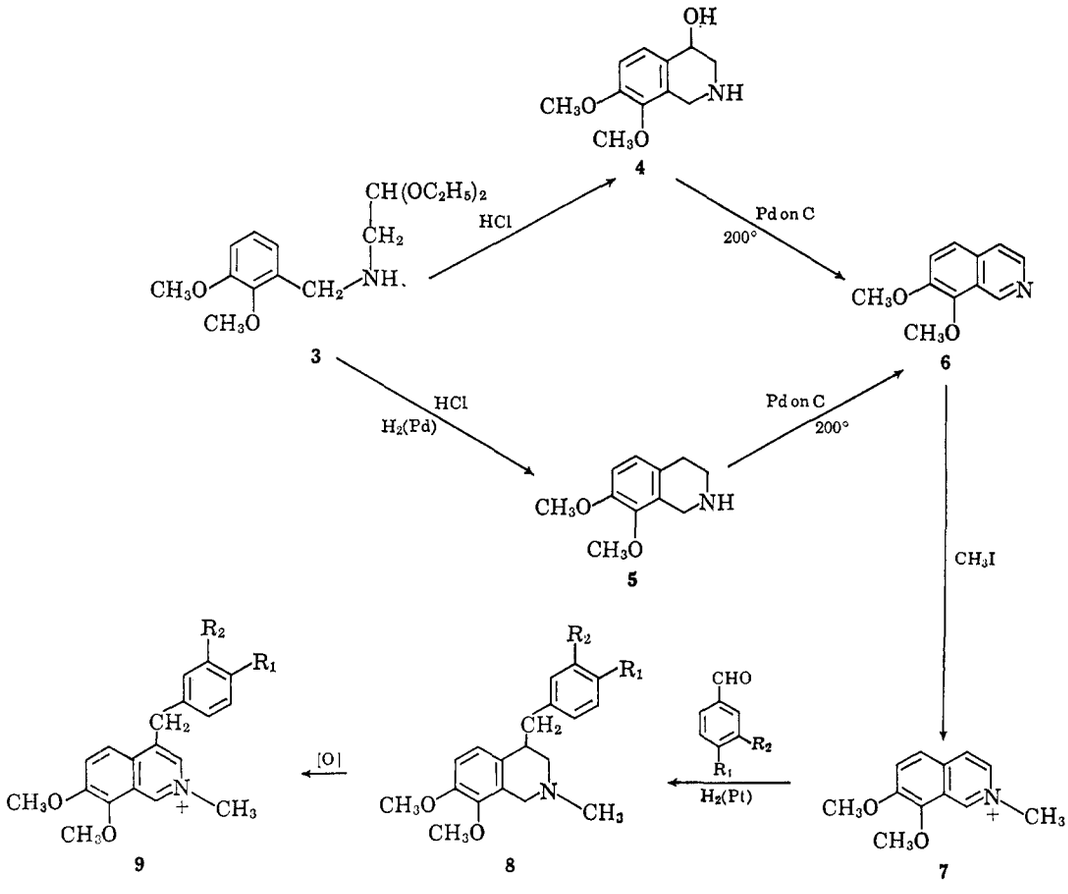
(5) J. M. Bobbitt, K. L. Khanna, and J. M. Kiely, *Chem. Ind.* (London), 1950 (1964); J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, **30**, 2247 (1965).

(6) In independent work, J. M. Bobbitt and J. C. Sih, utilizing a similar procedure, have isolated several analogous 4-hydroxytetrahydroisoquinolines [*J. Org. Chem.*, **33**, 856 (1968)]. Also *cf.* I. G. Hinton and F. G. Mann, *J. Chem. Soc.*, 599 (1959); T. Kondo and S. Tanaka, *J. Pharm. Soc. Jap.*, **50**, 923 (1930); *Chem. Abstr.*, **25**, 515 (1931).

(7) Related aromatizations of 4-ethoxy-1,2,3,4-tetrahydroisoquinolines have been reported by N. Vinot, *Bull. Soc. Chim. Fr.*, 617 (1960); *Ann. Chim.* (Paris), [13], **3**, 461 (1958).

(8) *Cf.* W. J. Gensler, *Org. Reactions*, **6**, 191 (1951). W. H. Perkin, Jr., and R. Robinson [*J. Chem. Soc.*, **105**, 2376 (1914)], using sulfuric acid in the Pomeranz–Fritsch cyclization of 2,3-dimethoxybenzalaminoacetal obtained 7,8-dimethoxyisoquinoline (**6**) in about 5% yield. C. Djerassi, F. K. Markley, and R. Ehrlich [*J. Org. Chem.*, **21**, 975 (1956)] using polyphosphoric acid brought the yield to 12–17%. In our hands, a variety of conditions produced **6** in yields no better than 8%.

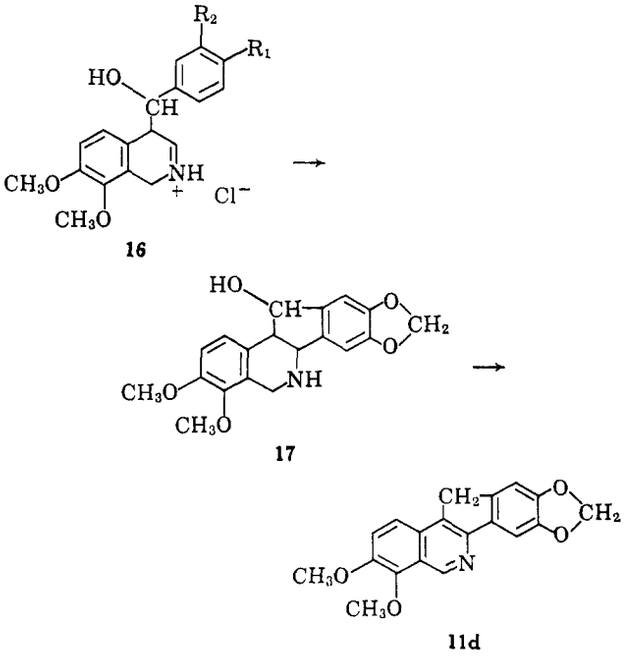
SCHEME I



when concurrent work on another approach began to show promising results, this plan was put aside.

In the alternate approach,[9] the starting material again was aminoacetal **3**. With benzaldehyde in the presence of hydrochloric acid, the aminoacetal furnished a solid hydrochloride (82%), evidently the same as that obtained by Dyke and Sainsbury[10] and formulated by them as **16a** ($R_1 = R_2 = H$). Exposing the hydrochloride to alkali generated the aromatic isoquinoline base **10a** in 72% yield. Methylation with methyl iodide formed the methiodide **9a**. The generality of this elegant method[9] was demonstrated by the use of *m*-anisaldehyde to give the corresponding 4-*m*-anisyl derivatives (**10b** and **9b**), of veratraldehyde to give the 4-veratryl derivatives (**10c** and **9c**), and of piperonal to give the 4-piperonyl derivatives (**10d** and **9d**). In every case, the acid-catalyzed condensation with the aromatic aldehydes precipitated product in the form of hydrochloride salts. The carbon content of the hydrochlorides from benzaldehyde and from piperonal was consistent with formulations **16a** and **16d**. The carbon content of the hydrochlorides from *m*-anisaldehyde and from veratraldehyde was consistent with that expected for the hydrochloride of the fully aromatic isoquinolines **10b** and **10c**. Whatever the nature of the precipitated hydrochlorides, alkali converted them smoothly into isoquinoline gases **10**.[10] (See Scheme II.)

In the reactions leading to the 4-piperonyl derivative **10d**, a side product was observed containing five aromatic protons instead of the expected seven. Methylation of this side product to indenoisoquinoline **15d** supported its formulation as **11d**. A reasonable sequence leading to **11d** would involve the intermediate condensation product **16d**,[4] which could cyclize to **17** by essentially the same mechanism as in the **12** to **13** conversion. Dehydration and dehydrogenation of **17** would lead to the observed side product.

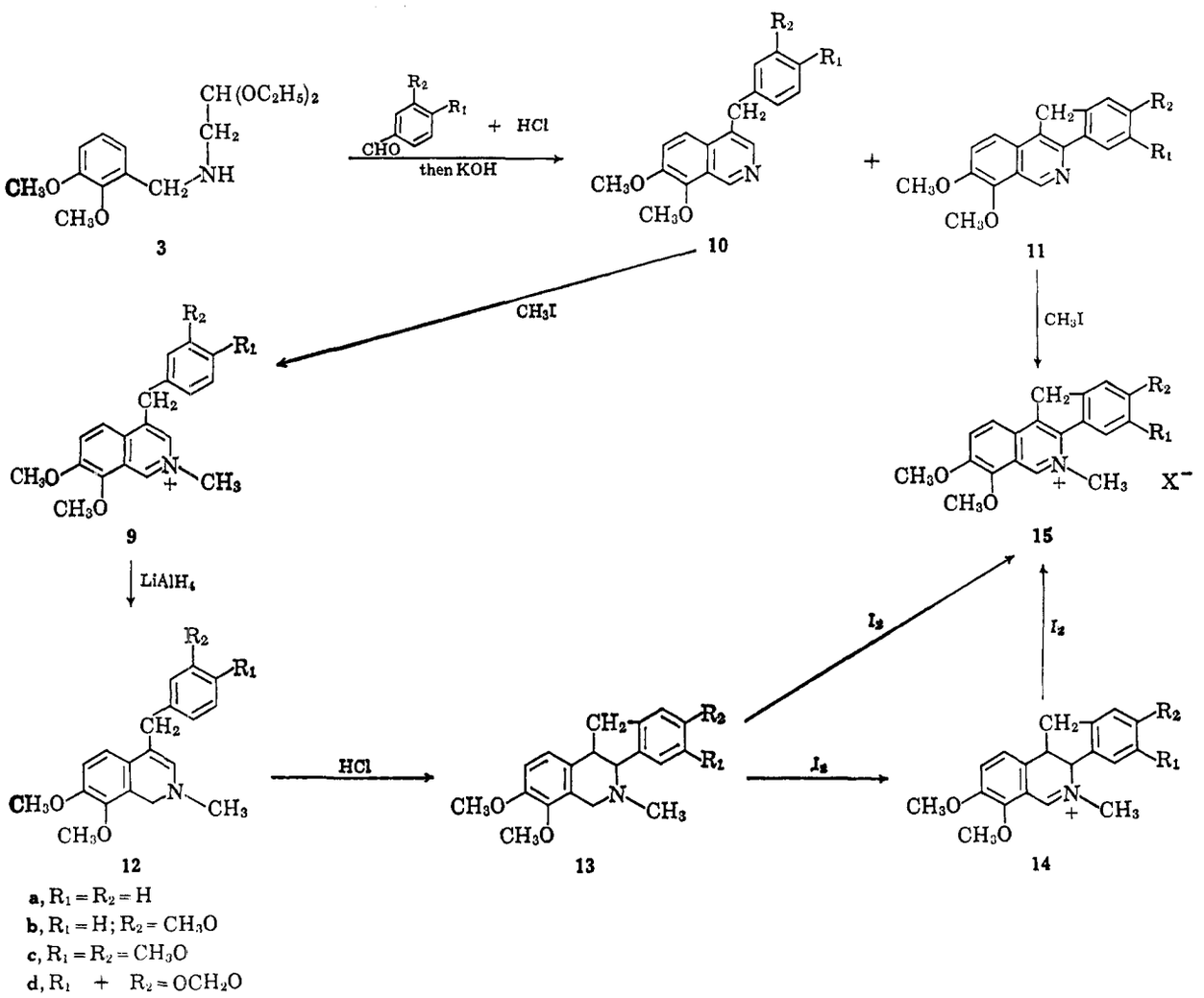


The final stages of the synthesis called for closing a ring on the 3 position of a 1,2-dihydroisoquinoline, as in

(9) J. M. Bobbitt, D. P. Winter, and J. M. Kiely, *J. Org. Chem.*, **30**, 2459 (1965).

(10) S. F. Dyke and M. Sainsbury, *Tetrahedron*, **23**, 3161 (1967).

SCHEME II



a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3O$
c, $R_1 = R_2 = CH_3O$
d, $R_1 + R_2 = OCH_2O$

12 to **13**. Related ring closures from the 1 position and from the 2 position have been reported;[11] ring closure from the isoquinoline 4 position have been considered but, so far as it can be determined, have not been realized.[12] In the authors' hands, the cyclization, carried through with the veratryl and piperonyl derivatives, proved to be both possible and practical. The necessary 1,2-dihydroisoquinolines **12c** and **12d** were obtained by reducing the corresponding isoquinolinium quaternary salts **9c** and **9d** with lithium aluminum hydride.[13] The structures of the dihydroisoquinolines, which were isolated as crystalline solids, are supported by the nmr spectra. Thus, the presence of a vinyl proton in piperonyl-1,2-dihydroisoquinoline (**12d**) is substantiated by a three-proton singlet at 5.92 ppm (coinciding OCH_2O and C=CH). The location and integration values of the signals for two methoxy groups, an N-methyl group, and five aromatic protons are also in accord with structure **12d**. The veratryl derivative **12c** shows its vinyl proton as a one-proton signal at 5.80 ppm.

Tetrahydroindenoisoquinoline **13d** was obtained when the 4-piperonyl-1,2-dihydroisoquinoline **12d** was exposed to the action of hydrochloric acid in methanol or in acetic acid. Several other conditions were tried but unsuccessfully. The tetramethoxy-1,2-dihydroisoquinoline **12c** also cyclized under the proper conditions. The nmr spectra of **13d** and **13c** proved to be consistent with the assigned structures (see Experimental Section). *A priori*, cyclization could lead either to *cis* or *trans* geometry at the tetrahydroindenoisoquinoline 12 and 13 positions of **13**. The nmr spectra did not help in deciding on the geometry, but on the basis of mechanistic speculation, the authors favor the *cis* arrangement. Ring closure *para* rather than *ortho* to the substituent oxygens is highly likely; electrophilic substitutions on veratroles or on methylenedioxybenzenes avoid the positions next to oxygen.

Dehydrogenation with ethanolic iodine plus potassium acetate at 40° converted the methylenedioxytetrahydroindenoisoquinoline **13d** into the triiodide of the corresponding quaternary dihydro derivative **14d**. Treatment with sulfite produced the simple iodide. Iodine dehydrogenation at 80° oxidized tetrahydroindenoisoquinoline **13d** as well as dihydro derivative **14d** to the fully aromatic indenoisoquinolinium iodide **15d**. Iodine dehydrogenation of tetrahydroisoquino-

(11) For a brief review see S. F. Dyke and M. Sainsbury, *Tetrahedron*, **21**, 1907 (1965); also, *cf.* D. W. Brown and S. F. Dyke, *ibid.*, **22**, 2429 (1966).

(12) A. R. Battersby, R. Binks, and P. S. Uzzell, *Chem. Ind.* (London), 1039 (1955); M. Sainsbury, S. F. Dyke, and A. R. Marshall, *Tetrahedron*, **22**, 2445 (1966); S. P. Pappas, Ph.D. Dissertation, University of Wisconsin, 1963; *Dissertation Abstr.*, **23**, 3125 (1963); S. F. Dyke, M. Sainsbury, and B. J. Moon, *Tetrahedron*, **24**, 1467 (1968).

(13) An adaptation of the procedure of H. Schmid and P. Karrer [*Helv. Chim. Acta*, **32**, 960 (1949)] who reduced 2-methylisoquinolinium iodide to 2-methyl-1,2-dihydroisoquinoline.

lines to 3,4-dihydroisoquinolines, as in **13** to **14**, observed before.[14] Structure **14d** is supported by the fact that further oxidation with iodine is possible to give **15d**, by the sharp infrared absorption peak at 1665 cm^{-1} (C=N+), and by the nmr singlet for one proton at 9.40 ppm, expected for the olefinic proton adjacent to nitrogen. The dehydrogenation of the tetramethoxy derivative **13c** was performed so as to lead directly to the indenoisoquinolinium iodide **15c**. Anion exchange conveniently converted the rather insoluble iodides **15d** and **15c** into the more soluble nitrates.

In summary, a six-step process has been described by which indeno[1,2-*c*]isoquinolines can be synthesized from readily available starting materials. One of the steps—cyclization of **12** to **13**—provides a further example of the versatility of the 1,2-dihydroisoquinoline system in permitting attachment of an activated aryl group to the isoquinoline 3 position. The new synthesis has been applied to the preparation of two indenoisoquinoline derivatives related to chelerythrine (**2**).

Experimental Section

General.—All melting points were determined in open capillary tubes in a melting point apparatus calibrated against standard samples. Infrared curves were taken with a recording spectrophotometer (Perkin-Elmer 137 and 237). Ultraviolet absorption curves were obtained with the help of a Bausch and Lomb 505 scanning spectrophotometer using 1-cm path length quartz cells. The nmr spectra were taken on a 60-Mc instrument (Varian A-60). For gas–liquid partition chromatography, we relied on an F & M dual column apparatus.

Analyses for elements were performed by Microchemical Laboratories, Massachusetts Institute of Technology, Cambridge, Mass., by Scandinavian Microanalytical Laboratory, Herlev, Denmark, by Spang Microanalytical Laboratory, Ann Arbor, Mich., and by Galbraith Laboratories, Inc., Knoxville, Tenn.

2,3-Dimethoxybenzylaminoacetal (3).[5,9]—Over a 6-hr period of stirring in an atmosphere of hydrogen, a mixture of *o*-veratraldehyde (3.3 g, 0.02 mol), aminoacetal (2.7 g, 0.02 mol), platinum oxide (0.2 g), and absolute alcohol (200 ml) absorbed 0.02 mol of hydrogen. Removal of catalyst and solvent left pale yellow 2,3-dimethoxybenzylaminoacetal (**3**) as a yellow oil (5.7 g, 99%), which was used without further purification.

2-Methyl-7,8-dimethoxyisoquinolinium Iodide (7) from 4-Hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4).—A solution of 2,3-dimethoxybenzylaminoacetal (**3**) in 6 *N* hydrochloric acid (5.7 g or 0.020 mol in 200 ml) was stirred for a day and then stored in the cold for 3 days. Adding crushed sodium hydroxide to the cold stirred mixture to pH >10 precipitated the 4-hydroxy compound **4**. Most of the product was collected by filtration; additional quantities were obtained by extracting the filtrate with ether. The total yield of product in the form of a dull white powder, mp 140–142°, was 3.0 g (70%). A sample of this 4-hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4**), prepared for elemental analysis by recrystallization from 1:1 ethanol–benzene, melted constantly at 141–142.5°.

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.80; H, 6.99; N, 6.52.

The nmr spectrum, taken in deuteriochloroform, showed signals at 2.98 (2 H, m, position 3), 3.24 (3 H, broad singlet, position 1 plus OH), 3.78 and 3.83 (6 H, 2 s, 2 OCH_3), 3.8–4.6 (2 H, m, positions 2 and 4), and 6.80 and 7.12 ppm (2 H, 2 d, *J*'s = 8 cps, positions 5 and 6).

A dibenzoyl derivative was prepared by vigorously shaking a mixture of 4-hydroxy compound **4** (51 mg), benzoyl chloride (280 mg), and 2.5 *N* aqueous sodium hydroxide solution (1 ml) for 10 min. The gummy brown precipitate was crystallized by gradually cooling its ethanolic solution. The fluffy white crystalline dibenzoyl derivative of **4** (37 mg) showed mp 125–126°.

Anal. Calcd for $C_{25}H_{23}NO_5$: C, 71.93; H, 5.55; N, 3.36. Found: C, 71.63; H, 5.60; N, 3.40.

A solution of the dibenzoyl derivative in chloroform showed no infrared absorption in the 3400–3600-cm^{-1} region but did show carbonyl maxima at 1720 (ester) and 1660 cm^{-1} (amide).

The 4-hydroxytetrahydroisoquinoline **4** (1.3 g, 7.5 mmol) was aromatized by boiling its solution in decalin (15 ml) containing 0.3 g of 30% palladium-on-carbon at 200° for 4 hr. An atmosphere of nitrogen was maintained over the reaction mixture. After catalyst was removed by filtering the cooled mixture, the filtrate was diluted with 10 ml of benzene and was extracted with several small volumes of 4 *N* hydrochloric acid. The combined aqueous acid extracts were rinsed once with benzene and then treated with 10% aqueous sodium hydroxide (cooling) until the mixture was strongly alkaline. Several extractions with ether removed the product as an ether solution, which was washed first with small portions of water and then with saturated potassium chloride. The ethereal solution, dried with magnesium sulfate, was stripped of solvent at room temperature under aspirator pressures. The yellow residual oil (1.1 g) was taken as 7,8-dimethoxyisoquinoline (**6**).

The nmr spectrum of **6** as a 10% solution in trifluoroacetic acid showed signals at 4.24 and 4.36 (two 3 H, 2 s, 2OCH_3), 8.16 and 8.38 (4 H, two broad singlets, positions 3, 4, 5, 6), and 9.77 ppm (1 H, broad singlet, position 1). For comparison, the spectrum of unsubstituted isoquinoline dissolved in trifluoroacetic acid was taken and was found to show a complex of signals at 8.00–8.85 (6 H, positions 3, 4, 5, 6, 7, 8) and a broad singlet at 9.73 ppm (1 H, position 1).

Treating the 7,8-dimethoxyisoquinoline (**6**) with methyl iodide (2.8 g) produced the lumpy yellow methiodide **7**. Washed once with a small volume of absolute alcohol, this product weighed 1.7 g (83% from the 4-hydroxy derivative **4**) and showed mp 181–183° with slight preliminary sintering. The same methiodide from authentic 7,8-dimethoxyisoquinoline prepared according to the Pomeranz–Fritsch procedure[8] melted at 182–183°; a mixture of the methiodides melted at 181–183° with sintering at 176°. The two methiodides as mulls with mineral oil gave identical infrared absorption curves.

Recrystallizations from methylene chloride–benzene furnished analytically pure 2-methyl-7,8-dimethoxyisoquinolinium iodide (**7**), mp 182–183° dec.

Anal. Calcd for $C_{12}H_{14}INO_2$: C, 43.51; H, 4.26; I, 38.32; N, 4.23. Found: C, 43.31; H, 4.35; I, 38.32; N, 4.24.

2-Methyl-7,8-dimethoxyisoquinolinium Iodide (7) from 7,8-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (5).[5]—A solution of 2,3-dimethoxybenzylaminoacetal (5.7 g, 0.020 mol) in 150 ml of 8 *N* hydrochloric acid was added to a suspension prepared by saturating a stirred mixture of 10% palladium on carbon (0.2 g) and ethanol with hydrogen. Stirring the reaction mixture for 10 hr under hydrogen resulted in the uptake of 1 molar equiv of hydrogen; hydrogen uptake stopped after this period. Removal of the catalyst and all solvent left a yellow pasty mass, which solidified on treatment with a few drops of ethanol. This crude product (3 g, mp 185–190°) on crystallization from absolute alcohol furnished 2.1 g (42%) of pale green crystalline hydrochloride of 7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5**), mp 192.5–193° dec.

The free base **5** was used for aromatization. A mixture of the hydrochloride (1.5 g, 7.0 mmol) in 15 ml of water was made strongly alkaline (pH >10) with sodium hydroxide, and the free base was extracted with several portions of decalin. The decalin solution was dried with potassium carbonate, mixed with 30% palladium on carbon, and boiled at 200° for 4 hr. Subsequent treatment, essentially the same as described above, gave rise to 1.2 g of 7,8-dimethoxyisoquinoline (**6**) as a yellow oil. The derived methiodide **7** weighed 1.8 g (79% from **5**·HCl) and melted either alone or mixed with authentic material at 180–183° (preliminary sintering). Mineral oil mulls of the two samples gave identical infrared absorption spectra.

2-Methyl-4-benzyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8a).[1]—Benzaldehyde (320 mg, 3.0 mmol) and 0.2 ml of 2 *N* NaOH solution were added to 2-methyl-7,8-dimethoxyisoquinolinium iodide (**7**, 820 mg, 2.5 mmol) in 25 ml of absolute alcohol. The mixture was subjected without delay to hydrogenation at atmospheric pressure over a catalyst prepared by saturating 30 mg of platinum oxide in 25 ml of alcohol with hydrogen. In 2.5 hr, 2.9 molar equiv of hydrogen was absorbed, after which time hydrogenation stopped. Aqueous 2 *N* sodium hydroxide (15 ml) was added, the turbid mixture was filtered, and

(14) W. J. Gensler in "Heterocyclic Compounds," Vol. IV, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p 396.

the filtrate was extracted with ether. The ether solution was washed with two small portions of water, dried with magnesium sulfate, and stripped of solvent. The brown residue was dissolved in concentrated hydriodic acid, and the solution was washed once with ether and then evaporated to dryness at moderate temperatures. Recrystallization of the crude residual iodide from absolute alcohol furnished 255 mg (24%) of bright yellow crystalline 2-methyl-4-benzyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinolinium iodide (**8a**·HI), mp 187–189°. Further crystallizations gave product melting no higher than 188–189°.

Anal. Calcd for $C_{19}H_{24}INO_2$: C, 53.66; H, 5.69; N, 3.29. Found: C, 53.47; H, 5.81; N, 3.38.

4-Benzyl-7,8-dimethoxyisoquinoline (10a).[9,10]—A mixture of benzaldehyde (2.12 g, 0.020 mol), 2,3-dimethoxybenzylaminoacetal (**3**, 2.85 g, 0.010 mol), ethanol (15 ml), and concentrated hydrochloric acid (15 ml) was boiled gently for 30 min. Cooling the mixture for 1 hr precipitated a yellow solid, which after crystallization from absolute ethanol appeared as bright yellow needles (2.8 g or 82%), mp 102–103° (sintering at 100°). Further crystallization did not change the melting point.

Anal. Calcd for $C_{18}H_{20}ClNO_3$: C, 64.77; H, 6.04; Cl, 10.62; N, 4.20. Found: C, 64.70; H, 6.30; Cl, 10.63; N, 4.15.

This solid in a mineral oil mull showed infrared absorption peaks at 1660 and 3350 (broad) cm^{-1}. With the exception of the color, these data correspond well to those reported for compound **16a**.[10]

Isoquinoline base **10a** was obtained by stirring a suspension of the above hydrochloride (1.25 g, 3.76 mmol) in aqueous alkali (pH >10) for 30 min. The precipitate was washed with cold water, dried, and then crystallized from ethanol to give 0.75 g (72%) of white crystalline 4-benzyl-7,8-dimethoxyisoquinoline (**10a**), mp 95–98° (sintering at 92°). The analytically pure material melted at 98–99°.

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.62; H, 6.29; N, 4.94.

Compound **10a** as a 10% solution in trifluoroacetic acid showed the following nmr signals: 4.21 and 4.36 (two 3 H, 2 s, $2OCH_3$), 4.62 (2 H, s, $ArCH_2$), 7.38 (5 H, two peaks, benzyl ArH's), 8.05 (1 H, d, J = 7 cps, position 3), 8.21 (2 H, two peaks, positions 5 and 6), and 9.67 ppm (1 H, d, J = 8 cps, position 1).

4-Piperonyl-7,8-dimethoxyisoquinoline (10d).—When the directions given above were followed with piperonal (3.0 g or 0.020 mol) taken in place of benzaldehyde, bright orange crystals (2.7 g, 68%), mp 100–102° (sintering at 98°), precipitated from the hydrochloric acid reaction mixture. Recrystallizations from ethanol gave crystals (**16d**·H_2O) with mp 102.5–103° (sintering at 100°).

Anal. Calcd for $C_{19}H_{20}ClNO_5 \cdot H_2O$: C, 57.65; H, 5.60; Cl, 8.96; N, 3.54. Found: C, 57.54; H, 5.97; Cl, 8.92; N, 3.28.

The crystals in a mineral oil mull showed infrared absorption peaks at 1660 and 3300 cm^{-1}.

Stirring a suspension of this material (3.50 g) in aqueous sodium hydroxide (pH >10) for 1–2 hr furnished a dull white solid, which after drying weighed 2.80 g. Fractional crystallization from absolute alcohol afforded two materials. The more soluble component was isolated as white powdery crystals (2.1 g, 65%) of 4-piperonyl-7,8-dimethoxyisoquinoline (**10d**), mp 124–125° (slight preliminary sintering). Further crystallizations brought the melting point to 124–125° (no sintering).

Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.58; H, 5.29; N, 4.32.

A 15% solution of **10d** in deuteriochloroform showed nmr signals at 3.98 (3 H, s, OCH_3), 4.09 (3 H, s, OCH_3), 4.25 (2 H, s, $ArCH_2$), 5.89 (2 H, s, OCH_2O), 6.70 (3 H, s, 3 ArH), 7.60–7.90 (2 H, m, 2 ArH), 8.30 (1 H, s, position 3), and 9.50 ppm (1 H, broad singlet, position 1).

The less soluble component (0.21 g, 6.5%, mp 238–242°), which was taken as 3,4-dimethoxy-8,9-methylenedioxy-11H-indeno[1,2-*c*]isoquinoline (**11d**), was crystallized from 1:1 ethanol–chloroform to a constant melting point of 242–243.5°.

Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 71.10; H, 4.81; N, 4.33.

A 15% solution of this indenoisoquinoline **11d** in trifluoroacetic acid showed the following nmr signals: 4.24 (5 H, s, OCH_3 plus $ArCH_2$), 4.39 (3 H, s, OCH_3), 6.17 (2 H, s, OCH_2O), 7.28 (1 H, s, position 7 or 10), 7.60 (1 H, s, position 7 or 10), 8.12 (2 H, s, positions 1 and 2), and 9.52 ppm (1 H, d J = 8 cps, position 5).

4-Veratryl-7,8-dimethoxyisoquinoline (10c).—Use of veratraldehyde in place of benzaldehyde in the above condensation furnished a red crystalline hydrochloride precipitate (70%) showing a color transformation to yellow at 135–140° and melting at 171–173°. Recrystallizations from absolute alcohol gave analytically pure 4-veratryl-7,8-dimethoxyisoquinoline hydrochloride (**10c**·HCl), mp 172–173°, with the same color change at 135–140°.

Anal. Calcd for $C_{20}H_{22}ClNO_4$: C, 63.91; H, 5.90; Cl, 9.43; N, 3.73. Found: C, 63.70; H, 6.08; Cl, 9.21; N, 3.84.

This compound as a mineral oil mull showed infrared absorption peaks at 1650, 2600 broad (unexplained), and 3400 cm^{-1}.

The free base **10c** in the form of white powdery crystals from benzene was obtained in 85% yield. The melting point, 251–252° (sintering at 233°), could not be improved by further recrystallizations.

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.68; H, 6.01; N, 4.13.

A 15% solution of 4-veratryl-7,8-dimethoxyisoquinoline (**10c**) in trifluoroacetic acid showed nmr signals at 3.78 and 3.91 (8 H, two singlets, two benzyl OCH_3 plus $ArCH_2$), 4.17 and 4.31 (6 H, two singlets, two isoquinoline OCH_3 groups), 6.68–8.60 (7 H, complex), and 9.64 ppm (1 H, d, J = 3 cps, position 1).

4-*m*-Anisyl-7,8-dimethoxyisoquinoline Hydrochloride (10b·HCl).—The crystalline yellow hydrochloride obtained when *m*-anisaldehyde was taken as starting aldehyde melted at 104–105° (sintering at 93°). A sample, prepared for analysis by recrystallization from ethanol, showed mp 104–105° (sintering at 100°).

Anal. Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; Cl, 10.25; N, 4.05. Found: C, 65.68; H, 5.84; Cl, 10.19; N, 4.17.

A mineral oil mull of this hydrochloride showed infrared absorption peaks at 1670 and 3400 cm^{-1}.

A 20% solution of 4-*m*-anisyl-7,8-dimethoxyisoquinoline hydrochloride in trifluoroacetic acid showed nmr signals at 4.04, 4.06, and 4.10 (9 H, 3 s, 3 OCH_3), 5.33 (2 H, s, $ArCH_2$), 7.21 s, 7.38 s, and 7.4–8.2 m (6 H, 6 ArH's), 8.59 (1 H, s, position 3), and 9.05 ppm (1 H, d, J = 10 cps, position 1).

2-Methyl-4-piperonyl-7,8-dimethoxyisoquinolinium Iodide (9d).—A mixture of the 4-piperonylisoquinoline **10d** (2.0 g, 6.2 mmol) and methyl iodide (9.0 g, 63 mmol) in 50 ml of 1:1 ethanol–benzene was boiled for 5 min. The mixture was cooled, and the orange upper layer was decanted from the underlying dark, viscous layer. The upper layer to which a few drops of alcohol was added was brought to a boil and then cooled. The precipitated crystals were collected by filtration, and the filtrate, treated with 3 g of methyl iodide, was allowed to react at room temperature for an hour. Cooling produced another crop of crystals. The mother liquor was combined with the original lower layer. Concentration and cooling deposited more product, which was crystallized from ethanol (decolorizing carbon used) before it was combined with the first two crops. The combined yellow methiodide **9d** (2.3 g or 81%) showed mp 190–192° with preliminary sintering. A sample prepared for analysis by recrystallization from ethanol melted at 192–193° (sintering at 183°).

Anal. Calcd for $C_{20}H_{20}INO_4$: C, 51.63; H, 4.33; I, 27.27; N, 3.01. Found: C, 51.86; H, 4.48; I, 27.16; N, 3.09.

2-Methyl-4-veratryl-7,8-dimethoxyisoquinolinium Iodide (9c).—A solution of the isoquinoline base **10c** (3.4 g, 0.010 mol) and methyl iodide (13.5 g, 0.095 mol) in 80 ml of benzene was boiled for 5 min. Ethanol (10 ml) was added, and the mixture processed for recovery of the iodide in a manner similar to that described above. Yellow crystals of methiodide **9c** (3.6 g, 75%) were obtained that gradually decomposed at temperatures over 160°. Recrystallization from ethanol changed the melting point behavior only slightly.

Anal. Calcd for $C_{21}H_{24}INO_4$: C, 52.40; H, 5.03; I, 26.36; N, 2.91. Found: C, 52.13; H, 4.94; I, 26.35; N, 2.91.

2-Methyl-4-*m*-anisyl-7,8-dimethoxyisoquinolinium Iodide (9b).—Treatment of the hydrochloride of isoquinoline **10b** (2.77 g, 8.0 mmol) with water at pH >10 released the free base, which was isolated in the usual way to give a dark, viscous oil (2.1 g). This oil was dissolved in benzene (100 ml) containing 12.0 g (0.090 mol) of methyl iodide, and the solution was boiled for 5 min. Two crops of yellow crystalline product **9b** were taken and were recrystallized from alcohol to give 2.53 g (70%) of yellow 2-methyl-4-*m*-anisyl-7,8-dimethoxyisoquinolinium iodide, mp 161–162° (red at 148°; sintering at 160°). Further crystallization did not affect the melting point significantly.

Anal. Calcd for $C_{20}H_{22}INO_3$: C, 53.23; H, 4.92; I, 28.12; N, 3.10. Found: C, 53.21; H, 5.05; I, 27.95; N, 3.08.

A 20% solution in trifluoroacetic acid showed nmr signals at 3.90, 4.18, 4.31, 4.54 (4 s, 4 CH_3), 4.58 (s, $ArCH_2$), and 6.80–8.35 ppm (complex, ArH).

2-Methyl-4-benzyl-7,8-dimethoxyisoquinolinium Iodide (9a).—This methiodide was formed in ethanol solvent. The two crops isolated melted at 295–298°. Recrystallization from ethanol raised the melting point to 297–298°.

Anal. Calcd for $C_{19}H_{20}INO_2$: C, 54.17; H, 4.79; I, 30.12; N, 3.33. Found: C, 53.96; H, 4.81; I, 30.30; N, 3.26.

2-Methyl-4-piperonyl-7,8-dimethoxy-1,2-dihydroisoquinoline (12d).—The mixture obtained on adding powdered dry 2-methyl-4-piperonyl-7,8-dimethoxyisoquinolinium iodide (**9d**, 0.91 g or 1.96 mmol) to an ice-cold suspension of lithium aluminum hydride (0.72 g or 19 mmol) in 100 ml of dry ether was stirred at room temperature for 12 hr. A slow stream of nitrogen blanketed the green reaction mixture. With the stirred mixture maintained at 0°, drops of ice–water were added until no hydrogen was evolved. Filtration through a layer of filter aid removed the gelatinous precipitate. The clear ethereal filtrate was extracted with 10-ml portions of cold 6 *N* hydrochloric acid until the aqueous layer was colorless. The combined acid extracts, after one washing with ether, was cooled and was added dropwise to 15 ml of ice-cold, stirred 28% aqueous ammonia. The precipitate was collected, washed with a small amount of cold water, and air-dried on the funnel. The gray 1,2-dihydroisoquinoline product **12d** obtained in this way weighed 0.47 g (71%) and melted at 95–98° (sintering at 90°). After crystallization from 1:1 aqueous alcohol, a sample appeared as shiny, off-white crystals, mp 97–98°.

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13; double bonds, 1.0. Found: C, 70.61; H, 6.21; N, 4.17; hydrogen absorbed on catalytic hydrogenation, 0.98 molar equiv.

The infrared absorption spectrum of this compound as a mineral oil mull showed a sharp peak at 1660 cm^{-1}, which was associated with C=C.

This dihydroisoquinoline as a 10% deuteriochloroform solution gave nmr signals at 2.75 (3 H, s, N-CH_3), 3.54 (2 H, s, position 1), 3.83 (6 H, s, 2 -OCH_3), 4.23 (2 H, s, $ArCH_2$), 5.92 (3 H, s, OCH_2O+ position 3), 6.69 (2 H, s, positions 5 and 6), and 6.80 ppm (3 H, s, piperonyl ArH's).

2-Methyl-4-veratryl-7,8-dimethoxy-1,2-dihydroisoquinoline (12c).—2-Methyl-4-veratryl-7,8-dimethoxyisoquinolinium iodide (**9c**, 0.96 g or 2.0 mmol) was added to a cold, stirred suspension of lithium aluminum hydride (0.76 g or 20 mmol) in 100 ml of ether. The procedure thereafter was essentially the same as for the piperonyl analog. The light gray dihydroisoquinoline product **12c** weighed 0.62 g (85%) and showed mp 92–94° (sintering at 85°). Crystallization from chloroform produced dull white crystals, mp 96–97°.

Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.82; H, 7.10; N, 3.88.

A mineral oil mull showed the expected infrared absorption peak for C=C at 1640 cm^{-1}.

A 20% deuteriochloroform solution of 2-methyl-4-veratryl-7,8-dimethoxy-1,2-dihydroisoquinoline (**12c**) revealed absorptions at 2.70 (3 H, s, N-CH_3), 3.55 (2 H, s, position 1), 3.78, 3.80, 3.82 (12 H, 3 s, 4 -OCH_3), 4.21 (2 H, s, $ArCH_2$), 5.80 (1 H, s, position 3), 6.66 (2 H, s, positions 5 and 6), and 6.82 ppm (3 H, s, veratryl ArH's).

Cyclization of 2-Methyl-4-piperonyl-7,8-dimethoxy-1,2-dihydroisoquinoline (12d) to 3,4-Dimethoxy-6-methyl-8,9-methylenedioxy-5,6,12,13-tetrahydro-11H-indeno[1,2-*c*]isoquinoline (13d).

A. Cyclization in Methanol–Hydrochloric Acid.—A solution of dihydroisoquinoline **12d** (0.30 g or 0.89 mmol) in a mixture of 5 ml of methanol plus 5 ml of concentrated hydrochloric acid was boiled under nitrogen for 0.5 hr and then allowed to cool to room temperature. The light orange precipitate was collected. Dilution of the filtrate with 3 ml of water produced more of this solid, which was combined with the first precipitate. The treatment of this orange solid (27 mg) is described below.

In a similar experiment starting with 0.5 g of dihydroisoquinoline **12d**, the cooled filtrate remaining after the orange precipitate had been removed, was treated with ice-cold aqueous ammonia until basic. The brown turbid mixture was extracted with three 15-ml portions of 1:1 chloroform–benzene. The combined extracts were washed with a small volume of water, dried with magnesium sulfate, and stripped of solvent at room temperature and under reduced pressure. The brown semisolid residue (0.3 g from 0.5 g of dihydroisoquinoline **12d**) was dissolved in 2 ml of chloroform and chromatographed through a 10 in. column of acid-washed Merck alumina (25 g). The developing solvents were first, 500 ml of benzene, and then three 250-ml portions of 1:1 benzene–chloroform. The last two 250-ml portions of eluate, containing material from a yellow band on the column, were combined and stripped of solvent to leave 105 mg (21%) of brown, semisolid tetrahydroindeno[1,2-*c*]isoquinoline **13d**.

This compound as a 15% carbon tetrachloride solution showed nmr signals as follows (see **1** for numbering): 2.35 (3 H, s, N-CH_3), 2.82 (2 H, s, position 5), 3.75 and 3.79 (6 H, 2 s, 2 -OCH_3), other peaks between 2.00 and 4.35 (4 H, complex, positions 11, 12, 13), 5.86 (2 H, s, OCH_2O), and 6.66 and 6.70 ppm (4 H, 2 s, 4 ArH's). The same material in trifluoroacetic acid (10% solution) gave peaks at 3.13 (3+ H, s, N-CH_3), 3.61 (2+ H, s, position 5), 4.04 (6 H, s, 2 -OCH_3), other peaks between 2.8–4.2 (4 H, complex, positions 11, 12, 13), 6.02 (2 H, s, OCH_2O), and 6.5–7.1 ppm (4 H, complex, 4 ArH's).

A solid derivative of tetrahydroindenoisoquinoline **13d** was prepared by allowing a solution of the brown semisolid (0.10 g) in 0.5 ml of trifluoroacetic acid to stand for 1 hr, adding 2 ml of ethanol, and cooling at 0° for several hours. The crystals were removed. A second crop could be isolated from the filtrate after it had been diluted with ether. The combined solids were crystallized from 1:1 ethanol–ether to give silky white crystals of the trifluoroacetate salt of tetrahydroindenoisoquinoline **13d**, mp 180–182°. The yield was 0.12 g, *i.e.*, 90% from the free base or 20% from precursor dihydroisoquinoline **12d**. Further crystallization brought the melting point to 182–182.5° (sintering at 181°).

Anal. Calcd for $C_{22}H_{22}F_3NO_6$: C, 58.28; H, 4.89; N, 3.09. Found: C, 58.52; H, 5.04; N, 3.33.

When the above-mentioned orange solid (mp 230–233° with preliminary changes) was crystallized from ethanol–ether, it melted at 232–233°. A sample was dried *in vacuo* at room temperature before analysis.

Anal. Calcd for $C_{19}H_{18}ClNO_5$ (*i.e.*, **11d**·HCl·H_2O): C, 60.73; H, 4.83; Cl, 9.43; N, 3.73. Found: C, 60.61; H, 5.30; Cl, 9.43; N, 3.98.

The nmr spectrum of this material dissolved in trifluoroacetic acid was identical with that of 3,4-dimethoxy-8,9-methylenedioxy-11H-indeno[1,2-*c*]isoquinoline (**11d**) in the same solvent. The trifluoroacetate salt of the orange side product was compared with the same salt of **11d**. The salts were prepared by allowing a solution of 20 mg of solid in 0.2–0.3 ml of trifluoroacetic acid plus 0.5 ml of ethanol to stand for a short while. The precipitate was collected, washed on the funnel with a few drops of ether–ethanol, and air dried. The two solids melted separately or when mixed in equal amounts at 238–240° (sintering at 237°). The infrared spectra of the two trifluoroacetate salts (mineral oil mulls) were identical.

Although the formulation of the side product as the hydrochloride of 3,4-dimethoxy-8,9-methylenedioxy-11H-indeno[1,2-*c*]-isoquinoline (**11d**) is consistent with its properties, how it appears at this point in the synthesis remains speculative. The compound was encountered in only one preparation.

B. Cyclization in Acetic Acid–Hydrochloric Acid.—A solution of 0.3 g (0.89 mmol) of 2-methyl-4-piperonyl-6,7-dimethoxy-1,2-dihydroisoquinoline (**12d**) in 10 ml of acetic acid containing 0.5 ml of concentrated hydrochloric acid was boiled under nitrogen for 1.5 hr. Cold 28% aqueous ammonia added in portions to the reaction mixture at temperatures below 15° made the mixture alkaline. Thereafter the processing was essentially the same as described above. The product, 3,4-dimethoxy-6-methyl-8,9-methylenedioxy-5,6,12,13-tetrahydro-11H-indeno-[1,2-*c*]isoquinoline (**13d**), weighed 0.23 g (75%). Its nmr spectrum was exactly the same as that obtained for the same compound from the methanol–hydrochloric acid cyclization. This material was suitable for use in the subsequent stages.

C. Unsuccessful Cyclizations.—When the **12d** to **13d** conversion was attempted with mixtures of 98% formic acid and 85% phosphoric acid at 100 or 80° and for periods ranging from 6–24 hr, no recognized product was isolated. Boiling a solution of dihydroisoquinoline **12d** in concentrated hydrochloric acid for 6, 3, or 1 hr again gave no useful product.

Cyclization of 2-Methyl-4-veratryl-7,8-dimethoxy-1,2-dihydroisoquinoline (12c) to 3,4,8,9-Tetramethoxy-6-methyl-5,6,12,13-tetrahydro-11H-indeno[1,2-*c*]isoquinoline (13c). A. Cyclization in Ethanol–Hydrochloric Acid.—A solution of the dihydroisoquinoline **12c** (0.20 g or 0.56 mmol) in 20 ml of concentrated hydrochloric acid and 5 ml of ethanol was boiled in an atmosphere

of nitrogen for 2 hr. The cooled mixture was extracted with small portions of ether to remove nonbasic materials and then made basic with ammonia in a manner similar to that already described for the piperonyl analog. The crude product **13c** (0.18 g) in 500 ml of 1:1 benzene–chloroform was passed through a 1 × 22 cm column of acid-washed alumina. The column was then washed with an additional 100 ml of the same solvent. The combined eluates, stripped of solvent under reduced pressures at room temperature, left 0.175 g (88%) of 3,4,8,9-tetramethoxy-6-methyl-5,6,12,13-tetrahydro-11H-indeno-[1,2-*c*]isoquinoline (**13c**) as a brown viscous oil, which was suitable for use in the next step.

As a 10% solution in carbon tetrachloride, this material showed nmr signals at 2.40 (2 H, m, positions 12 and 13), 3.30 (2 H, s, position 5), 3.68–4.00 (17 H, 5 s, 4 $-OCH_3$ plus $N-CH_3$ plus position 11), and 6.50–6.90 ppm (4 H, m, 4 ArH's).

B. Cyclization in Acetic Acid–Hydrochloric Acid.—A mixture of dihydroisoquinoline **12c** (0.20 g or 0.56 mmol), 0.3 ml of concentrated hydrochloric acid, and 10 ml of glacial acetic acid was boiled under nitrogen for 4 hr. The cooled reaction mixture, after dilution with 200 ml of water, was washed with several small portions of ether, and thereafter processed essentially as described above. The crude tetramethoxy cyclization product **13c** was obtained as a brown viscous oil (0.17 g, 86%) suitable for use without purification.

3,4-Dimethoxy-6-methyl-8,9-methylenedioxy-12,13-dihydro-11-H-indeno[1,2-*c*]isoquinolinium Salt of 14d.—A mixture of tetrahydro derivative **13d** (0.10 g, 0.30 mmol), iodine (0.23 g, 1.8 mmol), potassium acetate (0.35 g, 3.6 mmol), and 10 ml of ethanol was held at 40° with occasional swirling for 10 min. The initial turbidity disappeared on warming to 40°. Cooling the reaction mixture to room temperature deposited the black crystalline periodide of dihydroindenoisoquinolinium cation **14d**. Crystallization from ethanol furnished shiny orange crystals (0.132 g or 62%), mp 148.5–149°. Further crystallization did not affect the melting point.

Anal. Calcd for $C_{20}H_{20}I_3NO_4$: C, 33.41; H, 2.80; I, 52.94; N, 1.95. Found: C, 33.66; H, 2.74; I, 52.95; N, 1.97.

To get the simple iodide, the periodide (87 mg or 0.12 mmol) in 5 ml of warm methanol was treated with solid sodium sulfite in small portions until the red-brown color changed to bright orange-yellow. Cooling gave bright yellow crystals of 3,4-dimethoxy-6-methyl-8,9-methylenedioxy-12,13-dihydro-11H-indeno[1,2-*c*]isoquinolinium iodide of **14d**, (44 mg or 80%), mp 168.5–169° (sintering at 166°). Recrystallization did not change the melting point.

Anal. Calcd for $C_{20}H_{20}INO_4$: C, 51.63; H, 4.33; I, 27.27; N, 3.01. Found: C, 51.56; H, 4.09; I, 27.51; N, 2.87.

This dihydro iodide as a mull with mineral oil showed an infrared absorption peak at 1665 cm^{-1} attributable to $C{=}N^+$.

A 7% solution of the iodide of **14d** in deuteriochloroform was scanned in the nmr spectrophotometer. The signals were weak, so that a time-averaging computer had to be used. Peaks appeared as follows: 2.85 (2 H, m, positions 12 and 13), 3.78 (8 H, s, 2 $-OCH_3$ plus position 11), 4.12 (3 H, s, $N-CH_3$), 5.84 (2 H, s, OCH_2O), 6.2–7.5 (4 H, m, positions 1, 4, 7, 10), and 9.40 ppm (1 H, broad s, position 5).

3,4-Dimethoxy-6-methyl-8,9-methylenedioxy-11H-indeno-[1,2-*c*]isoquinolinium Iodide (15d). A. By Methylation of Free Base 11d.—A mixture of 3,4-dimethoxy-8,9-methylenedioxy-11H-indeno[1,2-*c*]isoquinoline (**11d**, 1.0 g, or 3.1 mmol) and methyl iodide (4.5 g or 31 mmol) in 25 ml of ethanol plus 25 ml of benzene was boiled for 2.5 hr. Allowing the yellow reaction mixture to stand overnight at room temperature produced bright yellow crystals. Recrystallization from ethanol afforded the methiodide **15d** (0.98 g or 71%), mp 248–250° (preliminary sintering). Further recrystallization from the same solvent brought the melting point to a constant value of 249–250° (preliminary sintering).

Anal. Calcd for $C_{20}H_{18}INO_4$: C, 51.85; H, 3.92; I, 27.39; N, 3.02. Found: C, 52.12; H, 4.02; I, 27.15; N, 3.19.

B. By Iodine Dehydrogenation of Dihydro Compound 14d.—Iodine (80 mg or 0.30 mmol) in 10 ml of ethanol was added to a solution of dihydroindenoisoquinolinium iodide of **14d** (50 mg or 0.15 mmol) in 10 ml of ethanol, and the mixture was boiled gently for 2 hr. Solvent was removed under vacuum at room temperature. Allowing the brown residue to stand overnight in 2 *N* sulfurous acid furnished a dull yellow powder, which on crystallization from 1:1 ethanol–acetone gave 3,4-dimethoxy-6-methyl-8,9-methylenedioxy-11H-indeno[1,2-*c*]isoquinolinium iodide (**15d**, 31 mg or 60%) as bright yellow crystals, mp 243–245° (sintering at 197°). Mixed with the same product from part A, this compound melted at 244–247° (sintering at 197°). The infrared absorption spectra of the two materials were identical.

C. By Iodine Dehydrogenation of Tetrahydroindenoisoquinoline 13d.—A mixture of tetrahydro compound **13d** (100 mg or 0.30 mmol), iodine (230 mg or 1.8 mmol), potassium acetate (350 mg or 3.6 mmol), and 10 ml of absolute alcohol was treated essentially as described in part B. The bright yellow crystals of the methiodide product **15d** (106 mg or 60% calculated from dihydroisoquinoline **12d**) showed mp 245–248° (sintering at 198°) by itself and mp 246–248° (sintering at 198°) when mixed with the product from part A. The two materials showed identical infrared absorption spectra.

3,4,8,9-Tetramethoxy-6-methyl-11H-indeno[1,2-*c*]isoquinolinium Iodide (15c).—A solution of tetramethoxytetrahydroindenoisoquinoline **13c** (0.175 g or 0.48 mmol), iodine (0.45 g or 1.77 mmol), potassium acetate (0.50 g or 5.1 mmol), and 1:1 methanol–ethanol (50 ml) was boiled for 2 hr. Treatment with 2 *N* sulfurous acid changed the dark color to bright orange. Cooling the concentrated mixture gave the desired iodide. A second crop could be obtained by further concentration. Recrystallization of the combined solids from ethanol afforded dark yellow crystals of 3,4,8,9-tetramethoxy-6-methyl-11H-indeno-[1,2-*c*]isoquinolinium iodide (**15c**, 0.18 g or 79%), mp 219–220° dec. Further crystallization did not change the melting point.

Anal. Calcd for $C_{21}H_{22}INO_4$: C, 52.62; H, 4.63; I, 26.48; N, 2.92. Found: C, 52.80; H, 4.80; I, 26.42; N, 2.89.

3,4-Dimethoxy-6-methyl-8,9-methylenedioxy-11H-indeno-[1,2-*c*]isoquinolinium Nitrate (15d).—Dowex 1 X-8, the ion-exchange resin used here, contains quaternary ammonium groups attached to a partially cross-linked styrene–divinylbenzene copolymer. A 1.25 × 40 in. column was prepared by adding a suspension of 400 g of thoroughly washed resin (100–200 mesh) in its chloride form to a glass tube. Care was taken to exclude air bubbles. Sodium nitrate solution (0.5 *M*) was passed through the column until the emergent liquid gave no precipitate with silver nitrate. The column was then washed with 2 l. of water.

A solution of **15d** iodide (1.4 g or 3.1 mmol) in 4 l. of distilled water was passed through the column at the rate of 200 ml/hr. This was followed by 2 l. of water. The combined solution and washings were evaporated under reduced pressure at room temperature. The residual orange solid was crystallized from absolute alcohol to give the desired indenoisoquinolinium nitrate **15d** (1.08 g or 90%), which decomposed in the range 200–220°. Further crystallization from the same solvent gave an analytically pure sample.

Anal. Calcd for $C_{20}H_{18}N_2O_7$: C, 60.30; H, 4.55. Found: C, 60.46; H, 4.79.

3,4,8,9-Tetramethoxy-6-methyl-11H-indeno[1,2-*c*]isoquinolinium Nitrate (15c).—The iodide of **15d** was converted to its nitrate essentially according to the above directions. Crystallization of the crude product from ethanol gave small golden yellow flakes of the nitrate (75%), mp 229–231° dec. Further crystallizations gave a sample for analysis still with the same melting point characteristics.

Anal. Calcd for $C_{21}H_{22}N_2O_7$: C, 60.86; H, 5.35. Found: C, 60.64; H, 5.48.

Registry No.—**4**, 16503-92-7; **4** dibenzoyl derivative, 16503-93-8; **5**·HCl, 15365-56-7; **6**, 16503-95-0; **7**, 16503-96-1; **8a**·HI, 16503-97-2; **9a**, 16503-98-3; **9b**, 16503-99-4; **9c**, 16520-66-4; **9d**, 16504-00-0; **10a**, 15539-33-0; **10b**·HCl, 16504-02-2; **10c**, 16504-03-3; **10c**·HCl, 17520-67-5; **10d**, 16504-04-4; **11d**, 16504-05-5; **11d**·HCl, 16504-06-6; **12c**, 16504-07-7; **12d**, 16504-08-8; **13c**, 16504-09-9; **13d**, 16504-10-2; **14d** periodide, 16482-30-7; **14d** iodide, 16504-11-3; **15c** iodide, 16504-12-4; **15d** iodide, 16504-13-5; **15d** nitrate, 16504-14-6; **15c** nitrate, 16504-15-7; **16a**, 15539-31-8; **16d**, 16503-34-7; chelerythrine, 2870-15-7.

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Acylindoles. I. The Synthesis and Transformations of 3-(2-Aminobenzoyl)indoles

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The acid-catalyzed rearrangement of appropriately substituted 3-(2-aminobenzoyl)indoles and 5-(3-indolyl)-2,3-dihydro-1,4-benzodiazepines was found to result in the formation of indolo[3,2-*c*]quinolines, 3-(2-aminophenyl)-4(1H)-quinolones, and an imidazo[1,2-*a*]indolo[3,2-*c*]quinoline. An independent synthesis of the 3-(2-aminophenyl)-4(1H)-quinolones is described. The requisite indolylbenzodiazepines were prepared from the corresponding 3-(2-fluorobenzoyl)indoles by treatment with ethylenediamine.

The synthesis of heterocyclic systems such as dibenzodiazocines,[1] quinazolines,[2] benzodiazepines,[3] indoles,[4] and quinolones[5] from aromatic *o*-amino ketones has now been well established, and consequently we have investigated the synthesis and subsequent transformations of some 3-(2-aminobenzoyl)indoles. While these compounds can be utilized as starting materials for the synthesis of other heterocyclic moieties, we have found that these indoles readily undergo acid-catalyzed rearrangements to give quinolones and indoloquinolines.

The preparation of the aminobenzoylindoles was effected by a nucleophilic exchange of fluorine for amines on 3-(2-fluorobenzoyl)indole (**1**)[6] (Scheme I). Compound **1** was obtained by the acylation of indolylmagnesium bromide with *o*-fluorobenzoyl chloride. Also isolated from this reaction was 1,3-di(2-fluorobenzoyl)indole which was readily converted into **1** by treatment with aqueous alkali. A Vilsmeier type of reaction carried out as described by Anthony,[7] for the synthesis of 3-benzoylindole was also utilized, but the yield of **1** was, in this instance, much lower than that obtained from the Grignard reaction. Alkylation of **1** with dimethyl sulfate in the presence of sodium hydroxide afforded the N-methyl derivative **2**.

Treatment of **1** with ethylenediamine gave the corresponding indolylbenzodiazepine **3**, while the amination of **2** with benzylamine gave the substituted aminobenzoylindole **4**. Treatment of these acyl- or iminoindoles with acid resulted in both cases in rearrangement. Thus, compound **4** when treated with hot aqueous acid afforded a mixture of the quinolone **5** and the indoloquinoline **6**.[8] Under somewhat similar conditions, compound **3** gave the corresponding quinolone **7**.

More energetic treatment of **3** with acid gave the indoloquinoline **8**, which could also be obtained from compound **7** under similar conditions. By heating **7**, in high-boiling solvents, either the previously described indoloquinoline **9**[9] or a mixture of **9** and the dealkylated quinolone **10** was obtained. Thus, by heating a solution of **7** in diphenyl ether under reflux, compound **9** was the only detectable product, while in nitrobenzene both **9** and **10** were obtained.

The mechanism of the rearrangement of **4** to the quinolone **5** can be explained by the initial protonation of **4** at the carbonyl oxygen[10] to give the indolenine intermediate A (Scheme II). Nucleophilic addition of the anilino N–H function to the polarized C=N bond of A, as shown, followed by hydrolytic cleavage of the resultant intermediate B at the C–N bond of the five-membered ring would then lead directly to the observed quinolone **5**.

Evidence that the mechanism for the conversion of **3** into **7** is similar and initially involves the hydrolytic cleavage of the azomethine bond was given by the observation that base cleavage of the 4-methyl quaternary salt of **3** (compound **11**) gave the corresponding methylaminoethylaminoindole **12**, which when subjected to hot mineral acid, underwent a similar rearrangement to give a 60% yield of the quinolone **13** (Scheme III). A minor product isolated from the reaction mixture was the indoloquinoline **14**, isolated as the dihydrochloride hemihydrate. The formation of the indoloquinolines from the intermediate quinolones is self-explanatory and would involve condensation of the anilino amine with the quinolone carbonyl group.

The proof of structure for the quinolones **5**, **7**, and **10** was given by the following unequivocal syntheses. Ethyl 2-nitrophenylacetate upon treatment with N,N-dimethylformamide diethyl acetal[11] afforded the aminoacrylate **15**. This was not isolated but was directly converted by acid treatment into the acrylate **16**[12] (Scheme IV).

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(7) W. C. Anthony, *ibid.*, **25**, 2049 (1960).

(8) For convenience and simplicity, the compounds described throughout the discussion will be referred to by number or letter corresponding to their correct structures.

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(10) R. L. Hinman and E. B. Whipple [*J. Amer. Chem. Soc.*, **84**, 2534 (1962)] have established that the principal conjugate acid of indole in strong acid is the 3-protonated isomer. The 3-acylindoles have been found to protonate primarily at the acyl oxygen [G. Berti and A. da Settimo, *Gazz. Chim. Ital.*, **91**, 728 (1961)].

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