Syntheses of 4-Substituted Isoquinolines

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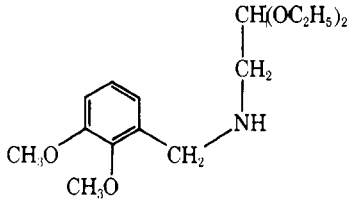
Several approaches to the synthesis of 4-substituted isoquinolines have been explored, as follows: preparation and α-alkylation of isoquinoline-4-acetic esters, alkylation of 3-cyanomeconin followed by ring expansion, α-alkylation and cyclization of *o*-carbomethoxyphenylacetonitrile, and oxidation of 4-hydroxy-1,2,3,4-tetrahydroisoquinoline to the oxo derivative with subsequent addition of a Grignard reagent. With the exception of the second, which was blocked at the last stage, all the methods were realized.

The work reported in this paper is presented as a contribution to the chemistry of 4-substituted isoquinolines, and especially to their syntheses, for which only a limited number of flexible methods are available.[1-3] The specific compounds were chosen with an eye to their structural relation with the benzophenanthridine alkaloids,[4] but the methods developed apply in general to 4-substituted isoquinolines. The approaches include: (1) alkylation of isoquinoline-4-acetic esters; (2) alkylation of a 3-cyanophthalide on its 3 position followed by ring expansion; and (3) alkylation of *o*-carbomethoxyphenylacetonitrile and cyclization to the corresponding homophthalimide. Also utilized was (4) Grignard addition to the carbonyl group of 4-oxo-1,2,3,4-tetrahydroisoquinoline, which could be prepared conveniently by oxidation of the readily accessible 4-hydroxy compound.



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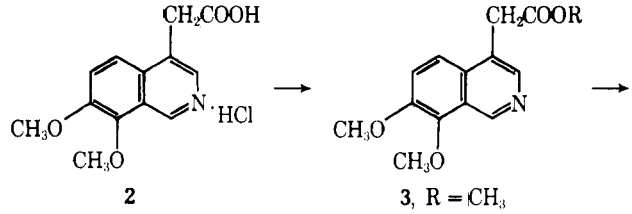
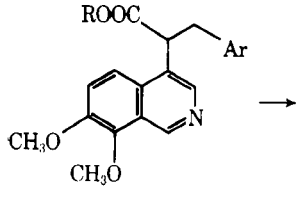
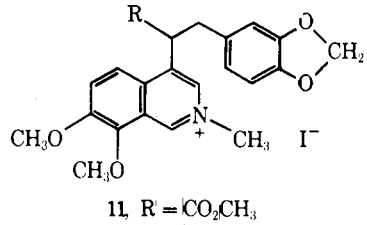


2 3, R = CH_3 4, R = C_2H_5

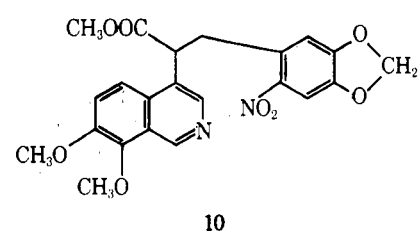


5, R = C_2H_5; Ar = 3′,4′-dimethoxyphenyl
6, R = CH_3; Ar = 3′,4′-dimethoxyphenyl
7, R = C_2H_5; Ar = phenyl
8, R = CH_3; Ar = 3′,4′-methylenedioxyphenyl
9, R = H; Ar = 3′,4′-methylenedioxyphenyl
10, R = CH_3; Ar = 3′,4′-methylenedioxy-6′-nitrophenyl



11, R = CO_2CH_3
12, R = CH_2OH

1. Alkylation of Isoquinoline-4-acetates. The elegant procedure of Bobbitt[1] was adapted to the preparation of isoquinoline-4-acetic acid **2** by allowing *N*-(2,3-dimethoxybenzyl)aminoacetal (**1**) to react with glyoxylic acid[5,6] in the presence of acid. The substituent at the 4 position of the corresponding esters **3** and **4** was elaborated by alkylating the ester enolates with benzyl chlorides. The yields of α-alkylation products **5–10** from the methyl ester (60–90%) were generally better than from the ethyl ester (30–35%). With variations possible in conditions, condensing base, and alkylating agent, this approach is adaptable to the synthesis of other kinds of 4-substituted isoquinolines. The methiodide **11** of the piperonyl derivative was reduced with lithium aluminum hydride both at the ester group and in the isoquinoline hetero ring; the product could be rearomatized directly to the quaternary alcohol salt **12**. No problem was encountered in the synthesis of nitro compound **10** despite exposure of the nitro group to strong base in liquid ammonia. However, when the nitro group in alkylation product **10** was reduced, cyclization could not be prevented, so that, instead of the amino compound, tetrahydroisoquinoline **13** was obtained.



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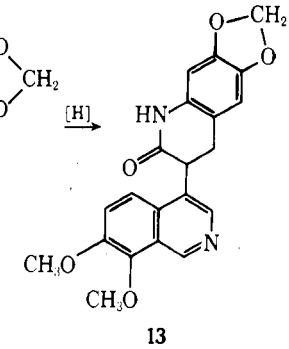

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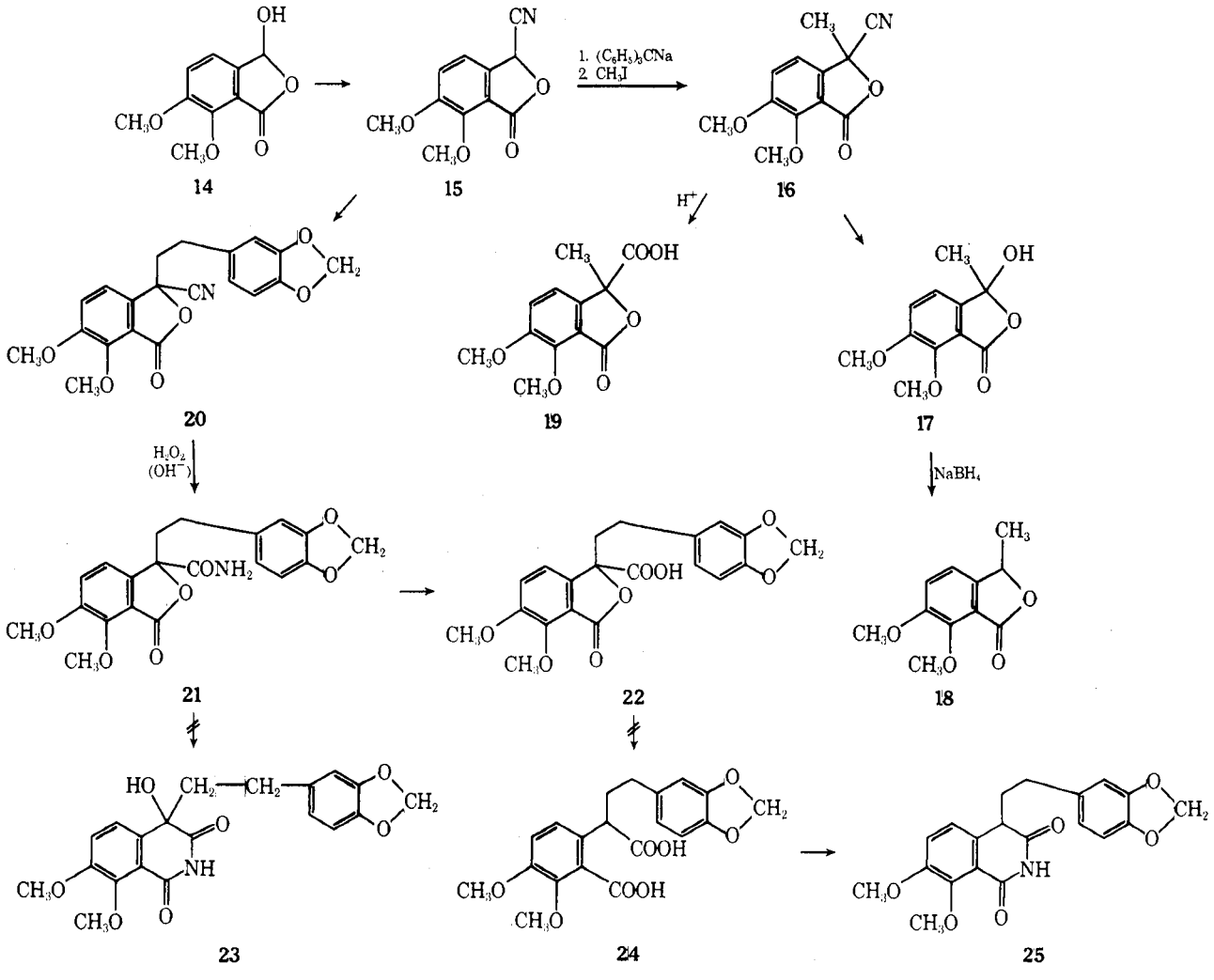
The acetic esters were hydrolyzed with exceptional ease to the corresponding acids, e.g., **8** to **9**. Since the acids are arylacetic acids, decarboxylation[7] appears quite feasible.

2. Alkylation of 3-Cyanomeconin (15). A second approach to the 4-substituted isoquinolines called for alkylation of the arylacetonitrile system, as in 3-cyano-6,7-dimethoxyphthalide (3-cyanomeconin, **15**), and conversion of the product, **20**, to the isoquinoline homophthalimide system, as in **23**. This series started with opianic acid (**14**), conveniently obtained from narcotine.[8] Cyanide ion reacts smoothly with opianic acid to give the necessary 3-cyanomeconin (**15**).[9] Methylation with the help of triphenylmethylsodium led to 3-cyano-3-methylmeconin (**16**), which on exposure to alkali lost cyanide ion. By reducing the resulting 3-methylopianic acid (**17**) to the known 3-methylmeconin (**18**),[10] the expected mode of alkylation on the 3 position was confirmed. When homopiperonyl iodide was substituted for methyl iodide in the alkylation step, 3-cyano-3-homopiperonylmeconin (**20**) was formed. Since di-



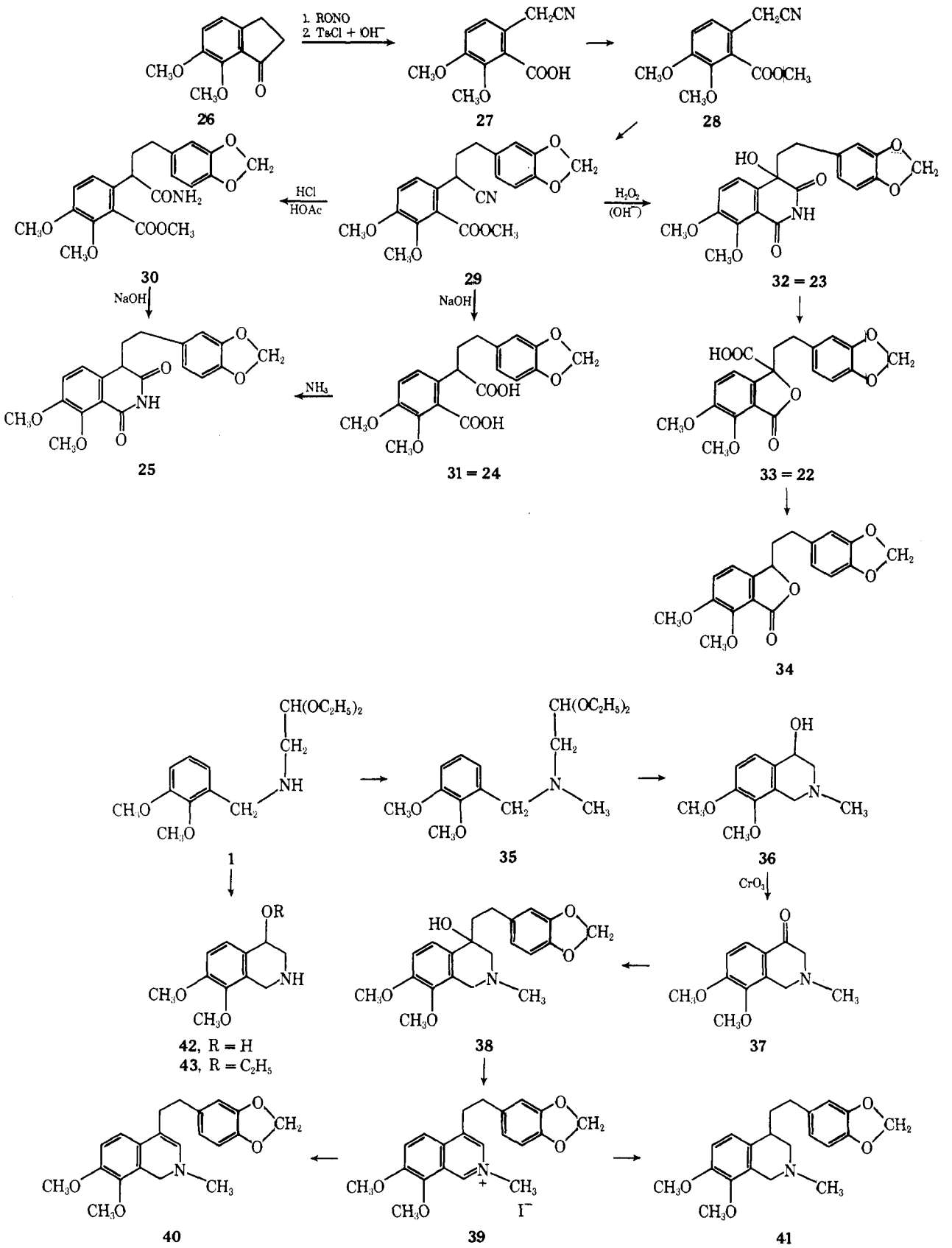
rect acid hydrolysis of **20** (analogous to **16** → **19**) failed, and direct alkaline hydrolysis eliminated the essential cyano group, a two-stage process was resorted to. Hydrogen peroxide with a catalytic amount of alkali[11] generated the amide **21**, which now could be safely hydrolyzed with alkali to 3-homopiperonylmeconin-3-carboxylic acid (**22**). This acid **22** was also obtained unexpectedly from α-homopiperonyl(2-carbomethoxy-3,4-dimethoxyphenyl)acetonitrile (**29**). Although the sequence broke down in its final stages, that is, in isomerizing phthalide **21** to **23**[12] and in reductively cleaving[13] phthalide **22** to homophthalic acid **24** (the intended precursor to homophthalimide **25**), we believe that this approach should not be lost sight of. So far as the reductive step **22** to **24** is concerned, cleavage of a benzyl-to-oxygen bond is involved, for which several alternate procedures are available.[13] For example, we have now confirmed the reported reduction of 6,7-dihydroxyphthalide-3-carboxylic acid to 3,4-dihydroxyhomophthalic acid with hydriodic acid.[14]

3. Alkylation of *o*-Carbomethoxyphenylacetonitrile. 2-Carboxy-3,4-dimethoxyphenylacetonitrile (**27**) is readily accessible by a two-step conversion from 6,7-dimethoxyindanone (**26**).[14] When sodium methoxide was used in the alkylation of the corresponding ester **28** with homopiperonyl iodide, the only products that could be identified were 7,8-dimethoxyhomophthalimide and 3,4-methylenedioxystyrene. Sodamide as condensing agent was more effective in furnishing the α-alkylation product **29**. Partial acid hydrolysis of **29** yielded the amide ester **30**, which under alkaline conditions cyclized to the desired 4-homopiperonyl-7,8-dimethoxyhomophthalimide (**25**).[15] The same homophthalimide **25** could be obtained also by hydrolyzing cyano ester **29** with alkali and cyclizing the resulting homophthalic acid **31** by heating it with ammonium carbonate.[15-17] Note that **31** is the same as **24**, so that the **24**-to-**25** step as projected before was realized here. Direct comparisons with a sample of 4-homopiperonyl-7,8-dimethoxyhomophthalimide synthesized elsewhere by a different route[15] confirmed the assigned structure of **25**.

When the Radziszewski hydrogen peroxide procedure[11] was applied to the cyano ester **29**, an oxidative step intruded, so that the product corresponded not to the expected amide ester **30**, but instead to 4-hydroxy-4-homopiperonyl-7,8-dimethoxyhomophthalimide (**32** or **23**). Hot aqueous alkali followed by acidification transformed 4-hydroxyhomophthalimide **32** to 3-homopiperonylmeconin-3-carboxylic acid (**33**), identical with the product **22** obtained before. Thermal decarboxylation to 3-homopiperonylmeconin (**34**) further confirmed the structure.

We have interpreted these transformations by postulating that hydrogen peroxide in the presence of a catalytic amount of alkali hydrolyzes cyano ester **29** readily to amide ester **30** in the usual way, and that in turn the amide ester with alkali cyclizes smoothly to 4-homopiperonyl-6,7-dimethoxyhomophthalimide (**25**). The enolate, readily formed by removal of hydrogen from the homophthalimide 4 position,[17] then oxidatively hydroxylates to yield the observed product **32**. Continued exposure of homophthalimide **32** to alkali would open the Py ring with loss of ammonia, and subsequent acidification would recyclize the intermediate hydroxyhomophthalic acid to phthalide **33**.

Since *o*-carbomethoxyphenylacetonitriles are smoothly



available from any indanone (cf. **26** to **27**), this alkylation–cyclization sequence provides a flexible approach to 4-substituted homophthalimides, which can then be modified in several ways.[17] If *o*-cyanophenylacetonitriles were generally accessible, they could serve equally as attractive starting materials.[18]

4. Oxidative Synthesis of 4-Oxotetrahydroisoquinoline Followed by Grignard Addition. Cyclization[1,5] of *N*-(2,3-dimethoxybenzyl)-*N*-methylaminoacetal (**35**) with acid produced 2-methyl-4-hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**36**) in high yield. After conditions were found for controlled oxidation at the 4-hydroxyl group, the 4-keto compound **37** became available, and this with homopiperonylmagnesium bromide gave rise to the desired 2-methyl-4-hydroxy-4-homopiperonyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**38**). Dehydration and

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Experimental Section

General. - Nuclear magnetic resonance spectra were determined at 60 MHz. Our thin-layer chromatograms utilized woven glass plates impregnated with silica gel (Gelman Type SG) as well as glass plates (Eastman 301R); they were developed with a spray of 1:1 sulfuric acid in ether or by exposure to iodine vapor. Analyses for elements were reported by the Microchemical Laboratories at Massachusetts Institute of Technology, Scandinavian Microanalytical Laboratory in Herlev, Denmark, Spang Microanalytical Laboratory in Ann Arbor, Michigan, Galbraith Laboratories in Knoxville, Tennessee, K. Ritter at Analytisches Laboratorium in Basel, and by C.K. Fitz, Needham Heights, Massachusetts (who reported percentage compositions to the tenth's place).

(7,8-Dimethoxyisoquinolyl-4)-acetic Acid (2). - 2,3-Dimethoxybenzylaminoacetal[5] (7.1 g; 25 mmol) in 50 ml of concentrated hydrochloric acid plus 90 ml of alcohol, was mixed with a solution of 40% aqueous glyoxylic acid (7.4 g containing 25 mmol) in 50 ml of alcohol. After refluxing the mixture 0.5 - 1 hr, it was evaporated under reduced pressures at 100°. Rubbing the almost dry residue with 3:1 alcohol-ether furnished needles, which were crystallized twice from ethanol to give the yellow needle-like hydrochloride of (7,8-dimethoxyisoquinolyl-4)-acetic acid (2), mp 178-181°, in 93% yield. Material melting at 194-195° (decomp.) could be obtained by crystallization from 2N hydrochloric acid. The hydrochloride showed a bright fluorescence under ultraviolet light; uv max (1.7×10^{-5} M in C_2H_5OH) 236 nm (log ε 4.37), 252 sh (4.22), 286 (3.64); ir (mineral oil mull) 1760 cm^{-1}; nmr (D_2O) δ 9.54 (s, 1, H-1), 8.35 (s, 1, H-3), 7.95 (s, 2, H-5,6), 4.30 (s, 2, CH_2), 4.08 ppm (s, 6, 2-CH_3O); nmr (F_3CCOOH) δ 9.81 (broad s, 1, H-1); 8.46 (broad s, 1, H-3), 8.18 (s, 2, H-5,6), 4.45 (s, 2, CH_2), 4.37 and 4.20 ppm (s's, 6, $2CH_3O$). *The spectra were not examined beyond δ 10 ppm.*

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Anal. Calcd. for $C_{13}H_{13}ClNO_6$: C, 55.00; H, 4.97; N, 4.97. Found: C, 54.87; H, 4.92; N, 5.25.

Methyl (7,8-Dimethoxyisoquinolyl-4)-acetate (3). - Thionyl chloride (6 ml) was added dropwise to a stirred suspension (-5°) of 2.8 g (10 mmol) of (7,8-dimethoxyisoquinolyl-4)-acetic acid hydrochloride in 20 ml of absolute methanol. After 15 min at -5°, the solution was stirred at room temperature for 3 hr, and then stripped of solvent at ca. 40°. Adding acetone to the gummy residue gave rise to solids, which on two crystallizations from ethanol or methanol afforded the highly fluorescent, yellow, crystalline hydrochloride of methyl (7,8-dimethoxyisoquinolyl-4)-acetate (3), mp 181-183°, in 84% yield; uv max (3×10^{-5} M in ab C_2H_5OH) 236 nm (log ε 4.48), 252 (4.34), 288 (3.56); ir (mineral oil mull) 1745 cm^{-1}; nmr (D_2O) δ 9.57 (s, 1, H-1), 8.33 (s, 1, H-3), 7.98 (q, J=9,1.5, 9 Hz, 2, H-5,6) 4.39 (s, 2, CH_2), 4.07 (s, 6, 7,8-diCH_3O), 3.78 ppm (s, 3, $COOCH_3$); nmr (F_3CCOOH) δ 10.05 (broad s, 1, H-1), 8.61 (broad s, 1, H-3), 8.25 (s, 2, H-5,6), 4.42 (s, 2, CH_2), 4.37 and 4.21 (s's, 6, 7,8-diCH_3O), 3.96 ppm (s, 3, $COOCH_3$).

Anal. Calcd. for $C_{14}H_{14}ClNO_4$: C, 56.47; H, 5.42; N, 4.71. Found: C, 56.74; H, 5.30; N, 4.46.

The picrate of methyl (7,8dimethoxyisoquinolyl-4)-acetate (3), precipitated from a saturated solution of picric acid in 95% ethanol, showed mp 182-184°.

Anal. Calcd. for $C_{20}H_{18}N_4O_{11}$: C, 50.29; H, 4.56; N, 16.08. Found: C, 50.00; H, 4.44; N, 15.97.

The free base 3 was released from its hydrochloride (2 g) by shaking the hydrochloride with sodium bicarbonate in 30 ml of methanol-water. The base was extracted into chloroform, and the extract was dried and stripped of solvent at room temperature. Methyl (7,8-dimethoxyisoquinolyl-4)-acetate (3) was obtained with mp 64-66° in 55% yield by recrystallizing the residue from a small volume of water: uv max (4×10^{-5} M in C_2H_5OH) 236 nm (log ε 4.63), 282 sh (3.80),

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290 sh (3.78), 349 (3.88); ir ($CHCl_3$) 1740 cm^{-1}; nmr (CCl_4) δ 9.31 (s, 1, H-1), 8.16 (s, 1, H-3), 7.44 (q, J=9,4.9 Hz, 2, H-5,6), 3.98 and 3.88 (s's, 6, 7,8-diCH_3O), 3.79 (s, 2, CH_2), 3.55 ppm (s, 3, $COOCH_3$); nmr (F_3CCOOH) δ 9.66 (broad s, 1, H-1), 8.26 (broad s, 1, H-3), 8.12 (s, 2, H-5,6), 4.40 (s, 2, CH_2), 4.33 and 4.19 (s's, 6, di-CH_3O), 3.95 ppm (s, 3, $COOCH_3$).

Ethyl (7,8-Dimethoxyisoquinolyl-4-)-acetate (4). - The hydrochloride of this ester 4 was prepared from the hydrochloride of acid 2 by using ethanol in place of methanol in the above procedure. Recrystallization from methanol gave the crystalline salt (81%) with mp 160-161°; ir (mineral oil mull) 1735 cm^{-1}; nmr (D_2O) δ 9.44 (s, 1, H-1), 8.26 (s, 1, H-3), 7.85 (q, J=9,4, and 9 hz, 2, H-5,6), 4.17 (s, CH_2), 4.01 (m, CH_2CH_3), 3.95 (s, 6, 7,8-diCH_3O), 1.17 ppm (t, J=9 Hz, 3, CH_2CH_3). Integration at δ 4.17 and 4.01 ppm indicated 4 protons.

The free base of ethyl (7,8-dimethoxyisoquinolyl-)-acetate (4) was recrystallized from water to give crystals, mp 80-81°; ir (CCl_4) 1740 cm^{-1}; nmr (CCl_4) δ 9.44 (s, 1, H-1), 8.21 (s, 1, H-3), 7.47 (q, J=9,5,9 Hz, 2, H-5,6), 4.11 (q, J=7 Hz, CH_2CH_3), 4.00 and 3.92 (s's, 7,8-di-CH_3O), 3.82 (s, CH_2), 1.25 ppm (t, J=7 Hz, 3, CH_2CH_3). Integration of the 4.11-3.82 signals corresponded to 10 protons as required.

The free base was converted to its picrate, mp 171-172°, for analysis.

Anal. Calcd. for $C_{21}H_{20}N_4O_{11}$: C, 50.01; H, 4.00; N, 11.11. Found: C, 49.96; H, 4.07; N, 11.29.

Ethyl α-(7,8-Dimethoxyisoquinolyl-4)-α-veratrylacetate (5). - Crystals of ethyl (7,8-dimethoxyisoquinolyl-4-)-acetate hydrochloride (4) (3.1 g; 10 mmol) were added in small portions to a stirred refluxing mixture of commercial sodamide (1.7 g; 43 mmol) in 500 ml of liquid ammonia that had been condensed directly into the reaction flask. The resulting red solution was stirred for 15 min before adding veratryl chloride (1.9 g; 10 mmol) and stirring further for 1-2 hr. Ammonium chloride (2.5 g; 50 mmol) was added in portions, after which the ammonia was allowed to evaporate.

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The residual solid was triturated with anhydrous acetone (50 ml), and acetone-insoluble material was discarded. The solution was dried and evaporated, and the remaining brown oil was dissolved in 25 ml of absolute ethanol. Adding drops of a saturated alcohol solution of picric acid gave a bright yellow precipitate, which was recrystallized from absolute ethanol to obtain the picrate of ethyl α-(7,8-dimethoxyisoquinolyl-4)-α-veratrylacetate (5), mp 120-130°, in 60% yield; ir ($CHCl_3$) 1735 cm^{-1}; nmr ($CDCl_3$) δ 9.72 (s, 1, H-1), 8.97 (s, 2, picrate Ar H's), 8.53 (s, 1, H-3), 7.98 (q, J=7,2,7 Hz, 2, H-5,6), 6.72 (s, 3, veratryl Ar H's), 4.26 and 4.12 (s's, 7,8-diCH_3O),4.0 (m, CH_2CH plus $COOCH_2$), 3.84 (s, veratryl CH_3O's), 1.23 ppm (t, J=7.5 Hz, 3, CH_2CH_3). The δ 4.26 - 3.84 ppm signals together corresponded to 17 protons.

Anal. Calcd. for $C_{26}H_{29}N_3O_{13}$: C, 55.04; H, 4.62. Found: C, 54.81; H, 4.85.

Methyl α-(7,8-Dimethoxyisoquinolyl-4)-α-veratryl acetate (6). - Alkylation of the methyl ester 3 with veratryl chloride was performed essentially the same as with the ethyl ester. The twice-crystallized picrate of methyl α-(7,8-dimethoxyisoquinolyl-4)-α-veratrylacetate, (6), mp 163.5-165°, was obtained in 35% yield; ir ($CHCl_3$) 1735 cm^{-1}; nmr ($CDCl_3$) δ 9.68 (s, 1, H-1), 8.90 (s, 2, picrate Ar H's), 8.55 (s, 1, H-3), 7.98 (s, 2, H-5,6), 6.68 (s, 3, veratryl Ar H's), 4.18 and 4.08 (s's, 6, 7,8-diCH_3O), 3.90 (m, 3, CH_2CH), 3.79 (s, 6, veratryl CH_3O's), 3.70 ppm (s, 3, $COOCH_3$).

None of the following showed signs of forming the enolate from methyl (7,8-dimethoxyisoquinolyl-4)acetate (3): triphenylmethyllithium, sodium hydride in dimethoxyethane, sodamide in boiling benzene, or sodium hydride in hexamethylphosphoramide.

Ethyl α-(7,8-Dimethoxyisoquinolyl-4)-α-benzylacetate (7). - The alkylation procedure was much the same as before, except that benzyl chloride was used. The picrate of ethyl α-(7,8-dimethoxyisoquinolyl-4)-α-acetate (7) was obtained after three crystallizations from alcohol as yellow crystals (30%) mp 153-155°.

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Anal. Calcd. for $C_{28}H_{28}N_4O_{11}$: C, 56.36; H, 4.42; N, 9.42. Found: C, 56.74; H, 4.70; N, 9.15.

The free base 5 could be obtained as an oil showing only a single spot on thin-layer chromatography (30-60° petroleum ether-ether, 1:1); nmr (CCl_4) δ 9.30 (s, 1, H-1), 8.28 (s, 1, H-3), 7.49 (q, J=11,14,11 Hz, 2, H-5,6), 7.02 (s, 3, phenyl Ar H's), 4.31 (m, 1, H-C-COO), 3.91 and 3.78 (s's, 6, 7,8-diCH_3O), 3.33 (m, 4, $ArCH_2$-C-CH_2), 0.96 ppm (t, J=7.5 Hz, 3, CH_2CH_3).

Methyl α-(7,8-Dimethoxyisoquinolyl-4)-α-piperonylacetate (8) and Its Methiodide (11). - Piperonyl chloride[21] was prepared by stirring a mixture of piperonyl alcohol (15.2 g; 0.10 mol), thionyl chloride (14 g; 0.11 mol) and solid sodium bicarbonate (14.4 g; 0.11 mol) in 100 ml of dry benzene for 2 hr at room temperatures. Filtration and distillation gave piperonyl chloride (13.2 g; 76%) with b.p 78-80° (0.05 mm).

The hydrochloride of methyl (7,8-dimethoxyisoquinolyl-4)-acetate (3) (2.0 g; 6.6 mmol) was allowed to react as above first with sodamide (1.0 g; 2.5 mmol) in 500 ml of liquid ammonia and then with piperonyl chloride (2.1 g; 6.6 mmol). After a 2-hr reaction period, 5.8 g (110 mmol) of ammonium chloride was added, after which the alkylation product, methyl α-(7,8-dimethoxyisoquinolyl-4)-α-piperonylacetate (8), was isolated as a yellow glass by the procedure described above.

A small sample, brought out of ethanol-ether, afforded crystalline material, mp 142-143°; nmr ($CDCl_3$) δ 9.36 (s, 1, H-1), 8.28 (s, 1, H-3), 7.55 (q, J=9,11,9 Hz, 2, H-5,6), 6.55 (s, 3, piperonyl Ar H's), 5.83 (s, 2, $CH_2(O)_2$), 4.00 and 3.91 (s's, 7,8-diCH_3O), 3.54 (m, $CHCH_2$), 3.52 ppm (s, CH_3OOC). Integration of the δ 4.0-3.52 ppm signals indicated 12 H's.

Another portion in solution with benzene was treated with hydrogen chloride. Recrystallization of the resulting gum from 95% ethanol gave the crystalline hydrochloride of methyl α-(7,8-dimethoxyisoquinolyl-4)-α-piperonylacetate, homo-

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geneous according to thin-layer chromatography and showing mp 130-132°; nmr ($CDCl_3$) δ 9.70 (s, 1, H-1), 8.95 (s, 1, H-3), 8.15 (s, 2, H-5,6), 6.68 (m, 3, piperonyl Ar H's), 5.96 (s, 2, $CH_2(O)_2$), 4.7-2.9 (m, CH_2CH), 4.23 and 4.18 (s's, 7,8-diCH_3O), 3.70 ppm (s, CH_3OOC). The last three signals corresponded to 12 protons.

The bulk of the yellow glassy product was dissolved in dry benzene, methyl iodide (10 ml) was added, and the solution was stirred in a nitrogen atmosphere for 3 hr. The yellow hygroscopic precipitate was collected and washed repeatedly with benzene to give 3.2 g (91% from 3) *of the desired methiodide of methyl α-*(7,8-dimethoxyisoquinolyl-4)-α-piperonylacetate (11), mp 101-103°. Recrystallization from alcohol did not change the melting point. This material showed one spot on thin-layer chromatography (4:1 benzene-ethanol); uv max (2×10^{-5} M in ab C_2H_5OH) 216 nm (log ε 4.59), 257 (4.6), 288 (3.84); ir ($CHCl_3$) 1725, 1645, 1620, 1575 cm^{-1}; nmr ($CDCl_3$) δ 10.00 (s, 1, H-1), 8.51 (s, 1, H-3), 7.96 (s, 2, H-5,6), 6.68 (s, piperonyl H-6'), 6.58 (s, piperonyl H-2',3'), 5.83 (s, 2, $CH_2(O)_2$), 4.76 (s, $CH_2\overset{+}{N}$), 4.57 (m, $HCOOCH_2$), 4.28 and 4.08 (s's, 6, 7,8-diCH_3O), 3.63 (s, $COOCH_3$), 3.40 ppm (m, piperonyl CH_2). Integration between δ 6.68-6.58 ppm corresponded to 3 protons, between 4.76-4.57 to 4 protons, and between 3.63-3.40 to 5 protons.

Anal. Calcd. for $C_{23}H_{24}INO_6$: C, 51.41; H, 4.50; N, 2.61. Found: C, 51.50; H, 4.56; N, 2.81.

α-(7,8-Dimethoxyisoquinolyl-4)-α-piperonylacetic Acid (9) from Its Methyl Ester 8. - Methyl α-(7,8-dimethoxyisoquinolyl)-α-piperonylacetate (8) was stirred for 1 hr at room temperature with 10% hydrochloric acid, after which period volatiles were removed under reduced pressures (100°). Two crystallizations of the residue from small volumes of ethanol afforded white crystals of α-(7,8-dimethoxyisoquinolyl-4)-α-piperonylacetic acid hydrochloride (9), mp 183-185°, in 80% yield; uv max (3×10^{-5} M in C_2H_5OH) 236 nm (log ε 4.43), 253 (4.30), 286 (3.78);

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ir (mineral oil mull) 1725, 2450 cm^{-1}; nmr (F_3CCOOH) δ 9.74 (s, 1, H-1), 8.43 (s, 1, H-3), 8.06 (s, 2, H-5,6), 6.54 (s, 3, piperonyl Ar H's), 5.73 (s, 2, $CH_2(O)_2$), 4.93 (t, J=10 Hz, 1, $HCOOH$), 4.23 and 4.13 (s's, 6, 7,8-diCH_3O), 3.33 ppm (m, 2, Ar CH_2).

Anal. Calcd. for $C_{21}H_{22}ClNO_6$: C, 60.36; H, 4.82; N, 3.35. Found: C, 60.13; H, 4.88; N, 3.35.

Methiodide of 8-(7,8-Dimethoxyisoquinolyl-4)-β-piperonyl-ethanol (12). - Lithium aluminum hydride (0.3 g; 8 mmol) was added to a stirred, ice-cold solution of the methiodide of methyl α-(7,8-dimethoxyisoquinolyl-4)-α-piperonylacetate (11) (0.5C g; 0.93 mmol) in 150 ml of tetrahydrofuran that had been dried with calcium hydride. Nitrogen covered the reaction mixture. The mixture was stirred for various periods (1 min - 1 day) at various temperatures (0°-30°) without significant difference in the results. Small portions of ice were introduced until no further bubbling was noted. After drying ($MgSO_4$), the mixture was filtered through diatomaceous earth, and the filtrate was stripped of solvent.

A portion (0.10 g; 0.25 mmol) of the residual frothy glass in 3 ml of methanol and 10 ml of 95% alcohol was refluxed for 6 hr with 0.20 g (0.79 mmol) of iodine and 0.40 g (4.2 mmol) of anhydrous potassium acetate. Then aqueous 6.7% sulfurous acid was added at room temperature until the red color changed to bright yellow-orange. Volatiles were removed (50° bath; reduced pressure), the remaining dry solid was thoroughly extracted with chloroform, and the chloroform-soluble material was recrystallized from 1:1 methanol-ether and from methanol to give the yellow methiodide of β-(7,8-dimethoxyisoquinolyl-4)-β-piperonyl-ethanol (12), mp 190-192°, in about 50% yield. This product showed a single spot on thin-layer chromatography (4:1 benzene-ethanol); uv max (4×10^{-5} M in ab C_2H_5OH) 230 nm (log ε 4.34), 256 (4.06), 287 (3.86); ir ($CHCl_3$) 2470, 1630 ($C=\overset{+}{N}H$) cm^{-1}; nmr ($CDCl_3$) δ 9.48 (s, 1, H-1), 8.49 (s, 1, H-3), 7.94 (q, J=8,5,8 Hz, 2, H-5,6), 6.66 and 6.60 (s's, 3, piperonyl Ar H's), 5.84

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(s, 2, $CH_2(O)_2$), 4.64 (s, 3, $CH_2\overset{+}{N}$), 4.17 and 4.05 (s's, 6, 7,8-diCH_3O), 3.94 (m, 3, piperonyl-CH_2CH), 3.07 ppm (m, 3, CH_2OH).

Anal. Calcd. for $C_{22}H_{24}INO_5$: C, 51.88; H, 4.76; N, 2.75. Found: C, 52.03; H, 5.06; N, 2.85.

Methyl α-(7,8-Dimethoxyisoquinolyl-4)-α-(6'-nitropiperonyl)-acetate (10). - 6-Nitropiperonyl chloride was prepared by adding piperonyl chloride (18.1 g) in portions to concentrated nitric acid (200 ml) at -15°. The mixture was then stirred for 2 hr at -10° and for 2 hr at room temperature. The reaction mixture was poured into a liter of water, and the solids were collected. After processing, recrystallized 6-nitropiperonyl chloride (8.6 g) was obtained with mp 78-80° [lit.[22] 83; 86°]. Another preparation gave light orange leaflets, mp 82-84°.

Anal. Calcd. for $C_8H_6ClNO_4$: C, 44.57; H, 2.80. Found: C, 44.67; H, 2.76.

According to the alkylation described above, 2.0 g (6.6 mmol) of methyl (7,8-dimethoxyisoquinolyl-4)-acetate hydrochloride (3) in liquid ammonia containing 0.4 g of sodamide (10 mmol) was combined with 1.5 g (6.6 mmol) of 6-nitropiperonyl chloride. Recrystallization of the crude product from methanol yielded faintly yellow methyl α-(7,8-dimethoxyisoquinolyl-4)-α-(6'-nitropiperonyl)-acetate (10), mp 150-151°, in 65% yield. This material showed one spot on thin-layer chromatography (chloroform); ir ($CHCl_3$) 1735, 1565, 1335, 875 cm^{-1}; nmr ($CDCl_3$) δ 9.31 (s, 1, H-1), 8.26 (s, 1, H-3), 7.32 (s, H-5'), 7.52 (q, J=9,12,9 Hz, H-5,6), 6.38 (s, 1, H-2'), 5.84 (s, 2, $CH_2(O)_2$), 4.53 (t, J=7 Hz, 1, $HCOOCH_3$), 3.93 and 3.74 (s's, 6, 7,8 diCH_3O), 3.45 (m, piperonyl CH_2), 3.42 ppm (s, $COOCH_3$). The integration from 7.32 and 7.52 indicated 3 H's, and from 3.45 and 3.42, 5 H's.

Anal. Calcd. for $C_{22}H_{22}N_2O_{10}$: C, 50.00; H, 4.58; N, 6.36. Found: C, 59.94; H, 4.54; N, 6.46.

Attempted alkylations in boiling 1,2-dimethoxyethane solvent with sodium hydride as condensing agent gave recovered nitropiperonyl chloride as the only

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product. Sodium hydride in hexamethylphosphoramide gave only recovered ester 3, whereas triphenylmethyllithium in tetrahydrofuran allowed recovery of both reactants.

Alkylation in boiling benzene with or without sodamide resulted in substitution on nitrogen instead of carbon. *The yellow crystals of the quaternary chloride (43%) obtained out of ether-ethanol with mp 174-175° (decomp), were* homogeneous according to thin-layer chromatography ($CHCl_3$-CH_3OH, 9:1); ir (mineral oil mull) 1725, 1520, 1350 cm^{-1}; nmr (F_3CCOOH) δ 9.22 (broad s, 1, H-1), 7.72 (d, J=5 Hz, 1, H-3), 7.50 (d, J=5 Hz, 2, $CH_2\overset{+}{N}$), 7.23 (s, 1, H-5'), 6.53 (s, 1, H-2'), 5.67 (s, $CH_2(O)_2$), 5.60 (broad s, together with preceding signal 4, H-5,6), 3.70 (m, 3, CH_2CHCH_2 plus $ArCH_2$), 3.58 (s, 3, $ArCH_3$), 3.30 ppm (s, 3, $COOCH_3$).

Anal. Calcd. for $C_{21}H_{21}ClN_2O_8$: C, 54.42; H, 4.44; Cl, 7.44; N, 5.86. Found: C, 54.69; H, 4.32; Cl, 7.61; N, 5.96.

Reduction and Cyclization of Nitro Compound 10 to 13. - A mixture of 0.60 g (1.3 mmol) of methyl α-(7,8-dimethoxyisoquinolyl-4)-α-(6-nitropiperonyl)-acetate (10) and prereduced platinum oxide catalyst (0.1 g) in 35 ml of ethanol was stirred under hydrogen for approximately 3 hr, at which time 115% of the calculated 3-molar equivalents of hydrogen had been absorbed. Removal of catalyst and of all solvent (7 below 40°) left a white residue, which was brought out of methanol to give *colorless crystals of 2-oxo-3-(7',8'-dimethoxyisoquinolyl-4')-*6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (13), mp 281-283°, in 59% yield; uv max (3×10^{-5} M ab C_2H_5OH) 213 nm (log ε 4.18), 236 (4.13), 278 sh; ir (mineral oil mull) 1680, 3220 cm^{-1}; nmr (F_3CCOOH) δ 9.51 (broad s, H-1'), 8.10 (broad s, H-3'), 7.98 (s, H-5',6') with the last 3 signals integrating to 3H's, 6.55 and 6.51 (s's, 2, H-5,8), 5.81 (s, 2, $CH_2(O)_2$), 4.77 (m, 1, H-3), 4.15 and 4.00 (s's, 6, 7',8'-diCH_3O), 3.28 ppm (m, 2, H-4).

Anal. Calcd for $C_{21}H_{18}N_2O_7$: C, 66.67; H, 4.79; N, 7.40. Found: C, 66.83; H, 4.90; N, 7.26.

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Reduction of 10 with tin and hydrochloric acid at 0° gave the same product 13 and offered no advantages.

Opianic Acid (14) from Narcotine. - The procedure described here is a considerably improved version of the reaction originally reported by Matthiessen and Foster.[8] A mixture of narcotine (225 g; 0.55 mol), manganese dioxide (203 g; 2.33 mol), and 3375 ml of 10% sulfuric acid was refluxed for 2.5 hrs. The hot mixture was filtered, the filtrate was cooled overnight, and the precipitated opianic acid (14) was collected, washed with cold water, and air-dried. Decolorization with charcoal followed by crystallization from 1.5 l. of water gave 85 g (75%) of cream-colored opianic acid (14), mp 145-146° [lit.[23], 142-146°].

3-Cyanonoconin (15) from Opianic Acid (14).[9] - Combining 42 g of opianic acid with potassium cyanide gave 3-cyanonoconin (15), mp 100-101°, in 70% yield, and twice-crystallized product, mp 102-103°, in 52% yield [lit.[9], mp 103-104].

3-Cyano-3-methylnoconin (16) by Methylation of 3-Cyanonoconin (15). - The methylation was performed in a manner similar to that described below for the homopiperonyl alkylation, except that the ether solvent was not replaced with benzene. An ether solution of 3-cyanonoconin (10 mmol) developed a permanent blood-red color only at the very end of the addition of ethereal triphenylmethylsodium[26] (122 ml containing 10 mmol). Methyl iodide in about 6-fold excess was introduced, and the mixture was allowed to stand at room temperature. Titration of aliquots showed that 93% of the base had disappeared after 18 hr, and that a total of 97% had disappeared after an additional 2 hr of reflux. 3-Cyano-3-methylnoconin (16) crystallized once from alcohol-water was obtained as a faintly yellow solid (1.6 g; 67%), mp 130-132.° Recrystallizations afforded colorless product, mp 134.5-135°.

Anal. Calcd. for $C_{13}H_{11}NO_4$: C, 61.80; H, 4.75. Found: C, 61.7; H, 4.8.

3-Methylnoconin (18) from 3-Cyano-3-Methylnoconin (16). - 3-Cyano-3-methylnoconin (0.1 g) was warmed on a steambath for 12 min with 2.5 ml of 8% aqueous

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sodium hydroxide. Acidification evolved HCN, and cooling gave a precipitate, which after one crystallization from water weighed 35 mg; mp 134-145°; mixture melting point with the starting material, 110-129°.

The crystals, taken as 3-methyl-3-hydroxymeconin (17), were allowed to stand for 3 hr with a solution of sodium borohydride (70 mg) in absolute ethanol (7 ml). Solvent was removed, hydrochloric acid was added, and the mixture was heated a short time on the steambath before chilling. The precipitate on crystallization from water furnished white glittering needles of 3-methylmeconin, mp 98-98.5°. [lit.[10], mp 101°]; ir max 1749 cm^{-1}.

Omitting alkali, and instead exposing 3-methyl-3-cyanomeconin directly to 25% hydrochloric acid on the steambath for 1 hr gave 3-methylmeconin-3-carboxylic acid (19) in 95% yield. On recrystallization from water, this acid showed mp 196.5-197° (effervescence).

Anal. Calcd. for $C_{13}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 57.41; H, 4.8.

Homopiperonyl Bromide and Iodide. - Phosphorous tribromide (10.2 g; 38 mmol) was added dropwise to a cold solution of homopiperonyl alcohol (15 g; 91 mmol) in 120 ml of benzene. The mixture was stirred at ice bath temperature for 0.5 hr, then refluxed for 1 hr, and finally allowed to stand overnight at room temperature. The reaction mixture was quenched over cracked ice, and the aqueous layer was extracted with ether. The combined organic phases were shaken with dilute carbonate solution, and with water, before drying over magnesium sulfate. Fractional distillation gave 8.6 g (83%) of homopiperonyl bromide, bp 129-131° (1.5 mm) or 97-100° (0.2 mm); n_D^{25} 1.573.

Anal. Calcd. for $C_8H_7BrO_2$: C, 47.30; H, 3.96. Found: C, 47.2; H, 4.0.

The quaternary salt derivative, N-homopiperonyl-pyridinium bromide, formed readily by warming the bromide in pyridine, showed mp 244.5-245° (decompose).

Anal. Calcd. for $C_{13}H_{12}BrNO_2$: C, 54.55; H, 4.58. Found: C, 54.6; H, 4.8.

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Crude dry homopiperonyl bromide obtained from 15 g of the alcohol was dissolved in 425 ml of acetone containing 27 g of sodium iodide. After 1 day at reflux temperature, solvent was removed, and the residue was extracted into ether. The ether-soluble material was crystallized from ethanol-water to get 19.5 g (78% from the alcohol) of colorless homopiperonyl iodide, mp 36-37°. The sample for analysis showed mp 40.1-40.4°.

Anal. Calcd. for $C_8H_7IO_2$: C, 38.73; H, 3.25. Found: C, 38.8; H, 3.3.

N-Homopiperonylpyridinium iodide, obtained from ethanol as glistening white crystals, melted at 205-206°.

Anal. Calc. for $C_{13}H_{12}INO_2$: C, 47.33; H, 3.97. Found: C, 47.7; H, 4.1.

3-Cyano-3-homopiperonylmeconin (20) by Alkylation of 3-Cyanomeconin (15). - The apparatus used here was scrupulously dry, and a current of dry nitrogen was maintained over the reaction mixtures throughout the reaction. Ether was distilled from lithium aluminum hydride and condensed directly onto 2.2 g (10 mmol) of 3-cyanomeconin (15). The resulting mixtures was titrated with ethereal triphenylmethylsodium[24] (ca. 0.1 M) until the red color persisted. Then over the course of 0.5 hr homopiperonyl iodide (6.2 g; 22 mmol) in a Soxhlet unit was extracted with ether directly into the boiling reaction mixture. Solvent was exchanged by condensing dry benzene vapors directly into the reaction vessel while distilling ether out. When the boiling point reached 80°, the resulting benzene solution (ca. 200 ml) was refluxed for 1 day.

Aqueous 2% acetic acid (100 ml) was added with cooling, and the aqueous layer was extracted with ether and benzene. The combined organic layers were rinsed with small portions of water, dried, and then warmed in a jet of clean nitrogen to remove solvent. After rinsing the slushy residue several times with 30-60° petroleum ether to remove triphenylmethane and unchanged homopiperonyl iodide, the remaining gum was recrystallized (charcoal) from 95% alcohol to give fine cream-colored crystals (0.89 g or 24%) of 3-cyano-3-homopiperonylmeconin

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(20), mp 144.5-145.5°; further recrystallizations brought this value to 146-146.5°.

Anal. Calcd. for $C_{21}H_{17}NO_6$: C, 65.39; H, 4.66. Found: C, 65.3; H, 4.7.

Processing the petroleum ether triturate afforded 2.1 g of unchanged homopiperonyl iodide or 70% of the excess. Approximately the same yield of alkylation product was obtained when the iodide was taken in equimolecular amounts. However, if ether alone was used as reaction solvent, the yield was 8%. The reaction with homopiperonyl bromide in place of the iodide was unsatisfactory in ether but was not tried in benzene solvent. When benzene suspensions of sodamide, sodium hydride, or sodium (dispersion) were used instead of ethereal triphenylmethylsodium, no reaction occured.

3-Homopiperonylmeconin-3-carboxamide 21. - Hydrogen peroxide (25 ml of 10% aqueous solution) plus 2 ml of 10% sodium hydroxide was added to a stirred suspension of 4.0 g of 3-cyano-3-homopiperonylmeconin (20) in 25 ml of acetone. Solution occured gradually over a 15 hr period. Removing volatiles left the crude solid product, which was crystallized from 30 ml of water to yield 3.5 g (83%) of crystalline 3-homopiperonylmeconin-3-carboxamide (21), mp 177-178° (prelim. softening). Another crystallization from benzene brought the melting point to 177.7-178.7°.

Anal. Calcd. for $C_{21}H_{19}NO_7$: C, 62.33; H, 4.97. Found: C, 62.2; H, 5.0.

Attempts at Isomerizing 3-Homopiperonylmeconin-3-carboxamide (21) to 4-Hydroxy-4-homopiperonyl-7,8-dimethoxyhomophthalimide (23). - Heating the dry carboxamide at 185-190° for 2.5 hr effected no change. Liquid ammonia with some methanol at room temperature for 1 day gave only unchanged starting material, as did alcoholic-concentrated aqueous ammonia at 100°, or sodamide in liquid ammonia at -43°.

While concentrated aqueous ammonia at 100° gave no reaction, raising the temperature to 150-180° produced a new compound, which on recrystallization

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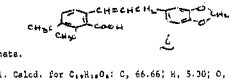
from 95% ethanol melted at 90-91°. This material, considered to be a disubstituted propene i, was soluble in aqueous alkali, and decolorized dilute



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permanganate.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 66.66; H, 5.30; O, 28.04. Found: C, 66.5; H, 5.7; O, 27.81.

In the light of a successful analogous conversion of 3-phenylphthalide-3-carboxamide to 4-hydro-4-phenylhomophthalimide,[12] this reluctance of 21 to isomerize is not clear. Possibly the methoxy group at the 6-position of meconin 21 tends to stabilize the lactone ring.[25]

3-Homopiperonylmeconin-3-carboxylic Acid (22) from the Amide 21. - A solution of the amide 21 (1.4 g) in 55 ml of 20% aqueous sodium hydroxide plus 17 ml of alcohol was refluxed for 3 hr. The reaction mixture was concentrated to about half its volume, diluted with an equal volume of water, and acidified with 20% sulfuric acid. The product was taken up in chloroform, and the extract was dried and then stripped of all solvent. Crystallization of the residue from benzene furnished 1.1 g (83%) of the desired 3-homopiperonylmeconin-3-carboxylic acid (22), mp 142.5-143.5°; ir (KBr) 3260, 2790, 1745, 1688 cm^{-1}. A sample further recrystallized for analysis showed mp 143.5-147°.

Anal. Calcd for $C_{20}H_{18}O_8$: C, 62.17; H, 4.70. Found: C, 62.2; H, 4.8.

Attempts at obtaining this acid by treating the amide 21 with nitrous acid failed, as did attempts at hydrolysing the precursor 3-cyano-3-homopiperonylmeconin (20) with acid. Thus 36% hydrochloric acid at 150° for 1 hr resulted in charring, while 24% hydrochloric acid at 130° for 1 hr gave only unchanged cyano compound. This resistance to acid hydrolysis, contrasting sharply with the facile hydrolysis of 3-cyano-3-methylmeconin (16), may be attributed to steric factors.

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3-Homopiperonylmeconin-3-carboxylic acid (33=22) was also obtained by an oxidative process from α-(homopiperonyl)-2-carbomethoxy-3,4-dimethoxyphenylacetonitrile (29) as described below.

2-Carboxy-3,4-dimethoxyphenylacetonitrile (27). - A solution of the 2-nitroso derivative[14] (22 g) of 6,7-dimethoxyindanone (26) in 200 ml of 8% aqueous sodium hydroxide was stirred and treated dropwise with 22 g of p-toluenesulfonyl chloride. The mixture was then warmed to 80° before chilling in an icebath and acidifying with 10% hydrochloric acid. The solids deposited overnight at icebox temperatures were collected, washed with water, and dried. Crystallization from benzene afforded 2-carboxy-3,4-dimethoxyphenylacetonitrile (27), mp 97-99° [lit.[14] mp 104-108°] in yields up to 72%. The same product 27 was obtained with phosphorus pentachloride,[14] but the yields were low.

2-Carbomethoxy-3,4-dimethoxyphenylacetonitrile (28). - 2-Carboxy-3,4-dimethoxyphenylacetonitrile (27) (7.5 g; 79 mmol) suspended in 20 ml of ether was treated with ethereal diazomethane in excess first in the icebath and then at room temperature. Crystallization of the crude product from ethanol-water gave pale yellow needles (5.4 g; 83%) of 2-carbomethoxy-3,4-dimethoxyphenylacetonitrile (28), mp 44.5-45°. A sample for analysis was prepared by distillation at bp 153° (0.7 mm).

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.3; H, 5.7; N, 6.0.

α-(Homopiperonyl)-2-carbomethoxy-3,4-dimethoxyphenylacetonitrile (29). - 2-Carbomethoxy-3,4-dimethoxyphenylacetonitrile (28; 10 g; 42 mmol) was added to benzene (150 ml freshly distilled from calcium hydride) containing commercial sodamide (1.67 g; 42 mmol), and the mixture was stirred and refluxed for 1hr. The glassware had been rigorously dried, and a slow stream of nitrogen was maintained through the apparatus during the course of the reaction. Homopiperonyl iodide was then added (8.8 g; 32 mmol), and the refluxing was continued for 1 day.

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Acetic acid (3.3 ml) in 100 ml of water was introduced, and the aqueous layer was extracted with benzene and with ether. The combined organic layers were rinsed with water, dried, and stripped of solvent. Fractionation of the oily residue (17.4 g) in a short-path, 3-bulb still gave a lower boiling mixture of starting materials (5.2 g), distilling at bath temperatures up to 185° (0.02 mm) and a higher boiling fraction (7.9 g), bp 180-240° (0.02 mm), containing the product. Two crystallizations of this material from acetic acid-water furnished α-(homopiperonyl-2-carbomethoxy-3,4-dimethoxyphenylacetonitrile (29), mp 60.5-62.0°, in yields of 26-36%; ir max 2240, 1731 cm^{-1}. Further recrystallization gave constant-melting material, mp 63.5-65.0°.

Anal. Calcd. for $C_{21}H_{21}NO_6$: C, 65.78; H, 5.52; N, 3.65; methoxy, 24.3. Found: C, 65.7; H, 5.4; N, 3.7, methoxy 24.1.

When the same alkylation was carried out at room temperature with the reactants in absolute methanol containing dissolved sodium, the initial alkalinity gradually decreased until after 16 hr, 35% had been lost. Two products could be isolated from this reaction: (a) 7,8-dimethoxyhomophthalimide, with the same melting point (208-210°) and infrared absorption curve as the identical material (mp 208-209.5°) obtained by baking 3,4-dimethoxyhomophthalic acid[14] with ammonium carbonate [Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 60.0; H, 4.8; N, 6.4.] and (b) a water-white liquid bp 40-45° (0.7 mm); n_D^{25} 1.5763; ir absorption max 3080, 2980, 1630, 988, 904 cm^{-1}, which decolorized bromine in carbon tetrachloride instantly and which was taken as 3,4-methylenedioxystyrene [Anal. Calcd. for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 72.8; H, 5.4].

4-Hydroxy-4-homopiperonyl-7,8-dimethoxyhomophthalimide (32) from Cyano-ester 29. - A solution of the cyano-ester 29 in acetone (35 ml) was treated with 1.5 ml of water containing 9 ml of 28% hydrogen peroxide followed by 2.1 ml of 8% aqueous sodium hydroxide, and the mixture was allowed to stand for 2 days.

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After volatiles were removed from the warm solution in a jet of air, the residue was taken up in ether, and the ether solution washed with water, dried, and stripped of solvent. The remaining solids, recrystallized from aqueous acetic acid, afforded 4-hydroxy-4-homopiperonyl-7,8-dimethoxyhomophthalimide, mp 118-119°, in low yield; ir max 3360, 3200, 1714, 1690 cm^{-1}; soluble in cold 8% aqueous sodium hydroxide.

Anal. Calcd. for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.64. Found: C, 62.2; H, 5.3; N, 3.6.

3-Homopiperonylmeconin-3-carboxylic Acid (33) from Cyano-ester 29. - A solution of cyano-ester 29 (3.0 g), 100 ml of acetone, 45 ml of water, 27 ml of 28% aqueous hydrogen peroxide, and 6.3 ml of 8% sodium hydroxide was kept at 15° for 1 hr, then at room temperature for 3 days, and thereafter treated essentially as in the isolation of crude 4-hydroxy-4-homopiperonyl-7,8-dimethoxyhomophthalimide (32).

A portion of this light-yellow oily material 32 (1.5 g) was refluxed with ethanol (17 ml) and 20% aqueous sodium hydroxide (60 ml) for 1 day in an atmosphere of nitrogen. After concentrating the mixture at steam-temperatures at reduced pressures, it was diluted with water, acidified with hydrochloric acid, and extracted with chloroform. The chloroform solution was dried, stripped of solvent, and the residue crystallized from aqueous acetic acid to give 3-homopiperonylmeconin-3-carboxylic acid (33), mp 142-143.5° in 38% yield; bicarbonate soluble; ir (KBr) 3280, 2860, 1740, 1690 cm^{-1}. Further recrystallization from aqueous acetic acid furnished colorless plates of 33, mp 143-144°.

Anal. Calcd. for $C_{20}H_{18}O_8$: C, 62.17; H, 4.70; neturalization eqv., 386.3. Found: C, 62.14; H, 4.56; N, 0.0; neturalization eq., 399.5.

The nonidentity of this product with the α-homopiperonyl-2-carboxy-3,4-dimethoxyphenylacetic acid described in the literature[15] was established by directly comparison with an authentic sample made available by Professor A.S.

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Bailey. The melting points, taken on a Fisher-Johns apparatus, were found to be 147-148° for compound 33, 152-153° for Bailey's homophthalic acid (cf. 31), and 123-128° (previous softening) for the mixture. The infrared absorption curves of the two materials showed many points of difference.

The identity of the product 33 described here with the 3-homopiperonylmeconin-3-carboxylic acid (22) obtained as described before from 3-homopiperonyl-3-carboxamide (21) was supported by melting point comparison (Fisher-Johns! 147-148° vs. 145.5-147°), by the virtual identity of the two infrared absorption spectra, and by decarboxylation of the present product to 3-homopiperonylmeconin (34).

3-Homopiperonylmeconin (34) from 3-Homopiperonylmeconin-3-carboxylic Acid (33). - A sample of the acid 33 was distilled in a wide-bore short-path still at outside temperatures of 240-300° (0.4 mm). Two crystallizations of the distillate from ethanol gave white, fluffy crystals of 3-homopiperonylmeconin (34), mp 81.5-82°; ir max 1748 cm^{-1}. The lactone carbonyl peak compares well with that observed for 3-methylmeconin (18) and for 3-homopiperonylmeconin-3-carboxylic acid (22).

Anal. Calcd. for $C_{19}H_{14}O_6$: C, 66.66; H, 5.30. Found: C, 66.5; H, 5.3.

4-Homopiperonyl-7,8-dimethoxyhomophthalimide (23). - No change noted when α-(homopiperonyl)-2-carbomethoxy-3,4-dimethoxyphenylacetonitrile (29) was heated at 200-320° for 0.5 hr or was exposed to the action of ethereal hydrogen chloride in the absence or presence of anhydrous zinc chloride.

1. Acid hydrolysis of cyano-ester 29 followed by cyclization with alkali. - Dry hydrogen chloride was bubbled for 5 hr into an ice-cold solution of 0.1 g of α-(homopiperonyl)-2-carbomethoxy-3,4-dimethoxyphenylacetonitrile (29) in 12 ml of acetic acid. The mixture was allowed to stand in the cold for 2 days. Stripping off all volatile material left a residue, which was dissolved in ether and washed with water. Removing the solvent furnished a partially puri-

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fied product, insoluble in warm 5% bicarbonate [ir max 3442, 3335, 1718, 1689, but not at 2240 cm^{-1} (nitrile)] and considered to be α-(homopiperonyl)-2-carbomethoxy-3,4-dimethoxyphenylacetamide (30). Solution occurred when this ester-amide was treated with 2 ml of oxygen-free 8% aqueous sodium hydroxide with intermittent warming on the steam for 15 min. Acidification of the cooled solution with dilute hydrochloric acid deposited a gum, which was collected, and rubbed with a small volume of cold ethanol. The resulting white crystals (0.05 g) of 4-homopiperonyl-7,8-dimethoxyhomophthalimide (25), mp 124.5-125°, showed an infrared absorption spectrum identical to that of the same compound described below. The mixture melting point was 125-126°.

2. Saponification of 29 followed by cyclization. - A mixture of 3.5 g (9.2 mmol) of cyano-ester 29 with 100 ml of 8% sodium hydroxide and 70 ml of ethanol was refluxed for 2 hr. The resulting solution, concentrated under reduced pressues to about $^1/_3$ its volume, was diluted with 100 ml of water and acidified with hydrochloric acid. After cooling the mixture overnight, it was filtered, and the solids (presumably homophthalic acid 31) were dissolved in concentrated aqueous ammonia. The solution was evaporated to dryness at 100° (reduced pressures), and the foamy residue was powdered and then thoroughly mixed with ammonia carbonate (1.1 g). The solids were heated for 30 min in an oilbath at 165° (reduced pressures). The reaction mixture was dissolved in ca. 75 ml of ethanol, and the solution was concentrated in the presence of decolorizing charcoal to ca. 30 ml, filtered, and finally cooled overnight. The precipitate was collected and crystallidetwice from ethanol to get 4-homopiperonyl-7,8-dimethoxyhomophthalimide (25) as fine white needles, mp 126-127°, in 61% yield; ir (mineral mull) 3155, 3079, 1700, 1670 cm^{-1}; insoluble in hot 5% aqueous sodium bicarbonate, but soluble in cold dilute sodium hydroxide to give a deep yellow solution.

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Anal. Calcd. for $C_{19}H_{17}NO_6$: C, 65.03; H, 5.19; N, 3.79; methoxy, 16.8. Found: C, 65.1; H, 5.3; N, 3.8; methoxy 16.7.

With determinations made using a Fisher-Johns apparatus instead of a melting-point bath, a sample of homophthalimide 25 prepared and provided by Bailey[15] showed mp 130-131.5°, and the product described above showed mp 128.5-130°; a mixture of the two showed mp 128.5-130°. The infrared absorption spectra of both samples taken as pellets in KBr were identical and included peaks at 3310 and 1672 cm^{-1}.

4-Hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinolinium Hydrochloride (42).[5] - A stoppered mixture of 2,3-dimethoxybenzylaminoacetal (1) (2.8 g; 0.010 mol) and 50 ml of 6 N hydrochloric acid was allowed to stand overnight at room temperature. *Evaporation of the mixture under reduced pressure (100°) left a red oil, which* was crystallized once from 1:1 ether-ethanol and three time from methanol. The desired product 42 as the hydrochloride[26] (1.7 g or 68%) was obtained with mp 170-171°; uv max (7×10^{-5} M in absolute ethanol) 229 nm (log ε 3.9), 278 (3.2);[27] ir (mineral oil mull) 3475, 1640, 1605, 1580 cm^{-1}.

Anal. Calcd. for $C_{11}H_{16}ClNO_3$: C, 53.77; H, 6.56; N, 5.70. Found: C, 53.69; H, 6.40; N, 5.70.

That the corresponding 4-ethoxy compound 43 was also present was shown by mixing the crude red oil with acetone, whereupon a pale yellow solid precipitated. Two crystallizations of this solid from ethanol gave crystals (20% yield) of 4-ethoxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinolinium chloride (43), mp 147-148° (preliminary coloration); ir (mineral oil mull) almost superposable with the curve from the 4-hydroxy compound 42; nmr (D_2O) δ 7.22 (q, J=8.5,2.5, 8.5, 2, H-5 and 6), 4.45 and 4.41 (s's, 2, 2H-1), 3.94 and 3.86 (s's, 7,8-diCH$_3$O), 3.67 (m, C*H*$_2$-O-C*H*-C*H*$_2$), 1.27 ppm (t, J=7, 3, C*H*$_3$CH$_2$-). Integration between δ 3.94 and 3.67 ppm showed 11 protons as required.

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The methiodide was prepared by treating the hydrochloride of 43 with dilute aqueous sodium carbonate, extracting the basic mixture with chloroform, and removing solvent from the dried chloroform solution. Distillation of the residual oil furnished the base, bp 141° (0.05 mm), corresponding to the 4-ethoxy compound 43. The distilled material was stirred with methyl iodide (3 molar equivalents) in benzene under nitrogen for 1 hr. The solids were collected and washed with dry benzene to give analytically pure 2,2-dimethyl-4-ethoxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinolinium iodide, mp 220-222°.

Anal. Calcd. for $C_{15}H_{24}INO_3$: C, 45.80; H, 6.15; N, 3.56. Found: C, 46.03; H, 6.22; N, 3.68.

Although we believe the 4-ethoxy compound 43 was present in the crude product, its formation from the 4-hydroxy compound during the crystallizations from ethanol has not been precluded.[28]

2-Methyl-4-hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (36). - The yellow solution obtained on mixing o-veratraldehyde (8.3 g; 0.050 mol) with aminoacetal (6.7 g; 0.050 mol) in 75 ml of absolute ethanol was hydrogenated over platinum to form 2,3-dimethoxybenzylaminoacetal (1).[5] Formaldehyde (4.5 g of 37% formalin, or 0.056 mol) plus 5 ml of acetic acid were added and the hydrogenation was continued until another 0.05 mol of hydrogen was taken up.[1] Removal of the catalyst and all volatiles left 14 g (97%) of colorless oily N-methyl-N-(2,3-dimethoxybenzyl)-aminoacetal (35).

Cyclization was effected by allowing a solution of this acetal (5.7 g or 0.020 mol) in 100 ml of 6N hydrochloric acid to stand at room temperature for one day. Bringing the reaction mixture to pH 10 by adding 6N sodium hydroxide at temperatures no higher than 10° precipitated almost pure 2-methyl-4-hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (36) in ca. 90% yield. Extracting the filtrate with ether afforded more of the same product, which when combined with the original crop melted at 135-136° either before or after

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crystallization from 1:1 ether-alcohol. This material should not be warmed unnecessarily. The free base 36 showed uv max (1×10^{-4} M in C_2H_5OH) 229 nm (sh)(log ε 3.67), 278 (2.93);[25] nmr ($CDCl_3$) δ 6.87 (q, J=8,10,8 Hz, 2, H-5,6), 4.45 (m, 1, *H*COH), 3.75 and 3.73 (s's, 6, 7,8-diCH$_3$O), 3.71, 3.08 (d, J=16 Hz, as AB, 2, 2H-1), 2.56 (m, 2, 2-H-3), 2.33 ppm (s, 3, N-CH$_3$).

The hydrochloride of 36 was prepared by bubbling dry hydrogen chloride into an ether solution of the base. Two crystallizations of the precipitate from ethanol gave yellow, analytically pure hydrochloride, mp 183-184°; uv max (7×10^{-5} in C_2H_5OH) 229 nm (log ε 4.1), 279 (3.3); ir ($CHCl_3$) 3325, 2575, 1605 cm^{-1}; nmr (D_2O) δ 7.96 (q, J=7,3,7, 2, H-5 and 6), 4.96 (t, J=2, 1, *H*COH), 4.38 (q, J=16,8,16, 2 2H-1), 3.77 and 3.73 (s's, 6, 7,8-diCH$_3$O), 3.53 (m, 2, 2H-3), 3.10 ppm (s, 3, $CH_3\overset{+}{N}$).

Anal. Calcd. for $C_{12}H_{18}ClNO_3$: C, 55.49; H, 6.98; N, 5.39;. Found: C, 55.45; H, 6.94; N, 5.44.

2-Methyl-4-oxo-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (37). - 4-Hydroxy compound 36 (2.2 g; 10 mmol) was added in portions to a stirred solution of 0.65 g (6.5 mmol) of chromium trioxide in 50 ml of water plus 15 ml of concentrated sulfuric acid. The reaction mixture protected with a blanket of nitrogen, and was held at temperatures below 10°. After stirring at 0-10° for 1 hr, the solution was stored overnight at room temperature. The cold solution was then rinsed with ether (discard), and with cooling was brought to pH 10. Without delay the basic mixture was extracted thoroughly with chloroform, and the dried extracts were stripped of all solvent (temperature below 40°). Crystallization of the residual yellow oil from chloroform yielded 1.3 g (55%) of 2-methyl-4-oxo-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (37), mp 95-97°; uv max (3×10^{-5} in C_2H_5OH) 229 nm (log ε 4.22), 279 (4.04); ir ($CHCl_3$) 1685 cm^{-1}; nmr ($CDCl_3$) δ 7.78 (d, $J_{5,6}$=8.5, 1, H-5), 6.87 (d, $J_{5,6}$=8.5, 1, H-6), 3.93 and 3.83 (s's, 7,8-diCH$_3$O), 3.75 (s, 2H-1), 3.24 (s, 2, 2H-3), 2.51 ppm (s, 3, CH$_3$-N). The integration between δ 3.93-3.75 ppm corresponded to 8 protons.

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The picrate of 37, recrystallized from methanol, showed mp 178-180°.

Anal. Calcd. for $C_{18}H_{18}N_4O_{10}$: C, 48.01; H, 4.03; N, 12.44. Found: C, 48.17; H, 3.84; N, 12.67.

Since the free base 37 was very susceptible to air oxidation, it was advantageous to store the material as its hydrochloride, which was precipitated by bubbling dry hydrogen chloride into a solution of the base in anhydrous ether. Crystallization without delay from 95% alcohol gave pale yellow crystals of 2-methyl-4-oxo-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinolinium chloride, mp 192-195° (decomp); ir (mineral oil mull) 1680 cm^{-1}; nmr (D_2O) δ 7.85 (d, J=8, 1, H-5), 7.20 (d, J=8, 1, H-6), 4.70 (s, 2, 2H-3), 4.20 (s, 2, 2H-1), 3.93 and 3.73 (s's, 6, 7,8-diCH$_3$O), 3.17 ppm (s, 3, $CH_3\overset{+}{N}$).

The N-benzyl derivative corresponding to the N-methyl compound 37 has been reported[29] with absorption constants that compare well with those given above.

2-Methyl-4-hydroxy-4-homopiperonyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (38) by Grignard Addition of Homopiperonylmagnesium Bromide to 4-Keto Compound 37. - A mixture of homopiperonyl bromide (2.8 g; 12 mmol), 0.3 g (12 mmol) of resublimed magnesium, and 35 ml of tetrahydrofuran freshly distilled from lithium aluminum hydride was refluxed for 0.5 hr until the magnesium had disappeared. The reaction was carried out under dry nitrogen in scrupulously dried glassware. 2-Methyl-4-oxo-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinolinium chloride 37 (1.7 g; 5.5 mmol) that had been carefully dried in vacuo was added in portions to the cold Grignard solution from a flask connected to the reaction vessel by a wide rubber hose. After 1 hr of reflux, the mixture was quenched over ice. Product was extracted into chloroform, and the chloroform solution was washed once with water, dried with magnesium sulfate, and stripped of all volatiles at room temperature under reduced pres-

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sure. Rubbing the residual yellow oil with a little methanol produced 1.4 g (69%) of almost pure addition product 38 as tan crystals, mp 112-115°. Recrystallization from methanol gave material, mp 118-118.5° which was homogeneous according to thin-layer chromatography (methanol-chloroform, 4:1); uv max (95% C_2H_5OH) 206 nm (log ε 4.57), 225 sh (4.05), 281 (3.61); ir (mineral oil mull) 3420, 1600 cm^{-1}; nmr ($CDCl_3$) δ 6.98 (d, J=8, 1, H-6), 6.55 (d, J=8, 1, H-5), 6.40 (s, 3, piperonyl Ar H's), 5.63 (s, 2, CH$_2$(O)$_2$), 3.65 (s, 6, 7,8-diCH$_3$O), 3.52 and 3.28 (d's, 2, 2H-1), 2.8-2.0 (m, C*H*$_2$-C-C*H*$_2$C*H*$_2$), 2.23 ppm (s, CH$_3$-N). Integration from δ 2.0-2.8 ppm indicated 9 protons.

Anal. Calcd. for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.94; N, 3.76. Found: C, 68.20; H, 6.99; N, 3.64.

When exposed to air for extended periods, the Grignard adduct 38 showed signs of change. The hydrochloride of 38 precipitated from aqueous-alcoholic hydrochloric acid and, when recrystallized from alcohol, was obtained as white crystals, mp 142-143°; uv max (2×10^{-5} M in C_2H_5OH) 229 nm (log ε 4.34), 281 (4.11).

Preliminary trials indicated that the Grignard addition using phenethylmagnesium bromide instead of homopiperonylmagnesium bromide would offer no complications.

4-Hydroxy compound 38 warmed in methanol containing various concentrations of hydrochloric acid gave mixtures. Exposure to hydrochloric acid in acetic acid converted the 4-hydroxy compound to the disproportionation products, the tetrahydro and the fully aromatic isoquinolines, 41 and 39, respectively.

2-Methyl-4-homopiperonyl-7,8-dimethoxyquinolinium Iodide (39). - A solution of the 4-hydroxy-4-homopiperonylisoquinoline 38 (0.50 g; 1.4 mmol) in 30 ml of methanol was added to a mixture of potassium acetate (2.5 g; 24 mmol) and 1.3 g (10 mmol) of iodine with 30 ml of 95% alcohol. After a 0.5 hr reflux

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period, the mixture was cooled, and the green precipitate was collected, dissolved in boiling methanol (20 ml), and treated with a few crystals of sodium sulfite until the color became yellow. Filtering the hot solution removed unwanted solids, and cooling the filtrate deposited yellow needles (0.55 g; 85%) of 2-methyl-4-homopiperonyl-7,8-dimethoxyisoquinolinium iodide (39), mp 176-178°. A sample recrystallized from CH_3OH melted at 180-181°; uv max (95% *C_2H_5OH) 217 nm (log ε 4.36), 254 (4.61), 287 (3.89);*[27] ir (mull) 1600, 1275 cm^{-1}; nmr (F_3CCOOH, external TMS) δ 9.00 (s, 1, H-1) 7.60 (s, 2, H-5,6), 7.40 (br s, 1, H-3), 6.20 (br s, 3 piperonyl Ar H's), 5.46 (s, 2, CH$_2$(O)$_2$), 4.05 (s, 3, $CH_3\overset{+}{N}$), 3.85 and 3.72 (s's, 6, 7,8-diCH$_3$O), 3.2-2.6 ppm (m, 4, CH$_2$CH$_2$).

2-Methyl-4-homopiperonyl-7,8-dimethoxy-1,2-dihydroisoquinoline (40). - 2-Methyl-4-homopiperonyl-7,8-dimethoxyisoquinolinium iodide (0.50 g; 1.0 mmol) was added in portions to a suspension of lithium aluminum hydride (0.8 g; 20 mmol) in 50 ml of dry ether.[19] The mixture under nitrogen was stirred for 4 hr at room temperature. Just enough aqueous 33% sodium potassium tartrate was added to coagulate the white precipitate. The supernatant ether was separated by decanting, solvent was removed in a stream of nitrogen at 35°, and the pink residue was crystallized quickly from 95% ethanol to give faintly pink needles (0.33 g; 93%) of 2-methyl-4-homoperonyl-7,8-dimethoxy-1,2-dihydro-

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isoquinoline (40), mp 60-64°. Further crystallization (nitrogen) raised the melting point to 64-65°.

Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.36; H, 6.56; N, 4.04. Found: C, 71.86; H, 6.32; N, 3.99.

Catalytic microhydrogenation showed that the dihydroisoquinoline 40 absorbed 0.90 mole of hydrogen as compared with the required 1.0 mole; ir (mineral oil mull) 1630 cm^{-1}; nmr ($CDCl_3$) δ 6.57 (s, 2, H-5,6), 6.50 (broad s, 3, piperonyl Ar H's), 5.70 (s, 2, CH$_2$(O)$_2$), 5.60 (broad s, 1, H-3), 3.98 (s, 2, 2H-1), 3.67 (s, 6, 7,8-diCH$_3$O), 3.0-2.15 (m, CH$_2$CH$_2$), 2.55 ppm (s, CH$_3$-N). The signals at δ 3.0-2.15 ppm corresponded to 7 protons.

Exposure of the dihydroisoquinoline 40 under a nitrogen atmosphere to hot methanolic hydrochloric acid led to disproportionation, with formation of tetrahydroisoquinoline 41 and the full aromatic isoquinoline 39 in approximate yields of 45-50% and 40% respectively. Exposure to acid at concentrations of *dihydroisoquinoline as low as 0.5 g in 5 liters gave essentially the same* results.

2-Methyl-4-homopiperonyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (41) by Borohydride Reduction of Isoquinoline Methiodide 39. - Excess sodium borohydride (0.9 g) was added in portions to a stirred solution of 2-methyl-4-homopiperonyl-7,8-dimethoxyisoquinolinium methiodide (39) (0.90 g; 1.8 mmol)

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in 100 ml of ethanol plus 100 ml of water. After warming on the steambath for 1 hr, solvent was removed under reduced pressure at 100°, and the residual gum was dissolved in ether. Introducing dry hydrogen chloride precipitated an oil, which was collected, suspended in water, and treated with 10% aqueous sodium hydroxide. Product was extracted from the alkaline mixture with chloroform, and the dried extract, concentrated to ca. 2 ml, was chromatographed through acid-washed alumina. The eluting solvents were benzene (125 ml) followed by 1:1 benzene-chloroform. The pale yellow oil (0.19 g; 30%) that emerged with the benzene-chloroform was taken as the desired tetrahydroisoquinoline 41; nmr ($CDCl_3$) δ 6.70 (d, J=5, 2, H-5,6), 6.58 (s, 3, piperonyl Ar H's), 5.76 (s, 2, CH$_2$(O)$_2$), 3.74 (s, 6, 7,8-diCH$_3$O), 3.9-3.3 (m, 2, 2H-1), 2.9-1.75 (m, CH$_2$CH$_2$CHCH$_2$), 2.4 ppm (s, CH$_3$-N). The 2.9-1.75 signals integrated to 10 protons.

The methiodide was prepared for characterization by allowing the tetrahydroisoquinoline 41 to stand for 3 days in a solution of methyl iodide (2 ml) in methanol (0.5 ml). Evaporation of volatile material from the reaction mixture followed by crystallization from alcohol gave white crystalline 2,2-dimethyl-4-homopiperonyl-7,8-dimethoxy-tetrahydroisoquinolinium iodide, mp 132-134°.

Anal. Calcd. for $C_{22}H_{28}INO_4$: N, 2.81. Found: N, 2.91.

dehydrogenation with iodine afforded the corresponding 4-substituted isoquinoline **39** in a minimum overall yield of 28% in the five steps from acetal **1**. The Py-reduced isoquinolines **40** and **41** were derived from **39** by treatment, respectively, with lithium aluminum hydride in ether[2,19] and with sodium borohydride in ethanol. When aminoacetal **1** was cyclized without N-methylation, the 4-hydroxytetrahydroisoquinoline **42**[5] was obtained, evidently mixed with the 4-ethoxy compound **43**. Oxidation of the hydroxy compound **42** to the 4-keto derivative was realized, but purification presented problems.

4-Ketotetrahydroisoquinolines analogous to **37** are

known[1] but, so far as we could find, they have not been prepared from 4-hydroxytetrahydroisoquinolines. Although related Grignard additions are also known,[20] they have been limited in number, probably because the 4-keto compounds have been hard to make.

In summary, we have described examples of several generally applicable syntheses of 4-substituted isoquinolines.

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Registry No.—**1**, 53762-16-6; **2** HCl, 55762-17-7; **3**, 53762-18-8; **3** HCl, 53762-19-9; **3** picrate, 53762-20-2; **3** quaternary chloride, 53762-66-6; **4**, 53762-21-3; **4** HCl, 53762-22-4; **4** picrate, 53798-66-6; **5** picrate, 53762-24-5; **6** picrate, 53762-26-8; **7**, 53762-27-9; **7** picrate, 53762-28-0; **8**, 53762-29-1; **8** HCl, 53762-30-4; **9** HCl, 53762-31-5; **10**, 53762-32-6; **11**, 53762-33-7; **12**, 53762-34-8; **13**, 53762-35-9; **14**, 519-05-1; **15**, 53783-46-3; **16**, 53762-36-0; **17**, 53762-37-1; **18**, 53762-38-2; **19**, 53762-39-3; **20**, 53762-40-6; **21**, 53762-41-7; **22**, 53762-42-8; **25**, 53762-43-9; **26**, 53762-44-0; **27**, 53762-45-1; **28**, 53762-46-2; **29**, 53762-47-3; **30**, 53762-48-4; **32**, 53762-49-5; **34**, 53762-50-8; **35**, 53762-51-9; **36**, 53366-13-5; **36** HCl, 53762-52-0; **37**, 53762-53-1; **37** picrate, 53762-54-2; **37** HCl, 53762-55-3; **38**, 53762-56-4; **38** HCl, 53762-57-5; **39**, 53762-58-6; **40**, 53762-59-7; **41**, 53762-60-0; **41** methiodide, 53762-61-1; **42** HCl, 53762-62-2; **43**, 53762-63-3; **43** HCl, 53762-64-4; **43** methiodide, 53762-65-5; i, 53762-67-7; glyoxylic acid, 298-12-4; veratryl chloride, 7306-46-9; benzyl chloride, 100-44-7; piperonyl chloride, 20850-43-5; piperonyl alcohol, 495-76-1; thionyl chloride, 7719-09-7; 6-nitropiperonyl chloride, 15862-98-3; narcotine, 128-62-1; homopiperonyl bromide, 23808-46-0; phosphorus tribromide, 7789-60-8; homopiperonyl alcohol, 6006-82-2; *N*-homopiperonylpyridinium bromide, 53762-68-8; homopiperonyl iodide, 53762-69-9; *N*-homopiperonylpyridinium iodide, 53762-70-2; 7,8-dimethoxyhomophthalimide, 53762-71-3; 3,4-dimethoxyhomophthalic acid, 3723-02-2; 3,4-methylenedioxystyrene, 7315-32-4.

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(27) Professor F. Santavý has determined related ultraviolet absorption maxima: (a) for the free base **42**,[5] uv max (ethanol) 226 nm (sh) (log ε 3.95), 274 (3.2), 278 (3.19); (b) for 2-methyl-7,8-dimethoxyisoquinolinium iodide,[5] uv max (ethanol) 219 nm (log ε 4.4), 258 (4.4), 296 sh (3.6), 3.96 (3.6).
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