184° (0.75 mm). For comparison, 3 g of **18** was dissolved in ether, and addition of excess isopropyl alcoholic hydrogen chloride furnished 3.1 g of crystalline hydrochloride, mp 111–115°. Recrystallization from acetone–ether gave pure hydrochloride of **18**, mp 112–117°, which was identical by melting point and infrared spectral data with material prepared by reaction of **9** with ethyl chloroacetate according to the general method described above.

2,3-Dihydro-7-methoxy-4(1H)-isoquinolone Hydrochloride (26).—The hydrochloride of **29** was obtained by dissolving the free base in methanol and adding 1 *N* methanolic hydrochloric acid. After addition of ether, the hydrochloride precipitated as a crystalline product, mp 213–215°. The hydrochloride (10 g) was dissolved in 200 ml of glacial acetic acid by heating to 70°. After addition of the catalyst (1.2 g, 10% palladium on charcoal), the mixture was hydrogenated at room temperature under normal pressure until the theoretical amount of hydrogen, necessary for debenzylation, had been consumed. This required about 2.5 hr. The catalyst was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The solid residue was washed with ether to give 6.6 g (94%) of **26**, mp 220–222°. Recrystallization from methanol–ether gave 5.7 g (81%) of pure **26**: mp 224–225°; λ_{max} 225 mμ (ε 12,100), 229 (12,100), 287 (18,000); ν_{max}^{KBr} 2790, 2650, and 2500 (*sec*-amine salt), 1690 (C=O), and 1280 and 1250 cm^{-1} (OCH_3).

2,3-Dihydro-7-methoxy-1-methyl-4(1H)-isoquinolone Hydrochloride (30).—Hydrogenation of **32** under similar conditions gave **30** in 78% yield, mp 208–210° after recrystallization from ethanol. A sample was recrystallized several times from ethanol to give analytically pure **30**: mp 213–214°; λ_{max} 227 mμ (ε 11,750), 288 (16,900); ν_{max}^{KBr} 2760, 2660, and 2480 (*sec*-amine salt), 1700 (C=O), and 1280 and 1250 cm^{-1} (OCH_3).

2,3-Dihydro-6,7-dimethoxy-4(1H)-isoquinolone Hydrochloride (35).—Hydrogenation of **37** under the conditions described above afforded **35** in 94% yield: mp 237–238° after recrystallization from methanol; λ_{max} 235 mμ (ε 18,700), 280–281 (11,160), 316–317 (8650); $\lambda_{max}^{0.1\ N\ KOH}$ 226–227 mμ (ε 18,120), 264 (11,900), 277–278 (9710), 318 (7400); ν_{max}^{KBr} 2760, 2610, and 2510 (*sec*-amine salt), 1685 (C=O), and 1290 and 1260 cm^{-1} (OCH_3).

1,2,3,4-Tetrahydro-7-methoxy-4-isoquinolinol Hydrochloride (38).—A mixture of 1 g (3.74 mmoles) of the free base of **29** and 150 mg of 5% palladium on charcoal in 50 ml of glacial acetic acid was hydrogenated at normal pressure and room temperature until the hydrogen uptake ceased. Removal of the catalyst by filtration was followed by evaporation of the filtrate to dryness under vacuum. The oily residue was dissolved in ether and, upon addition of isopropyl alcoholic hydrogen chloride, crystalline **38** was obtained. Recrystallization from ethanol gave 500 mg (62%) of the isoquinolinol hydrochloride **38**: mp 168–170°; λ_{max} 227 mμ (ε 10,200), 277–278 (1750), 284 (1670); ν_{max}^{KBr} 3340 (OH), 2950, 2840 and 2670 (*sec*-amine salt), and 1260 cm^{-1} (OCH_3).

Anal. Calcd for $C_{10}H_{13}NO_2 \cdot HCl$ (215.67): C, 55.69; H, 6.54. Found: C, 56.01; H, 6.56.

1,2,3,4-Tetrahydro-7-methoxy-1-methyl-4-isoquinolinol Hydrochloride (39).—Hydrogenation of the free base of **32** as described in the preceding experiment gave **39** in 61% yield: mp 174–175° after recrystallization from ethanol; λ_{max} 228 mμ (ε 8900), 276 (1620), 284 (1480); ν_{max}^{KBr} 3320 (OH), 2780, 2660 and 2500 (*sec*-amine salt), and 1290 and 1260 cm^{-1} (OCH_3).

Anal. Calcd for $C_{11}H_{15}NO_2 \cdot HCl$ (229.72): C, 57.51; H, 7.02; N, 6.10. Found: C, 57.19; H, 7.19; N, 6.08.

Registry No.—**6**, 3459-14-1; **6** free base, 5071-96-5; **7**, 5071-92-1; **8**, 5120-82-1; **9**, 5077-16-7; **10**, 5077-14-5; **11**, 5077-11-2; **12**, 5077-08-7; **13**, 5077-05-4; **13** free base, 13174-24-8; **14**, 5071-94-3; **15**, 5071-93-2; **16**, 5071-91-0; **17**, 5077-21-4; **18**, 5077-15-6; **18** hydrochloride, 15297-11-7; **19**, 5077-20-3; **20**, 5077-19-0; **21**, 5077-13-4; **22**, 5077-18-9; **23**, 5077-10-1; **24**, 5077-06-5; **24** free base, 5077-07-6; **25**, 5077-04-3; **25** hydrochloride, 5120-80-9; **26**, 5119-79-9; **27**, 5071-90-9; **28**, 5120-83-2; **29**, 5120-75-2; **29** hydrochloride, 15297-22-0; **30**, 15297-23-1; **31**, 5120-81-0; **32**, 5077-12-3; **33**, 5077-17-8; **34**, 5077-09-8; **35**, 15297-27-5; **36**, 5489-51-0; **37**, 5077-03-2; **38**, 15297-30-5; **39**, 15297-31-1.

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Syntheses in the Isoquinoline Series. Synthesis and Chemical Transformation of 2,3-Dihydro-4(1H)-isoquinolones[1]

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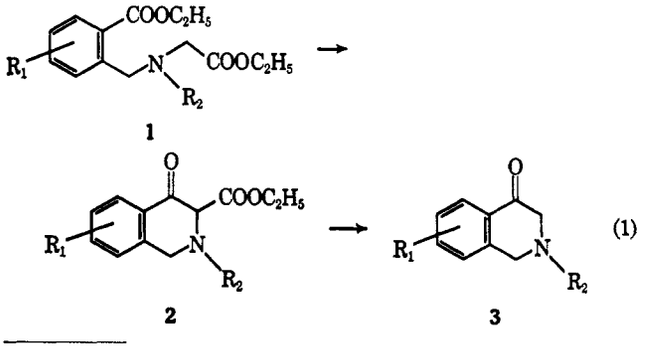
Several 2,3-dihydro-4(1H)-isoquinolones have been prepared by Dieckmann cyclization of suitable N-(*o*-carbalkoxybenzyl)glycine ester derivatives followed by hydrolysis and decarboxylation of the intermediate β-keto esters. The importance of these compounds as useful intermediates is shown by their conversion into various isoquinoline derivatives.

In the preceding paper we reported the preparation of 2,3-dihydro-4(1H)-isoquinolones by acid-catalyzed cyclization of suitably substituted N-benzylglycine esters.[2] In the 6,7-dimethoxy series this method gave poor results. Another route to 2,3-dihydro-4(1H)-isoquinolones consists of a Dieckmann cyclization of a diester followed by hydrolysis and decarboxylation of the intermediate β-keto ester. This synthetic scheme is illustrated (eq 1) by the conversion of **1** into **3** *via* **2** as reported by Hinton and Mann[3] where R_1 = H and R_2 = CH_3. The availability of a variety of substituted *o*-

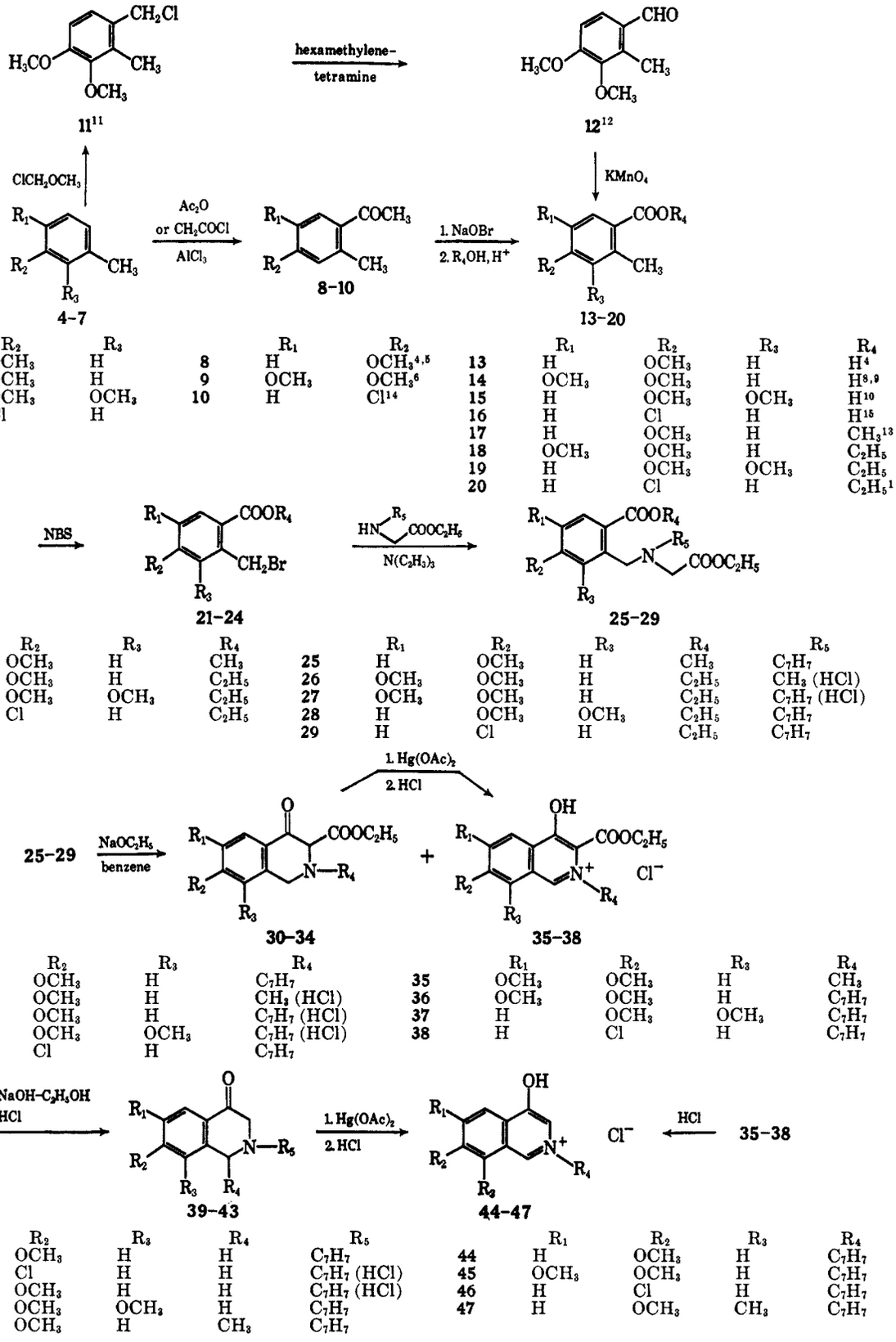


(1) Presented in part by one of us (A. B.) before the section of Chemical Science at the New York Academy of Sciences, March 1966; *Trans. N. Y. Acad. Sci.*, [II] **28**, 685 (1966).

(2) G. Grethe, H. L. Lee, M. Uskoković, and A. Brossi, *J. Org. Chem.*, **33**, 491 (1968).

(3) I. G. Hinton and F. G. Mann, *J. Chem. Soc.*, 599 (1959).

SCHEME I



	R_1	R_2	R_3
4	H	OCH_3	H
5	OCH_3	OCH_3	H
6	H	OCH_3	OCH_3
7	H	Cl	H

	R_1	R_2
8	H	OCH_3[4,5]
9	OCH_3	OCH_3[6]
10	H	Cl[14]

	R_1	R_2	R_3	R_4
13	H	OCH_3	H	H[4]
14	OCH_3	OCH_3	H	H[8,9]
15	H	OCH_3	OCH_3	H[10]
16	H	Cl	H	H[15]
17	H	OCH_3	H	CH_3[13]
18	OCH_3	OCH_3	H	C_2H_5
19	H	OCH_3	OCH_3	C_2H_5
20	H	Cl	H	C_2H_5[1]

	R_1	R_2	R_3	R_4
21	H	OCH_3	H	CH_3
22	OCH_3	OCH_3	H	C_2H_5
23	H	OCH_3	OCH_3	C_2H_5
24	H	Cl	H	C_2H_5

	R_1	R_2	R_3	R_4	R_5
25	H	OCH_3	H	CH_3	C_7H_7
26	OCH_3	OCH_3	H	C_2H_5	CH_3 (HCl)
27	OCH_3	OCH_3	H	C_2H_5	C_7H_7 (HCl)
28	H	OCH_3	OCH_3	C_2H_5	C_7H_7
29	H	Cl	H	C_2H_5	C_7H_7

	R_1	R_2	R_3	R_4
30	H	OCH_3	H	C_7H_7
31	OCH_3	OCH_3	H	CH_3 (HCl)
32	OCH_3	OCH_3	H	C_7H_7 (HCl)
33	H	OCH_3	OCH_3	C_7H_7 (HCl)
34	H	Cl	H	C_7H_7

	R_1	R_2	R_3	R_4
35	OCH_3	OCH_3	H	CH_3
36	OCH_3	OCH_3	H	C_7H_7
37	H	OCH_3	OCH_3	C_7H_7
38	H	Cl	H	C_7H_7

	R_1	R_2	R_3	R_4	R_5
39	H	OCH_3	H	H	C_7H_7
40	H	Cl	H	H	C_7H_7 (HCl)
41	OCH_3	OCH_3	H	H	C_7H_7 (HCl)
42	H	OCH_3	OCH_3	H	C_7H_7
43	H	OCH_3	H	CH_3	C_7H_7

	R_1	R_2	R_3	R_4
44	H	OCH_3	H	C_7H_7
45	OCH_3	OCH_3	H	C_7H_7
46	H	Cl	H	C_7H_7
47	H	OCH_3	CH_3	C_7H_7

toluic acid esters, which can be used to prepare **1** and the possibility of using N-benzylglycine ester intermediates instead of N-methylglycine derivatives prompted us to study this synthetic approach in more detail. The intermediate β-keto esters of type **2** were also considered to be interesting compounds *per se*.

Synthesis of 2,3-Dihydro-4(1H)-isoquinolones.—The synthesis of some specific 2,3-dihydro-4(1H)-isoquinolones *via* the route indicated is outlined in Scheme I. The toluenes **4** and **5** were transformed to the acetophenones **8**[4,5] and **9** by the Friedel–Crafts reaction. The reported method for the preparation of **9**[6] was improved by using acetic anhydride in tetrachloroethane

(4) J. F. Eykmann, *Chem. Zentr.*, [I] **75**, 1597 (1904).
(5) R. Adams and C. R. Noiler, *J. Am. Chem. Soc.*, **46**, 1889 (1924).
(6) V. J. Harding and C. Weizmann, *J. Chem. Soc.*, **97**, 1126 (1910).

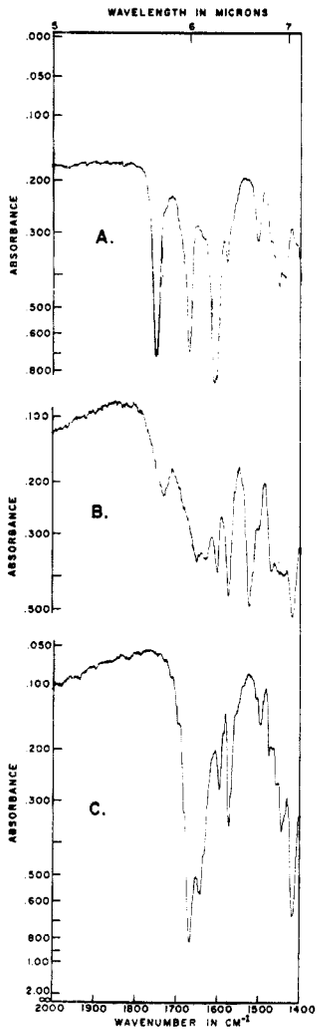
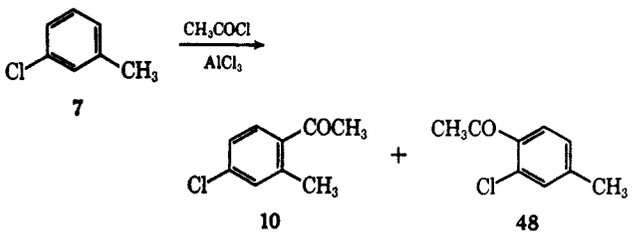


Figure 1.

at low temperature. Oxidation with hypobromite[7] afforded the *o*-toluic acid derivatives **13** and **14**. This route avoided the more tedious procedure described previously[4,8,9] for the preparation of these compounds. The 3,4-dimethoxy-*o*-toluic acid **15**[10] was obtained from 3-methylveratrol by chloromethylation, Sommelet formylation, and oxidation (**6** → **11**[11] → **12**[12] → **15**). Esterification of the acids **13–15** gave the esters **17**[13]**–19**.

The Friedel–Crafts acylation of *m*-chlorotoluene (**7**) afforded a 1:1 mixture of acetophenones **10**[14] and **48** (nmr and glpc), which could not be separated by fractional distillation. Oxidation of the mixture with sodium hypobromite gave the corresponding acids, the esters of which could be separated by fractional distillation thus affording the desired 4-chloro-*o*-toluic acid ethyl ester **20**.[15] The esters **17–20** were converted into the bromides **21–24** by reaction with N-



bromosuccinimide in carbon tetrachloride solution. The crude benzyl bromides were allowed to react with the appropriate N-substituted glycine ethyl esters in refluxing ether in the presence of 1 equiv of triethylamine to yield compounds **25–29**. The subsequent Dieckmann cyclizations were carried out in refluxing benzene in the presence of sodium ethoxide and the ethanol formed was continuously removed by azeotropic distillation. The desired products **30–34** were thus obtained in yields of approximately 60%.

The structure of the β-keto esters was confirmed by positive ferric chloride tests in conjunction with infrared and ultraviolet spectra. The infrared spectra (in potassium bromide) of some of these compounds (salts) are shown in Figure 1. The 7-chloro derivative **34** (hydrobromide) is completely enolized as indicated by absorption bands at 1665 and 1640 cm^{-1}, which can be ascribed to the ester carbonyl group chelated to the enolic hydroxyl group and to the C=C linkage,[16] respectively. In contrast, the monomethoxy compound **30** exhibits absorption bands at 1670 and 1750 cm^{-1}, which correspond to the ketone and to the ester carbonyl group.[16] The 6,7-dimethoxy derivative **32** exists as an enol–ketone mixture. The degree of enolization of these compounds can also be estimated by the intensity of the long-wave maximum at about 350 mμ in the ultraviolet spectra which is due to the extended conjugation of the enol forms. Figure 2 shows the ultraviolet spectra of the partially enolized **32**.

The β-keto esters were transformed to the isoquinolones **39**, **40**, **41**, and **42** by hydrolysis and decarboxylation. It may be noted, that the 6,7-dimethoxy-2,3-dihydro-4(1H)-isoquinolone **41** was obtained in much better over-all yield than by the method previously described.[2]

Chemical Transformations.—The isoquinolinium salts **35–37**, characterized by elemental analysis and spectral data, were obtained as by-products of the Dieckmann cyclization in yields varying from 1 to 10%. None of the corresponding by-products could be detected in the reaction mixture from **25** and **29**. The conversion of keto esters such as **31–33** to isoquinolinium compounds is presumably facilitated by the presence of methoxy groups at C-6 or C-8. Compounds **36** and **38** were obtained in good yields from **32** and **34**, respectively, by mercuric acetate oxidation. The characteristic uv absoption of these isoquinolinium compounds is illustrated by the spectrum of 2-benzyl-3-carbethoxy-4-hydroxy-6,7-dimethoxyisoquinolinium chloride (**36**) as shown in Figure 2, which also includes the spectra of the corresponding 2,3-dihydro-4(1H)-isoquinolone **41** and the 3-carbethoxy-2,3-dihydro-4(1H)-isoquinolone **32**.

(7) M. S. Newman and H. L. Holmes, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 428.
(8) W. H. Perkin and H. Weizmann, *J. Chem. Soc.*, **89**, 1649 (1906); L. Gattermann, *Ann. Chem.*, **357**, 313 (1907).
(9) R. H. F. Manske and A. E. Ledingham, *Can. J. Res.*, **22B**, 115 (1944).
(10) W. H. Perkin, *J. Chem. Soc.*, **113**, 722, 762 (1918).
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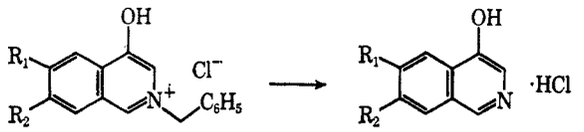
(15) A. Claus and E. Stapelberg, *Ann. Chem.*, **274**, 285 (1893).
(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1962, p 184.

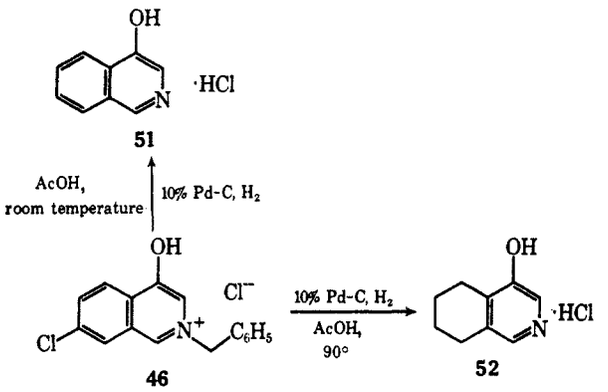
The isoquinolinium salts **36** and **38** were converted to compounds **45** and **46** by hydrolysis and decarboxylation. Alternatively, **46** was obtained by mercuric acetate oxidation of the isoquinolone **40** as were the 4-hydroxyisoquinolinium salts **44** and **47** from **39** and **43**, respectively. The N-benzylisoquinolinium salts **44** and **45** were readily debenzylated to the isoquinolines **49** and **50** by catalytic hydrogenation. When



44, $R_1 = H$; $R_2 = OCH_3$
45, $R_1 = R_2 = OCH_3$

49, $R_1 = H$; $R_2 = OCH_3$
50, $R_1 = R_2 = OCH_3$

this reaction was performed with compound **46**, depending on the reaction temperature, two different products were obtained. Hydrogenolysis of **46** at room temperature in acetic acid solution over palladium on carbon gave the hydrochloride of the known 4-isoquinolinol **51**,[17] whereas at 90° the reaction afforded the hydrochloride of 5,6,7,8-tetrahydro-4-isoquinolinol **52**.[18]

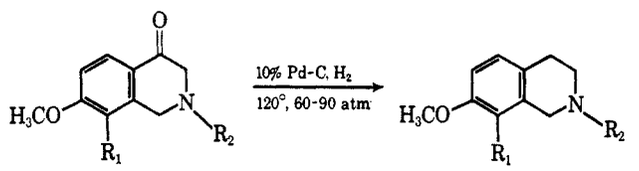


51

46

52

Having synthesized different substituted 2,3-dihydro-4-(1H)-isoquinolones we studied their conversion to 1,2,3,4-tetrahydroisoquinolines by taking advantage of the benzylic character of the intermediate carbinol. As expected, hydrogenation of the free bases **39**, **42**, and **53** in glacial acetic acid at elevated temperatures



39, $R_1 = H$; $R_2 = C_7H_7$
42, $R_1 = OCH_3$; $R_2 = C_7H_7$
53, $R_1 = H$; $R_2 = CH_3$[2]

54, $R_1 = R_2 = H$[19]
55, $R_1 = OCH_3$; $R_2 = H$
56, $R_1 = H$; $R_2 = CH_3$[19]

and high pressure resulted in the formation of the 1,2,3,4-tetrahydroisoquinolines, **54–56**.

(17) H. Gilman and G. C. Gainer, *J. Am. Chem. Soc.*, **69**, 1946 (1947); M. M. Robison and B. L. Robison, *J. Org. Chem.*, **21**, 1337 (1956).
(18) E. Ochiai and M. Ikehara, *Chem. Pharm. Bull. Japan*, **2**, 72 (1954).
(19) P. Fritsch, *Ann. Chem.*, **286**, 1 (1885).

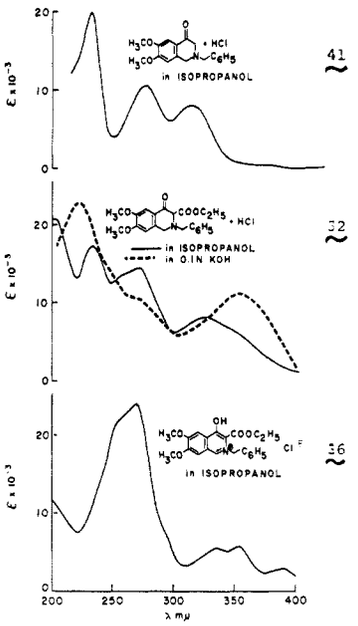
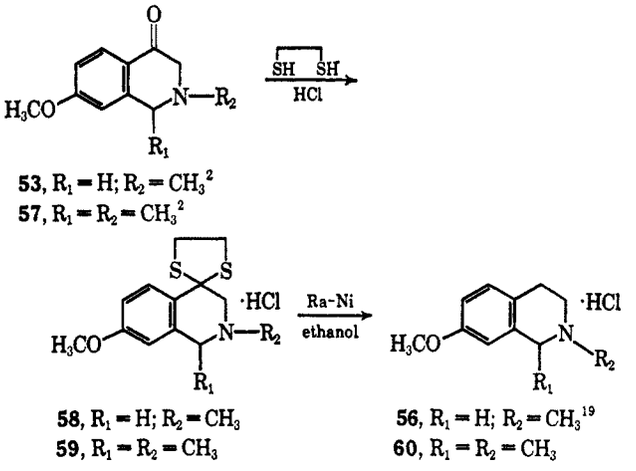


Figure 2.

Alternatively, compounds of this type were prepared by the following modification. The 2,3-dihydro-4(1H)-isoquinolones **53** and **57** were converted to the thioketals **58** and **59** which, in turn, were desulfurized to the 1,2,3,4-tetrahydroisoquinolines **56** and **60** with Raney nickel in boiling ethanol.



53, $R_1 = H$; $R_2 = CH_3$[2]
57, $R_1 = R_2 = CH_3$[2]

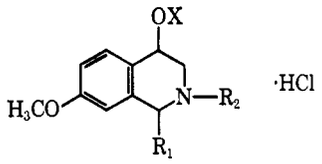
58, $R_1 = H$; $R_2 = CH_3$
59, $R_1 = R_2 = CH_3$

56, $R_1 = H$; $R_2 = CH_3$[19]
60, $R_1 = R_2 = CH_3$

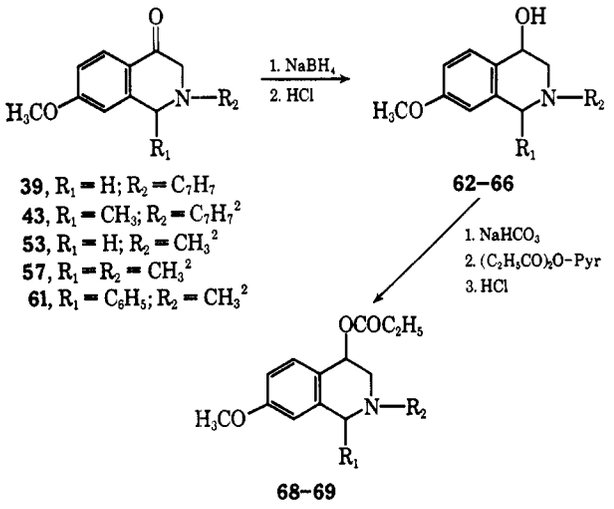
Reduction of the 2,3-dihydro-4(1H)-isoquinolones **39**, **43**, **53**, **57**, and **61** with sodium borohydride afforded good yields of the 1,2,3,4-tetrahydro-4-isoquinolinols **62–66**. The infrared spectra (KBr pellets) showed a sharp band at about 3300 cm^{-1} due to a free OH stretching vibration and the ultraviolet spectra (in 2-propanol) showed the typical absorption curve of 1,2,3,4-tetrahydroisoquinolines with maxima at 277–278 mμ (ε ~2000), 287 (~2000), and about 225 (10,000–11,000). Esterification of **63** and **65** with propionic anhydride and catalytic amounts of pyridine afforded the propionates **68** and **69**. Compound **67** was best prepared by hydrogenolytic debenzylation of **68** with palladium on charcoal as catalyst. The 1,2,3,4-tetrahydro-4-isoquinolinols prepared by reduction with sodium borohydride and some of their esters are summarized in Table I.

TABLE I

1,2,3,4-TETRAHYDRO-4-ISOQUINOLINOLS (X = H) AND PROPIONATES (X = COC_2H_5)



Compd	R_1	R_2	X	Yield, %	Mp, °C	Crystn solvent	Calcd % C	Calcd % H	Calcd % N	Found, % C	Found, % H	Found, % N
62	H	CH_3	H	35	173–174	Ethanol	57.51	7.03	6.10	57.67	7.11	6.12
63	H	C_7H_7	H	91	184–185	Methanol	66.77	6.59	4.58	66.87	6.86	4.43
64	CH_3	CH_3	H	90	159–161	2-Propanol	59.13	7.44	5.75	58.95	7.44	5.78
65	CH_3	C_7H_7	H	70	169–170	Acetone–ethanol	67.60	6.93	4.38	67.92	7.02	4.46
66	C_6H_5	CH_3	H	69	173–174	2-Propanol	66.77	6.59	4.58	66.74	6.83	4.46
67	H	H	COC_2H_5	96	184–185	Ethanol	57.46	6.68	5.16	57.53	6.71	5.22
68	H	C_7H_7	COC_2H_5	78	177–178	Ethanol	66.38	6.69	3.87	66.73	6.94	3.68
69	CH_3	C_7H_7	COC_2H_5	81	180–181	Ethanol	67.10	6.97	3.73	67.33	7.19	3.95



39, $R_1 = H$; $R_2 = C_7H_7$
43, $R_1 = CH_3$; $R_2 = C_7H_7$[2]
53, $R_1 = H$; $R_2 = CH_3$[2]
57, $R_1 = R_2 = CH_3$[2]
61, $R_1 = C_6H_5$; $R_2 = CH_3$[2]

62–66

68–69

Experimental Section[20]

4,5-Dimethoxy-2-methylacetophenone (**9**).—To a solution of 60.8 g (0.359 mole) of 3,4-dimethoxytoluene (**5**) and 39.6 ml (0.42 mole) of acetic anhydride in 500 ml of tetrachloroethane cooled to 0° was added with stirring 112 g (0.84 mole) of aluminum chloride at a rate so as to keep the temperature of the reaction mixture at 0–5°. After the addition was completed, the solution was stored for 2 days at 0–5°, and then was poured onto 800 g of ice. The product was extracted with dichloromethane; the combined organic extracts were washed with aqueous sodium carbonate solution and subsequently with water, dried, and filtered. The filtrate was evaporated to dryness under reduced pressure, and the residue was recrystallized from ether–petroleum ether (30–60°) giving 69.8 g (87%) of **9**, mp 73–75° (lit.[6] mp 68°).

4-Methoxy-*o*-toluic Acid (**13**).—A solution of sodium hypobromite, prepared at 0° by dissolving 84 g (2.1 moles) of sodium hydroxide and 30 ml (0.552 mole) of bromine in 400 ml of water, was added slowly during 30 min to a stirred solution of 22 g (0.134 mole) of **8** in 250 ml of dioxane. During the addition the temperature was allowed to rise to 30°. The mixture was warmed to 40° and stirred for an additional 15 min at this temperature, the suspension was treated with enough sodium bisulfite to destroy the excess hypobromite, and 1.5 l. of water was added. The mixture was allowed to stand at room temperature overnight. After removal of ~400 ml of the solvents under reduced pressure, the hot solution was acidified with 3 *N* hydrochloric acid to give a crystalline precipitate which was collected by filtration and dried under vacuum at 50°. Recrystallization from benzene gave 14.4 g (65%) of acid **13**, mp 178–180° (lit.[4] mp 176°).

4,5-Dimethoxy-*o*-toluic acid (**14**) was prepared by sodium hypobromite oxidation from 25 g (0.129 mole) of **9** as described in the preceding experiment. Without recrystallization 24.5 g (97%) of crystalline **14** was obtained, mp 146–148° (lit.[8] mp 145°).

3,4-Dimethoxy-*o*-toluic Acid (**15**).—A solution of 42.1 g (0.268 mole) of potassium permanganate in 1 l. of water was added dropwise to a stirred solution of 36 g (0.2 mole) of 2-methylveratraldehyde in 700 ml of acetone at 70°. The mixture was stirred for an additional hour at the same temperature and filtered through Celite Analytical Filter-Aid (Johns-Manville). The filtrate was washed with ether and acidified with concentrated hydrochloric acid. The precipitated acid **15** was collected by filtration and dried at 50° overnight. It weighed 26 g (66%), mp 186–188° (lit.[10] mp 183–184°).

4-Methoxy-*o*-toluic Acid Ester (**17**).—A solution of 125 g (0.752 mole) of **13** and 12 ml of concentrated sulfuric acid in 1 l. of anhydrous methanol was refluxed for 15 hr. After removal of 500 ml of the solvent under vacuum, 500 ml of ether was added to the residue, and the solution was washed once with dilute aqueous sodium carbonate and then with water. The ethereal solution was dried and filtered and the filtrate evaporated to dryness under reduced pressure. The oily residue was distilled under vacuum to give 113 g (83%) of methyl ester **17**, bp 92° (0.25 mm) (lit.[13] bp 143° (16 mm)).

4,5-Dimethoxy-*o*-toluic Acid Ethyl Ester (**18**).—A solution of 100 g (0.51 mole) of **14** and 10 ml of concentrated sulfuric acid in 1 l. of anhydrous ethanol was refluxed for 2 days. After 500 ml of solvent was removed under reduced pressure, 500 ml of ether was added to the solution, and the mixture was washed once with dilute aqueous sodium carbonate and then with water. The ethereal solution was dried and filtered. The filtrate was evaporated to dryness under reduced pressure, and the solid residue was crystallized from ether–petroleum ether (30–60°) giving 89.8 g (78%) of ethyl ester **18**, mp 62–63°. An analytical sample was recrystallized twice from ether–petroleum ether: mp 64–65°; $\lambda_{max}^{CH_3OH}$ 217–218 mμ (ε 22,800), 259–260 (10,900), 294–296 (4800); $\nu_{max}^{CHCl_3}$ 1705 (C=O) and 1265 cm^{-1} (OCH_3); nmr ($CDCl_3$), δ 1.37 (3 H, t, J = 7 cps, CH_2–CH_3), 2.55 (3 H, s, CH_3), 3.87 (6 H, s, OCH_3), 4.32 (2 H, q, J = 7 cps, CH_2–CH_3), 6.64 (1 H, s, C_3–H), 7.43 (1 H, s, C_6–H).

Anal. Calcd for $C_{12}H_{16}O_4$ (224.26): C, 64.27; H, 7.19; O, 28.54. Found: C, 64.32; H, 7.21; O, 28.91.

3,4-Dimethoxy-*o*-toluic acid ethyl ester (**19**) was prepared from 78 g (0.398 mole) of 2-methylveratric acid (**15**) as described in the previous experiment. A crystalline residue was obtained which weighed 82.1 g (92%), mp 47–49°. An analytical sample was obtained by two recrystallizations from petroleum ether

(20) Melting points were taken in capillaries with a Thomas–Hoover melting point apparatus and are uncorrected. Boiling points are not corrected. Infrared spectra were determined with a Beckman infrared spectrophotometer Model-IR-5 or IR-9. The uv spectra were recorded on a Cary spectrophotometer Model 14 using 2-propanol as solvent unless otherwise indicated. Nuclear magnetic resonance spectra were obtained on a Varian Associates Model A-60 or HA-100 spectrophotometer, and chemical shifts are reported in δ using tetramethylsilane as internal reference (δ 0). The following abbreviations are used in connection with the nmr data: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (b) broad, featureless peak, (cp) complex band pattern, (m) multiplet. Gas–liquid partition chromatography (glpc) was done on a Beckman Model GC-2A Thermotrac instrument. Thin layer chromatography (tlc) was done with silica gel F_{254} precoated plates (manufactured by E. Merck, A. G., Darmstadt, Germany; distributed by Brinkman Instruments, Inc., Westbury, N. Y.). Unless otherwise specified, organic solutions were dried over sodium sulfate.

(30–60°): mp 49–50°; $\lambda_{max}^{CH_3OH}$ 256 mμ (ε 13,200); $\nu_{max}^{CHCl_3}$ 1708 (C=O) and 1270 cm^{-1} (OCH_3); nmr ($CDCl_3$), 1.37 (3 H, t, J = 7 cps, CH_2–CH_3), 2.53 (3 H, s, CH_3), 3.78 and 3.90 (3 H each, s, OCH_3), 4.35 (2 H, q, J = 7 cps, CH_2–CH_3), 6.77 and 7.74 (2 H, AB pattern, J = 9 cps, C_5–H and C_6–H).

Anal. Calcd for $C_{12}H_{16}O_4$ (224.26): C, 64.27; H, 7.19. Found: C, 64.60; H, 7.06.

4-Chloro-*o*-toluic Acid Ethyl Ester (20).—To a boiling mixture of 190 g (1.5 moles) of *m*-chlorotoluene and 229.5 g (1.74 moles) of aluminum chloride in 1.5 l. of carbon disulfide was added with stirring 123 ml (2.18 moles) of acetyl chloride. Refluxing and stirring were continued for 1 hr. The mixture was poured onto 2 l. of a mixture of ice and concentrated hydrochloric acid (ratio 1:1) and extracted several times with a benzene–ether mixture. The combined organic extracts were washed with water, dried, and filtered. After removal of the solvents the residue was purified by fractional distillation to give 179.1 g of a clear liquid, bp 126° (16 mm). Analysis by glpc (10% DEGS on Anakrom ABS; 0.25 in. × 6 ft; 125°; 100 cc of N_2/min) showed that the material consisted of the two isomers, **10** and **48**, in a ratio of 52:46 with retention times of t_o = 19.2 and 21.5 min, respectively. In addition a small impurity (2%) with t_0 = 14.0 min was present.

This mixture was added within 5 min at 20–25° to a solution of sodium hypobromite, prepared at 0° by dissolving 537 g (13.45 moles) of sodium hydroxide and 171 ml (2.93 moles) of bromine in 2.2 l. of water. Stirring was continued for 1.5 hr at room temperature. After ~250 g of sodium bisulfite was added, the mixture was stirred for 30 min, washed with ether, acidified with concentrated hydrochloric acid, and extracted repeatedly with chloroform. The combined organic extracts were washed with water, dried, and filtered. After removal of the solvent under vacuum 120 g of solid material, consisting mainly of the two isomeric acids, was obtained. Because fractional crystallization of these two compounds was difficult the mixture was dissolved in 1.2 l. of anhydrous ethanol, 20 ml of concentrated sulfuric acid was added, and the solution was refluxed for 3 days. After removal of most of the solvent under reduced pressure, the residue was diluted with a benzene–ether mixture and washed twice with dilute aqueous sodium bicarbonate and then once with water. The organic solution was dried and filtered. Evaporation of the filtrate to dryness under vacuum gave an oily residue, which was purified by fractional distillation under reduced pressure. The collected fractions were analyzed by glpc (10% DEGS on Anakrom ABS, 0.25 in. × 6 ft; 125°; 100 cc of N_2/min). The first fraction (31.3 g of a light oil, bp 132° (14 mm) (lit.[15] bp 258°), $n^{24}\alpha$ 1.5268) contained 95% of 4-chloro-*o*-toluic acid ethyl ester (**20**) with t_0 = 15 min; the nmr spectrum (CCl_4) showed peaks at δ 1.37 (3 H, t, J = 7 cps, CH_2–CH_3), 2.57 (3 H, s, CH_3), 4.31 (2 H, q, J = 7 cps, CH_2–CH_3), 7.13 (1 H, q, J_o = 9 cps, J_m = 2 cps, C_5–H), 7.21 (1 H, s, C_3–H), 7.83 (1 H, d, J_o = 9 cps, C_6–H). The next fractions became progressively richer with the other isomer, 2-chloro-*p*-toluic acid ethyl ester:[21] bp 146–154° (14.5 mm); $n^{24}\alpha$ 1.5239 (lit.[21] $n^{21.4}\alpha$ 1.5197); t_0 = 28 min; nmr (CCl_4), 1.37 (3 H, t, J = 7 cps, CH_2–CH_3), 2.35 (3 H, s, CH_3), 4.32 (2 H, q, J = 7 cps, CH_2–CH_3), 7.02 (1 H, q, J_o = 8 cps, J_m = 2 cps, C_5–H), 7.19 (1 H, s, C_3–H), 7.68 (1 H, d, J_o = 8 cps, C_6–H). The fractions contaminated with up to 20% of this isomer could be used for the next steps.

α-Bromo-4,5-dimethoxy-*o*-toluic Acid Ethyl Ester (22).—A mixture of 48.5 g (0.216 mole) of **18**, 35.5 g (0.2 mole) of N-bromosuccinimide, and 1 g of dibenzoyl peroxide in 500 ml of carbon tetrachloride was refluxed for 2 hr. The succinimide which was formed during the reaction was removed by filtration and washed with carbon tetrachloride. The filtrate was washed with dilute aqueous sodium hydroxide and then twice with water, dried, and filtered. The filtrate was evaporated to dryness under reduced pressure. Crystallization of the residue from ether–petroleum ether (30–60°) furnished 48.6 g (74%) of **22**, mp 78–81°. A sample was recrystallized twice from ether to give analytically pure **22**: mp 81°; $\nu_{max}^{CHCl_3}$ 1710 (C=O), 1605 (phenyl), and 1290 and 1275 cm^{-1} (OCH_3); λ_{max} 232 mμ (ε 30,400), 273–274 (9560); nmr ($CDCl_3$), 1.43 (3 H, t, J = 7 cps, CH_2–CH_3), 3.95 (6 H, s, OCH_3), 4.41 (2 H, q, J = 7 cps, CH_2–CH_3), 4.98 (2 H, s, CH_2–Br), 6.93 and 7.53 (1 H each, s, C_3–H and C_6–H).

Anal. Calcd for $C_{12}H_{15}BrO_4$ (303.17): C, 47.56; H, 4.99; Br, 26.36. Found: C, 47.63; H, 4.90; Br, 26.14.

α-Bromo-4-methoxy-*o*-toluic acid methyl ester (21) was prepared from 18 g (0.1 mole) of **17**, with 17.8 g (0.1 mole) of N-bromosuccinimide as described above. A 250-W infrared lamp (G. E.) served as the heating source. An oily product (25.6 g) was obtained which was crystallized with ether–petroleum ether (30–60°) to give 15.3 g (58%) of **21**: mp 66–67°; $\nu_{max}^{CHCl_3}$ 1715 (C=O), 1608 (phenyl), and 1280 and 1260 cm^{-1} (OCH_3); λ_{max} 220 mμ (ε 24,000), 260 (12,220).

Anal. Calcd for $C_{10}H_{11}BrO_3$ (259.11): C, 46.35; H, 4.28. Found: C, 46.12; H, 4.22.

α-Bromo-3,4-dimethoxy-*o*-toluic acid ethyl ester (23) was prepared from 9 g (0.04 mole) of ester **19** with 7.15 g (0.04 mole) of N-bromosuccinimide as described in the previous experiment. After work-up, 12.6 g of crystalline benzyl bromide **23** was obtained. An analytical sample was obtained by three recrystallizations from ether–petroleum ether (30–60°), mp 69.5–70.5°; $\nu_{max}^{CHCl_3}$ 1710 (C=O) and 1275 and 1240 cm^{-1} (OCH_3); $\lambda_{max}^{CH_3OH}$ 223 mμ (ε 28,700), 258 (9900), 298 (4350); nmr ($CDCl_3$), 1.40 (3 H, t, J = 7 cps, CH_2–CH_3), 3.92 and 3.98 (3 H each, s, OCH_3), 4.39 (2 H, q, J = 7 cps, CH_2–CH_3); 5.13 (2 H, s, CH_2–Br), 6.92 and 7.80 (2 H, AB pattern, J = 9 cps, C_5–H and C_6–H).

Anal. Calcd for $C_{12}H_{15}BrO_4$ (303.17): C, 47.56; H, 4.99. Found: C, 47.72; H, 4.82.

α-Bromo-4-chloro-*o*-toluic acid ethyl ester (24) was prepared from 155.6 g (0.785 mole) of ester **20** with 139.2 g (0.785 mole) of N-bromosuccinimide as described. An oily product (233.2 g) was obtained which crystallized slowly on standing. This material contained 64% of **24** and 21% of starting material **20** as seen by nmr and glpc analysis.[22] An analytical sample was recrystallized from ethanol and dried for 15 hr at 25° under reduced pressure to give pure **24**: mp 51–52°; $\nu_{max}^{CHCl_3}$ 1720 cm^{-1} (C=O); λ_{max} 242 mμ (ε 11,750), 283 (4500); nmr ($CDCl_3$), 1.42 (3 H, t, J = 7 cps, CH_2–CH_3), 4.41 (2 H, q, J = 7 cps, CH_2–CH_3), 4.90 (2 H, s, CH_2–Br), 7.2–8.0 (3 H, aromatic protons); glpc (4% SE-30 on Chromosorb W, 0.25 in. × 6 ft; 125 + 2.5°/min; 100 cc of N_2/min) gave a retention time of t_0 = 11 min.

Anal. Calcd for $C_{10}H_{10}BrClO_2$ (277.56): C, 43.27; H, 3.63. Found: C, 43.42; H, 3.59.

N-(2-Carbethoxy-4,5-dimethoxybenzyl)sarcosine Ethyl Ester Hydrochloride (26).—Sarcosine ethyl ester was prepared by passing dry hydrogen chloride through a suspension of 50 g of sarcosine in 500 ml of anhydrous ethanol, the heat of the reaction eventually causing the solution to boil. The resulting clear solution was refluxed for 2 hr while hydrogen chloride was introduced. The solvent was removed under reduced pressure, and 30 ml of 8 *N* sodium hydroxide was added to the syrupy residue. Ether (100 ml) was added, and then enough potassium carbonate to transform the aqueous layer into a thick semisolid. The ether was decanted, the residue was extracted two more times with ether, and the combined ether solutions were dried (K_2CO_3) overnight, filtered, and evaporated to dryness at room temperature under vacuum. Vacuum distillation of the residue gave 33.3 g (50%) of **sarcosine ethyl ester**, bp 68° (41 mm) (lit.[23] bp 52° (15 mm)); nmr (neat), 1.25 (3 H, t, J = 7 cps, CH_2–CH_3), 1.73 (1 H, s, NH), 2.33 (3 H, s, NH–CH_3), 3.25 (2 H, s, CH_2–CO), 4.13 (2 H, q, J = 7 cps, CH_2–CH_3).

A solution of 16.22 g (0.139 mole) of **sarcosine ethyl ester** and 21 g (0.068 mole) of benzyl bromide **22** in 120 ml of anhydrous ether was refluxed with stirring for 15 hr. The mixture was diluted with 100 ml of benzene and washed twice with water. The organic solution was dried, filtered, and concentrated. A yellow oil (22.1 g) was obtained which was dissolved in excess 0.1 *N* ethanolic hydrogen chloride. The solvent was removed under reduced pressure, and the oily residue crystallized on standing. After addition of acetone the crystalline material was collected by filtration to give 15.1 g (58%) of **26**, mp 120–127°. An analytical sample was recrystallized twice from acetone–ethyl acetate: mp 128–131°; λ_{max} 227 mμ (ε 33,100), 272 (9800), 297 (5500) (sh); $\nu_{max}^{CHCl_3}$ 2450 and 2350 (broad, *t*-amine salt), 1775 and 1710 (C=O), and 1280 (OCH_3) cm^{-1}; the nmr spectrum ($CDCl_3$) showed four peaks resulting from two overlapping

(21) K. v. Auwers and L. Harres, *Z. Physik. Chem.* (Leipzig), *Sect. A*, **143**, 18 (1929).

(22) When the bromination was carried out with a mixture of the two isomeric esters the crude reaction product consisting mainly of the two benzyl bromides and some starting material could be analyzed easily by glpc (4% PEG 4000 MS on Chromosorb W, 0.25 in. × 6 ft; 150 + 2.5°/min; 100 cc of N_2/min) with retention times of t_o = 5 min for **20**, t_0 = 7 min for **48**, t_0 = 12 min for **24**, and t_0 = 18 min for the isomeric bromide.

(23) C. E. Dagliesh and F. G. Mann, *J. Chem. Soc.*, 658 (1947).

triplets centered at 1.32 and 1.43 (6 H, J = 7 cps, CH_2–CH_3), five peaks resulting from overlap of two quartets centered at 4.32 and 4.43 (4 H, J = 7 cps, CH_2–CH_3); further peaks were at 3.12 (3 H, s, broad, ^+N–CH_3), 4.00 (3 H, s, OCH_3), 4.10 (5 H, s, OCH_3 and ^+N–CH_2–CO), 5.07 (2 H, s, broad, ^+N–CH_2), 7.57 and 7.98 (1 H each, s, aromatic protons), 12.00 (1 H, s, broad, ^+NH).

Anal. Calcd for $C_{17}H_{25}NO_6 \cdot HCl$ (375.86): C, 54.33; H, 6.97; N, 3.73; Cl, 9.43. Found: C, 54.61; H, 7.13; N, 3.90; Cl, 9.65.

N-Benzyl-N-(2-carbethoxy-4,5-dimethoxybenzyl)glycine Ethyl Ester Hydrochloride (27).—To a stirred solution of 35.4 ml of ethyl chloroacetate in 150 ml of anhydrous ether was dropped a solution of 68.1 ml of benzylamine and 126 ml of triethylamine within 20 min. The reaction mixture was refluxed and stirred for 3 days. The precipitated triethylamine hydrochloride was removed by filtration, and the filtrate was concentrated under reduced pressure. Vacuum distillation of the residue gave 43.2 g (77%) of **N-benzylglycine ethyl ester**, bp 103–107° (0.3 mm) (lit.[24] bp 160–165° (10–20 mm)). A solution of 19.3 g (0.1 mole) of **N-benzylglycine ethyl ester** and 14 ml (0.1 mole) of triethylamine was added dropwise to a stirred solution of 30.3 g (0.1 mole) of **22** in 100 ml of anhydrous ether. After refluxing and stirring for 20 hr, the reaction mixture was diluted with ether–benzene, washed with water, dried, and filtered. Concentration of the filtrate gave an oil which was dissolved in ethanol. The ethanolic solution was saturated with dry hydrogen chloride, and addition of ether gave 30.4 g (67%) of crystalline **27**, mp 137–139°. Two recrystallizations from chloroform–ether gave analytically pure **27**: mp 137.5–140°; $\nu_{max}^{CHCl_3}$ 2450 (broad, t-amine salt), 1755 and 1705 (C=O), and 1285 cm^{-1} (OCH_3); λ_{max} 225–226 mμ (ε 30,400), 265–266 (8500), 295½(5000) (sh). The nmr ($CDCl_3$) showed five peaks resulting from two overlapping triplets centered at 1.18 and 1.43 (6 H, J = 7 cps, CH_2–CH_3); further peaks were at 3.95 and 4.10 (3 H each, s, OCH_3), 4.13 and 4.45 (2 H each, q, J = 7 cps, CH_2–CH_3), ~4.1 (2 H, s, broad, ^+N–CH_2–CO) buried underneath the signals of the ester methylene and the methoxy protons, 4.75 and 5.17 (2 H each, s, broad, ^+N–CH_2), 7.5–8.2 (7 H, cp, aromatic protons).

Anal. Calcd for $C_{23}H_{29}NO_6 \cdot HCl$ (451.96): C, 61.12; H, 6.69; N, 3.10. Found: C, 61.38; H, 6.79; N, 3.26.

N-Benzyl-N-(2-carbethoxy-3,4-dimethoxybenzyl)glycine Ethyl Ester (28).—To a stirred solution of 69.7 g (0.23 mole) of benzyl bromide **23** in 300 ml of anhydrous ether was added dropwise a mixture of 44.4 g (0.23 mole) of **N-benzylglycine ethyl ester** and 32.7 ml (0.235 mole) of triethylamine. After the addition was completed the mixture was refluxed for 36 hr. The crystalline precipitate was removed by filtration, and the filtrate was extracted with three 300-ml portions of 3 N hydrochloric acid. The aqueous solutions were combined, made alkaline with dilute aqueous sodium hydroxide, and immediately extracted repeatedly with ether. The combined ether solutions were dried and filtered, and, after evaporation of the solvent under reduced pressure, 68.7 g of a yellow, viscous oil was obtained. A small amount of this material was distilled in a molecular still under a pressure of 0.015 mm at a bath temperature of 250°.

Infrared bands were at $\nu_{max}^{CHCl_3}$ 1735–1720 (C=O), 1600 (phenyl), and 1280 and 1238 cm^{-1} (OCH_3); ultraviolet peaks were at $\lambda_{max}^{CH_3OH}$ 249–250 mμ (ε 10,100), 284 (3030) (sh); the nmr spectrum ($CDCl_3$) showed peaks at δ 1.24 and 1.36 (3 H each, t, J = 7 cps, CH_2–CH_3), 3.23 (2 H, s, N–CH_2–CO), 3.84 and 3.88 (3 H each, s, OCH_3), 3.8–4.6 (8 H, cp, N–CH_2, CH_2–CH_3), 6.83 and 7.54 (2 H, AB pattern, J = 8.5 cps, C_5–H and C_6–H), 7.23 (5 H, s, phenyl).

Anal. Calcd for $C_{23}H_{29}NO_6$ (415.49): C, 66.49; H, 7.04; N, 3.37. Found: C, 66.99; H, 6.87; N, 3.55.

3-Carbethoxy-2,3-dihydro-6,7-dimethoxy-2-methyl-4(1H)-isoquinolone Hydrochloride (31) and 3-Carbethoxy-6,7-dimethoxy-4-hydroxy-2-methylisoquinolinium Chloride (35).—A solution of 7.55 ml of ethanol containing 362 mg (5.32 mmoles) of sodium ethoxide was added to a solution of 2 g (5.32 mmoles) of **26** in 20 ml of ethanol. The solvent was removed under reduced pressure, the residue was suspended in 25 ml of dichloromethane, and the insoluble part was removed by filtration. Concentration of the filtrate under vacuum gave the oily free base of **26** which was dissolved in 15 ml of azeotropically dried benzene. The solution was added under nitrogen to 480 mg (7.06 mmoles) of sodium ethoxide within 15 min. After the addition was completed, the mixture was heated under nitrogen (oil-bath temperature 90°) with stirring for 45 min with slow distillation of an azeotropic ethanol–benzene mixture which was collected in a Dean–Stark trap. The mixture was cooled to room temperature, diluted with 50 ml of benzene and 50 ml of water, and acidified to the Congo Red end point by adding concentrated hydrochloric acid. After adding excess sodium bicarbonate, the organic layer was separated, and the aqueous layer was extracted with benzene. The combined organic solution was washed with water, dried, and filtered. Concentration of the filtrate under vacuum gave an oil which was dissolved in 0.1 N ethanolic hydrogen chloride. Addition of ether to the solution gave 330 mg (19%) of the yellow crystalline isoquinolinium chloride **35**, mp 230–231° dec. An analytical sample was recrystallized from ethanol–ether and dried for 20 hr at 60° under vacuum: mp 221–223°; ν_{max}^{KBr} 3420 (OH), 1713 (C=O), 1610 (phenyl), 1580 (C=N^+), and 1285 and 1255 cm^{-1} (OCH_3); λ_{max} 244 mμ (ε 32,000), 281–282 (27,200), 295 (11,250) (sh), 325 (2800) (sh), 365 (11,500) (sh), 381 (14,200); $\lambda_{max}^{0.1\ N\ KOH}$ 244–245 mμ (ε 29,600), 273–274 (20,400), 355 (11,600) (sh), 368–369 (14,000); $\lambda_{max}^{0.1\ N\ HCl}$ 274 mμ (ε 52,100), 335 (10,000), 350 (11,600); nmr (DMSO-d_6), δ 1.40 (3 H, t, J = 7 cps, CH_2–CH_3), 4.01 and 4.08 (3 H each, s, OCH_3), 4.31 (3 H, s, ^+N–CH_3), 4.53 (2 H, q, J = 7 cps, CH_2–CH_3), 7.75, 8.38, and 9.40 (1 H each, s, aromatic protons), ~5.75 (1 H, b, OH).

Anal. Calcd for $C_{15}H_{18}ClNO_5$ (327.78): C, 54.97; H, 5.54; N, 4.27. Found: C, 55.06; H, 5.53; N, 3.92.

The mother liquor from the crystallization of **35** was concentrated under reduced pressure, the residue was dissolved in ethanol, and dry hydrogen chloride was passed through the solution to pH 1. Addition of ether gave 621 mg (35%) of yellow, crystalline **31**, mp 131°. Recrystallization from ethanol–ether and drying for 3 days at 40° under reduced pressure afforded analytically pure **31**: mp 105–152° (under vacuum);[25] ν_{max}^{KBr} 2490 (broad, t-amine salt), 1740 (ester C=O), 1675 (C=O), 1605 (phenyl), 1270 cm^{-1} (broad, OCH_3); λ_{max}^{EtOH} 236–237 mμ (ε 18,200), 273–275 (12,500), 323–324 (6600), 355 (4600) (sh), 380 (4000) (sh); $\lambda_{max}^{0.1\ N\ KOH}$ 227–229 mμ (ε 18,200), 272 (11,600), 357–360 (10,100); $\lambda_{max}^{0.1\ N\ HCl}$ 242–243 mμ (ε 13,200), 274 (24,700), 333–336 (9600), 349 (8500) (sh). The nmr spectrum (DMSO-d_6) is quite complex, but indicates that **31** exists as keto–enol mixture as seen by two triplets for CH_2–CH_3 at δ 1.23 (major) and 1.38 (minor) (J = 7 cps), two singlets for ^+N–CH_3 at 2.70 (minor) and 2.88 (major), and a singlet at 5.02, exchangeable with D_2O and calculating for one proton (enolic OH).

Anal. Calcd for $C_{15}H_{19}NO_5 \cdot HCl$ (329.80): C, 54.63; H, 6.11; N, 4.25. Found: C, 54.37; H, 5.93; N, 4.27.

2-Benzyl-3-carbethoxy-2,3-dihydro-6,7-dimethoxy-4(1H)-isoquinolone Hydrochloride (32).—To a solution of 30 g (0.0665 mole) of **27** in 200 ml of ethanol was added a solution of 4.52 g (0.0665 mole) of sodium ethoxide in 128 ml of absolute ethanol. The solvent was removed under reduced pressure, the residue was suspended in 200 ml of dichloromethane, and the insoluble part was removed by filtration. The filtrate was concentrated under vacuum and the free base of **27** thus obtained was dissolved in 150 ml of azeotropically dried benzene.[26] The solution was added, in a nitrogen atmosphere, with stirring to 5.65 g (0.0831 mole) of sodium ethoxide within 25 min. After the addition was completed, the clear solution was heated (oil-bath temperature 92–94°) under nitrogen with stirring and slow distillation of an azeotropic mixture of ethanol–benzene. After heating for 1 hr the solution became turbid. Heating was continued for 2 hr and, after cooling to room temperature, 150 ml of water was added to the mixture. Concentrated hydrochloric acid was added dropwise with shaking until the aqueous layer reached pH 4. The benzene solution was separated, the aqueous layer was extracted several times with ether, and the combined organic solution was washed with water, dried, and filtered. Concentration under reduced pressure gave 20.6 g of an oil which was dissolved in excess saturated ethanolic hydrogen chloride. Upon addition of ether 19.2 g (71%) of crystalline **32** was obtained, mp 170–172°. To the aqueous layer was added excess sodium bicarbonate and, after extraction with chloroform, the organic extracts were washed with water, dried, filtered, and concen-

(24) A. T. Mason and G. R. Winder, *J. Chem. Soc.*, **65**, 187 (1894).

(25) The discrepancy between the melting points of the crude keto ester and the analytical sample may be attributed to different degrees of enolization of the material.

(26) In later experiments the crude free base of **27** was used for the cyclization without purification *via* the hydrochloride. The yields of both reactions were compatible.

trated under vacuum. The oily residue (2 g) was dissolved in excess saturated ethanolic hydrogen chloride and, upon addition of ether, another fraction of crystalline **32** (1.3 g) was obtained, mp 166–167°. Evaporation of the filtrate left a residue which, after several crystallizations, gave 500 mg of the isoquinolinium salt **36**. A sample of **32** was recrystallized three times from ethanol and dried 3 days at 50° under vacuum to give yellow, analytically pure **32**: mp 153–156°[25] (for the ir spectrum, see Figure 1; for the uv spectra in 2-propanol and 0.1 *N* KOH, see Figure 2); $\lambda_{max}^{0.1\ N\ HCl}$ 242 mμ (ε 18,750), 265–267 (15,300), 303 (8450), 339 (13,500); nmr (DMSO-d_6), δ 1.23 (3 H, t, J = 7 cps, CH_2–CH_3), 3.82 and 3.85 (3 H each, s, OCH_3), cumulation pattern between 3.9 and 4.7 for six methylene protons, 6.9–7.8 (7 H, cp, aromatic protons), 9.37 (2 H, s, broad, $^+$N–H and enolic OH).

Anal. Calcd for $C_{21}H_{23}NO_5 \cdot HCl$ (405.89): C, 62.14; H, 5.96; N, 3.45. Found: C, 62.14; H, 6.09; N, 3.73.

2-Benzyl-3-carbethoxy-2,3-dihydro-7,8-dimethoxy-4(1H)-isoquinolone Hydrochloride (33) and 2-Benzyl-3-carbethoxy-4-hydroxy-7,8-dimethoxyisoquinolinium Chloride (37).—Reaction of the crude diester **28** (11.87 g, 0.0286 mole) with sodium ethoxide (2.23 g, 0.0328 mole) and work-up of the reaction mixture followed the procedure described in the preceding experiment. Crystallization from acetone–ether gave 6.8 g of **33**, mp 134–135°. For analysis a sample was recrystallized by dissolving it in acetone in a nitrogen atmosphere and removing part of the solvent at room temperature under reduced pressure. The analytical sample, after drying, had mp 134–135°; $\nu_{max}^{CHCl_3}$ 2300 (broad, *t*-amine salt), 1660 (ester C=O, chelated), 1630 (C=C of enol), and 1280 and 1240 cm^{-1} (OCH_3); $\lambda_{max}^{CH_3OH}$ 229 mμ (ε 12,500), 286 (11,100), 324–325 (10,820); $\lambda_{max}^{0.1\ N\ HCl}$ 230 mμ (ε 12,960) (sh), 235–236 (13,350), 262 (4920), 323 (20,400); $\lambda_{max}^{0.1\ N\ KOH}$ 255–256 mμ (ε 9620), 295 (6950) (sh), 346 (11,100); nmr ($CDCl_3$), δ 1.37 (3 H, t, J = 7 cps, CH_2–CH_3), 3.87 and 4.00 (3 H each, s, OCH_3), 4.14 (2 H, q, J = 7 cps, CH_2–CH_3), 4.28 and 4.72 (2 H each, s, $^+$N–CH_2), 7.05 and 7.67 (2 H, AB pattern, J = 8.5 cps, C_5–H and C_6–H), 7.40 (5 H, s, phenyl), 12.25 (2 H, b, NH, enol OH).

Anal. Calcd for $C_{21}H_{23}NO_5 \cdot HCl$ (405.89): C, 62.14; H, 5.96; N, 3.45. Found: C, 62.48; H, 6.12; N, 3.52.

The combined mother liquors from the crystallization of **33** were evaporated to dryness under reduced pressure, and the residue was recrystallized several times from acetone–ether to afford the isoquinolinium salt **37**: mp 141–143°; $\nu_{max}^{CHCl_3}$ 2800–2400 (broad, OH), 1725 (C=O, ester), and 1295 and 1260 cm^{-1} (OCH_3); $\lambda_{max}^{CH_3OH}$ 260 mμ (ε 21,000), 300 (8360) (sh); 387 (6150) (sh), 403–404 (7020); $\lambda_{max}^{0.1\ N\ HCl}$ 261 mμ (ε 29,300), 325 (5290) (sh), 388–390 (6400); $\lambda_{max}^{0.1\ N\ KOH}$ 224 mμ (ε 19,600), 252 (17,500), 301 (9350), 380 (7100), 398 (9350); nmr ($CDCl_3$), δ 1.10 (3 H, t, J = 7 cps, CH_2–CH_3), 4.02 and 4.16 (3 H, each, s, OCH_3), 4.26 (2 H, q, J = 7 cps, CH_2–CH_3), 6.28 (2 H, s, broad, $^+$N–CH_2), 7.23 (5 H) (phenyl), 7.75 and 8.55 (2 H, AB-pattern, J = 9 cps, C_5–H and C_6–H), 8.75 (1 H, b, OH).

Anal. Calcd for $C_{21}H_{22}NO_5Cl$ (403.87): C, 62.46; H, 5.49; N, 3.47. Found: C, 62.75; H, 5.64; N, 3.73.

2-Benzyl-3-carbethoxy-2,3-dihydro-7-methoxy-4(1H)-isoquinolone (30).—The required **N-benzyl-N-(2-carbomethoxy-5-methoxybenzyl)glycine ethyl ester (25)** was prepared from 25.9 g of benzyl bromide **21** as described for the preparation of **27**. Purification of the crude reaction product by vacuum distillation gave 23.6 g of **25**: bp 215–220° (0.4 mm); $\nu_{max}^{CHCl_3}$ 1720 cm^{-1} (broad band, C=O); nmr ($CDCl_3$), δ 1.23 (3 H, t, J = 7 cps, CH_2–CH_3), 3.28 (2 H, s, CH_2–CO), 3.85 (8 H, s, OCH_3, $COOCH_3$ and N–CH_2–C_6H_5), 4.23 (2 H, s, CH_2–N), 4.18 (2 H, q, J = 7 cps, CH_2–CH_3), 6.6–8.0 (8 H, aromatic protons).

Reaction of the diester **25** (15.75 g, 0.0425 mole) with sodium ethoxide (3.44 g, 0.051 mole) and work-up of the reaction mixture as described above gave an oil which crystallized upon addition of ethanol and afforded 9.4 g (68%) of **30**, mp 103–107°. Recrystallization from ethanol gave pure **30**: mp 101–107°; $\nu_{max}^{CHCl_3}$ 1730 (ester C=O), 1680 (C=O), 1640 (ester C=O chelated with enolic OH), 1610 infl (enolic C=C), 1605 (phenyl), and 1280 and 1245 cm^{-1} (OCH_3); λ_{max} 217–218 mμ (ε 20,500), 283 (13,700), 310 (8600), 346 (12,500); $\lambda_{max}^{0.1\ N\ HCl}$ 235 mμ (ε 16,600), 260–262 (5000), 321–322 (23,000); $\lambda_{max}^{0.1\ N\ KOH}$ 256 mμ (ε 11,000), 347 (14,250).

Anal. Calcd for $C_{20}H_{21}NO_4$ (339.40): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.99; H, 6.15; N, 4.12.

The hydrochloride of **30** was prepared by solution of the free base in an excess of 1 *N* ethanolic hydrogen chloride and addition of ether. The crystalline precipitate was collected by filtration. Recrystallization from ethanol–ether furnished analytically pure hydrochloride of **30**: mp 170–174° dec; see Figure 1 for ir; λ_{max} 282 mμ (ε 13,600), 343–344 (7000).

Anal. Calcd for $C_{20}H_{21}NO_4 \cdot HCl$ (375.86): C, 63.91; H, 5.90; N, 3.73. Found: C, 64.16; H, 6.13; N, 3.77.

2-Benzyl-3-carbethoxy-7-chloro-2,3-dihydro-4(1H)-isoquinolone (34).—To a stirred solution of 41.9 g of crude benzyl bromide which by glpc analysis contained 27.8 g (0.1 mole) of **24** in 100 ml of anhydrous ether was added a mixture of 19.3 g (0.1 mole) of **N-benzylglycine ethyl ester** and 14 ml (0.1 mole) of triethylamine within 15 min. After the addition was completed, the mixture was refluxed with stirring for 25 hr. The precipitate was removed by filtration and washed with ether. The filtrate was diluted with 50 ml of benzene and extracted with two 100-ml portions of 3 *N* hydrochloric acid. The organic solution was washed with water, dried, filtered, and concentrated under reduced pressure. The oily residue was shown by thin layer chromatography (silica gel DF-5, Camag, benzene) to consist mainly of *o*-toluic acid ethyl ester **20**.[27] The aqueous solution was made alkaline by adding 3 *N* sodium hydroxide, and the mixture was extracted immediately with two 100-ml portions of ether. The combined ethereal solution was washed with water, dried and filtered. Concentration under reduced pressure gave 35 g of crude oily **29**. Reaction of the crude diester **29** (15 g) with sodium ethoxide (2.75 g) and work-up of the reaction mixture as described before gave an oily residue which crystallized on standing at room temperature. A sample was recrystallized from ethanol to give analytically pure **34**: mp 91–93°; $\nu_{max}^{CHCl_3}$ 1645 (ester C=O, chelated) and 1610 cm^{-1} (enolic C=C and phenyl); $\lambda_{max}^{CH_3OH}$ 260 mμ (ε 10,700) (sh), 272 (11,000), 310 (4800) (sh), 348 (7750); $\lambda_{max}^{0.1\ N\ KOH}$ 239 mμ (ε 11,700), 250 (11,600), 295 (4600) (sh), 357–358 (10,300); $\lambda_{max}^{0.1\ N\ HCl}$ 218 mμ (ε 15,200), 225 (16,400), 232 (14,200), 248 (6150), 305 (17,400); nmr ($CDCl_3$), δ 1.42 (3 H, t, J = 7 cps, CH_2–CH_3), 3.68 (2 H, s, N–CH_2–C_6H_5), 3.88 (2 H, s, CH_2-1), 4.38 (2 H, q, J = 7 cps, CH_2–CH_3), 7.0–7.8 (8 H, aromatic protons), 11.67 (1 H, s, enolic OH).

Anal. Calcd for $C_{19}H_{18}ClNO_3$ (343.82): C, 66.38; H, 5.28; N, 4.07. Found: C, 66.21; H, 5.42; N, 4.05.

The crude **34** was dissolved in an excess of freshly prepared saturated ethanolic hydrogen bromide. Addition of ether precipitated the crystalline hydrobromide of **34** which was collected by filtration, washed with ethanol–ether, and dried in a desiccator to afford 10.1 g of crystalline compound, mp 154–157°. A sample, recrystallized from ethanol–ether and dried at 60° for 15 hr under reduced pressure, gave analytically pure hydrobromide of **34**, mp 146–151° dec.[25]

Anal. Calcd for $C_{19}H_{18}ClNO_3 \cdot HBr$ (424.74): C, 53.73; H, 4.51; N, 3.30. Found: C, 53.93; H, 4.72; N, 3.28.

2-Benzyl-2,3-dihydro-7-methoxy-4(1H)-isoquinolone (39).[2]—A solution of 1 g (2.66 mmoles) of **30** in a mixture of 15 ml of 2 *N* sodium hydroxide and 20 ml of ethanol was heated at 100° for 90 min. To the hot solution was added excess concentrated hydrochloric acid, and heating was continued for 15 min. After cooling to room temperature the mixture was made alkaline by addition of 6 *N* sodium hydroxide and extracted several times with chloroform. The combined organic solution was washed with water, dried, and filtered. Evaporation of the filtrate under reduced pressure gave 700 mg (87%) of crystalline **39**, mp 141–144°, after recrystallization from benzene–petroleum ether (30–60°); mixture melting point with material prepared by acid-catalyzed cyclization[2] was 141–145°. Infrared and ultraviolet spectra were superimposable: $\nu_{max}^{CHCl_3}$ 1680 (C=O), 1605 (phenyl), and 1280 cm^{-1} (OCH_3); λ_{max} 276 mμ (ε 16,080); $\lambda_{max}^{0.1\ N\ KOH}$ 223–224 mμ (ε 13,400), 286 (15,240). Nmr ($CDCl_3$) had δ 3.33 (2 H, s, CO–CH_2–N), 3.70 (4 H, s, broad CH_2–N–CH_2), 3.80 (3 H, s, OCH_3), 6.50–8.10 (eight aromatic protons).

2-Benzyl-2,3-dihydro-6,7-dimethoxy-4(1H)-isoquinolone Hydrochloride (41).[2]—Hydrolysis and decarboxylation of 15 g (0.037 mole) of **32** as described above gave 10.4 g (85%) of crystalline **41**, mp 220–222°; mixture melting point with material obtained by acid-catalyzed cyclization[2] was 219–220°. Infrared and ultraviolet spectra were superimposable: ν_{max}^{KBr} 2350 (broad, *t*-amine salt), 1670 (C=O), 1600 (phenyl), and 1285 cm^{-1} (OCH_3); λ_{max} (see Figure 2); $\lambda_{max}^{0.1\ N\ KOH}$ 234 mμ (ε 19,800), 278 (11,420), 318 (7420).

2-Benzyl-2,3-dihydro-7,8-dimethoxy-4(1H)-isoquinolone (42).—Prepared as described above from 20 g (49.2 mmoles) of **33**.

(27) The ester could be reused for other brominations.

The yield was 13.8 g (94%), mp 123–125°. An analytical sample was prepared by recrystallization from methanol: mp 125–126°; $\nu_{max}^{CHCl_3}$ 1690 (C=O), 1600 (phenyl), and 1287 and 1237 cm^{-1} (OCH_3); $\lambda_{max}^{CH_3OH}$ 227 mμ (ε 16,960), 280 (14,550), $\lambda_{max}^{0.1\ N\ KOH}$ 226 mμ (ε 14,800), 287 (14,610); $\lambda_{max}^{0.1\ N\ HCl}$ 231 (ε 13,900), 293 (14,500); nmr ($CDCl_3$), δ 3.30 (2 H, s, $N-CH_2-CO$), 3.75 and 3.87 (2 H each, s, CH_2-N-CH_2), 3.77 and 3.92 (3 H each, s, (OCH_3), 6.90 and 7.86 (2 H, AB pattern, J = 8.5 cps, C_5–H and C_6–H), 7.32 (5 H, s, phenyl).

Anal. Calcd for $C_{18}H_{19}NO_2$ (297.36): C, 72.71; H, 6.44; N, 4.71. Found: C, 73.00; H, 6.63; N, 4.79.

The **hydrochloride** of **42** was prepared by dissolving the free base in ethanol and precipitating the salt with 2-propanolic hydrogen chloride, mp 206–214° dec, after recrystallization from ethanol.

Anal. Calcd for $C_{18}H_{19}NO_2 \cdot HCl$ (333.83): C, 64.78; H, 6.03; N, 4.19. Found: C, 64.75; H, 5.64; N, 3.94.

2-Benzyl-7-chloro-2,3-dihydro-4(1H)-isoquinolone Hydrochloride (40).—A stirred solution of 16 g (0.0378 mole) of the hydrobromide of **34** in a mixture of 200 ml of concentrated hydrochloric acid and 60 ml of ethanol was refluxed in a nitrogen atmosphere for 2 days. The precipitate was collected by filtration, washed with methanol–ether, and dried in a desiccator to give 8.6 g (74%) of **40**, mp 261–264°. Two recrystallizations from methanol gave analytically pure **40**: mp 262–266°; ν_{max}^{KBr} 2450 (broad, t-amine salt), 1710 (C=O), 1605 (phenyl), and 1285 cm^{-1} (OCH_3); λ_{max} 257 mμ (ε 16,550); $\lambda_{max}^{0.1\ N\ HCl}$ 265 mμ (ε 16,100) (unstable in 0.1 N KOH); nmr (DMF-d_7), δ 4.28 (2 H, s, $CO-CH_2-N$), 4.65 and 4.72 (2 H each, s, CH_2-N-CH_2), 7.3–8.2 (8 H, aromatic protons).

Anal. Calcd for $C_{16}H_{14}ClNO \cdot HCl$ (308.22): C, 62.35; H, 4.91; N, 4.55. Found: C, 62.40; H, 5.06; N, 4.55.

2-Benzyl-3-carbethoxy-4-hydroxy-6,7-dimethoxyisoquinolinium Chloride (36).—To a solution of **32** in water was added excess ammonia, and the mixture was extracted with chloroform. Usual work-up of the combined organic solution gave the free base of **32**. To a solution of 9 g (24.4 mmoles) of the free base in 200 ml of 50% acetic acid was added a solution of 40 g (0.125 mole) of mercuric acetate in 300 ml of 50% acetic acid. The mixture was stirred under nitrogen at room temperature for 15 hr. The precipitated mercurous acetate was removed by filtration and hydrogen sulfide was passed into the filtrate. The black precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethanol and treated with excess 2-propanolic hydrogen chloride. Addition of ether produced crystalline material. Recrystallization from ethanol–ether gave 7 g (71%) of pure isoquinolinium chloride **36**: mp 187–188°; ν_{max}^{KBr} 2600 (very broad, OH), 1740 (C=O), 1617 (phenyl), and 1250 cm^{-1} (broad, OCH_3); λ_{max} (see Figure 2); nmr (DMSO-d_6), 1.10 (3 H, t, J = 7 cps, CH_2-CH_3), 4.02 and 4.10 (3 H each, s, OCH_3), 4.26 (2 H, q, J = 7 cps, CH_2-CH_3), 5.93 (2 H, s, $^+N-CH_2$), 7.35 (5 H, s, phenyl), 7.84, 8.42, and 9.65 (1 H each, s, aromatic protons).

Anal. Calcd for $C_{21}H_{22}ClNO_5$ (403.87): C, 62.46; H, 5.49; N, 3.47. Found: C, 62.34; H, 5.65; N, 3.55.

2-Benzyl-3-carbethoxy-7-chloro-4-hydroxyisoquinolinium Chloride (38).—A mixture of 16 g (46.7 mmole) of **34** and 72 g (0.226 mole) of mercuric acetate in 1 l. of 50% acetic acid was treated and worked up as in the preceding experiment to give 9 g (51%) of pure **38**: mp 154–155° (recrystallized from methanol–ether); ν_{max}^{KBr} 2400 (broad, OH), 1730 (C=O), and 1570 cm^{-1} (phenyl); λ_{max} 225 mμ (ε 46,500), 270 (7500) (sh), 287–290 (7600), 350 (6500) (sh), 400–402 (11,000); nmr (DMSO-d_6), 1.07 (3 H, t, J = 7 cps, CH_2-CH_3), 4.22, (2 H, q, J = 7 cps, CH_2-CH_3), 6.02 (2 H, s, $^+N-CH_2$), 7.37 (5 H, s, phenyl), 8.19 (1 H, q, J_o = 9 cps, J_m = 2 cps, C_6–H), 8.60 (1 H, d, J_m = 2 cps, C_8–H), 8.84 (1 H, d, J_o = 9 cps, C_5–H), 9.13 (1 H, s, broad, OH), 9.98 (1 H, s, C_1–H).

Anal. Calcd for $C_{19}H_{17}Cl_2NO_3$ (378.27): C, 60.33; H, 4.53; N, 3.70. Found: C, 60.40; H, 4.76; N, 3.67.

2-Benzyl-4-hydroxy-7-methoxyisoquinolinium Chloride (44).—To a solution of 13.5 g (50.5 mmoles) of **39** in 400 ml of 50% acetic acid was added a solution of 65 g (0.202 mole) of mercuric acetate in 100 ml of 50% acetic acid. The mixture was stirred under nitrogen at 60° for 6 hr. The work-up was the same as in the preceding experiment and afforded 7.1 g (47%) of crystalline **44**, mp 252–254°. A sample was recrystallized from methanol to give analytically pure **44**: mp 251–253° (under vacuum); ν_{max}^{KBr} 2400 (broad, OH), 1610 (phenyl), 1220 (OH), and 1250 cm^{-1} (OCH_3); λ_{max} 239–240 mμ (ε 41,200), 262–263 (21,900), 284–286 (5700), 364–365 (5250); $\lambda_{max}^{0.1\ N\ KOH}$ 231–232 mμ (ε 38,400), 278 (16,700), 308–309 (2950), 378 (9100).

Anal. Calcd for $C_{17}H_{16}ClNO_2$ (301.78): C, 67.66; H, 5.34; N, 4.64; Cl, 11.75. Found: C, 67.87; H, 5.48; N, 4.43; Cl, 11.88.

2-Benzyl-4-hydroxy-7-methoxy-1-methylisoquinolinium Chloride (47).—A solution of 4.5 g (16 mmoles) of **43** and 20.4 g (64 mmoles) of mercuric acetate in 270 ml of 10% acetic acid was stirred at 60° under nitrogen for 19 hr. The work-up, as in the preceding experiments, gave 0.9 g (18%) of crystalline **47**: mp 243–244° (recrystallized from ethanol); ν_{max}^{KBr} 2500 (broad, OH), 1605 (phenyl), 1280 (OCH_3), and 1230 cm^{-1} (OH); λ_{max} 240 mμ (ε 44,200), 260 (19,500), 267 (19,250), 287 (4300), 297 (3800) (sh), 354–355 (5500) (sh), 369–370 (6900); $\lambda_{max}^{0.1\ N\ KOH}$ 230 mμ (ε 39,500), 280 (16,900), 314 (2600), 382–383 (9700); nmr (DMSO-d_6), δ 3.05 (3 H, s, CH_3), 4.05 (3 H, s, OCH_3), 6.05 (2 H, s, broad, $^+N-CH_2$), 7.1–8.5 (9 H, aromatic protons).

Anal. Calcd for $C_{18}H_{18}ClNO_2$ (315.81): C, 68.46; H, 5.75; N, 4.44; Cl, 11.23. Found: C, 68.09; H, 5.55; N, 4.36; Cl, 11.22.

2-Benzyl-7-chloro-4-hydroxyisoquinolinium Chloride (46). A.—A solution of 3.8 g (14 mmoles) of the free base of **40** and 18.3 g (57.5 mmoles) of mercuric acetate in 150 ml of 50% acetic acid was stirred under nitrogen at 55° for 14 hr. Work-up as before gave 1.6 g (37%) of crystalline **46**, mp 280–285° dec. A sample was recrystallized from methanol and dried at 65° for 3 days under reduced pressure to give analytically pure isoquinolinium chloride **46**: mp 279–281°; ν_{max}^{KBr} 2580 (broad, OH), 1595 (phenyl), and 1210 cm^{-1} (OH); λ_{max} 222 mμ (ε 45,700), 274–275 (9200), 283 (9550), 341 (5850), 391–392 (9500).

Anal. Calcd for $C_{16}H_{13}Cl_2NO$ (306.21): C, 62.76; H, 4.28; N, 4.58. Found: C, 62.82; H, 4.19; N, 4.66.

B.—A solution of 3.8 g (10 mmoles) of **38** in a mixture of 60 ml of 2 N sodium hydroxide and 40 ml of ethanol was refluxed under nitrogen for 90 min. To the hot solution was added concentrated hydrochloric acid to bring the pH of the solution to 1. After addition of a mixture of 10 ml of concentrated hydrochloric acid and 10 ml of ethanol, refluxing was continued overnight. The precipitated crystalline material was collected by filtration and washed with ethanol and then with acetone. After drying, 2.6 g (85%) of **46**, mp 280–282°, was obtained.

2-Benzyl-4-hydroxy-6,7-dimethoxyisoquinolinium Chloride (45).—Hydrolysis and decarboxylation of 6 g of **36** as described in the preceding experiment under method B gave 4.8 g (97%) of **45**, mp 235–236°. Recrystallization from ethanol and drying at 72° under reduced pressure for 20 hr gave analytically pure **45**: mp 238–239°; ν_{max}^{KBr} 2550 (broad, OH), 1610 (phenyl), 1290 and 1240 (OCH_3), and 1210 cm^{-1} (OH); λ_{max} 256 mμ (ε 55,000), 323 (11,900), 346 (8700); nmr (DMSO-d_6), δ 4.03 and 4.10 (3 H each, s, OCH_3), 5.93 (2 H, s, $^+N-CH_2$), 7.3–7.8 (7 H, cp, phenyl, C_5–H, C_8–H), 8.35 and 9.5 (1 H each, s, C_1–H and C_3–H).

Anal. Calcd for $C_{18}H_{18}ClNO_3$ (331.81): C, 65.16; H, 5.46; N, 4.22. Found: C, 65.04; H, 5.70; N, 4.11.

7-Methoxy-4-isoquinolinol Hydrochloride (49).—A mixture of 2 g of **44** and 0.8 g of 10% palladium on charcoal in 140 ml of glacial acetic acid was hydrogenated at 70° under atmospheric pressure for 6 hr. After cooling to room temperature and filtration of the catalyst, the filtrate was concentrated under reduced pressure. The solid residue was recrystallized twice from methanol to give 0.4 g (30%) of **49**: mp 279–280°; ν_{max}^{KBr} 2750 (broad, t-amine salt and OH), 1620 and 1600 (isoquinoline and phenyl), 1240 (OCH_3), and 1205 cm^{-1} (OH); λ_{max} 235 mμ (ε 35,500), 253 (18,000), 261 (16,950), 281–282 (3950), 291 (3450), 347–348 (5450), 358–359 (5300).

Anal. Calcd for $C_{10}H_9NO_2 \cdot HCl$ (211.66): C, 56.75; H, 4.76; N, 6.62. Found: C, 56.79; H, 4.83; N, 6.75.

6,7-Dimethoxy-4-isoquinolinol Hydrochloride (50).—A mixture of 4 g of **45** and 1.2 g of 10% palladium on charcoal in 400 ml of ethanol was hydrogenated at room temperature and under atmospheric pressure for 6 hr. After filtration of the catalyst, the filtrate was concentrated to 150 ml. The crystalline precipitate was collected by filtration and recrystallized from methanol to give 2.5 g (86%) of **50**: mp 264–265°; ν_{max}^{KBr} 2750–3100 (broad, t-amine salt and OH), 1635, 1615, and 1595 (isoquinoline and phenyl), 1280 and 1230 (OCH_3), and 1205 cm^{-1} (OH); λ_{max} 253 mμ (ε 47,500), 317 (7700), 340–341 (6450); nmr (DMSO-d_6), δ 3.98 and 4.05 (3 H each, s, OCH_3), 7.53, 7.78, 8.03, and 9.12 (1 H each, s, C_8–H, C_5–H, C_1–H, and C_3–H).

Anal. Calcd for $C_{11}H_{11}NO_3 \cdot HCl$ (241.68): C, 54.67; H, 5.01; N, 5.80. Found: C, 54.94; H, 5.06; N, 5.60.

4-Isoquinolinol Hydrochloride (51).[28]—Hydrogenation of 1 g of **46** as described in the preceding experiment gave 0.35 g (59%) of analytically pure **51**: mp 207–208° after recrystallization from ethanol–ether; ν_{max}^{KBr} 2600–3100 (*t*-amine salt and OH), and 1645, 1615, and 1595 cm^{-1} (isoquinoline and phenyl); λ_{max} 233 mμ (ε 25,400), 286 (3240), 298 (3330), 331–332 (7540), 342–343 (7400).

Anal. Calcd for $C_9H_7NO \cdot HCl$ (181.63): C, 59.52; H, 4.44; N, 7.71. Found: C, 59.40; H, 4.30; N, 7.73.

5,6,7,8-Tetrahydro-4-isoquinolinol Hydrochloride (52).[29]—The isoquinolinium chloride **46** (0.5 g) was dissolved in 50 ml of glacial acetic acid at 90°, 0.2 g of 10% palladium on charcoal was added, and the mixture was hydrogenated at 90° for 3 hr under atmospheric pressure. Work-up as in preceding experiments gave 0.258 g (85%) of analytically pure **52**: mp 191–192° after recrystallization from ethanol–ether; ν_{max}^{KBr} 2600–3100 (broad, *t*-amine salt and OH), 1625 (pyridine), and 1270 cm^{-1} (OH); λ_{max} 233 mμ (ε 2780), 282–283 (6500).

Anal. Calcd for $C_9H_{11}NO \cdot HCl$ (185.65): C, 58.23; H, 6.52; N, 7.55. Found: C, 58.57; H, 6.72; N, 7.52.

1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinoline Hydrochloride (55).—A solution of 400 mg of **42** in 30 ml of glacial acetic acid was hydrogenated at 80 atm and 120° over 100 mg of 10% palladium on charcoal until the hydrogen uptake ceased. The catalyst was filtered, and the solvent was removed under reduced pressure. The residue was dissolved in ethanol, and the solution was treated with excess methanolic hydrogen chloride. Upon standing, 24 mg of crystalline **55**, mp 192–194°, was obtained. From the mother liquor a second crystalline fraction of **55** (95 mg, mp 191–193°) was isolated. An analytical sample was recrystallized from ethanol: mp 194–195°; ν_{max}^{KBr} 2770 (broad, *sec*-amine salt), 1615 and 1590 (phenyl), and 1285 and 1240 cm^{-1} (OCH_3); λ_{max}^{EtOH} 226 mμ (ε 6600), 276 (1700) (sh), 282 (1760).

Anal. Calcd for $C_{11}H_{15}NO_2 \cdot HCl$ (229.71): C, 57.52; H, 7.02; N, 6.10. Found: C, 57.43; H, 6.92; N, 6.13.

1,2,3,4-Tetrahydro-7-methoxyisoquinoline Hydrochloride (54).[30]—Hydrogenation of **39** (68 g) under the same reaction conditions gave 32.7 g (65%) of **54**, mp 230–232°. An analytical sample was recrystallized from methanol–ether: mp 231.5–232°;[31] ν_{max}^{KBr} 2800 (*sec*-amine salt), 1615 and 1595 (phenyl), and 1255 cm^{-1} (OCH_3); λ_{max} 225–226 mμ (ε 8790), 280 (2630), 287 (2510).

Anal. Calcd for $C_{10}H_{13}NO \cdot HCl$ (199.68): C, 60.15; H, 7.07; N, 7.02. Found: C, 60.46; H, 7.13; N, 7.17.

1′,2′-Dihydro-7′-methoxy-2′-methylspiro[1,3-dithiolane-2,4′-(3′H)-isoquinoline] Hydrochloride (58).—Dry hydrogen chloride was passed into a solution of 8 g (35.2 mmoles) of **53**[2] and 16 g (0.17 mole) of ethanedithiol in 220 ml of glacial acetic acid for 40 min. After standing overnight at room temperature a crystalline precipitate was obtained, then collected by filtration, and recrystallized from methanol to give 10 g (94%) of **58**: mp 252–253°; ν_{max}^{KBr} 2670 (*t*-amine salt) and 1260 cm^{-1} (OCH_3).

Anal. Calcd for $C_{13}H_{17}NOS_2 \cdot HCl$ (303.88): C, 51.38; H, 5.97; N, 4.61; S, 21.10. Found: C, 51.11; H, 6.05; N, 4.59; S, 21.08.

1′,2′-Dihydro-1′,2′-dimethyl-7′-methoxyspiro[1,3-dithiolane-2,4′(3′H)-isoquinoline] Hydrochloride (59).—By the same procedure as described above 2 g of **57**[2] gave 2 g (76%) of **59**: mp 194–195°; $\nu_{max}^{CHCl_3}$ 2270 (*t*-amine salt) and 1250 cm^{-1} (OCH_3).

Anal. Calcd for $C_{14}H_{19}NOS_2 \cdot HCl$ (317.89): C, 52.89; H, 6.34; N, 4.41; S, 20.17. Found: C, 53.16; H, 6.41; N, 4.41; S, 20.31.

1,2,3,4-Tetrahydro-7-methoxy-1,2-dimethylisoquinoline Hydrochloride (60).—To a solution of 0.5 g of **59** in 20 ml of ethanol was added 5 g of Raney nickel. The mixture was refluxed for 4 hr. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ether and 2-propanolic hydrogen chloride was added slowly. The crystalline precipitate was collected by filtration and recrystallized from acetonitrile–ether to give 0.25 g (70%) of **60**, mp 168–170°. A sample was recrystallized once more from acetonitrile–ether to furnish analytically pure **60**: mp 171–173°; $\nu_{max}^{CHCl_3}$ 2390 (*t*-amine salt) and 1250 cm^{-1} (OCH_3).

Anal. Calcd for $C_{12}H_{17}NO \cdot HCl$ (227.73): C, 63.24; H, 7.97; N, 6.15. Found: C, 63.54; H, 7.98; N, 6.31.

1,2,3,4-Tetrahydro-7-methoxy-2-methylisoquinoline Hydrochloride (56). A.—Compound **58** gave **56** by the method given above in 23% yield: mp 207–208°[32] after recrystallization from ethanol–ether; $\nu_{max}^{CHCl_3}$ 2350 (*t*-amine salt), 1620 and 1595 (phenyl), and 1280 and 1240 cm^{-1} (OCH_3).

Anal. Calcd for $C_{11}H_{15}NO \cdot HCl$ (213.72): C, 61.81; H, 7.55; N, 6.56. Found: C, 61.69; H, 7.55; N, 6.60.

B.—Hydrogenation of **53**[2] (1.7 g) as described for the preparation of **55** gave 1.2 g (71%) of crystalline **56**, mp 205–207°, mixture melting point with the analytical sample 206–208°; the infrared spectra were superimposable.

Reduction of 2,3-Dihydro-4(1H)-isoquinolones with Sodium Borohydride. General Method.—To a solution of the free base of the isoquinolones (0.1 mole) in 400 ml of methanol was added portionwise 0.44 mole of sodium borohydride. The mixture was stirred overnight at room temperature and then evaporated to dryness under reduced pressure. To the residue was added 200 ml of water, and the mixture was extracted repeatedly with ether. The combined ether solution was washed with water, dried, and filtered. Addition of excess 2-propanolic hydrogen chloride gave the crystalline 1,2,3,4-tetrahydro-4-isoquinolinol hydrochlorides (Table I).

Preparation of Propionates of 1,2,3,4-Tetrahydro-4-isoquinolinols. General Method.—A mixture of 0.1 mole of tetrahydroisoquinolinol, 65 ml of propionic anhydride, and 1 ml of pyridine was heated at 100° with stirring for 4 hr. The cooled mixture was poured into water and treated with excess sodium bicarbonate. The aqueous solution was extracted with ether and the combined ether solution was dried and filtered. Addition of excess 2-propanolic hydrogen chloride to the filtrate gave the crystalline 1,2,3,4-tetrahydro-4-isoquinolinol propionate hydrochlorides (Table I).

1,2,3,4-Tetrahydro-7-methoxy-4-isoquinolinol Propionate Hydrochloride (67).—To a solution of 3.6 g of **68** in 100 ml of glacial acetic acid was added 400 mg of 10% palladium on charcoal. The mixture was hydrogenated at room temperature and atmospheric pressure until the hydrogen uptake ceased (4 hr). The catalyst was filtered and the filtrate was evaporated to dryness under reduced pressure. The crystalline residue was washed with ether and recrystallized from ethanol–methanol to give 2.6 g (96%) of **67**, mp 183–184°.

Registry No.—**18**, 15364-83-7; **19**, 15364-84-8; **20**, 15393-58-5; **21**, 15365-25-0; **22**, 15365-26-1; **23**, 15365-27-2; **24**, 15365-28-3; **25**, 15365-29-4; **26**, 15365-30-7; **27**, 15365-31-8; **28**, 15365-32-9; **30**, 15365-33-0; **30** HCl, 15365-34-1; **31**, 15365-35-2; **32**, 15365-36-3; **33**, 15365-37-4; **34**, 15365-38-5; **35**, 15365-39-6; **36**, 15365-40-9; **37**, 15365-41-0; **38**, 15365-42-1; **39**, 5120-75-2; **40**, 15365-44-3; **41**, 5077-03-2; **42**, 15365-46-5; **42** HCl, 15365-47-6; **44**, 15412-13-2; **45**, 15365-48-7; **46**, 15365-49-8; **47**, 15365-50-1; **49**, 15365-51-2; **50**, 15365-52-3; **51**, 15365-53-4; **52**, 15365-54-5; **54**, 1745-05-7; **55**, 15365-56-7; **56**, 15365-57-8; **58**, 15365-58-9; **59**, 15393-45-0; **60**, 15393-46-1; **62**, 15393-59-6; **63**, 15393-47-2; **64**, 15393-48-3; **65**, 15393-49-4; **66**, 15393-50-7; **67**, 15393-51-8; **68**, 15393-52-9; **69**, 15393-53-0.

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(28) The free base of **51** is described in ref 17, mp 223°.

(29) The free base of **52** is described in ref 18, mp 192–193°.

(30) This compound was prepared by Dr. F. Schenker of these laboratories.

(31) In ref 19 the melting point is reported as 228–229°.

(32) In ref 19 the melting point is reported as 201–202°.