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(22) Reduction of **1** oxalate in D_2O with D_2/PtO_2 gave **4**, which was exchanged against 6 *N* HCl (to convert $-ND_2$ to $-NH_2$), and purified by GC. NMR revealed that some loss of the methine proton had occurred during the reduction. This does not demand, but could be consistent with, simultaneous racemization.
(23) (a) $\alpha^{31.5}_{365}$ −0.040° (1 dm). The specific rotation given in the text is corrected for the optical purity of the amine precursor. (b) $\alpha^{31.5}D$ −0.033° (1 dm). The specific rotation is corrected for the optical purity of the amine.
(24) $\alpha^{25}D$ −0.457° (*c* 2.902, benzene, 1 dm). The specific rotation is corrected for the optical purity of the diazotate precursor.
(25) Reaction of 95.6% optically pure (*S*)-(−)-**3** with hydroxylamine-*O*-sulfonic acid gave 8% of pure (*S*)-**1**, $[\alpha]^{25}D$ −29.0° (*c* 0.784, benzene).[15]
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(39) Microanalyses were done by Micro-Tech Laboratories, Skokie, Ill.

Synthesis of Phenyl-Substituted 1-Aminotetralines

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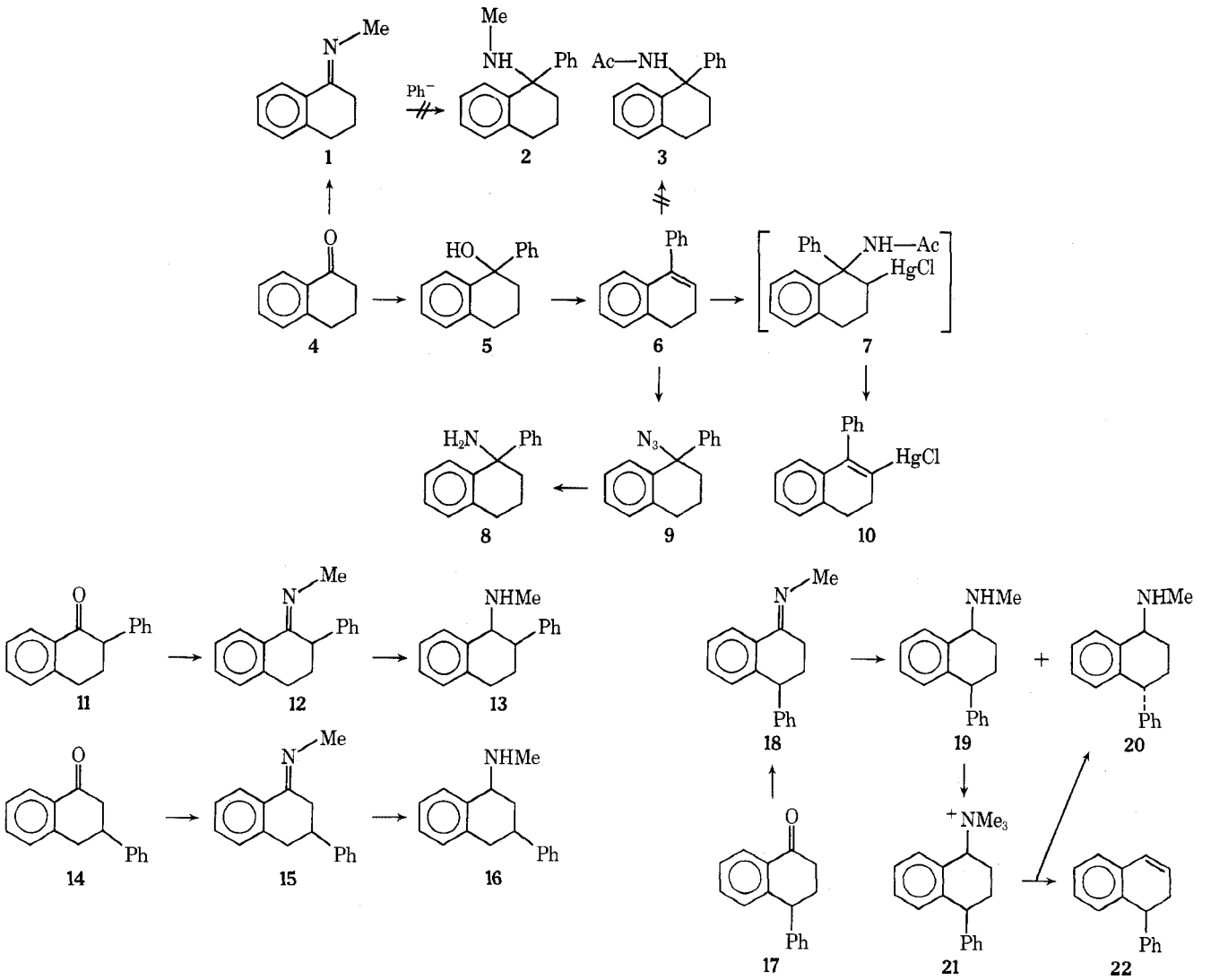
Received October 9, 1974

Synthetic methods were developed for 1-, 2-, 3-, or 4-phenyl-substituted 1-aminotetraline derivatives. 1-Phenyl-1-aminotetraline was obtained by hydrazoic acid addition to 1-phenyl-3,4-dihydronaphthalene, followed by lithium aluminum hydride reduction. The cis isomers of 2- or 3-phenyl-substituted *N*-methyl-1-aminotetraline resulted from sodium borohydride reduction of the methylimines derived from the corresponding ketones. Sodium borohydride treatment of the methylimine derived from 4-phenyl-1-tetralone gave a 1:1 mixture of *cis*- and *trans*-4-phenyl-1-aminotetraline, but stereoselective conversions were achieved by catalytic hydrogenation over palladium/carbon (cis isomer) and by zinc–acetic acid reduction (trans isomer). These reactions were extended to the synthesis of the corresponding 5-methoxy-8-chloro substituted analogs and to the preparation of a series of 4-phenyl-1-aminotetralines with modified nitrogen substituents. In addition, two useful reactions were discovered: the oxidation of 1-phenyltetraline to 4-phenyl-1-tetralone with potassium permanganate and the conversion of *N*-methyl-4-phenyl-1-aminotetraline to the corresponding ketone by aqueous potassium permanganate.

The interesting pharmacological activity exhibited by certain 1-aminotetralines,[1] especially the 5-methoxy-8-halogen derivatives, prompted us to investigate the synthesis of 1-aminotetralines substituted with phenyl groups in the alicyclic ring. Initially, we explored the synthesis of the simple 1-, 2-, 3-, or 4-phenyl-substituted 1-aminotetralines bearing no substituents in the aromatic ring. The synthesis of 1-phenyl-1-aminotetraline was approached in three ways. Addition of phenylmagnesium bromide or phenyllithium to the methylimine (**1**) derived from 1-tetralone (**4**) failed to give, even in the presence of polarizing agents such as BF_3, the desired 1-phenyl-1-aminotetraline derivative **2** (Scheme I), although this type of reaction had been successful in the preparation of the corresponding 1-methyl derivatives.[1] While this failure may be due to steric factors, this explanation is not entirely satisfactory, since the reaction of phenylmagnesium bromide with 1-tetralone (**4**) itself proceeded in good yield in accordance with published results[2,3] to the alcohol **5**. Compound **5** was dehydrated to 3,4-dihydro-1-phenyltetraline (**6**),[2] which proved to be inert in the Ritter reaction[4] (acetonitrile, sulfuric acid). The modified conditions of Chow et al.[5] (acetonitrile, mercuric nitrate) led, presumably via **7**, to the mercurated olefin **10**. The addition of hydrazoic acid to **6** in the presence

Scheme I



of trichloroacetic acid[6] gave small yields of the azide **9**, which was in turn reduced to the desired 1-phenyl-1-aminotetraline (**8**) with lithium aluminum hydride or zinc–hydrochloric acid. The yield of **9** could not be increased by using different solvents, different acid catalysts, or moderately elevated temperature, although we confirmed that this reaction sequence leads to good yields of 1,1-diphenylethylamine from the closely related "ring open" 1,1-diphenylethylene.[6]

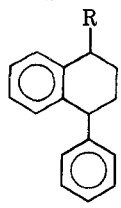
The synthesis of 2-phenyl-1-aminotetraline was straightforward. 2-Phenyl-1-tetralone (**11**)[3,7,8] was converted to the methylimine **12** with the aid of titanium tetrachloride;[1,9] reduction of **12** with sodium borohydride[1,10] yielded exclusively *cis*-*N*-methyl-2-phenyl-1-aminotetraline (**13**), presumably as a consequence of the steric influence of the phenyl group. Similarly, 3-phenyl-1-tetralone (**14**)[3,7] was converted to the methylimine derivative **15**, sodium borohydride reduction of which led to *cis*-*N*-methyl-3-phenyl-1-aminotetraline (**16**). The apparently exclusive formation of the cis isomer is somewhat surprising in this instance, since no particular steric hindrance to the approach of the reducing species from either side would be anticipated from molecular models. Sodium borohydride reduction of the methylimine (**18**) derived from 4-phenyl-1-tetralone[11] (**17**) gave the expected 1:1 mixture of *cis*- and *trans*-*N*-methyl-4-phenyl-1-aminotetraline (**19** and **20**), which were easily separated by fractional crystallization.

The intriguing "antidepressant" pharmacological activity exhibited by the trans isomer **20**[12] prompted us to investigate the stereochemical control of the reduction of **18** more thoroughly, and to develop a stereoselective synthesis of **20**. As expected, catalytic hydrogenation of **18** over palladium/carbon in ethanol gave exclusively the cis derivative **19**. Attempts to convert **19** to **20** were only partially successful: **19** proved to be stable to treatment with methylamine, and quaternization of **19** to **21**, followed by reaction with methylamine, favored elimination to **22** (70% yield) over displacement to **20** (30% yield).

All efforts to increase the trans to cis ratio by modifying the sodium borohydride reduction conditions of **18** (pH, solvent, temperature) or by using different hydrides (BH_3, $LiAlH_4$, $LiBH_4$, Redal) failed. Conceivably, the use of reducing conditions which result in the formation of radical anions, such as dissolving metal reductions, would lead to the presumably thermodynamically favored trans isomer **20**, if the reaction intermediate has an appreciable half-life. However, treatment of **18** with sodium in ethanol resulted in only a 50% yield of the trans isomer **20**. On the other hand, reduction of **18** with zinc in acetic acid produced mainly the desired trans isomer **20**. This difference between sodium and zinc may be a consequence of the size and/or the complexing properties of zinc.

Since the pharmacological profile of simple 1-aminotetralines is highly configuration specific,[1] **20** was resolved

Table I



No.	R	Configuration
23	NMe_2	Trans
24	NMe_2	Cis
25	NH_2	Trans
26	NH_2	Cis
27	NHEt	Trans
28	NHEt	Cis
29	NH-*i*-Pr	Trans
30	NH-*i*-Pr	Cis
31	NH- 	Trans
32	NH- 	Cis
33		Trans
34		Cis
35	 N-Me	Trans
36	 N-Me	Cis

into its enantiomers using D-mandelic acid and *N*-acetyl-L-tyrosine. On the basis of previous experience,[1] the isomer which precipitated with *N*-acetyl-L-tyrosine was assigned the 1*S*,4*R* configuration, and this assignment was confirmed by an X-ray analysis of its hydrobromide.[12]

The "antidepressant" activity resides exclusively in the 1*R*,4*S* isomer[12] of **20**. An economical synthesis of this isomer would require a recycling of the unwanted isomer. Consequently, we examined various conditions for the oxidation of secondary amines to the corresponding ketones, using the oxidation of **19** to **17** as a model system. Whereas literature methods[13] proved to be inadequate on a preparative scale, treatment of **19** with potassium permanganate in 50% aqueous acetone at room temperature for 1 hr gave a clean conversion to the ketone in acceptable yields.

For pharmacological comparison,[12] several analogs of **19** and **20** with modified nitrogen substituents were prepared, and these are listed in Table I. The dimethyl derivatives **23** and **24** were prepared by methylation of **20** and **19**, respectively, since treatment of the enamine obtained from dimethylamine and the tetralone **17** with formic acid resulted in hydrolysis to **17**. Conversion of **17** to the oxime, followed by catalytic hydrogenation over palladium/carbon in ethanol, gave a 1:2 mixture of the trans and cis primary amines, **25** and **26**. The trans isomer **23** was also obtained in moderate yield by zinc–acetic acid reduction[1] of the phenylhydrazone of **17**. The *N*-ethyl, *N*-isopropyl, and *N*-cyclopropyl derivatives **27–32** were obtained as mixtures of cis and trans isomers by sodium borohydride reduction of the corresponding ketimines; in all these cases catalytic hydrogenation over palladium/carbon gave predominantly the cis isomers. The pyrrolidine derivatives **33** and **34** were obtained by reaction of **25** or **26** with 1,4-dibromobutane.[1] Compounds **35** and **36** resulted from reduction of the corresponding enamine with lithium borohydride in the presence of formic acid,[1] and the cis isomer **35** was formed exclusively by catalytic hydrogenation of the enamine. Recently, compounds **19**, **20**, **23**, **24**, **25**, and **26** have been described.[30]

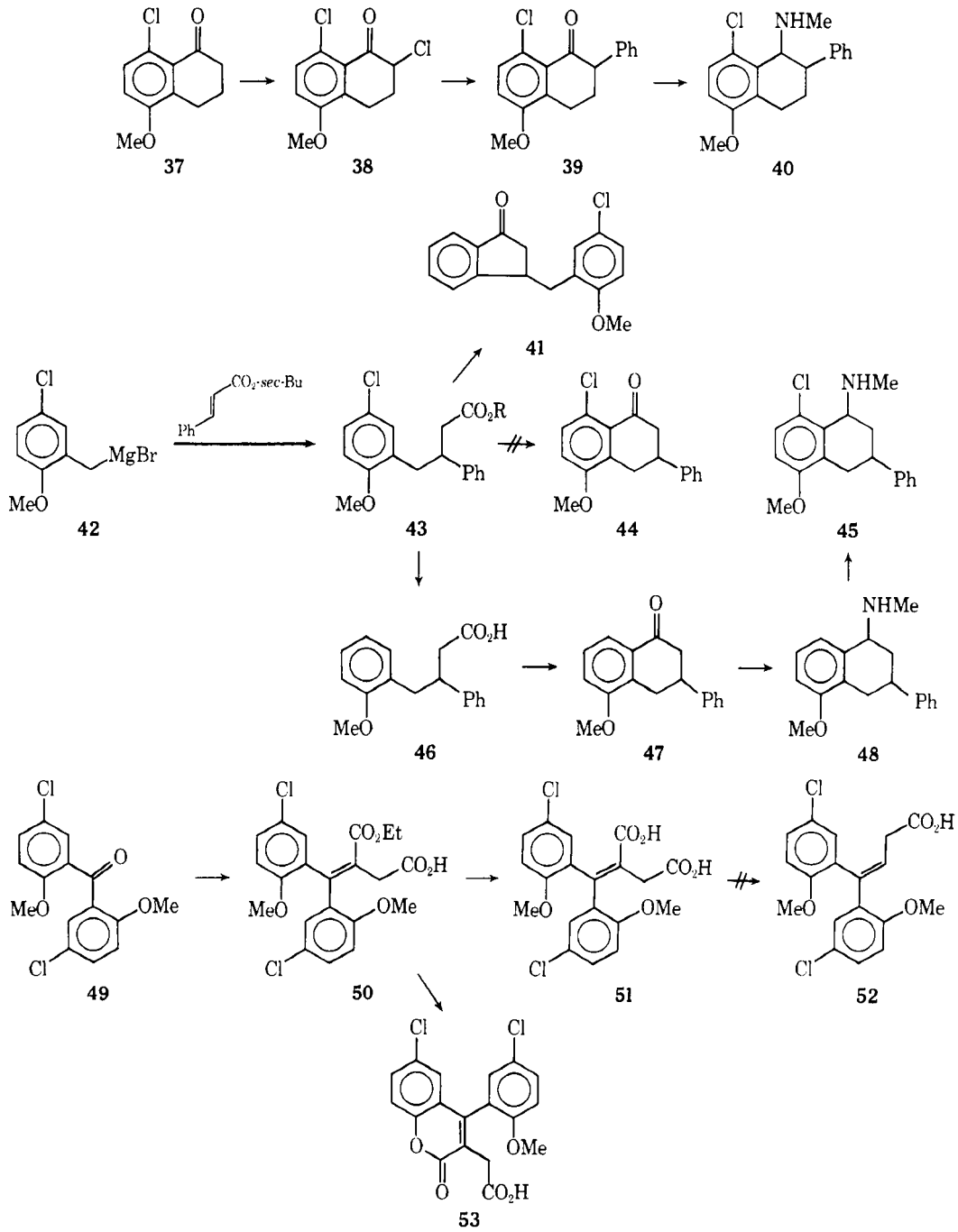
We then turned our attention to the synthesis of phenyl-substituted 5-methoxy-8-chloro-1-aminotetralines. Chlorination of 5-methoxy-8-chloro-1-tetralone[1,14] (**37**) in acetic acid,[15] followed by treatment with phenylmagnesium bromide,[15,16] gave 2-phenyl-1-tetralone (**39**) (Scheme II). This compound was converted to the methylimine and reduced with sodium borohydride to give again exclusively the cis isomer **40**. Addition of 5-chloro-2-methoxybenzylmagnesium bromide to the *sec*-butyl ester[17] of cinnamic acid in the presence of cuprous chloride, followed by saponification of the resulting ester **43** (R = *sec*-butyl) to the acid (R = H) and cyclization with polyphosphoric acid,[1] gave the 3-benzyl-substituted 1-indanone **41** instead of the desired 3-phenyl-substituted tetralone **44**. However, after removal of the deactivating chlorine function in **43** by catalytic hydrogenation, the resulting acid **46** was cyclized to give the desired tetralone **47**, indicating that formation of the six-membered ring is favored despite the presence of the deactivating *m*-methoxy group. Conversion of **47** to the methylimine, followed by reduction with sodium borohydride, resulted in mixtures of cis and trans isomers which could not be separated. Catalytic hydrogenation of the methylimine gave exclusively the cis isomer **48**, which was converted by chlorination in acetic acid[1] to the desired derivative **45**.

The synthesis of 4-phenyl-substituted chloromethoxy derivatives was initially approached from the symmetrical 5,5′-dichloro-2,2′-dimethoxybenzophenone[18] (**49**). However, both the Stobbe condensation product **50** and the diacid **51** obtained by base hydrolysis of **50** proved to be resistant to the standard hydrolysis and decarboxylation conditions (HBr–acetic acid),[19] as lactone **53** was formed instead of the expected acid **52**. Other attempts to decarboxylate **51**, such as heating either neat or in the presence of thioglycolic acid, thiophenol, copper–quinoline,[20] toluenesulfonic acid, or toluenesulfonic acid–sulfolane, led either to no reaction, partial formation of lactone **53** or an intractable mixture of products. An alternate route, reduction of the double bond of **51** followed by ring closure to the tetralone and decarboxylation under nonselective conditions, was considered. However, reduction of **50** or **51** over palladium/carbon, rhodium/carbon, or with sodium borohydride failed, presumably owing to the inaccessibility of the tetrasubstituted double bond.

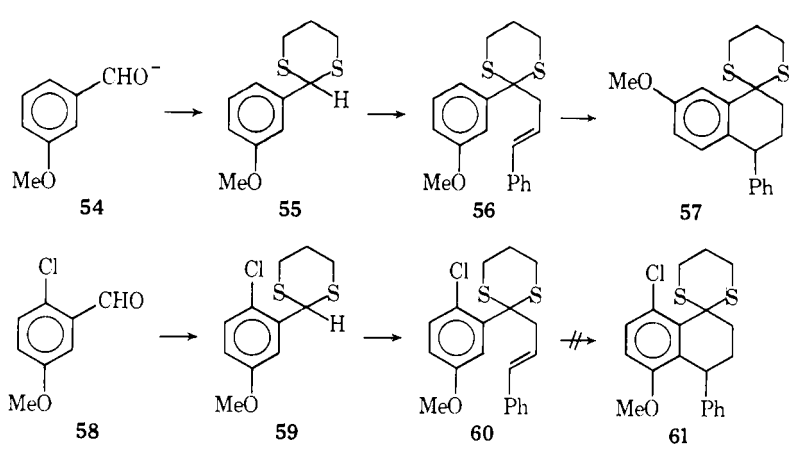
A second approach involving cyclization of an olefin containing a protected ketone group was also explored. Conversion of 3-methoxybenzaldehyde (**54**) to the 1,3-dithiane derivative **55**, followed by alkylation of the anion of **56**[21] with cinnamyl bromide, gave an excellent yield of **56** (Scheme III). Cyclization of **56** with BF_3 in methylene chloride proceeded in moderate yield, but to the undesired isomer **57**. In order to guide the cyclization into the proper direction we planned to block the position para to the methoxy group with chlorine. Conversion of 2-chloro-5-methoxybenzaldehyde[22,23] (**58**) to the dithiane derivative **59** was uneventful, but generation of the anion of **59** proved to be difficult. Even the best conditions found, methyllithium in tetrahydrofuran at 0°, resulted only in poor yields of the alkylated product **60**. The presence of the chlorine atom in **59** apparently interfered with formation of the anion and led to side reactions involving the aromatic ring, as suggested by NMR data. Furthermore, attempts to cyclize **60** were futile, presumably owing to the deactivating effects of the chlorine atom.

A successful synthesis was ultimately developed starting with 5-chloro-8-methoxy-1-tetralone (**62**).[24] Tetralone **62** was converted in three steps to the phenyltetraline derivative **65**. Although the literature[25] claims that V_2O_5–H_2O_2 gives good yields of 4-phenyl-1-tetralone from the tetraline, this oxidation procedure, as well as those employing SeO_2 or chromic acid, failed with **65**. However, treatment of **65**

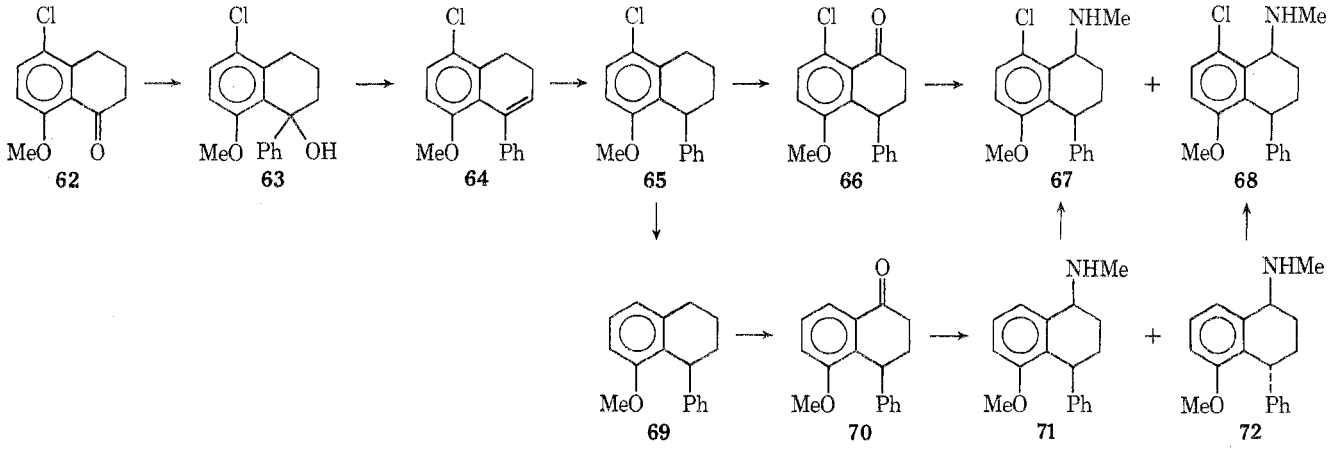
Scheme II



Scheme IIIA



Scheme IIIB



with potassium permanganate gave a clean conversion to the ketone **66**. Since this reaction proceeded rather slowly, we decided to investigate whether **69**, the dechloro analog of **65**, would react faster in the absence of the bulky chlorine atom. Indeed, **69** was oxidized more readily to give the ketone **70**. Surprisingly, conversion of either **66** or **70** to the methylimine, followed by reduction with sodium borohydride, gave predominantly the cis 1-aminotetralines, **67** and **71**, respectively. This result must be attributed to the presence of the 5-methoxy group. However, reduction of the methylimine derived from **70** with zinc–acetic acid again, as in the unsubstituted compound, gave predominantly the thermodynamically more stable trans isomer **72**. Compounds **71** and **72** were then converted by chlorination in acetic acid[1] to compounds **67** and **68**, respectively.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by the Analytical Department of Pfizer Central Research. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-60 spectrometer. NMR spectra were obtained on Varian T-60 and A-60 instruments.

1-Phenyl-1,2,3,4-tetrahydro-1-naphthylamine (8). A solution of 10.4 g (0.064 mol) of trichloroacetic acid and 2.75 g (0.0134 mol) of 1-phenyl-3,4-dihydronaphthalene[2] in 100 ml of benzene containing 2.58 g (0.06 mol) of hydrazoic acid[26] was kept at room temperature for 15 hr. The mixture was washed with H_2O, dried over $MgSO_4$, and filtered, and the filtrate was evaporated. The residue was dissolved in 50 ml of Et_2O and added dropwise to a suspension of 510 mg (0.0134 mol) of lithium aluminum hydride in 150 ml of Et_2O. After refluxing overnight, the mixture was quenched with H_2O, filtered, and treated with 12 *N* HCl until a pH of 2 was reached. After three extractions with Et_2O, 2.62 g (95.5%) of starting material was recovered from the combined organic layers. Basification of the aqueous phase with 4 *N* NaOH, followed by three extractions with Et_2O and evaporation of the combined organic layers, afforded 104 mg of basic material. After treatment with HCl in Et_2O and two recrystallizations of the resulting solids from EtOH–Et_2O there was obtained 40 mg (1%) of **8** as the hydrochloride: mp 237–238°; mass spectrum *m/e* 223 (M^+), 206 (base peak), 194, 178, 146, 123.

Anal. Calcd for $C_{16}H_{17}N \cdot HCl$: C, 73.97; H, 6.99; N, 5.39. Found: C, 73.83; H, 6.81; N, 5.17.

2-Chloromercuri-1-phenyl-3,4-dihydronaphthalene (10). To a suspension of 3.24 g (0.01 mol) of mercuric nitrate in 20 ml of acetonitrile (distilled from P_2O_5) was added 0.05 ml of concentrated nitric acid and then dropwise a solution of 2.06 g (0.01 mol) of 1-phenyl-3,4-dihydronaphthalene (**6**) in 5 ml of acetonitrile; the resulting clear solution was kept at room temperature for 14 hr. The mixture was poured into 50 ml of H_2O, treated with 5 ml of 5 *N* aqueous NaCl, stirred for 5 min, and extracted three times with 50 ml of $CHCl_3$. The exracts were dried and evaporated, and the residue was crystallized from CH_2Cl_2–hexane to give 1.5 g (34%) of **10**: mp 159–160°; NMR ($CDCl_3$) δ 2.3–3.2 (m, 4 H), 6.6–7.3 (m, 4 H), 7.35 (s, 5 H).

Anal. Calcd for $C_{16}H_{13}ClHg$: C, 43.55; H, 2.98. Found: C, 43.40; H, 2.95.

***cis*-*N*-Methyl-2-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (13).** A solution of 2.22 g (0.01 mol) of 2-phenyl-3,4-dihydro-1(2*H*)-naphthalenone (**11**) and 1.85 g (0.06 mol) of methylamine in 50 ml of benzene was cooled to 0° and treated dropwise with 0.55 ml (0.005 mol) of $TiCl_4$, keeping the temperature below 10°. The mixture was kept at room temperature overnight and then heated to reflux for 24 hr. After cooling and filtration, the filtrate was evaporated in vacuo, and the residue was dissolved in 50 ml of MeOH and treated with 0.54 g (0.02 mol) of $NaBH_4$. After stirring at room temperature for 30 min, the mixture was evaporated, and the residue was treated with 2 *N* NaOH and extracted with three 50-ml portions of CH_2Cl_2. The combined organic extracts were dried and evaporated, and the residue was dissolved in Et_2O and treated with HCl gas to give 1.7 g of crude **13** as the hydrochloride. After recrystallization from CH_2Cl_2–hexane there was obtained 1.6 g (59%): mp 257–258°; NMR (free base in $CDCl_3$) δ 1.2 (d, 2 H, J = 5 Hz), 2.15 (s, 3 H), 2.2–3.4 (m, 3 H), 3.7 (d, 1 H, J = 3.5 Hz), 7.2, 7.3 (2 s, 9 H).

Anal. Calcd for $C_{17}H_{19}N \cdot HCl$: C, 74.56; H, 7.36; N, 5.11. Found: C, 74.53; H, 7.38; N, 5.00.

***cis*-*N*-Methyl-3-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (16).** 3-Phenyl-3,4-dihydro-1(2*H*)-naphthalenone (2.2 g, 0.01 mol) was treated with methylamine–$TiCl_4$ and subsequently with $NaBH_4$ as described above to give after conversion to the hydrochloride 2.0 g of crude **16**. After recrystallization from EtOH–hexane there was obtained 1.73 g (63%) of **16** as the hydrochloride: mp 177–179°; NMR (free base in $CDCl_3$) δ 1.55 (m, 2 H), 2.4 (m, 1 H), 2.45 (s, 3 H), 2.95 (m, 3 H), 4.0 (d of d, 1 H, J = 5, 10 Hz), 6.9–7.7 (m, 9 H).

Anal. Calcd for $C_{17}H_{19}N \cdot HCl$: C, 74.56; H, 7.36; N, 5.11. Found: C, 74.48; H, 7.27; N, 4.92.

***cis*-*N*-Methyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (19) and Its Trans Isomer (20).** A solution of 11.2 g (0.05 mol) of 4-phenyl-3,4-dihydro-1(2*H*)-naphthalenone (**17**) in 250 ml of benzene was treated with 9.3 g of methylamine and 2.75 ml of $TiCl_4$ as described above, but the mixture was kept at room temperature overnight. After filtration and evaporation the residue was crystallized from hexane to give 11 g (93%) of the methylimine derivative **18**, mp 69–70°. A solution of 5 g (0.021 mol) of **18** in 150 ml of MeOH was treated with 2 g of $NaBH_4$ and the mixture was kept at room temperature for 30 min. After the usual work-up and conversion to the hydrochlorides, the cis isomer **19** was separated by fractional crystallization of the crude mixture from water. After two recrystallizations from MeOH–Et_2O there was obtained 2.3 g (40%) of **19** as the hydrochloride: mp 241–242°; NMR (CD_3OD) δ 1.9–2.3 (m, 4 H), 2.8 (s, 3 H), 4.1 (br t, 1 H), 4.5 (br s, 1 H), 4.9 (DOH), 6.7–7.7 (m, 9 H, sharp s at 7.23).

Anal. Calcd for $C_{17}H_{19}N \cdot HCl$: C, 74.56; H, 7.36; N, 5.11. Found: C, 74.44; H, 7.46; N, 5.11.

From the aqueous mother liquor of **19** there was obtained after two recrystallizations from acetone–MeOH–Et_2O 1.9 g (33%) of the trans isomer **20** as the hydrochloride: mp 224–225°; NMR (CD_3OD) δ 1.7–2.5 (m, 4 H), 2.75 (s, 3 H), 4.25 (br t, 1 H), 4.6 (br t, 1 H), 4.9 (DOH), 6.7–7.7 (m, 9 H).

Anal. Calcd for $C_{17}H_{19}N \cdot HCl$: C, 74.56; H, 7.36; N, 5.11. Found: C, 74.42; H, 7.30; N, 4.99.

Alternatively, **19** was obtained in 92% yield by hydrogenation of

18 in ethanol over 10% Pd/C at atmospheric pressure. Only trace amounts of the trans isomer **20** were found under these conditions according to VPC analysis (3% SE-30 on Varaport 30, 100/120 mesh, 3 ft × 0.125 in. column). On the other hand, treatment of 235 mg (0.001 mol) of **18** in 10 ml of glacial acetic acid with 0.5 g of activated zinc dust at 65° for 2 hr, followed by stirring at room temperature overnight, resulted after the usual work-up in the isolation of 180 mg (66%) of the trans isomer of **20** as the hydrochloride. VPC analysis of the crude reaction mixture indicated an 80:20 ratio of trans to cis isomer.

Resolution of the Trans Isomer 20. A mixture of 34 g (0.143 mol) of the cis and trans amines **19** and **20**, obtained by $NaBH_4$ reduction of **18**, and 15.9 g (0.0715 mol) of *N*-acetyl-L-tyrosine were dissolved in 300 ml of hot MeOH. After the addition of 700 ml of Et_2O, the mixture was kept at room temperature for 1 hr and at 0° for 30 min. The solids which had separated (13.6 g, mp 222–226°) were filtered and recrystallized from MeOH–Et_2O (1:2) to give 11.72 g of the *N*-acetyl-L-tyrosine salt of the 1*S*,4*R* isomer of **20**, mp 230–231°. After conversion to the hydrochloride and recrystallization from MeOH–Et_2O there was obtained 6.06 g (15%) of the hydrochloride of the 1*S*,4*R* isomer of **20**, mp 230–231°, $[\alpha]^{24}D$ −41.4° (*c* 1, MeOH). This sample was identical with a sample obtained by resolution of a specimen of pure **20**.

Anal. Calcd for $C_{17}H_{19}N \cdot HCl$: C, 74.56; H, 7.36; N, 5.11. Found: C, 74.34; H, 7.31; N, 4.99.

The original mother liquor of the *N*-acetyl-L-tyrosine salt was evaporated, treated with 200 ml of 1 *N* NaOH, and extracted with three 200-ml portions of Et_2O. The combined organic extracts were dried and evaporated, and the residue (27 g) was dissolved in 300 ml of hot MeOH and treated with 8.7 g of D-(−)-mandelic acid. After cooling and the addition of 1 l. of Et_2O, the mixture was kept in the refrigerator overnight. The solids which had separated were filtered off and recrystallized twice from MeOH–Et_2O (1:2) to give 11.8 g of the D-mandelate of the 1*R*,4*S* isomer of **20**, mp 130–131°. After conversion to the hydrochloride and two recrystallizations from $CHCl_3$–Et_2O (1:3) there was obtained 6.3 g (16%) of the 1*R*,4*S* isomer of **20** as the hydrochloride, mp 230–231°, $[\alpha]^{24}D$ 41.2° (*c* 1, MeOH). Again, this compound was identical with a sample obtained previously by direct resolution of pure **20**.

Anal. Calcd for $C_{17}H_{19}N \cdot HCl$: C, 74.56; H, 7.36; N, 5.11. Found: C, 74.73; H, 7.36; N, 5.09.

***cis*-4-Phenyl-*N,N,N*-trimethyl-1,2,3,4-tetrahydro-1-naphthylammonium Iodide (21).** A mixture of 165 mg (0.65 mmol) of **24** and 184 mg (1.3 mmol) of methyl iodide in 7 ml of MeOH was heated to 50° for 24 hr. After the addition of 50 ml of Et_2O, the precipitated solids were filtered and recrystallized from MeOH–Et_2O to give 155 mg (61%) of **21**, mp 174–175° dec.

Anal. Calcd for $C_{19}H_{24}IN$: C, 58.01; H, 6.16; N, 3.56. Found: C, 57.54; H, 6.12; N, 3.42.

A mixture of 10 mg of **21** and 1 ml of anhydrous methylamine in 10 ml of dimethylformamide was heated in a steel bomb to 98° for 30 min. VPC analysis of this mixture indicated the formation of ~30% trans amine **20**, in addition to 70% elimination product **22**.[27]

Oxidation of 19 with Aqueous Permanganate. To a solution of 23.7 g (0.1 mol) of **19** (free base) in 750 ml of acetone was added a solution of 23.7 g (0.15 mol) of $KMnO_4$ in 750 ml of H_2O over a period of 15 min, causing the temperature to rise to 42°. After stirring at room temperature for 1 hr, the mixture was filtered, and the filter cake was washed well with 500 ml of acetone. The combined filtrates were concentrated in vacuo to approximately 500 ml, and the mixture was extracted with CH_2Cl_2. After the usual work-up there was obtained 7.7 g (28%) of unreacted **19** as the hydrochloride, and 13.25 g (60%) of 4-phenyltetralone (**17**), mp 73–74°. In a similar run, using 0.3 mol of $KMnO_4$, the yield of **17** was 61%.

***trans*-*N,N*-Dimethyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (23).** A mixture of 390 mg (1.64 mmol) of 20 (free base), 5 ml of 37% formaldehyde, and 5 ml of 98% formic acid was heated on a steam bath for 1 hr. After evaporation and the usual work-up there was obtained after crystallization from MeOH–Et_2O 402 mg (85%) of **23** as the hydrochloride, mp 228–230° dec. Similarly was obtained the cis isomer **24** in 85% yield, mp 192–194° after crystallization from acetone–Et_2O.

Anal. Calcd for $C_{18}H_{21}N \cdot HCl$: C, 75.12; H, 7.71; N, 4.86. Found (**23**): C, 74.87; H, 7.80; N, 4.71. Found (**24**): C, 75.18; H, 7.66; N, 4.74.

4-Phenyl-3,4-dihydro-1(2*H*)-naphthalenone Oxime. To a stirred solution of 4.9 g (0.022 mol) of **17** in 18 ml of EtOH was added 16 ml of H_2O, 1.72 g (0.025 mol) of hydroxylamine hydrochloride, and then 4.4 g of powdered NaOH. After 10 min, a clear solution had formed, which was then heated on the steam bath for 45 min. After cooling and evaporation, the residue was dissolved in $CHCl_3$ and washed with 1 *N* HCl. The organic layer was evaporated and the residue was crystallized from $CHCl_3$–hexane to give 3.58 g (69%) of the oxime, mp 114–115°.

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.74; H, 6.48; N, 5.90.

4-Phenyl-3,4-dihydro-1(2*H*)-naphthalenone Phenylhydrazone. To a solution of 11.1 g (0.05 mol) of **17** in 200 ml of EtOH was added 10.8 g (0.1 mol) of phenylhydrazine and 40 ml of glacial acetic acid. The solution was heated on a steam bath for 30 min. After cooling, the crystals which had separated were collected and recrystallized from EtOH to give 13.4 g (86%) of the phenylhydrazone, mp 124–126°.

Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.26; H, 6.48; N, 8.97.

4-Phenyl-1,2,3,4-tetrahydro-1-naphthylamine (25 and 26). Hydrogenation of 2 g (8.4 mmol) of the oxime of **17** in 100 ml of EtOH over 1 g of 10% Pd/C at 50 psi for 2 hr gave after the usual work-up and fractional crystallization from MeOH–Et_2O 0.71 g (32%) of the trans isomer **25** as the hydrochloride, mp 301–302°, and 1.4 g (64%) of the cis isomer **26** as the hydrochloride, mp 279–281°. The stereochemical assignments are based on the conversion of **25** to **23** with formic acid–formaldehyde.

The trans isomer **25** was also obtained in 18% yield by suspending 10 g of the phenylhydrazone of **17** in 400 ml of acetic acid and treating the mixture with 26 g of activated zinc dust at 60° overnight, followed by the usual work-up.

Anal. Calcd for $C_{16}H_{17}N \cdot HCl$: C, 73.97; H, 6.99; N, 5.39. Found (**25**): C, 73.82; H, 6.85; N, 5.31. Found (**26**): C, 73.96; H, 7.03; N, 5.37.

***N*-Ethyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (27 and 28).** A solution of 6.66 g (0.03 mol) of **17** in 100 ml of benzene was treated with 8.1 g of ethylamine and 1.65 ml of $TiCl_4$ as described above to give, after crystallization of hexane, 5.4 g of the ethylimine derivative, mp 89–90°. Reduction of 4.9 g of this imine with 1 g of $NaBH_4$ in 75 ml of MeOH as described above gave, after fractional crystallization from MeOH–Et_2O, 490 mg (9%) of the trans isomer **27** as the hydrochloride, mp 224–225°, and 1.85 g (34%) of the cis isomer **28** as the hydrochloride, mp 261–262°. Catalytic hydrogenation of 1.5 g of the ketimine in 50 ml of EtOH over 200 mg of 10% Pd/C at 50 psi gave exclusively the cis isomer **28** according to VPC analysis.

Anal. Calcd for $C_{18}H_{21}N \cdot HCl$: C, 75.12; H, 7.71; N, 4.86. Found (**27**): C, 75.00; H, 7.78; N, 5.11. Found (**28**): C, 74.88; H, 7.63; N, 4.85.

***N*-Isopropyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (29 and 30).** When 6.66 g of **17** was treated with 10.6 g of isopropylamine as described above, there was obtained, after crystallization from hexane, 5.7 g of the ketimine, mp 74–75°. A 5.2-g sample was reduced with $NaBH_4$ to give, after multiple fractional crystallizations from MeOH–Et_2O, 2.59 g (44%) of the trans isomer **29** as the hydrochloride [mp 283–284°; NMR ($CDCl_3$ + NaOD) δ 1.1 (d, 3 H, *J* = 7 Hz), 1.14 (d, 3 H, *J* = 7 Hz), 1.3–2.4 (m, 4 H), 3.1 (m, *J* = 7 Hz), 3.7–4.3 (m, 2 H), 6.7–7.6 (m, 9 H)] and 0.65 g (11%) of the cis isomer **30** as the hydrochloride [mp 228–229°; NMR ($CDCl_3$ + NaOD) δ 1.25 (d, 6 H, *J* = 7 Hz), 1.9–2.2 (m, 4 H), 3.3 (m, *J* = 7 Hz), 3.8–4.6 (m, 2 H), 6.7–7.8 (m, 9 H; sharp s at 7.23)]. Catalytic hydrogenation of the ketimine gave again exclusively the cis isomer **30**.

Anal. Calcd for $C_{19}H_{23}N \cdot HCl$: C, 75.61; H, 8.01; N, 4.64. Found (**29**): C, 75.39; H, 7.96; N, 4.53. Found (**30**): C, 75.43; H, 7.97; N, 4.64.

***N*-Cyclopropyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (31 and 32).** When 6.66 g of **17** was converted to the ketimine with 10.05 g of cyclopropylamine, followed by reduction with $NaBH_4$ and multiple fractional crystallizations of the hydrochloride salts, there was ultimately obtained 1.15 g (13%) of the trans isomer **31** as the hydrochloride, mp 218–220°, and 0.4 g (4%) of the cis isomer **32** as the hydrochloride, mp 223–224°, NMR of **32** ($CDCl_3$ + NaOH) δ 0.3–0.6 (m, 4 H), 1.8–2.5 (m, 5 H), 3.8–4.2 (m, 2 H), 6.7–7.4 (m, 9 H).

Catalytic hydrogenation of the ketimine gave again predominantly the cis isomer **32**.

Anal. Calcd for $C_{19}H_{21}N \cdot HCl$: C, 76.10; H, 7.39; N, 4.67. Found (**31**): C, 75.84; H, 7.31; N, 4.67. Found (**32**): C, 75.85; H, 7.36; N, 4.68.

***N*-(4-Phenyl-1,2,3,4-tetrahydro-1-naphthyl)pyrrolidine (33 and 34).** A mixture of 380 mg (1.7 mmol) of **25** as the free base, 360 mg (1.7 mmol) of 1,4-dibromobutane, 25 ml of xylene, and 286 mg

of $NaHCO_3$ was refluxed for 62 hr. After the usual work-up there was obtained 190 mg (36%) of the trans isomer **33** as the hydrochloride, mp 258–259°. Similarly, **26** was converted to **34**, mp of the hydrochloride 256–257°.

Anal. Calcd for $C_{20}H_{23}N \cdot HCl$: C, 76.53; H, 7.70; N, 4.46. Found (**33**): C, 76.44; H, 7.70; N, 4.30. Found (**34**): C, 76.11; H, 7.89; N, 4.32.

1-(4-Phenyl-1,2,3,4-tetrahydro-1-naphthyl)-4-methylpiperazine (35 and 36). A solution of 2.2 g (0.01 mol) of **17** in 50 ml of benzene was treated with 6 g of 1-methylpiperazine and 0.55 ml of $TiCl_4$ as described above, but the mixture was kept at room temperature for 20 hr. After filtration and evaporation, the resulting enamine was dissolved in 75 ml of tetrahydrofuran and treated with 2 g of $LiBH_4$ and then dropwise with 5 ml of 98% formic acid. The mixture was refluxed for 15 min and then worked up in the usual manner to give after multiple fractional crystallizations of the hydrochlorides from MeOH–Et_2O 300 mg (9%) of **35** as the hygroscopic hydrochloride, mp 254–255°, and 560 mg (16%) of **36** as the hydrochloride, mp 249–250°. The stereochemical assignments are based on the result of a catalytic hydrogenation of a sample of the enamine which gave exclusively **36**.

Anal. Calcd for $C_{21}H_{26}N_2 \cdot HCl$: C, 73.56; H, 7.93; N, 8.17. Calcd for $C_{21}H_{26}N_2 \cdot HCl \cdot \frac{1}{4}H_2O$: C, 72.60; H, 7.94; N, 8.07. Found (**35**): C, 72.87; H, 8.07; N, 8.25. Found (**36**): C, 73.45; H, 7.92; N, 8.23.

2,8-Dichloro-5-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (38). A solution of 21 g (0.1 mol) of 8-chloro-5-methoxy-3,4-dihydro-1(2*H*)-naphthalenone[1,14] (**37**) in 500 ml of glacial acetic acid was cooled to 5° and 7.1 g of chlorine gas was introduced. After stirring for 2 hr at room temperature, the mixture was evaporated and the residue was suspended in 250 ml of 1 *N* HCl. Extraction with chloroform, evaporation of the organic solvents, and two recrystallizations of the residue from $CHCl_3$–hexane yielded 17.3 g (71%) of **38**: mp 112–113°; NMR ($CDCl_3$) δ 2.25–2.65 (m, 2 H), 2.85–3.2 (m, 2 H), 3.83 (s, 3 H), 4.55 (d of d, 1 H, J = 4.5, 6.5 Hz), 6.9 (d, 1 H, J = 9 Hz), 7.3 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{11}H_{10}Cl_2O_2$: C, 53.91; H, 4.11. Found: C, 53.72; H, 4.41.

8-Chloro-5-methoxy-2-phenyl-3,4-dihydro-1(2*H*)-naphthalenone (39). To a solution of 17 g (0.0695 mol) of **38** in 150 ml of benzene was added to a solution of phenylmagnesium bromide (obtained from 11 g of bromobenzene and 1.7 g of magnesium shavings in Et_2O) over a period of 15 min, causing a temperature rise. The mixture was kept for 2 days at room temperature and then refluxed for 1 hr. After addition of 200 ml of H_2O and 200 ml of 1 *N* HCl, the organic layer was separated and evaporated, and the residue (20 g) was crystallized from EtOAc–hexane to give 4.77 g (24%) of **39**: mp 126–128°; NMR ($CDCl_3$) δ 2.25–2.7 (m, 2 H), 2.8–4.2 (m, 3 H), 3.83 (s, 3 H), 6.85 (d, 1 H, J = 9 Hz), 7.0–7.8 (m, 6 H).

Anal. Calcd for $C_{17}H_{15}ClO_2$: C, 71.21; H, 5.27. Found: C, 71.50; H, 5.36.

***cis*-8-Chloro-5-methoxy-*N*-methyl-2-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (40).** A solution of 4.3 g (0.015 mol) of **39** in benzene was converted to the ketimine with methylamine and $TiCl_4$ as described above, refluxing the reaction mixture for 19 hr. After reduction with $NaBH_4$ and the usual work-up there was obtained 0.99 g (20%) of **40** as the hydrochloride, mp 238–239° (from $CHCl_3$–Et_2O), which was indistinguishable from a sample obtained by catalytic hydrogenation of the ketimine.

Anal. Calcd for $C_{18}H_{20}ClNO \cdot HCl$: C, 63.91; H, 6.26; N, 4.14. Found: C, 64.19; H, 6.40; N, 4.19.

4-(2-Methoxy-5-chlorophenyl)-3-phenylbutyric Acid (43, R = H). A solution of 20.4 g (1 mol) of the *sec*-butyl ester of cinnamic acid[17] in 300 ml of Et_2O was added dropwise at 0° to a solution of 5-chloro-2-methoxybenzylmagnesium chloride [prepared from 47.8 g (0.25 mol) of 5-chloro-2-methoxybenzyl chloride[28] and 36 g of magnesium shavings] and 150 mg of cuprous chloride in 300 ml of Et_2O. After standing at room temperature overnight, the mixture was poured onto ice and 100 ml of concentrated HCl. The organic layer was collected, dried, and evaporated. The residue (51 g) was distilled and the fraction (21 g, 58%) boiling at 180–182° (0.15 mm) was collected. A 15-g (0.0415 mol) portion of this fraction was saponified with 37.5 g of 87% KOH, 150 ml of EtOH, and 37.5 ml of H_2O at reflux temperature for 3 hr to give, after a crystallization of the acidic product from hexane, 8.6 g (68%) of **43** (R = H): mp 99–100°; NMR ($CDCl_3$) δ 2.5–3.0 (m, 4 H), 3.1–3.7 (m, 1 H), 3.7 (s, 3 H), 6.67 (d, 1 H, J = 9 Hz), 6.95 (d of d, J = 3, 9 Hz), 7.2 (br s, 6 H), 11.5 (br s, 1 H).

Anal. Calcd for $C_{17}H_{17}ClO_3$: C, 67.01; H, 5.62. Found: C, 67.18; H, 5.87.

3-(5-Chloro-2-methoxybenzyl)-1-indanone (41). A mixture of 7.6 g (0.025 mol) of **43** and 200 g of polyphosphoric acid was heated to 110° for 45 min and then poured onto ice. After extraction with EtOAc and washing with 10% aqueous Na_2CO_3, the organic layer was dried and evaporated and the residue was crystallized from ETOH–hexane to give 3.19 g (44%) of **41**: mp 73–74°; NMR ($CDCl_3$) δ 2.15–3.8 (m, 5 H), 3.8 (s, 3 H), 6.78 (d, 1 H, J = 9 Hz), 7.0–7.85 (m, 6 H).

Anal. Calcd for $C_{17}H_{15}ClO_2$: C, 71.21; H, 5.27. Found: C, 71.13; H, 5.57.

4-(2-Methoxyphenyl)-3-phenylbutyric Acid (46). A solution of 10.8 g (0.035 mol) of **43** in 400 ml of MeOH and 14.2 ml of NEt_3 was hydrogenated in the presence of 2 g of 10% Pd/C at 50 psi and ambient temperature for 40 min. After the usual work-up the acidic product was crystallized from EtOAc–hexane (1:10) to give 8.55 g (89%) of **46**: mp 98–99°; NMR ($CDCl_3$) δ 2.6 (d, 2 H, J = 7.5 Hz), 2.85 (d, 2 H, J = 7.5 Hz), 3.5 (m, 1 H), 3.7 (s, 3 H), 6.6–7.1 (m, 4 H), 7.2 (s, 5 H), 10.9 (s, 1 H).

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.45; H, 6.65.

5-Methoxy-3-phenyl-3,4-dihydro-1(2*H*)-naphthalenone (47). This compound was obtained from **46** according to the method of Johnson and Glenn[7] in 24% yield after chromatography over a SiO_2 column with benzene. After crystallization from EtOAc–hexane (1:5), **47** had mp 158–160°; NMR ($CDCl_3$) δ 2.6–3.7 (m, 5 H), 3.85 (s, 3 H), 7.05 (d of d, 1 H, J = 9 Hz), 7.2–7.45 (m, 1 H), 7.3 (s, 5 H), 7.7 (d of d, 1 H, J = 7.5, 2 Hz).

Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.92; H, 6.57.

***cis*-5-Methoxy-*N*-methyl-3-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (48).** A solution of 1 g (3.95 mmol) of **47** in 50 ml of benzene was converted with 1.0 g of methylamine and 0.25 ml $TiCl_4$ at room temperature to the ketimine. Hydrogenation of the ketimine in EtOH in the presence of 500 mg of 10% Pd/C at 50 psi gave, after conversion to the hydrochloride and recrystallization from MeOH–Et_2O (1:1), 850 mg (70%) of **48**: mp 270–271°; NMR (free base in $CDCl_3$) δ 2.5–4.1 (m, 7 H), 2.45 (s, 3 H), 3.75 (s, 3 H), 6.4–7.4 (m, 3 H), 7.3 (s, 5 H).

Anal. Calcd for $C_{18}H_{21}NO \cdot HCl$: C, 71.15; H, 7.30; N, 4.61. Found: C, 70.89; H, 7.37; N, 4.58.

***cis*-8-Chloro-5-methoxy-*N*-methyl-3-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (45).** A solution of 304 mg (1 mmol) of **48** hydrochloride in 10 ml of AcOH was treated at room temperature with a solution of 71 mg of Cl_2 in 2 ml of AcOH[1] for 30 min to give, after evaporation and two recrystallizations of the residue from MeOH–Et_2O (1:10), 190 mg (56%) of **45** hydrochloride: mp 246–247° dec; NMR (CD_3OD) δ 2.0–3.3 (m, 5 H), 2.75 (s, 3 H), 3.85 (s, 3 H), 4.85 (s, DOH), 5.05 (t, 1 H, J = 9 Hz), 7.05 (d, 1 H, J = 9 Hz), 7.1–7.5 (m, 6 H).

Anal. Calcd for $C_{18}H_{20}ClNO \cdot HCl$: C, 63.91; H, 6.26; N, 4.14. Found: C, 63.88; H, 6.23; N, 4.02.

4,4-Di(5-chloro-2-methoxyphenyl)-3-ethoxycarbonyl-3-butenoic Acid (50). 5,5′-Dichloro-2,2′-dimethoxybenzophenone[18] was converted to the title compound in 35% yield using the conditions of Johnson et al.[19] The product melted at 98–100° after recrystallization from EtOAc–hexane: NMR ($CDCl_3$) δ 0.9 (t, 3 H, J = 7 Hz), 3.3 (br s, 2 H), 3.7 (s, 3 H), 3.73 (s, 3 H), 4.0 (q, 2 H, J = 7 Hz), 6.77 (d, 1 H, J = 9 Hz), 6.82 (d, 1 H, J = 9 Hz), 7.0–7.4 (m, 4 H), 10.3 (br s, 1 H).

Anal. Calcd for $C_{21}H_{20}Cl_2O_6$: C, 57.42; H, 4.56. Found: C, 58.01; H, 5.00.

4,4-Di(5-chloro-2-methoxyphenyl)-3-carboxy-3-butenoic Acid (51). This compound was prepared in 72% yield by treating a solution of 4 g of **50** in 30 ml of EtOH with 60 ml of 4 *N* NaOH at room temperature overnight. After a crystallization from EtOH–hexane, **51** melted at 238–239°. This compound was also obtained as a by-product in various attempts to hydrolyze and decarboxylate **50** under acidic conditions.

Anal. Calcd for $C_{19}H_{16}Cl_2O_6$: C, 55.49; H, 3.89. Found: C, 55.45; H, 4.19.

3-Carboxymethyl-6-chloro-4-(5-chloro-2-methoxyphenyl)-coumarin (53). This compound was isolated in up to 24% yield during attempts to hydrolyze and decarboxylate **50**.[19] **53** melted at 228–229° after recrystallization from EtOAc: NMR (DMSO-d_6) δ 3.2 (br s, 2 H), 3.73 (s, 3 H), 6.8–7.8 (m, 6 H).

Anal. Calcd for $C_{18}H_{12}Cl_2O_5$: C, 57.00; H, 3.17; Cl, 18.71. Found: C, 57.21; H, 3.16; Cl, 18.64.

2-(3-Methoxyphenyl)-1,3-dithiane (55). A mixture of 80.5 g (0.592 mol) of *m*-anisaldehyde and 60 ml (0.592 mol) of 1,3-propanedithiol in 450 ml of $CHCl_3$ was saturated with HCl gas,[29]

keeping the temperature at 30–40° with external cooling. The solution was stirred at room temperature for 30 min, washed with H_2O (2 × 200 ml), 1 *N* KOH (3 × 250 ml), and H_2O, dried, and evaporated. The residue was crystallized from 200 ml of MeOH to give 123 g (92%) of **55**: mp 62–63°; NMR ($CDCl_3$) δ 1.7–2.2 (m, 2 H), 2.8–3.2 (m, 4 H), 3.77 (s, 3 H), 5.13 (s, 1 H), 6.7–7.4 (m, 4 H).

Anal. Calcd for $C_{11}H_{14}OS_2$: C, 58.40; H, 6.24. Found: C, 58.60; H, 6.31.

2-Cinnamyl-2-(3-methoxyphenyl)-1,3-dithiane (56). A solution of 6.8 g (0.03 mol) of **55** in 50 ml of tetrahydrofuran was cooled to −40°, and 20 ml of a 1.6 *M* solution of butyllithium (0.032 mol) was added dropwise with stirring, keeping the temperature below −30° during the addition. The mixture was then allowed to stand at room temperature for 1 hr (at that time NMR analysis of an aliquot quenched with D_2O indicated complete conversion to the lithio derivative) and cooled again to −40° while 5.8 g (0.03 mol) of cinnamyl bromide in 10 ml of tetrahydrofuran was added dropwise. After standing at room temperature overnight, the mixture was diluted with 50 ml of H_2O, concentrated in vacuo, and extracted with three 50-ml portions of $CHCl_3$. The organic layers were combined, dried, and evaporated. The residue afforded, after crystallization from MeOH, 9.5 g (93%) of **56**: mp 84–85°; NMR ($CDCl_3$) δ 1.7–2.2 (m, 2 H), 2.45–2.9 (m, 6 H), 3.8 (s, 3 H), 5.9 (d of d, 1 H, *J* = 6.5, 16 Hz), 6.35 (d, 1 H, *J* = 16 Hz), 6.6–7.7 (m, 9 H).

Anal. Calcd for $C_{20}H_{22}OS_2$: C, 70.16; H, 6.48. Found: C, 70.47; H, 6.63.

Spiro[1,3-dithiane-2,1′-(7′-methoxy-4′-phenyl-1′,2′,3′,4′-tetrahydronaphthalene)] (57). Boron trifluoride gas was introduced for 3.5 min into a solution of 680 mg (0.002 mol) of **56** in 50 ml of CH_2Cl_2. The orange mixture was kept at room temperature overnight, diluted with H_2O, and extracted twice with 50 ml of CH_2Cl_2. The organic layers afforded, after evaporation and crystallization of the residue from CH_2Cl_2–Et_2O, 310 mg (36%) of **57** as the HBF_4 adduct: mp 163–164°; NMR (DMSO-d_6) δ 1.8–4.5 (m, 10+ H), 3.83 (s, 3 H), 6.7–6.9 (m, 2 H), 7.0–7.5 (m, 7 H).

Anal. Calcd for $C_{20}H_{22}OS_2 \cdot HBF_4$: C, 55.82; H, 5.39. Found: C, 55.82; H, 5.47.

2-(2-Chloro-5-methoxyphenyl)-1,3-dithiane (59). This compound was prepared in 67% yield from 22.5 g of 2-chloro-5-methoxybenzaldehyde[23] as described above for **55**. After crystallization from MeOH, **59** melted at 66–68°; NMR ($CDCl_3$) δ 1.8–2.2 (m, 2 H), 2.8–3.2 (m, 4 H), 3.77 (s, 3 H), 5.57 (s, 1 H), 6.75 (d of d, 1 H, *J* = 3, 9 Hz), 7.20 (d, 1 H, *J* = 3 Hz), 7.23 (d, 1 H, *J* = 9 Hz).

Anal. Calcd for $C_{11}H_{13}ClOS_2$: C, 50.66; H, 5.02. Found: C, 50.70; H, 5.08.

2-(2-Chloro-5-methoxyphenyl)-2-cinnamyl-1,3-dithiane (60). A solution of 1.8 g (0.0069 mol) of **59** in 12 ml of tetrahydrofuran was cooled to 0° and treated dropwise with 3.4 ml of a 2.1 *M* solution of MeLi in Et_2O. After stirring at 0° for 1 hr, NMR analysis of an aliquot quenched with D_2O indicated only a 50% conversion. Therefore, another 3.5 ml of the MeLi solution was added and the mixture was kept for another hour at 0°. At that time, NMR analysis indicated complete conversion to the lithio derivative, and 1.3 g (0.0069 mol) of cinnamyl bromide was added and the mixture was kept at room temperature overnight. The work-up procedure was identical with that described above for **56**, and afforded 0.7 g (27%) of **60**: mp 106–108° after two crystallizations from isopropyl alcohol; NMR ($CDCl_3$) δ 1.8–2.2 (m, 2 H), 2.6–2.9 (m, 4 H), 3.38 (d, 2 H, *J* = 7 Hz), 3.86 (s, 3 H), 5.85 (d of d, 1 H, *J* = 7, 16 Hz), 6.43 (d, 2 H, *J* = 16 Hz), 6.73 (d of d, 1 H, *J* = 3, 9 Hz), 7.19 (s, 5 H), 7.32 (d, 1 H, *J* = 9 Hz), 7.73 (d, 1 H, *J* = 3 Hz).

Anal. Calcd for $C_{20}H_{21}ClOS_2$: C, 63.73; H, 5.61. Found: C, 63.57; H, 5.70.

5-Chloro-8-methoxy-1-phenyl-1,2,3,4-tetrahydro-1-naphthol (63). A solution of 2.1 g (0.01 mol) of 5-chloro-8-methoxy-3,4-dihydro-1(2*H*)naphthalenone[24] (**62**) in 20 ml of Et_2O was added dropwise to a boiling solution of phenylmagnesium bromide, prepared from 0.486 g of magnesium shavings and 3.14 g of bromobenzene in 40 ml of Et_2O. After refluxing for 2 hr, the mixture was treated with 10 ml of H_2O and washed with 100 ml of 10% aqueous NH_4Cl and 200 ml of H_2O. The organic layer afforded ultimately, after crystallization from hexane, 2.2 g (76%) of **63**, mp 91–92°.

Anal. Calcd for $C_{17}H_{17}ClO_2$: C, 70.70; H, 5.93. Found: C, 70.66; H, 6.09.

5-Chloro-8-methoxy-1-phenyl-3,4-dihydronaphthalene (64). A solution of 2.2 g of **63** in 60 ml of benzene was heated to reflux in the presence of 10 mg of *p*-toluenesulfonic acid in a Dean-Stark apparatus for 1.5 hr. After evaporation and crystallization from hexane and from EtOH, 2.02 g (98%) of **64**, mp 106–107°, was obtained.

Anal. Calcd for $C_{17}H_{15}ClO$: C, 75.43; H, 5.58. Found: C, 75.62; H, 5.28.

5-Chloro-8-methoxy-1-phenyl-1,2,3,4-tetrahydronaphthalene (65). This compound was prepared in 84% yield by hydrogenation of 1.8 g of **64** at atmospheric pressure in 55 ml of EtOH containing a few drops of concentrated HCl in the presence of 500 mg of 10% Pd/C until the theoretical amount of hydrogen had been taken up (2 hr). After crystallization from MeOH, **65** melted at 91–92°.

Anal. Calcd for $C_{17}H_{17}ClO$: C, 74.85; H, 6.28. Found: C, 74.66; H, 6.48.

8-Chloro-5-methoxy-4-phenyl-3,4-dihydro-1(2*H*)-naphthalenone (66). A solution of 1 g of $KMnO_4$ in 50 ml of H_2O was added to a solution of 820 mg (3 mmol) of **65** in 120 ml of acetone. After stirring at room temperature for 2 days, an analysis of an aliquot of the purple mixture indicated only partial conversion to the ketone. The reaction mixture was then heated to reflux while 3 g of $KMnO_4$ in 50 ml of H_2O was added at such a rate that the color of the mixture remained purple (45 min). After filtration, the filtrate was concentrated to 50 ml in vacuo and the mixture was extracted twice with Et_2O; the combined organic layers were washed, dried, and evaporated to an oil (756 mg) which was separated by column chromatography (25 g of silica gel, 70–325 mesh, 1.5 × 50 cm column), using benzene as the solvent. From the early fractions was recovered, after a crystallization from MeOH, 447 mg (54%) of starting material, and from the later fractions, after crystallizations from MeOH, 250 mg (29%) of **66**: mp 123–124°; NMR ($CDCl_3$) δ 2.1–2.6 (m, 4 H), 3.65 (s, 3 H), 4.7 (br s, 1 H), 6.9 (d, 1 H, *J* = 9 Hz), 6.9–7.3 (m, 5 H), 7.38 (d, 1 H, *J* = 9 Hz); mass spectrum *m/e* 286 (M^+, base peak), 271, 258, 251, 243, 199.

8-Methoxy-1-phenyl-1,2,3,4-tetrahydronaphthalene (69). This compound was obtained in 79% yield by hydrogenation of 2.06 g of **65** over 1 g of 10% Pd/C in 50 ml of EtOH, containing 2 ml of triethylamine, at atmospheric pressure (2 hr). **69** had mp 101–103° after recrystallization from EtOH.

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.39; H, 7.76.

5-Methoxy-4-phenyl-3,4-dihydro-1(2*H*)-naphthalenone (70). A solution of 1.02 g of **60** in 100 ml of acetone was treated with 10 ml of H_2O and 10 g of $KMnO_4$. The mixture was heated on the steam bath until the purple color had disappeared (4 hr). Another 10 g of $KMnO_4$ was added and the mixture was refluxed for 3 hr. The mixture was then filtered, and the filtrate was treated with 100 ml of acetone, 10 ml of H_2O, and 10 g of $KMnO_4$ and refluxed for another 3 hr. Upon work-up (concentration in vacuo, extraction with $CHCl_3$, drying, and evaporation) there was obtained, after crystallization on $CHCl_3$–hexane, 655 mg (61%) of **70**: mp 117–118°; NMR ($CDCl_3$) δ 2.1–2.7 (m, 4 H), 3.68 (s, 3 H), 4.65 (m, 1 H), 6.9–7.85 (m, 8 H).

Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.90; H, 6.64.

***cis*-5-Methoxy-*N*-methyl-4-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (71) and Its Trans Isomer 72.** Reduction of the methylimine, obtained from **70** and methylamine in the usual manner, with $NaBH_4$ gave **71** in 72% yield as the hydrochloride, mp 285–286°.

Anal. Calcd for $C_{18}H_{21}NO \cdot HCl \cdot \frac{1}{4}H_2O$: C, 70.11; H, 7.35; N, 4.54. Found: C, 70.55; H, 7.26; N, 4.37.

On the other hand, reduction of the methylimine derivative with zinc–acetic acid (see above for the preparation of **20**) gave a 42% yield of the trans isomer **72**; mp of the hydrochloride 240–242°.

Anal. Calcd for $C_{18}H_{21}NO \cdot HCl \cdot \frac{1}{4}H_2O$: C, 70.11; H, 7.35; N, 4.54. Found: C, 69.88; H, 7.10; N, 4.15.

***cis*-8-Chloro-*N*-methyl-5-methoxy-4-phenyl-1,2,3,4-tetrahydro-1-naphthylamine (67) and Its Trans Isomer (68).** Conversion of **66** to the methylimine in the usual manner, followed by reduction with $NaBH_4$ in MeOH, gave the cis isomer **67** in 85% yield. Only traces of the trans isomer **68** were detected by TLC analysis. This isomer was identical with the one obtained by catalytic hydrogenation of the ketimine or by chlorination of **71** in acetic acid.[1] The melting point of **67** as the hydrochloride was 255–257° (from $CHCl_3$–Et_2O); NMR (CD_3OD) δ 2.0–2.25 (m, 4 H), 2.86 (s, 3 H), 3.47 (s, 3 H), 4.3 (m, 1 H), 4.8 (m, 1 H), 4.85 (CD_3OH), 6.9–7.3 (m, 6 H), 7.5 (d, 1 H, *J* = 9 Hz).

Anal. Calcd for $C_{18}H_{20}ClNO \cdot HCl \cdot \frac{1}{2}H_2O$: C, 62.25; H, 6.39; N, 4.03. Found: C, 62.26; H, 6.17; N, 3.87.

The trans isomer **68** was obtained in 40% yield by chlorination of **72** in acetic acid;[1] the melting point of **68** as the hydrochloride was 250–252°; mass spectrum *m/e* 301 (M^+), 286, 270 (base peak), 266, 235, 193, 179.

Acknowledgments. The skillful assistance of Messrs. Edmund G. Andrews, Werner H. Kappeler, and Frank W. Rusek is greatly appreciated.

Registry No.—**6,** 7469-40-1; **8** HCl, 54308-10-0; **10,** 54308-11-1; **11,** 7498-87-5; **13** HCl, 54308-12-2; **14,** 14944-26-4; **16** HCl, 54308-13-3; **17,** 14578-68-8; **17** oxime, 50845-35-7; **17** phenylhydrazone, 54308-14-4; **18,** 52789-19-2; **19,** 54308-15-5; **19** HCl, 52371-38-7; **20,** 54308-16-6; **20** HCl, 52371-37-6; (1*S*,4*R*)-**20** *N*-acetyl-L-tyrosine salt, 52795-05-8; (1*S*,4*R*)-**20** HCl, 52760-48-2; (1*R*,4*S*)-**20** D-(−)-mandelate, 52795-03-6; (1*R*,4*S*)-**20** HCl, 52760-47-1; **21,** 54308-17-7; **23** HCl, 52371-39-8; **24,** 52371-40-1; **24** HCl, 54308-18-8; **25** HCl, 52371-31-0; **26** HCl, 52371-32-1; **27** HCl, 54308-19-9; **28** HCl, 54308-20-2; **29** HCl, 54308-21-3; **30** HCl, 54308-22-4; **31** HCl, 54308-23-5; **32** HCl, 54308-24-6; **33** HCl, 54308-25-7; **34** HCl, 54308-26-8; **35** HCl, 54308-27-9; **36** HCl, 54308-28-0; **37,** 34910-81-1; **38,** 54308-29-1; **39,** 54308-30-4; **40** HCl, 54308-31-5; **41,** 54308-32-6; **43** (R = H), 54308-33-7; **45** HCl, 54308-34-8; **46,** 54308-35-9; **47,** 54308-37-1; **48,** 54308-36-0; **48** HCl, 54308-38-2; **49,** 54308-39-3; **50,** 54308-40-6; **51,** 54308-41-7; **53,** 54308-42-8; **54,** 591-31-1; **55,** 54308-43-9; **56,** 54308-44-0; **57** HBF_4 adduct, 54308-46-2; **58,** 13719-61-4; **59,** 54308-47-3; **60,** 54308-48-4; **62,** 54308-49-5; **63,** 54308-50-8; **64,** 54308-51-9; **65,** 54308-52-0; **66,** 54308-53-1; **67** HCl, 54308-54-2; **68** HCl, 54308-55-3; **69,** 54308-56-4; **70,** 54308-57-5; **71** HCl, 54308-58-6; **72** HCl, 54308-59-7; mercuric nitrate, 10045-94-0; methyl iodide, 74-88-4; hydroxylamine hydrochloride, 5470-11-1; phenylhydrazine, 100-63-0; isopropylamine, 75-31-0; 4-phenyl-3,4-dihydro-1(2*H*)-naphthalenone isopropyl ketimine, 54308-60-0; 1-methylpiperazine, 109-01-3; *sec*-butyl cinnamate, 7726-62-7; 5-chloro-2-methoxybenzyl chloride, 7035-11-2; 1,3-propanedithiol, 109-80-8; boron trifluoride, 7637-07-2; *N*-acetyl-L-tyrosine, 537-55-3; ethylamine, 75-04-7; cyclopropylamine, 765-30-0; 1,4-dibromobutane, 110-52-1; bromobenzene, 108-86-1; D-(−)-mandelic acid, 611-71-2.

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Novel Synthesis of Aminoethanethiols[1]

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Received December 11, 1974

The reaction of α,α'-dithiodiisobutyraldehyde (**1**) with primary aromatic or aliphatic amines afforded novel Schiff bases (**2–8**). The reduction of these Schiff bases with sodium borohydride furnished a novel synthesis of 1,1-dimethyl 2-substituted aminoethanethiols (**9–15**). Two of the aminoethanethiols (**13** and **14**) were further characterized by the reaction with carbon disulfide to give the corresponding 3-substituted 5,5-dimethyl-2-thiazolidinethione (**16** and **17**).

Aminoethanethiols are among the most effective radiation-protective compounds known.[2,3] 2-Aminoethanethiols have been synthesized by the addition of aromatic or aliphatic amines to episulfides or episulfide precursors.[4] However, this method requires high temperatures in sealed tubes and gives low yields because of further mercaptoethylation on sulfur or nitrogen to give bis products or polymers. The addition of excess amine has been successfully used to repress these side reactions[4,5a] but also requires separation of the excess amine from the product. Recently, Luhowy and Meneghini[6] reported that the mercaptoethylation of primary aliphatic amines can be carried out at room temperature with equimolar amounts of episulfide and amine in aqueous media containing amine–silver ion complex.

We wish to report a novel synthesis for 1,1-dimethyl 2-substituted aminoethanethiols. The key intermediate, α,α-dithiodiisobutyraldehyde[7] (**1**), was prepared by the reaction of isobutyraldehyde with sulfur monochloride. The reaction of **1** with primary aromatic or aliphatic amines in refluxing heptane containing a catalytic amount of *p*-toluenesulfonic acid or in methyl alcohol at 25–30° gave the Schiff bases **2–8** in yields of 82–99%. Reduction of these products with sodium borohydride in refluxing ethanol furnished the aminoethanethiols (**9–15**) in good yields. The structures of the Schiff bases and aminoethanethiols were