tars and were combined. The hexane solution was added to the second fraction and evaporated to dryness to give 38 g (84.0%) of the base of **11** as an oil.

A solution of 200 mg of the base in anhydrous Et_2O was treated with an excess of HCl gas. The ether solution was then evaporated to dryness and the residual oil was crystallized from Me_2CO–Et_2O to give pure **11**·HCl, white prisms, mp 214–218°. *Anal.* ($C_{23}H_{25}ClFN_3O_3$·HCl) C, H.

7-Chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one (12).—A solution of 12.0 g (0.0248 mole) of **11** in 230 ml of EtOH was treated with 28.0 ml (0.028 mole) of 1 *N* NaOH. The reaction mixture was allowed to stand for 16 hr at room temperature and was then evaporated to dryness. The residual oil was partitioned between 200 ml of H_2O and 200 ml of CH_2Cl_2. A 50% K_2CO_3 solution was added until the pH of the aqueous layer was approximately 11. The layers were separated and the CH_2Cl_2 extract was washed (H_2O, four 200-ml portions, and saturated brine solution), dried (Na_2SO_4), and evaporated to dryness. The residual oil was dissolved in Et_2O and cooled in an ice bath, and gaseous HCl was bubbled into the solution. The ether solution of the salt was evaporated to dryness and the residual oil was crystallized from Me_2CO–Et_2O to give 8.0 g (73.0%) of the pure salt of **12** as white prisms, mp 196–203° dec. *Anal.* ($C_{21}H_{23}ClFN_3O_2$·HCl) C, H.

A solution of 1.5 g of the salt was dissolved in 30 ml of H_2O and 50% K_2CO_3 was added to pH 11. The mixture was extracted with 30 ml of CH_2Cl_2, the layers were separated, and the organic layers were washed (H_2O, three 50-ml portions, and saturated brine solution), dried (Na_2SO_4), and evaporated to dryness. The residual oil was crystallized from a mixture of ether and petroleum ether (30–60°) to give the pure base as white prisms, mp 118–121°. *Anal.* ($C_{21}H_{23}ClFN_3O_2$) C, H.

7-Chloro-1-(2-diethylaminoethyl)-4,5-dihydro-5-(2-fluorophenyl)-1H-1,4-benzodiazepine-2,3-dione (13).—A solution of 2.0 g (0.0045 mole) of the hydrochloride of **11** in 25 ml of EtOH was treated with 9 ml (0.009 mole) of 1 *N* NaOH. The reaction mixture was allowed to stand at room temperature for 16 hr and was then treated with 1 *N* HCl to pH 6. The solution was made basic again with 50% K_2CO_3 and the resulting mixture was evaporated to dryness. The residual oil was dissolved in 150 ml of CH_2Cl_2 which was washed (H_2O, three 150-ml portions, and saturated brine solution), dried (Na_2SO_4), and evaporated to dryness. The residual yellow oil (1.8 g) was crystallized from Me_2CO–petroleum ether (30–60°) to give 1.2 g (65.5%) of the pure product as white prisms, mp 169–171°. *Anal.* ($C_{21}H_{23}ClFN_3O_2$) C, H.

3-Acetoxy-7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (14).—A solution of 10 g (0.0328 mole) of **9** in 150 ml of Ac_2O was heated with stirring on a steam bath for 3.5 hr. Ac_2O was removed under reduced pressure and the residue was dissolved in 100 ml of CH_2Cl_2. The organic solution was washed with 75 ml of dilute NH_4OH, two 75-ml portions of H_2O, and 75 ml of saturated brine, dried (Na_2SO_4), and evaporated to dryness. The product was recrystallized from MeOH to give 8.6 g (76%) of **14** as white prisms, mp 239–247° (sealed tube). *Anal.* ($C_{17}H_{12}ClFN_2O_3$) C, H.

7-Chloro-5-(2-fluorophenyl)-3-hydroxy-1,3-dihydro-2H-1 4-benzodiazepin-2-one (15).—A solution of 5 g (0.0145 mole) of **14** in 200 ml of EtOH was treated with 36.3 ml (0.036 mole) of 1 *N* NaOH. After 5 min a white precipitate separated which was redissolved after an additional 10 min by the addition of 200 ml of H_2O. The solution was then acidified with AcOH and EtOH was removed under reduced pressure. The product separated as a white precipitate and was recrystallized from a mixture of THF and hexane to give 4.2 g (96%) of **15** as white rods, mp 197–200°.

Acknowledgment.—We are indebted to Dr. F. Vane and Dr. T. Williams for the nmr spectra, to Mr. S. Traiman for the infrared spectra, and to Dr. A. Steyermark and Dr. F. Scheidl for the microanalyses.

Tetrahydroisoquino[2,1-*d*][1,4]benzodiazepines. Synthesis and Neuropharmacological Activity

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The synthesis and neuropharmacological activities for a series of tetrahydroisoquinobenzodiazepines are described. These substances produce qualitatively similar pharmacological activities to the well-known benzodiazepines, although similar structure–activity relationships could not be developed. One significant difference between compounds of the present series and the standard benzodiazepines was obtained in the dihydroxyphenylalanine-potentiation test (indicating possible "antidepressant" activity residing in the isoquinobenzodiazepine molecule). The most active compound in the present series was the dextrorotatory isomer of 2-chloro-5-methyl-5,9,10,14b-tetrahydroisoquino[2,1-*d*][1,4]benzodiazepin-6(7H)-one. Only those substances possessing electronegative substituents at position 2 demonstrated significant CNS depressant effects.

The pharmacological and clinical spectra of 5-phenyl-1,4-benzodiazepines (**1**) have been well documented since the advent of chlordiazepoxide.[1–5] A review of reports in which attempts were made to modify the chemical structure of the parent molecule with no concomitant loss in biological activity has brought out the fact that the benzene ring in the 5 position is important for neuropharmacological activity.[6] One might assume that such a molecule combines with the enzyme at the receptor site in one specific rotational conformation. Based on this idea we became interested in the biological activities of 5-phenyl-1,4-benzodiazepines (**1**) in which the free rotation of the phenyl group is blocked by an ethylene bridge between position 2′ and 4. The resulting novel tetracyclic

(1) L. O. Randall, *Diseases Nervous System (Suppl. 3)*, **21**, 7 (1960).

(2) L. O. Randall, G. A. Heise, W. Schallek, R. E. Bagdon, R. Banziger, A. Boris, R. A. Moe, and W. B. Abrams, *Current Therap. Res.*, **3**, 405 (1961).

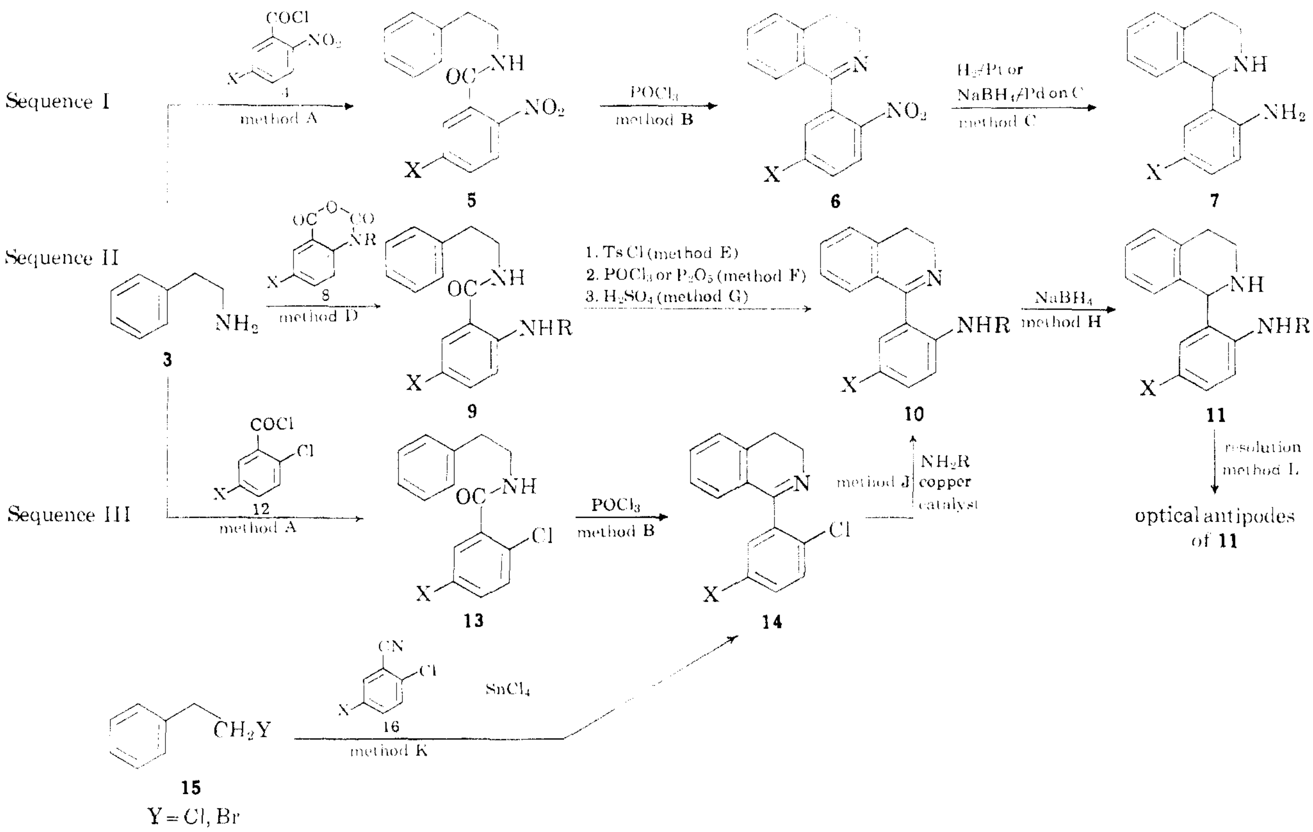
(3) L. O. Randall, W. Schallek, C. Scheckel, R. E. Bagdon, and J. Rieder, *Schweiz. Med. Wochschr.*, **95**, 334 (1965).

(4) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).

(5) E. Kingstone, A. Villeneuve, and I. Kossatz, *Current Therap. Res.*, **8**, 159 (1966).

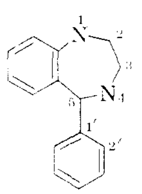
(6) S. C. Bell, C. Gochman, and S. J. Childress, *J. Med. Pharm. Chem.*, **5**, 63 (1962).

Chart I

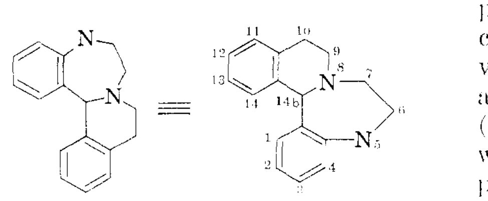


X = H, Cl, NO_2, CF_3, etc.
R = H or lower alkyl

ring system (2)[7] represents a combination of the isoquinoline system with the 1,4-benzodiazepine system. These compounds exhibit pharmacological features similar to those observed with chlordiazepoxide or diazepam and, in addition, provide certain indications of possible central nervous system stimulant activity.



1



2

The key intermediates for the synthesis of our hexahydroisoquino[2,1-*d*][1,4]benzodiazepines were 1-(*o*-aminophenyl)-1,2,3,4-tetrahydroisoquinolines bearing substituents in various positions. The general procedures which we used for the preparation of these intermediates are outlined in Chart I[8] and shall be briefly discussed. The choice of one or the other procedure depended on practical considerations (availability of starting materials, reactivity, or sensitivity of particular substituents, etc.) and on the experience obtained in the course of this work. To build up the isoquinoline ring system the classical Bischler–Napieralski reaction was applied except in two cases where a newer method proceeding through nitrilium salts[9] was used (method K).

Reaction Sequence I.—The cyclodehydration of N-phenethyl-2-nitrobenzamide (**5**, X = H) to the 3,4-dihydroisoquinoline (**6**, X = H) with phosphorus pentoxide in xylene has been described earlier.[10] We preferred to use $POCl_3$ in this and analogous cyclizations with equally good results and greater convenience. Simultaneous reduction of the nitro group and the carbon–nitrogen double bond of **6** to the 1-(*o*-aminophenyl)-1,2,3,4-tetrahydroisoquinolines (**7**) was achieved by catalytic hydrogenation with either platinum in acetic acid or with a combination of Pd–C and $NaBH_4$[11] in aqueous–alcoholic suspension. The latter procedure gave excellent and reproducible results in contrast to the catalytic hydrogenation.

Reaction Sequence II.—The first step (method D) consisted of the condensation of phenethylamine (**3**) with a substituted isatoic anhydride (**8**) by heating the reactants in an inert solvent and led to the benzamides (**9**) in high yields. Prior to the Bischler–Napieralski cyclization the anilino function in these benzamides (**9**) had to be protected and the tosyl group proved very satisfactory for this purpose. It should be mentioned that when in some preliminary experiments the anilino function was acetylated no conclusive results could be obtained in the attempted isoquinoline ring closure with $POCl_3$, P_2O_5, or polyphosphoric acid.

(7) (a) Sandoz Inc., South African Patent 65/4606 (1965); (b) M. Mueller and P. Zeller, *Helv. Chim. Acta*, **49**, 1222 (1966).

(8) For the sake of clarity the reactions represented in Chart I are exemplified with phenethylamine as a starting material, although variously substituted phenethylamines have been used. The types and positions of such substituents become apparent from Table VI.

(9) M. Lora-Tamayo, R. Madronero, and G. G. Munoz, *Ber.*, **93**, 289 (1959).

(10) V. M. Rodionov and E. V. Yavorskaya, *J. Gen. Chem. USSR*, **13**, 491 (1943); *Chem. Abstr.*, **38**, 3282 (1943).

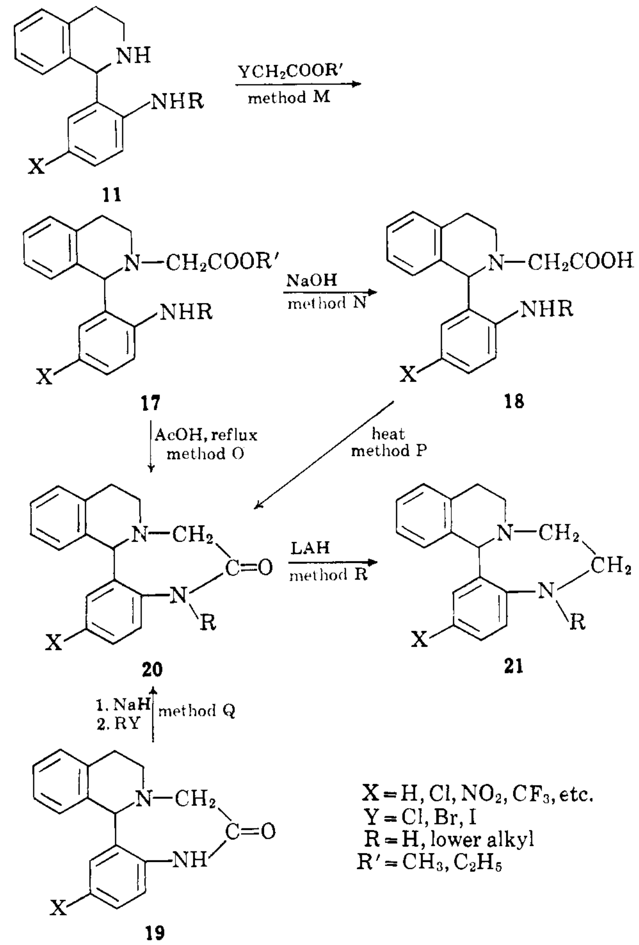
(11) T. Neilson, H. C. S. Wood, and A. G. Wylie, *J. Chem. Soc.*, 371 (1962).

Furthermore, only P_2O_5 and not $POCl_3$ resulted in satisfactory yields in the cyclodehydration of primary tosylates. The tosyl group was then easily and quantitatively removed on treatment with concentrated sulfuric acid at ambient temperature for several hours (method G) and the resulting 3,4-dihydroisoquinolines (**10**) were reduced with $NaBH_4$ to the key intermediates (**11**).

Reaction Sequence III.—It was conceivable that the chlorine in 1-(*o*-chlorophenyl)-3,4-dihydroisoquinolines (**14**) with X representing an electronegative substituent is reactive enough to undergo an Ullmann exchange reaction[12] with ammonia or primary amines. Displacement reactions of this type have recently been reported with *o*-halo-substituted benzophenones[13] and benzophenononimines.[14] Our required intermediates (**14**) were obtained either by cyclodehydration of the corresponding benzamides (**13**) or in a one-step procedure (method K) *via* a nitrilium salt[9] prepared from β-phenethyl chloride (**15**, Y = Cl) and a benzonitrile (**16**). The Ullmann reaction (method J) was indeed successfully carried out with the 3,4-dihydroisoquinolines (**14**, X = NO_2 or CF_3). In both cases the reactions with methylamine gave substantially higher yields than with ammonia.

Chart II outlines the final steps in our synthesis of tetrahydroisoquino[2,1-*d*][1,4]benzodiazepines. The key intermediates (**11**) reacted preferentially on the isoquinoline nitrogen when refluxed with ethyl chloro- or bromoacetate in the presence of triethylamine (method M). High yields of the amino esters (**17**, R′ = C_2H_5) were obtained particularly when X represented an electron-attracting substituent, *e.g.*, Cl, NO_2, or CF_3, which decreased the nucleophilicity of the aniline nitrogen. In a few instances where X was a hydrogen atom, however, the alkylation reaction was not entirely selective and we were able to isolate some N,N′-dialkylation products as well. Two methods for the formation of the diazepine ring of compounds (**20**) proved equally satisfactory. The first one consisted in heating the amino acids (**18**), obtained in quantitative yield by alkaline hydrolysis of the corresponding amino esters (**17**), to 150–160° for 1–2 hr (method P). The second and more direct method was to reflux the amino esters (**17**) in glacial acetic acid (method O). The use of acetic acid seems to be rather specific since refluxing of the amino ester (**17**) in other solvents like ethanol, pyridine, xylene, or toluene (in presence of catalytic amounts of *p*-toluenesulfonic acid) or simply heating them to 160° without a solvent[15] was unsuccessful. These facts clearly indicate that this lactam formation is catalyzed by weak acids. Tetrahydroisoquino[2,1-*d*][1,4]benzodiazepinones (**20**) with R representing a substituent other than lower alkyl (*e.g.*, R = allyl, propargyl, dialkylaminoalkyl, etc.) were best prepared by direct alkylation of **19** through their sodium salt in a well-known manner (method Q). The undesirable quaternization of the

CHART II



tertiary N-8 could be suppressed essentially by using molar amounts of the corresponding halide. Lithium aluminum hydride reduction of several benzodiazepinones (**20**) led to 5,6,7,9,10,14b-hexahydroisoquino-[2,1-*d*][1,4]benzodiazepines (**21**).

The synthesis of isoquino[2,1-*d*][1,4]benzodiazepines (**19–21**) described above resulted in racemic products since these compounds contain one asymmetric carbon atom in position 14b. The pharmacologically most prominent representative in this series proved to be 2-chloro-5-methyl-5,9,10,14b-tetrahydroisoquino-[2,1-*d*][1,4]benzodiazepin-6(7H)-one (**20**, X = Cl; R = CH_3). We decided at that point to resolve this racemate in order to establish the question whether only one or both of the enantiomers contribute to the over-all activity of the racemate. Our attempts to obtain any crystalline salt of **20** (X = Cl; R = CH_3) with an optically active acid, like camphorsulfonic acid, tartaric acid, mandelic acid, etc., met with no success. This failure must be attributed essentially to the low basicity of this molecule (pK_a = 3.3, in Methyl Cellosolve–water, 8:2) which prevents the formation of stable salts.[16]

The first racemic intermediate in our synthesis of **20** (X = Cl, R = CH_3), the tetrahydroisoquinoline **11** (X = Cl, R = CH_3), is a much stronger base, however (pK_a = 6.4), and was indeed easily resolved into its optical antipodes with D- or L-tartaric acid,

(12) See Houben–Weyl "Methoden der Organischen Chemie," Vol. 11/1, p 32.

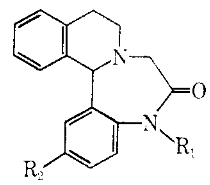
(13) G. Saucy and L. H. Sternbach, *Helv. Chim. Acta*, **45**, 2226 (1962).

(14) M. Gordon, I. J. Pachter, and J. W. Wilson, *Arzneimittel-Forsch.*, **13**, 802 (1963).

(15) Mueller and Zeller[7b] reported the direct ring closure of the amino ester (**17**, X = R = H) to the corresponding benzodiazepinone (**20**) by heating the amino ester to 200°.

(16) The crystalline hydrochloride of **20** (X = Cl, R = CH_3) loses hydrochloric acid on drying under high vacuum at temperatures as low as 50°.

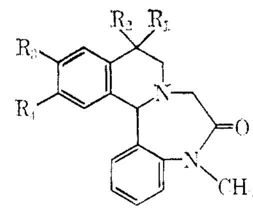
TABLE I



Compd	R_1	R_2	LD_{50},[a] mg/kg ip	ND_{50},[b] mg/kg ip	Amphet antag[c] ED_{50}, mg/kg ip	Anticonvul act. ED_{50} Strych[d]	N-SA[e]	Max elect.[f]	Hxb reinduction[g] RD_{50}, mg/kg ip	Dopa potentiation[h] at 25 mg/kg ip	Flexor refl,[i] mg/kg iv
I	CH_3	H	367	91	100	75	>100	>100	18.3	Neg	*j*
II	H	Cl	*j*	17	25	10	28	37	17.5	Neg	2.4
III(±)	CH_3	Cl	233	32	60	38	16	38	4.5	++	1.7
IV(+)[k]	CH_3	Cl	325	8	22	17	6	30	1.5	+++	1.0
V(−)	CH_3	Cl	300	*j*	*j*	58	>150	70	18.8	*j*	5.0
VI	CH_3	NO_2	>800	37	*j*	44	17	38	18.8	Neg	1.2
VII	H	NO_2	733	11	17	19	19	17	10.4	++	1.2
VIII	CH_3	CF_3	275	13	47	92	29	38	44	Neg	*j*
IX	CH_3	Br	367	12	75	50	18	38	38	++	*j*

[a] Modification of method described in ref 17; ten animals per dose. [b] Method of ref 18; ten animals per dose. [c] Determined in mice using standard photocell activity cages, Woodard Research Corporation, Herndon, Va. [d] Method of ref 20; ten animals per dose. [e] See text. [f] Method of ref 21; ten animals per dose. [g] Modified method of ref 25 in which animals were administered compound immediately following recovery from hexobarbital anesthesia (70 mg/kg iv) and reinduction of "anesthesia" (loss of righting) was measured from that time. [h] Modification of the method described in ref 26. [i] Dose (intravenous) required to produce 50% depression of the flexor reflex (obtained by stimulation of the peroneal branch of the sciatic nerve and recording contraction of the achilles tendon) in chloralose-anesthetized cats, as described by E. F. Domino, *Ann. N. Y. Acad. Sci.*, **64**, 705 (1956). Patellar reflex was not affected by any of the compounds studied. Each compound was studied in three animals. [j] Not tested. [k] Neuropharmacologic activity originally presented by J. H. Gogerty, H. Ott, G. O'Neill, and J. H. Trapold, *Fed. Proc.*, **25**, 503 (1966). Extensive description of neuropharmacologic activity to be published.

TABLE II



Compd	R_1	R_2	R_3	R_4	LD_{50},[a] mg/kg ip	ND_{50},[b] mg/kg ip	Amphet antag[c] ED_{50}, mg/kg ip	Anticonvul act. ED_{50} Strych[d]	N-SA[e]	Max elect.[f]	Hxb reinduction[g] RD_{50}, mg/kg ip	Dopa potentiation[h] at 25 mg/kg
III	H	H	H	H	233	32	60	38	16	38	4.5	++
X	CH_3	CH_3	H	H	650	*i*	25	>600	>600	>600	>600	Neg
XI	CH_3	H	H	H	275	*i*	>100	100	23	>100	>100	Neg
XII	H	CH_3	H	H	>800	81	>100	>300	>300	>300	>300	Neg
XII	H	H	OCH_3	OCH_3	*i*	80	100	>100	>100	100	100	Neg
XIV	H	H	Cl	Cl	>800	*i*	>100	252	>300	>300	>300	*i*

[a–h] See corresponding footnotes in Table I. [i] See footnote *j*, Table I.

respectively (method L). Both enantiomers were then converted into the optically pure antipodes of compound **20** (X = Cl; R = CH_3). The pharmacological evaluation clearly revealed the fact that only the (+) antipode possesses significant activity and is approximately twice as active as the racemate. No such separation of pharmacological activities could be seen, however, with the optical antipodes of the $LiAlH_4$ reduction products (**21**, X = Cl; R = CH_3). No attempt has been made to establish the absolute configuration of these optically active intermediates or final products.

Biological Evaluation.—Because of the obvious chemical similarities to chlordiazepoxide and diazepam, compounds presented in this paper have been compared, pharmacologically, to these benzodiazepines and to other relevant centrally acting substances. The neuropharmacological profiles of the series under investigation are presented in Tables I–IV, with Table V listing the data obtained with standard substances.

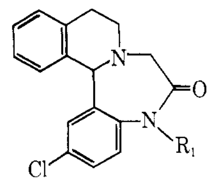
Compounds were originally submitted for acute toxicity and behavioral studies in mice, using modifications of the methods described by Irwin.[17] The ability to produce neurologic deficit in mice was determined using the rotarod method,[18] and interaction with amphetamine was studied in standard photocell activity cages.[19] Anticonvulsant activities were defined in mice using a modification of the method de-

(17) S. Irwin in "Animal and Clinical Pharmacologic Techniques in Drug Evaluation," J. H. Nodine and P. E. Siegler, Ed., Year Book Medical Publishers, Inc., Chicago, Ill., 1964.

(18) N. W. Dunham and T. S. Miya, *J. Pharm. Sci.*, **46**, 208 (1957).

(19) Woodard Research Corp., Herndon, Va.

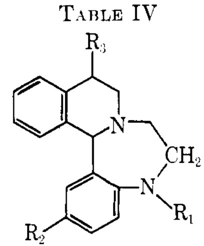
TABLE III



Compd	R_1	LD_{50},[a] mg/kg ip	ND_{50},[b] mg/kg ip	Amphet antag[c] ED_{50}, mg/kg ip	Anticonvul act. ED_{50} Strych[d]	N-SA[e]	Max elect.[f]	Hxb reinduction[g] RD_{50}, mg/kg ip	Dopa potentiation[h] at 25 mg/kg ip
II	H	*i*	17	25	10	28	37	17.5	Neg
III	CH_3	233	32	60	38	16	38	4.5	++
XV	C_2H_5	600	36	*i*	81	46	94	75.0	*i*
XVI	C_3H_7	>800	*i*	77	225	>300	>300	>300	Neg
XVII	$CH_2CH{=}CH_2$	>800	71	93	138	150	150	90	*i*
XVIII	$CH_2C{\equiv}CH$	600	36	25	150	75	>200	167	Neg
XIX	CH_2OCOCH_3	764	>200	88	>300	>300	>300	>300	+
XX	$CH_2CONHCH_3$	>800	>200	50	>300	>300	>300	>300	Neg
XXI	$(CH_2)_3N(CH_3)_2$	300	81	>75	92	92	>100	117	Neg

[a–h] See corresponding footnotes in Table I. [i] See footnote *j* in Table I.

TABLE IV

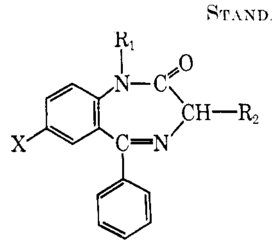


Compd	R_1	R_2	R_3	LD_{50},[a] mg/kg ip	ND_{50},[b] mg/kg ip	Amphet antag[c] ED_{50}, mg/kg ip	Anticonvul act. ED_{50} Strych[d]	N-SA[e]	Max elect.[f]	Hxb reinduction[g] RD_{50}, mg/kg ip	Dopa potentiation[h] at 25 mg/kg ip
XXII	CH_3	H	H	217	74	100	>75	>75	>75	46	Neg
XXIII	H	Cl	H	467	85	41	69	>100	75	75	Neg
XXIV(±)	CH_3	Cl	H	600	>400	87	>400	>400	300	>400	Neg
XXV(+)	CH_3	Cl	H	233	38	90	69	69	88	29	Neg
XXVI(−)	CH_3	Cl	H	363	150	36	>75	>75	56	>75	Neg
XXVII	CH_3	Cl	CH_3	394	144	91	200	>200	183	>200	Neg

[a–h] See corresponding footnotes in Table I.

TABLE V

STANDARDS



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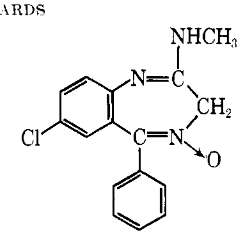


Chlordiazepoxide

Compd	R_1	R_2	X	LD_{50},[a] mg/kg ip	ND_{50},[b] mg/kg ip	Amphet antag[c] ED_{50}, mg/kg ip	Anticonvul act. ED_{50} Strych[d]	N-SA[e]	Max elect.[f]	Hxb reinduction[g] RD_{50} mg/kg ip	Dopa potentiation[h] at 25 mg/kg ip	Flexor refl,[i] mg/kg iv
Chlordiazepoxide				272	13.5	46	7.3	6.3	43.8	4.7	Neg	1.3
Diazepam	CH_3	H	Cl	220	2.5	21	3.0	1.0	8.5	0.38	Neg	0.2
Oxazepam	H	OH	Cl	767	1.3	8	8.6	3.1	3.1	16.5	Neg	0.4
Mogadon	H	H	NO_2	733	0.9	23	4.5	1.0	36.0	0.83	Neg	0.04
Prazepam	$CH_2-\triangleleft$	H	Cl	*j*	6.7	*j*	*j*	1.3	*j*	7.5	Neg	*j*
Meprobamate				667	85.0	180	127	93	108	92	Neg	70
Phenobarbital				325	32.5	*k*	24.4	13.5	20.0	*j*	Neg	*j*
Glutethimide				*j*	61.5	*k*	38	68.8	38	42	Neg	20

[a–j] See corresponding footnotes in Table I. [k] Potentiation of amphetamine at low doses.

scribed by Orloff, *et al.*,[20] for antagonism of strychnine and the method of Toman, *et al.*,[21] for antagonism of maximal electroshock convulsions. Because of the sensitivity of pentamethylenetetrazole-induced convulsions to standard benzodiazepines,[22] the antagonism of pentamethylenetetrazole convulsions in mice[23] was initially used to study compounds of the present series. However, this test was subsequently replaced by one in which convulsions were produced by N-sulfamoylazepine. This substance, synthesized in these laboratories, had previously been found to produce a pentamethylenetetrazole-like spectrum of convulsant activity but was noted to be approximately three times more active than pentamethylenetetrazole and to provide more reproducible results.[24] Consequently, the antagonism of convulsions produced by this substance became one of our primary test procedures for examining compounds within the series under discussion and selected standards. The over-all central nervous system depressant activity was defined by interacting the compounds with hexobarbital, using a modification of the test described by Winter, *et al.*,[25] in which mice were injected intravenously with 70 mg/kg of hexobarbital and, upon recovery of their righting reflex, were administered the test substance intraperitoneally. The ability of substances to modify the aggressive behavior in mice produced by dihydroxyphenylalanine (DL-dopa) was analyzed according to a modification of the method described by Everett, and Wiegand.[26]

Secondary evaluation of selected substances and of standards included analysis of effects on spinal reflexes and behavioral alterations in cats.

a. Acute Toxicity and Effects on Behavior in Mice.—In general, all compounds of the series provided moderate to low toxicities with depression of behavior and reflexes being the dominant symptoms. Substances lacking substitution in the 2 position or lacking the carbonyl group in position 6 produced mixed CNS activity with thrashing and clonic convulsions at lethal doses. Most of the compounds demonstrated qualitatively similar effects to those observed with chlordiazepoxide, oxazepam, or diazepam.

b. Neuropharmacologic Profile.—As can be seen from the respective tables, the substance demonstrating the greatest over-all activity was IV, the dextrorotatory isomer of III. Because III and XXIV represented the only compounds of the series resolved into their antipodes (IV, V and XXV, XXVI, respectively), structure–activity relationships within the series were made relative to the racemic form. Interestingly, the neuropharmacological activity appears to reside in the dextrorotatory isomer IV with the levorotatory form V being significantly less active, but more toxic than IV. A similar structure–activity relationship could not, however, be developed with the reduced congeners (XXIV–XXVI) in that both optical antipodes were more active and more toxic than their racemic form.

Structural alterations of III show that removal of the methyl group on the amide nitrogen (II) enhances the protection against strychnine convulsions but provides no significant improvement as regards antagonism of maximal electroshock convulsions. On the other hand, the ability to antagonize N-sulfamoylazepine-induced seizures was significantly reduced. These relationships are to a certain extent in contrast to those reported for diazepam and its demethylated derivative.[27]

Comparison of the data obtained with I–III, VI–IX (Table I) allows one to conclude that substitution in the 2 position, particularly with electronegative groups, is necessary for anticonvulsant activity and for muscle relaxant activity (as defined by the rotarod test). Interestingly, the nonmethylated nitro derivative is pharmacologically similar to the nonmethylated chlorine derivative with both substances showing similar decreases in activity when compared to the methylated substances (VII *vs.* VI and II *vs.* III). This relationship agrees with that reported by Sternbach, *et al.*,[28] and by Gordon, *et al.*,[14] for similar amino-1,4-benzodiazepines. However, nitro-substituted compounds were not more active than chlorine-substituted ones, as previously reported and reproduced in the present investigation. The 2-trifluoromethyl derivative (VIII) was also found to be significantly less active than the parent substance, again in contrast with previously reported structure–activity relationships for benzodiazepines.[29] These differences in activity are demonstrated most prominently in the strychnine antagonism and hexobarbital reinduction tests.

To the extent that substitution was made on the benzene ring of the isoquinoline portion of the molecule, it has been found that either the 12,13-dimethoxy or the 12,13-dichloro derivatives (XIII and XIV) abolish the neuropharmacologic activity observed with the parent compound. Similarly, 10,10-dimethyl substitution (X) also abolishes activity. However, the two isomeric 10-methyl-substituted compounds[30] (XI and XII, respectively) provided an interesting structure–activity relationship in that only one form (XI) provided "specific" antagonism of N-sulfamoylazepine- and pentamethylenetetrazole-induced convulsions.

Replacement of the N-methyl group by a number of other groups (XV–XXI, Table III) results in marked reduction of all measured activities. Interestingly, the activity seen with XX appears to agree with that reported for the related 1,4-benzodiazepine insofar as comparisons can be made.

Substances related to **21**, Chart II, lacking the amide carbonyl group at the 6 position, demonstrate a modified behavioral picture in that a mixture of CNS stimulation and depression occurs (*e.g.*, thrashing and

(20) M. J. Orloff, H. L. Williams, and C. C. Pfeiffer, *Proc. Soc. Exp. Biol. Med.*, **70**, 254 (1949).

(21) J. E. P. Toman, E. A. Swinyard, and L. S. Goodman, *J. Neurophysiol.*, **9**, 231 (1946).

(22) S. J. Childress and M. I. Gluckman, *J. Pharm. Sci.*, **53**, 577 (1964).

(23) G. M. Everett and R. K. Richards, *J. Pharmacol. Exp. Ther.*, **81**, 402 (1944).

(24) J. H. Gogerty, G. Leslie, and J. H. Trapold, to be published.

(25) C. F. Winter, *J. Pharmacol. Exp. Ther.*, **94**, 7 (1948).

(26) G. M. Everett and R. G. Wiegand, First International Pharmacological Meeting, Stockholm, 1961, Vol. 8, The Macmillan Co., New York, N. Y., 1962, p 85.

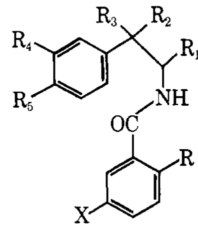
(27) L. O. Randall, C. L. Scheckel, and R. F. Banziger, *Current Therap. Res.*, **7**, 590 (1965).

(28) L. H. Sternbach, R. I. Fryer, O. Keller, W. Metlesicz, G. Sach, and N. Steiger, *J. Med. Pharm. Chem.*, **6**, 261 (1963).

(29) L. H. Sternbach, G. A. Archer, J. V. Earley, R. I. Fryer, E. Reeder, N. Wasyliw, L. O. Randall, and R. Banziger, *ibid.*, **8**, 815 (1965).

(30) The introduction of an additional asymmetric carbon atom (C-10) resulted in two diastereoisomeric forms. Their relative configuration has not been clearly established. Chemical evidence (ratio of reduction products obtained in method H) favors the "*cis*" configuration for XI and the "*trans*" configuration for XII, "*cis*" and "*trans*" referring to the spacial arrangements of the hydrogen atoms at C-10 and C-14b.

TABLE VI
SUBSTITUTED N-PHENETHYLBENZAMIDES



X	R	R_1	R_2	R_3	R_4	R_5	Method	Recrystn[a] solvent	Mp, °C	Yield, %	Formula	Analyses[b]
H	NH_2						D	Et–Pe	90–91	83	$C_{15}H_{16}N_2O$	C, H, N, O
H	$NHCH_3$						D	Al	106–107	76	$C_{16}H_{18}N_2O$	C, H, N, O
Cl	NH_2						D	Al	128–129	80	$C_{15}H_{15}ClN_2O$	C, H, Cl, N, O
Cl	$NHCH_3$						D	Et	131–132	98	$C_{16}H_{17}ClN_2O$	C, H, Cl
Cl	$NHCH_3$	CH_3[c]					D	Al–Wa	90–91	99	$C_{17}H_{19}ClN_2O$	C, H, Cl, N, O
Cl	$NHCH_3$	CH_3[d]					D	Ac–Wa	102–105	97	$C_{17}H_{19}ClN_2O$	C, H, Cl
Cl	$NHCH_3$					Cl	D	Ea–Et	130–132	93	$C_{16}H_{16}Cl_2N_2O$	C, H, Cl
Cl	$NHCH_3$				Cl	Cl	D	Al	148–149	91	$C_{16}H_{15}Cl_3N_2O$	C, H, Cl, N, O
Cl	$NHCH_3$					OCH_3	D	Al–Wa	95–96	100	$C_{17}H_{19}ClN_2O_2$	C, H, Cl, N
Cl	$NHCH_3$				OCH_3	OCH_3	D	Ea–Et	96–98	97	$C_{18}H_{21}ClN_2O_3$	C, H, Cl
Cl	$NHCH_3$				O–CH_2–O		D	Mc–Et	153–154	93	$C_{17}H_{17}ClN_2O_3$	C, H, Cl, N
Cl	$NHCH_3$		CH_3[e]				D	Et	100–103	88	$C_{17}H_{19}ClN_2O$	C, H, Cl
Cl	$NHCH_3$		CH_3	CH_3			D	Et–Pe	126–128	88	$C_{18}H_{21}ClN_2O$	C, H, Cl, N, O
NO_2	NH_2						D	Mc	160	87	$C_{15}H_{15}N_3O_3$	C, H, N, O
NO_2	$NHCH_3$						D	Mc	170	94	$C_{16}H_{17}N_3O_3$	C, H, N, O
H	NO_2						A	Dt–Wa	115–116[f]	96	$C_{15}H_{14}N_2O_3$	
Cl	NO_2						A	Ea–Et	102–104	82	$C_{15}H_{13}ClN_2O_3$	C, H, N
H	NO_2	CH_3[d]					A	Et	85–87	98	$C_{16}H_{16}N_2O_3$	C, H, N, O
Cl	NO_2	CH_3[d]					A	Di–Wa	96–98	99	$C_{16}H_{15}ClN_2O_3$	
Cl	NO_2				Cl	Cl	A	Al	129–130	82	$C_{15}H_{11}Cl_3N_2O_3$	C, H, Cl, N
H	NO_2				OCH_3	OCH_3	A	Al–Wa	142–143[g]	94	$C_{17}H_{17}N_2O_5$	
NO_2	Cl						A	Et	155	90	$C_{15}H_{13}ClN_2O_3$	C, H, Cl, N
H	NHTs						E	Ea	154–155	99	$C_{22}H_{22}N_2O_3S$	C, H, N, O
Cl	NHTs						E	Mc–Et	49–52	80	$C_{22}H_{21}ClN_2O_3S$	C, H, O
Cl	$N(CH_3)\cdot Ts$						E				$C_{23}H_{23}ClN_2O_3S$	
Cl	$N(CH_3)\cdot Ts$		CH_3[e]				E	Et	89–91	83	$C_{24}H_{25}ClN_2O_3S$	C, H, Cl[h]
Cl	$N(CH_3)\cdot Ts$		CH_3	CH_3			E	Et	129–130	90	$C_{25}H_{27}ClN_2O_3S$	C, H, N, O
NO_2	NHTs						E	Ea–Et	165	75	$C_{22}H_{21}SN_3O_5S$	C, O; H[i]

[a] Al, ethanol; Ac, acetone; Di, dioxane; Ea, ethyl acetate; Et, dimethyl ether; Mc, methylene chloride; Pe, petroleum ether (bp 30–60°); Wa, water. [b] Analytical results obtained for the elements indicated by symbols were within ±0.4% of the theoretical values. [c] From DL-amphetamine. [d] From D-amphetamine. [e] From DL-2-phenylpropylamine. [f] Lit.[10] mp 115–116°. [g] S. Rajagopalan [*Proc. Indian Acad. Sci.*, **14A**, 126 (1941); *Chem. Abstr.*, **36**, 1603[7] (1942)] reported mp 142°. [h] *Anal.* Calcd: C, 63.1; H, 5.5; Cl, 7.8. Found: C, 62.1; H, 5.1; Cl, 8.3. [i] H: calcd, 4.8; found, 5.8.

clonic convulsions). In spite of this, a structure–activity relationship similar to that of the benzodiazepinones (**20**) is obtained, albeit the level of activity is much weaker (compare XXII, XXIII, XXIV, XXV, and XXVI *vs.* I, II, III, IV, and V). The specific antagonism of N-sulfamoylazepine observed with XI was not apparent with its reduced congener XXVII.

A comparison of the neuropharmacological profiles of compounds in the present series *vs.* those of "standard" benzodiazepines elicits one significant difference: when the various substances were interacted with DL-dihydroxyphenylalanine in mice (delayed dopa test of Everett, *et al.*[26]), the isoquinobenzodiazepines tended, if anything, to potentiate the CNS stimulant activities of dopa, whereas the "standard" substances provided only antagonism to dopa-induced stimulation. Because this test has been proposed as a means of identifying antidepressant activity of compounds, the most active of the present series (IV) was further tested for its ability to reverse the behavioral depression and hypothermia obtained with reserpine in mice and the catalepsy observed in rats with tetrabenazine. In all respects, the results with IV were negative. The utility of the dopa test for defining antidepressant activity is presently being examined clinically, using compound IV as the test substance.

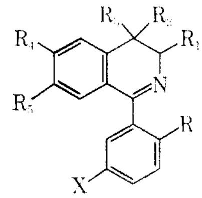
The apparent discrepancy obtained in these studies between interaction of substances with DL-dopa and with amphetamine has not been resolved, although the end points and criteria for defining the respective interactions are recognizably important. However, the fact that substances which potentiate the behavioral effects of DL-dopa will antagonize the stimulant activities of amphetamine provide suggestive evidence that these two methods for obtaining stimulation of CNS sympathetic activity are not one and the same.

More specific neuropharmacological and behavioral studies with IV form the basis of another investigation presently being completed.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and have not been corrected. The optical rotations were measured with a photoelectric Zeiss polarimeter at the mercury line wavelength of 546 mμ. Pmr spectra were obtained on a Varian Associates A-60 spectrometer, ir

TABLE VII
SUBSTITUTED 1-PHENYL-3,4-DIHYDROISOQUINOLINES



X	R	R_1	R_2	R_3	R_4	R_5	Method	Recrystn[a] solvent	Mp, °C	Yield, %	Formula	Analyses[b]
H	NHTs						$F(P_2O_5)$	Al–Pe	131–133	65	$C_{22}H_{20}N_2O_2S$	C, H, N, O
H	NH_2						G	Al	95–96[c]	94	$C_{15}H_{14}N_2$	C, H, N
H	$N(CH_3)\cdot Ts$						$F(POCl_3)$	Et	138–140	43	$C_{23}H_{22}N_2O_2S$	C, H, N
H	$NHCH_3$						G		Oil	95	$C_{16}H_{16}N_2$	
Cl	NHTs						$F(P_2O_5)$	Et	102–103	39	$C_{22}H_{18}N_2O_2S\cdot HCl$	C, H, Cl; N[d]
Cl	NH_2						G		Oil	98	$C_{15}H_{13}ClN_2$	C, H, Cl, N
Cl	$N(CH_3)\cdot Ts$						$F(POCl_3)$	Al	250–252	71	$C_{17}H_{17}ClN_2O_2S\cdot HCl$	C, H, Cl
Cl	$NHCH_3$						G	Al–Wa	80–100	95	$C_{16}H_{15}ClN_2$	C, H, Cl, N
Cl	$N(CH_3)\cdot Ts$				OCH_3	OCH_3	$F(P_2O_5)$	Al–Et	222–223	83	$C_{25}H_{25}ClN_2O_4S\cdot HCl$	C, H, Cl, N, O
Cl	$NHCH_3$				OCH_3	OCH_3	G	Al	110–112	85	$C_{18}H_{19}ClN_2O_2$	C, H, Cl
Cl	$N(CH_3)\cdot Ts$[e]				O–CH_2–O		$F(POCl_3)$	Et–Pe	144–145	91	$C_{24}H_{21}ClN_2O_4S$	C, H, N
Cl	$N(CH_3)\cdot Ts$		CH_3[f]				$F(POCl_3)$	Al–Et	252 dec	55	$C_{24}H_{23}ClN_2O_2S\cdot HCl$	C, H, Cl
Cl	$NHCH_3$		CH_3[f]				G	Al	108–110	72	$C_{17}H_{17}ClN_2$	C, H, Cl, N
Cl	$N(CH_3)\cdot Ts$		CH_3	CH_3			$F(POCl_3)$	Al–Et	260–268	67	$C_{25}H_{25}ClN_2O_2S\cdot HCl$	C, H, N, O
Cl	$NHCH_3$		CH_3	CH_3			G	Al	125–128	65	$C_{18}H_{19}ClN_2$	C, H, Cl, N
NO_2	NH_2						J	Et	152	53	$C_{15}H_{13}N_3O_2$	C, H, O; N[g]
NO_2	$NHCH_3$						J	Et	148	92	$C_{16}H_{15}N_3O_2$	C, H, N, O
H	NO_2						$F(POCl_3)$	Et	86–87[h]	68	$C_{15}H_{12}N_2O_2$	
Cl	NO_2						$F(P_2O_5)$	Ppt from Wa	128–130[i]	53	$C_{15}H_{11}ClN_2O_2$	C, H, Cl, N, O
H	NO_2	CH_3[j]					$F(P_2O_5)$	Et	125–127	40	$C_{16}H_{14}N_2O_2$	C, H, O
Cl	NO_2	CH_3[j]					$F(POCl_3)$	Ea	118–120	53	$C_{16}H_{13}ClN_2O_2$	C, H, O
NO_2	Cl						$F(P_2O_5)$	Et	150	73	$C_{15}H_{11}ClN_2O_2$	C, H, O
CF_3	Cl						K	Ac–Et	212–214	40	$C_{16}H_{11}ClF_3N\cdot HCl$	H, Cl, N; C[k]
CF_3	$NHCH_3$						J		Oil	75	$C_{17}H_{15}F_3N_2$	C, H, N

[a,b] See corresponding footnotes in Table VI. [c] Lit.[10] mp 95–96°. [d] N: calcd, 15.7; found, 14.7. [e] Detosylation of this compound resulted in unidentified mixtures. [f] From DL-2-phenylpropylamine. [g] N: calcd, 15.7; found, 14.9. [h] Lit.[10] mp 84–85°. [i] Lit.[7b] mp 131–134°. [j] From D-amphetamine. [k] C: calcd, 55.5; found, 56.1.

spectra (CH_2Cl_2) using a Perkin-Elmer Infracord. Structure determinations were based essentially on microanalysis and comparison of ir and pmr spectra within a given class of compounds. Since no unusual spectral features have been observed with the compounds described herein, no absorption peaks are listed in the Experimental Section. Where analytical results are represented only by the symbols of the elements, analytical values obtained were within ±0.4% of the calculated values.

Each method discussed in the theoretical part of this paper is described here by only one representative example. The methods used in the preparation of analogs are indicated in Tables VI–X.

Method A. N-(β-Phenethyl)-2-nitro-5-chlorobenzamide (5, X = Cl).—To a mixture of 121 g (1.0 mole) of phenethylamine and 35 g (0.87 mole) of NaOH in 420 ml of H_2O and 150 ml of dioxane were added dropwise under vigorous stirring 192 g (0.87 mole) of 2-nitro-5-chlorobenzoyl chloride dissolved in 200 ml of dioxane. The addition took ~1 hr and the reaction temperature was kept below 35° by external cooling. Stirring was continued for 1 hr at ambient temperature. The reaction mixture was diluted with 2 l. of H_2O and extracted with three 500-ml portions of CH_2Cl_2. The extracts were combined, washed (H_2O), dried (Na_2SO_4), filtered, and evaporated to dryness *in vacuo*. Crystallization of the residue from EtOAc gave 250 g (82%) of white prisms, mp 102–104°. *Anal.* ($C_{15}H_{13}ClN_2O_3$) C, H, Cl, N.

Method B. 1-(2-Nitrophenyl)-3,4-dihydroisoquinoline (6, X = H) from N-(β-Phenethyl)-2-nitrobenzamide with $POCl_3$.—A solution of 100 g (0.370 mole) of the benzamide (4, X = H) in 500 ml of $POCl_3$ was heated to reflux for 17 hr. The volatile parts were then removed *in vacuo* as thoroughly as possible. The dark brown oily residue was dissolved in 500 ml of CH_2Cl_2, 300 ml of ice-cold 2 *N* NaOH was added, and this mixture was shaken for 0.5 hr to decompose the remaining $POCl_3$. The organic phase was separated and the aqueous phase was extracted twice with 200-ml portions of CH_2Cl_2. The combined extracts were washed (NaOH solution, H_2O), dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The oily residue was dissolved in 300 ml of acetone and HCl gas was bubbled in to precipitate the product as its hydrochloride (73 g, 68%), mp 225°. The base was set free from its hydrochloride in the usual way and crystallized from ether in light yellow crystals of mp 86–87° (identical with the melting point reported in the literature).[10]

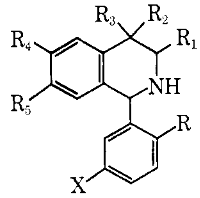
Compound 6 (X = Cl) from N-Phenethyl-2-nitro-5-chlorobenzamide with P_2O_5.—To a hot solution of 57 g (0.18 mole) of the benzamide (5, X = Cl) in 250 ml of xylene was added with stirring 110 g of P_2O_5. This mixture was refluxed for 5 hr. After cooling the xylene was decanted and the sticky residue was carefully decomposed with H_2O and ice. The acid solution was extracted with two 300-ml portions of ether to remove unreacted starting material. The aqueous phase was then made alkaline with concentrated NaOH. The precipitated product was filtered off and dried, yield 28.5 g (53%), white crystals, mp 128–130°. For analysis a sample was recrystallized from EtOAc–Et_2O without a change in melting point. *Anal.* ($C_{15}H_{11}ClN_2O_2$) C, H, N, Cl.

Method C. 1-(2-Amino-5-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (7, X = Cl). a. Catalytic Hydrogenation.—A solution of 2.86 g (10 mmoles) of **6** (X = Cl) in 20 ml of AcOH was shaken under H_2 in the presence of 250 mg of PtO_2 at room temperature and at atmospheric pressure. When no further H_2 uptake was observed, the catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo*. To purify the product, the crystalline residue was recrystallized (EtOAc) to yield 2.10 g (81%) of white crystals, mp 135–136°. *Anal.* ($C_{15}H_{15}ClN_2$) C, H, N, Cl.

b. Reduction of 6 (X = Cl) with Pd–$NaBH_4$.—In a suspension of 0.5 g of 10% Pd–C in 15 ml of H_2O and 50 ml of MeOH, 5.0 g of $NaBH_4$ was dissolved quickly. To this mixture was added dropwise with stirring a solution of 10.0 g of **6** (X = Cl) in 40 ml of MeOH and 20 ml of dioxane within 45 min, keeping the reaction temperature between 50 and 60°. Stirring was continued for 1 hr. The excess sodium borohydride was carefully decomposed by addition of AcOH, the catalyst was filtered off, and the filtrate was basified with 2 *N* NaOH and further diluted with H_2O to precipitate 7.5 g (83%) of the product described above.

Method D. N-Phenethyl-2-methylamino-5-chlorobenzamide (9, X = Cl; R = CH_3).—To a solution of 60.0 g (0.50 mole) of phenethylamine in 270 ml of dioxane, 93.8 g (0.44 mole) of N-methyl-5-chloroisatoic anhydride (**8**, X = Cl; R = CH_3) was added. An exothermic reaction set in under vigorous evolution

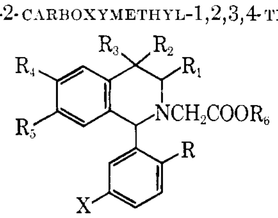
TABLE VIII
SUBSTITUTED 1-PHENYL-1,2,3,4-TETRAHYDROISOQUINOLINES



X	R	R1	R2	R3	R4	R5	Method	Recrystn[a] solvent	Mp, °C	Yield, %	Formula	Analyses[b]
H	NH_2						C (Pt)	Et–Pe	108[c]	83	$C_{15}H_{16}N_2$	
H	$NHCH_3$						H		Oil	98	$C_{16}H_{18}N_2$	
Cl	NH_2						C (Pt)	Ea–Et	128–130	81	$C_{15}H_{15}ClN_2$	C, H, Cl, N
Cl	$NHCH_3$						H	Et–Pe	140–142	72	$C_{16}H_{17}ClN_2$	C, H, Cl, N
Cl	$NHCH_3$	(+) isomer, $[\alpha]^{25}{}_{546}$ +48.3° ($CHCl_3$)					L	Al	98–99	39[d]	$C_{16}H_{17}ClN_2$	
Cl	$NHCH_3$	(−) isomer, $[\alpha]^{25}{}_{546}$ −48.0° ($CHCl_3$)					L	Al	98–99	37[d]	$C_{16}H_{17}ClN_2$	
Cl	$NHCH_3$				OCH_3	OCH_3	C (Pt)	Ea–Et	145–147	85	$C_{18}H_{21}ClN_2O_2$	C, H, N, O
Cl	$NHCH_3$		CH_3[e]				H	Et	142–144	60	$C_{17}H_{19}ClN_2$	C, H, Cl, N
Cl	$NHCH_3$		CH_3[e]				H	Et–Pe	81–84	12	$C_{17}H_{19}ClN_2$	C, H, Cl, N
Cl	$NHCH_3$		CH_3	CH_3			H	Et–Pe	110–112	82	$C_{18}H_{21}ClN_2$	C, H, Cl, N
NO_2	NH_2						H	Me[f]	192	75	$C_{15}H_{15}N_3O_2$	C, H, N, O
NO_2	$NHCH_3$						H	Et	182	76	$C_{16}H_{17}N_3O_2$	C, H, O; N[g]
H	NH_2	CH_3[h]					C (Pd)	Et	92–94	45	$C_{16}H_{18}N_2$	C, H, N
Cl	NH_2	CH_3[e,h]					C (Pt)	Ea–Et	168–170		$C_{16}H_{17}ClN_2$	C, H, O, N
Cl	NH_2	CH_3[e,h]					C (Ra Ni)	Et	135–137		$C_{16}H_{17}ClN_2$	C, H, O, N
H	NH_2				OCH_3	OCH_3	C (Pd)	Ppt from Wa	157–160[i]	88	$C_{17}H_{20}N_2O_2$	
Br	$NHCH_3$						H	Al	146–147	58	$C_{16}H_{17}BrN_2$	C, H, N
CF_3	$NHCH_3$						H	Et–Pe	131–133	40	$C_{17}H_{17}F_3N_2$	C, H, N
CF_3	NH_2						H	Et–Pe	122–124	45	$C_{16}H_{15}F_3N_2$	C, H, N

[a,b] See corresponding footnotes in Table VI. [c] Lit.[10] mp 108–109°. [d] Based on a theoretical yield of 50%. [e] Relative configuration at the two asymmetric C atoms speculative. [f] Me, methanol. [g] N: calcd, 14.8; found, 14.1. [h] From D-amphetamine. [i] Lit. (footnote *g*, Table VI) mp 162°.

TABLE IX
SUBSTITUTED 1-PHENYL-2-CARBOXYMETHYL-1,2,3,4-TETRAHYDROISOQUINOLINES



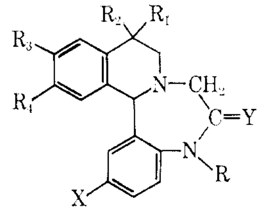
X	R[c]	R2	R3	R4	R5	R6	Method	Recrystn[a] solvent	Mp, °C	Yield, %	Formula	Analyses[b]
H	NH_2						M, N	Ppt from Wa	~95–130	59	$C_{17}H_{18}N_2O_2$	H, N; C, O[d]
H	$NHCH_3$					C_2H_5	M	Al	98–100		$C_{20}H_{24}N_2O_2$	...
H	$NHCH_3$					H	N	Ppt from Wa	125 dec		$C_{18}H_{20}N_2O_2$	...
Cl	NH_2					C_2H_5	M		Oil		$C_{19}H_{21}ClN_2O_2$	...
Cl	NH_2					H	M, N	Al	163–165	76	$C_{17}H_{17}ClN_2O_2$	C, H, Cl
Cl	$NHCH_3$					C_2H_5	M	Al	83–84	53	$C_{20}H_{23}ClN_2O_2$	C, H, Cl, N
Cl	$NHCH_3$					H	N	Al–Wa	115–122	84	$C_{18}H_{19}ClN_2O_2$	C, H, Cl, N
Cl	$NHCH_3$	(+) isomer, $[\alpha]^{22}{}_{546}$ +126° ($CHCl_3$)				C_2H_5	M	Al–Wa	113–114	82	$C_{20}H_{23}ClN_2O_2$	...
Cl	$NHCH_3$	(+) isomer, $[\alpha]^{22}{}_{546}$ +64.5° (C_2H_5OH)				H	N	Amorphous		91	$C_{18}H_{19}ClN_2O_2$	...
Cl	$NHCH_3$	(−) isomer, $[\alpha]^{22}{}_{546}$ −128° ($CHCl_3$)				C_2H_5	M	Al	112–113	78	$C_{20}H_{23}ClN_2O_2$	C, H, Cl, N, O
Cl	$NHCH_3$	(−) isomer, $[\alpha]^{22}{}_{546}$ −62° (C_2H_5OH)				H	N	Amorphous		91	$C_{18}H_{19}ClN_2O_2$	...
Cl	$NHCH_3$			OCH_3	OCH_3	CH_3	M		Oil		$C_{21}H_{25}ClN_2O_4$	...
Cl	$NHCH_3$			OCH_3	OCH_3	H	N		Amorphous		$C_{20}H_{23}ClN_2O_4$	...
Cl	$NHCH_3$	CH_3[e]				CH_3	M	Et–Pe	111–113	55	$C_{20}H_{23}ClN_2O_2$	C, H, Cl, O
Cl	$NHCH_3$	CH_3[e]				CH_3	M	Pe	99–102	40	$C_{20}H_{23}ClN_2O_2$	O
Cl	$NHCH_3$	CH_3[e]				H	N	Ppt from Wa	260–266	56	$C_{19}H_{21}ClN_2O_2$	...
Cl	$NHCH_3$	CH_3	CH_3			CH_3	M	Et–Pe	111–113	56	$C_{21}H_{25}ClN_2O_2$	C, H, Cl, N, O
Cl	$NHCH_3$	CH_3	CH_3			H	N	Al–Wa	212–216	66	$C_{20}H_{23}ClN_2O_2$	C, H, Cl, N, O
NO_2	NH_2					C_2H_5	M	Et–Pe	150	90	$C_{19}H_{21}N_3O_4$	C, H, O
NO_2	NH_2					H	M, N	Ppt from Wa	210	54	$C_{17}H_{17}N_3O_4$	...
NO_2	$NHCH_3$					C_2H_5	M	Ea	119–120	73	$C_{20}H_{23}N_3O_4$	C, H, N, O
NO_2	$NHCH_3$					H	N	Ppt from Wa	155	90	$C_{18}H_{19}N_3O_4$	...
CF_3	$NHCH_3$					C_2H_5	M	Pe	81–83	90	$C_{21}H_{23}F_3N_2O_2$	C, H, N

[a,b] See corresponding footnotes in Table VI. [c] R_1 is always H in this table since a methyl group in that position completely inhibited carbethoxy methylation on the isoquinoline nitrogen, probably because of steric hindrance. [d] C: calcd, 72.3; found, 70.9. O: calcd, 11.3; found, 12.1. [e] Relative configuration at the asymmetric C atoms speculative.

of CO_2. To complete the reaction, the mixture was heated on the water bath for 1 hr. On slow addition of 500 ml of H_2O, the product precipitated was filtered, washed (H_2O), and dried (126 g, 98%). For analysis it was recrystallized from Et_2O to give white prisms, mp 131–132°. *Anal.* ($C_{16}H_{17}ClN_2O$) C, H, Cl.

Method E. N-(Phenethyl)-2-methyltosylamino-5-chlorobenzamide.—A solution of 126 g (0.437 mole) of **9** (X = Cl; R =

TABLE X
SUBSTITUTED ISOQUINO[2,1-*d*][1,4]BENZODIAZEPINES



Compd	X	Y	R	R_1	R_2	R_3	R_4	Method	Recrystn[a] solvent	Mp, °C	Yield, %	Formula	Analyses[b]
	H	O	H					P	Al	248–250[c]	42	$C_{17}H_{16}N_2O$	C, H, N, O
I	H	O	CH_3					P	Ea	260–262	82	$C_{18}H_{18}N_2O \cdot HCl$	C, H, N, O
II	Cl	O	H					P	Al	228–230[d]	70	$C_{17}H_{15}ClN_2O$	H, Cl, C[e]
III	Cl	O	CH_3					P	Al–Wa	95–97	81	$C_{18}H_{17}ClN_2O$	C, H, Cl, O
IV	Cl	O	CH_3	(+) isomer, $[\alpha]^{25}_{546}$ +410° (C_2H_5OH)				O	Al	156–157	90	$C_{18}H_{17}ClN_2O$	C, H, N, O
V	Cl	O	CH_3	(−) isomer, $[\alpha]^{25}_{546}$ −404° (C_2H_5OH)				P	Al	156–157	65	$C_{18}H_{17}ClN_2O$	C, H, N, O
XIII	Cl	O	CH_3			OCH_3	OCH_3	P	Al–Et	275–280	24	$C_{20}H_{21}ClN_2O_3 \cdot HCl$	C, H, Cl, N, O
XI	Cl	O	CH_3	CH_3[f]				O	Et	179–181	58	$C_{19}H_{19}ClN_2O$	C, H, Cl, N, O
XII	Cl	O	CH_3	CH_3[f]				O	Et	187–189	63	$C_{19}H_{19}ClN_2O$	C, H, Cl, N, O
X	Cl	O	CH_3	CH_3	CH_3			P	Me–Et	190–194	51	$C_{20}H_{21}ClN_2O$	C, H, Cl, N, O
IX	Br	O	CH_3					O	Al–Pe	151–152	68	$C_{18}H_{17}BrN_2O$	C, H, Br
VII	NO_2	O	H					O	Et	160	49	$C_{17}H_{15}N_3O_3$	C, H, N; O[g]
VI	NO_2	O	CH_3					O	Ea–Et	223	76	$C_{18}H_{17}N_3O_3$	C, H, O
XIV	Cl	O	H			Cl	Cl	O	Al	245–246	31	$C_{17}H_{13}Cl_3N_2O$	C, H, Cl, N, O
XV	Cl	O	C_2H_5					Q	Al	171–173	50	$C_{19}H_{19}ClN_2O$	C, H, Cl, N, O
XVI	Cl	O	C_3H_7					Q	Me	187–190	45	$C_{20}H_{21}ClN_2O$	C, H, Cl, N, O
XVII	Cl	O	$CH_2CH{=}CH_2$					Q	Me	159–160	25	$C_{20}H_{19}ClN_2O$	C, H, Cl, N, O
XVIII	Cl	O	$CH_2C{\equiv}CH$					Q	Al–Pe	168–170	48	$C_{20}H_{17}ClN_2O$	C, H, Cl, N, O
VIII	CF_3	O	CH_3					O	Ea	221–225	23	$C_{19}H_{17}F_3N_2O \cdot HCl$	C, H, Cl, N
XIX	Cl	O	CH_3COOCH_3					Q	Me–Al	218–221	50	$C_{20}H_{19}ClN_3O_2$	C, H, Cl, N, O
XX	Cl	O	$CH_2CONHCH_3$					h	Me–Al	259–261	75	$C_{20}H_{20}ClN_3O_2$	C, H, Cl, N, O
XXI	Cl	O	$(CH_2)_3N(CH_3)_2$					Q	Ea–Al	193–200[i]	34	$C_{22}H_{26}ClN_3O \cdot 2HCl$[i]	C, H, Cl, N, O
XXII	H	H_2	CH_3					R[j]	Al–Ea	123–124	60	$C_{18}H_{20}N_2 \cdot (CH_2COOH)_2$	C, H, N, O
XXIII	Cl	H_2	H					R[k]	Al–Ea	157–159	51	$C_{17}H_{17}ClN_2 \cdot (CH_2COOH)_2$	C, H, Cl, N, O
XXIV	Cl	H_2	CH_3					R[l]	Et	142–144	70	$C_{18}H_{19}ClN_2$	C, H, Cl, N
XXV	Cl	H_2	CH_3	(+) isomer, $[\alpha]^{25}_{546}$ +296° (Wa)				R[l]	Al	130–132	71	$C_{18}H_{19}ClN_2 \cdot$ tartrate	C, H, Cl, N, O
XXVI	Cl	H_2	CH_3	(−) isomer, $[\alpha]^{25}_{546}$ −275° (Wa)				R[l]	Me–Al	125–128	45	$C_{18}H_{19}ClN_2 \cdot$ tartrate (+1 mole of C_2H_5OH)	C, H, Cl, N, O
XXVII	Cl	H_2	CH_3	CH_3[f]				R[l]	Al–Ea	158–160		$C_{19}H_{21}ClN_2 \cdot (CH_2COOH)_2$	C, H, Cl, N, O

[a,b] See corresponding footnotes in Table VI. [c] Lit.[7b] mp 253–255°. [d] Lit.[7b] mp 233–235°. [e] C: calcd, 68.3; found, 67.7. [f] Relative configuration at the two asymmetric C atoms speculative. [g] O: calcd, 15.5; found, 14.9. [h] Prepared from the corresponding methyl ester with methylamine in 2-propanol. [i] Crystals contained 0.25 mole of EtOH according to analysis and particularly the nmr spectrum. [j] LAH reduction in PhH. [k] LAH reduction in PhMe. [l] LAH reduction in Et_2O.

CH_3) and 102 g (0.536 mole) of *p*-toluenesulfonyl chloride in 450 ml of pyridine stood overnight at room temperature. Excess tosyl chloride was hydrolyzed by adding 100 ml of Me_2CO and 100 ml of H_2O and shaking this mixture for 0.5 hr at room temperature. The reaction mixture was then concentrated *in vacuo*. The oily residue was dissolved in 2 l. of EtOAc, and this solution was extracted with two 500-ml portions of 2 *N* HCl and one 500-ml portion of saturated $NaHCO_3$ solution. The organic phase was dried (Na_2SO_4), filtered, and evaporated to dryness *in vacuo* to yield 199 g (theoretical amount 192 g) of the product as an oil which proved to be practically pure by tlc. All attempts to crystallize it failed. The absorption bands of the ir spectrum (CH_2Cl_2) were as expected.

Method F. 1-(2-Methyltosylamino-5-chlorophenyl)-3,4-dihydroisoquinoline Hydrochloride.—A solution of 10.0 g of crude N-phenethyl-2-methyltosylamino-5-chlorobenzamide in 50 ml of $POCl_3$ was heated to reflux for 20 hr. The work-up procedure was analogous to that described under method B. The oily residue (~10 g) was dissolved in 30 ml of acetone and HCl gas was bubbled in to precipitate 7.44 g (71%) of the product in white prisms. For analysis the product was recrystallized from EtOH; mp 250–252°. *Anal.* ($C_{23}H_{22}Cl_2N_2O_2S$) C, H, Cl, S.

Method G. 1-(2-Methylamino-5-chlorophenyl)-3,4-dihydroisoquinoline (10, X = Cl; R = CH_3).—Concentrated H_2SO_4 (50 ml) was gradually added to 18.0 g (39 mmoles) of 1-(2-methyltosylamino-5-chlorophenyl)-3,4-dihydroisoquinoline hydrochloride (strong HCl evolution) and the thus obtained solution stood at room temperature overnight. The reaction mixture was then poured on crushed ice and made alkaline with 30% NaOH. The oily precipitate was extracted with three 100-ml portions of CH_2Cl_2. The extracts were combined, washed (H_2O), dried (Na_2SO_4), filtered, and evaporated to an oily residue (11.0 g, theoretical 10.6 g). This raw product was pure enough to be used in the following step. For analysis it was crystallized from EtOH–H_2O; yield 10.0 g (95%), mp 80–100°. *Anal.* ($C_{16}H_{15}ClN_2$) C, H, Cl, N.

Method H. DL-1-(2-Methylamino-5-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (11, X = Cl; R = CH_3).—A solution of 193 g (0.716 mole) of **10** (X = Cl; R = CH_3) in 2 l. of 95% EtOH was warmed to 50° and then 40 g of $NaBH_4$ was added. This reaction mixture was refluxed under stirring for 2 hr, whereby a boron complex crystallized out gradually. Excess $NaBH_4$ was destroyed by careful addition of 50 ml of AcOH. After distilling off 1 l. of EtOH *in vacuo*, 1 l. of 2 *N* HCl was added and the solution was kept at 30° for 30 min to decompose the boron complex. This aqueous solution was made alkaline with 30% NaOH and extracted with three 500-ml portions of CH_2Cl_2. The extracts were combined, washed (H_2O), dried (Na_2SO_4), filtered, and evaporated to dryness *in vacuo*. The oily residue (195 g, 100%) was practically pure **11** by tlc. The product could be crystallized from EtOH as white prisms, mp 140–141°. *Anal.* ($C_{16}H_{17}ClN_2$) C, H, Cl, N.

Method J. 1-(2-Methylamino-5-trifluoromethylphenyl)-3,4-dihydroisoquinoline (10, X = CF_3; R = CH_3).—A mixture of 35.0 g (0.1 mole) of 1-(2-chloro-5-trifluoromethylphenyl)-3,4-dihydroisoquinoline hydrochloride (**14**, X = CF_3), 1.7 g of Cu powder, and 1.7 g of Cu_2Cl_2 in 500 ml of liquid $MeNH_2$ was heated in an autoclave to 55–60° for 18 hr. The $MeNH_2$ was evaporated and the residue was treated with CH_2Cl_2. The filtered organic phase was extracted (H_2O), dried (Na_2SO_4), and evaporated *in vacuo*. The resulting oily reaction product (31.0 g) could not be obtained in crystalline form either as the free base or as a salt.

The crude product contained only small amounts of starting material according to tlc and the ir and nmr spectra ($CDCl_3$) confirmed the structure.

Method K. 1-(2-Chloro-5-trifluoromethylphenyl)-3,4-dihydroisoquinoline Hydrochloride (14, X = CF_3).—A mixture of 122 g (0.6 mole) of phenethyl bromide (**15**, Y = Br), 134 g (0.72 mole) of 4-chloro-3-cyanobenzotrifluoride (**16**, X = CF_3) and 80 ml of $SnCl_4$ was refluxed for 5 hr. The clear solution was poured on 500 g of ice and made alkaline with 50% NaOH. The product was extracted with EtOAc. The obtained crude residue was dissolved in 200 ml of CH_2Cl_2. On saturation with HCl gas and addition of ~200 ml of Et_2O, the hydrochloride crystallized out; yield 110 g (53%). For analysis the compound was recrystallized from CH_2Cl_2–Et_2O; mp 213–216°. *Anal.* ($C_{16}H_{12}Cl_2F_3N$) C, H, Cl, N.

Method L. Optical Resolution of 1-(2-Methylamino-5-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline into Its Enantiomers.—To a hot solution of 15.0 g (0.055 mole) of DL-1-(2-methylamino-5-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline in 200 ml of EtOH was added 8.25 g (0.055 mole) of D-(+)-tartaric acid. On cooling, a neutral tartrate crystallized out and was filtered off and dried (9.0 g, 47%), mp 219–220°. The free base was liberated from this salt with dilute NaOH and extracted with two 50-ml portions of CH_2Cl_2. The combined extracts were washed (H_2O), dried (Na_2SO_4), filtered, and evaporated to an oily residue (7.0 g). On crystallization from EtOH 5.9 g (39%) of the (+) isomer was obtained as white prisms, mp 98–99°, $[\alpha]^{25}_{546}$ +48.3° (*c* 2.1, $CHCl_3$).

(−)-1-(2-Methylamino-5-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline was prepared in the same way from 15.0 g of the racemate by using 8.25 g of (−)-tartaric acid; 5.5 g (37%) of this isomer was obtained, mp 97–99°, $[\alpha]^{25}_{546}$ −48° (*c* 1.5, $CHCl_3$).

Method M. DL-1-(2-Methylamino-5-chlorophenyl)-2-carbethoxymethyl-1,2,3,4-tetrahydroisoquinoline (17, X = Cl; R = CH_3; R′ = C_2H_5).—A mixture of 15 g (55 mmoles) of **12** (X = Cl, R = CH_3), 20.0 g (120 mmoles) of ethyl bromoacetate, 12.2 g (120 mmoles) of Et_3N, and 135 ml of EtOH was refluxed for 3 hr. The clear yellow solution was concentrated to half its volume, diluted with 200 ml of H_2O, and extracted with three 100-ml portions of C_6H_6. The combined extracts were washed three times with dilute HCl to remove Et_3N and unreacted starting material. The C_6H_6 solution was dried (Na_2SO_4), filtered, and evaporated to dryness. The oily residue (15.5 g) was crystallized from EtOH to yield 10.5 g (53%) of product, mp 83–84°. *Anal.* ($C_{20}H_{23}ClN_2O_2$) C, H, Cl, N.

Method N. DL-1-(2-Methylamino-5-chlorophenyl)-2-carboxymethyl-1,2,3,4-tetrahydroisoquinoline (18, X = Cl; R = CH_3).—A solution of 7.5 g (21 mmoles) of **17** (X = Cl, R = CH_3, R′ = C_2H_5) in 40 ml of Me_2CO and 21 ml of 2 *N* aqueous NaOH was refluxed for 30 min. The acetone was removed *in vacuo*, 30 ml of EtOH was added and then 21 ml of 2 *N* HCl. The product crystallized on cooling in an ice bath and was filtered off. On concentrating the filtrate, a second crop was obtained, yield 5.85 g (84%) of white needles, mp 115–122°. *Anal.* ($C_{18}H_{19}ClN_2O_2$) C, H, Cl, N.

Method O. (+)-2-Chloro-5-methyl-5,9,10,14b-tetrahydroisoquino[2,1-*d*][1,4]benzodiazepin-6(7H)-one (20, X = Cl; R = CH_3).—A solution of 35.9 g (100 mmoles) of (−)-**17** (X = Cl; R = CH_3; R′ = C_2H_5) in 150 ml of AcOH was refluxed for 2 hr. The solution was evaporated to dryness *in vacuo* and the residue crystallized from EtOH as white prisms, yield 26.6 g (85%), mp 157–158°, $[\alpha]^{25}_{546}$ +410° (*c* 0.7, EtOH). *Anal.* ($C_{18}H_{17}ClN_2O$) C, H, N, O.

Method P. Compound (−)-20 (X = Cl; R = CH_3).—Crude amorphous (+)-**18** (X = Cl; R = CH_3), prepared by alkaline hydrolysis of 35 g (78 mmoles) of the corresponding (+)-ethyl ester (**17**, X = Cl; R = CH_3; R′ = C_2H_5), was heated in an oil bath at 140–150° for 2 hr. The product crystallized from EtOH as white prisms, mp 158°; $[\alpha]^{25}_{546}$ −411° (*c* 0.6, EtOH). A total of 25.2 g (83% over two steps) was obtained. *Anal.* ($C_{18}H_{17}ClN_2O$) C, H, N, O.

Method Q. Compound 20 (X = Cl; R = $CH_2CH{=}CH_2$).—To a solution of 6.0 g (20 mmoles) of 2-chloro-5,9,10,14b-tetrahydroisoquino[2,1-*d*][1,4]benzodiazepin-6(7H)-one (**19**, X = Cl) in 100 ml of DMF, 0.57 g (24 mmole) of NaH was added. After 30 min this mixture was heated to 75° and a solution of 2.9 g (24 mmoles) of allyl bromide in 10 ml of DMF was added dropwise over a period of 1 hr. The reaction mixture was maintained at 75° for another 30 min. The volatile parts were then removed *in vacuo*, the residual oil was dissolved in $CHCl_3$, and the organic phase was washed twice with H_2O. After drying and evaporating the solvent, the product was crystallized from CH_2Cl_2–pentane; yield 4.6 g (78%), mp 159–160°. *Anal.* ($C_{20}H_{19}ClN_2O$) C, H, Cl, O.

Method R. 2-Chloro-5-methyl-5,6,7,9,10,14b-hexahydroisoquino[2,1-*d*][1,4]benzodiazepine (21, X = Cl; R = CH_3).—2-Chloro-5-methyl-5,9,10,14b-tetrahydroisoquino[2,1-*d*][1,4]benzodiazepin-6(7H)-one (15.0 g) in 200 ml of ether was reduced by the Soxhlet method with 5.0 g of LAH. After 20 hr of reflux the reaction mixture was diluted with 200 ml of C_6H_6 and the excess LAH was destroyed by careful addition of H_2O. The organic phase was washed (H_2O), dried (Na_2SO_4), and evaporated *in vacuo*. The reduction product crystallized from ether–pentane; yield 12.5 g (85%), mp 142–144°. *Anal.* ($C_{18}H_{19}ClN_2$) C, H, Cl, N. The ir and pmr spectra confirmed the structure of the expected product.

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