

Tetrahydroisoquinolines. I. The Preparation and Analgetic Activity of Some 1-Thiophenoxyethyltetrahydroisoquinolines and 1-Phenoxyethyltetrahydroisoquinolines¹

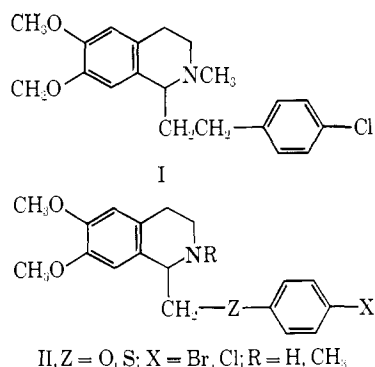
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A series of substituted 1-thiophenoxyethyltetrahydroisoquinolines (IV), their sulfoxide and sulfone analogs, and several substituted 1-phenoxyethyltetrahydroisoquinolines (IX) were synthesized and evaluated for analgetic activity. Some of these compounds demonstrated good analgetic activity when tested in mice. The preparation of 7,8-dimethoxy-3-methyl-3,4,5,9b-tetrahydroazetidino[2,1-a]isoquinolinium *p*-bromobenzenesulfonate (VIII), a key intermediate in the synthesis of IV and IX, is described.

Several 1-phenethyltetrahydroisoquinoline compounds are known to possess good analgetic activity.^{2,3} In particular, methopholine (I) has been evaluated clinically and shown to be approximately equal to codeine in analgetic potency. Recently, the syntheses of a few 1-phenoxyethyltetrahydroisoquinolines and 1-thiophenoxyethyltetrahydroisoquinolines (II) have been reported.^{4,5} These compounds show little if any analgetic activity. We have prepared several substituted 1-thiophenoxyethyltetrahydroisoquinolines,



their sulfoxide and sulfone analogs, and several 1-phenoxyethyltetrahydroisoquinolines (see Tables I-IV). A few of these compounds have shown strong analgetic activity when tested in mice.

Chemistry.—Three methods of synthesis were used for the preparation of the tetrahydroisoquinolines. The standard Bischler-Napieralski⁶ cyclization of several homoveratrylamides (III) with POCl₃ or PCl₅ followed by NaBH₄ reduction and formaldehyde-formic acid methylation worked for several of the thio compounds (IV) as shown in Chart I. The Pictet-Spengler procedure⁷ was used for the preparation of V but was generally an unsatisfactory procedure (Chart II).

Since these two synthetic methods were not satis-

(1) Some of these compounds have been described by T. A. Montzka, U. S. Patents 3,378,561 (1968) and 3,389,141 (1968).

(2) A. Brossi, H. Besendorf, L. A. Pirk, and A. H. Rheiner, Jr., in "Analgetics," G. deStevens, Ed., Academic Press, New York, N. Y., 1965, Chapter 6.

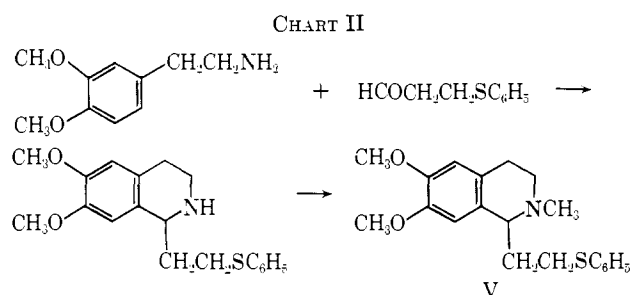
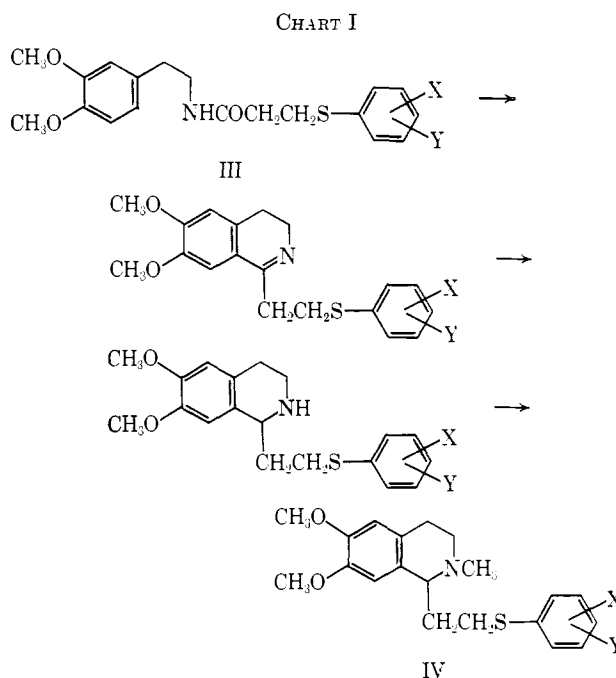
(3) (a) A. Brossi, H. Besendorf, B. Pellmont, M. Walter, and O. Schider, *Helv. Chim. Acta*, **43**, 1459 (1960); (b) M. Walter, H. Besendorf, and O. Schider, *ibid.*, **46**, 1127 (1963).

(4) I. Jirkovsky and M. Protiva, *Collect. Czech. Chem. Commun.*, **32**, 1197 (1967).

(5) R. Dorme, P. Rumpf, C. Viel, R. Morin, D. Vigier, and C. Menillet, *Bull. Soc. Chim. Fr.*, 2582 (1965).

(6) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **6**, 74 (1951).

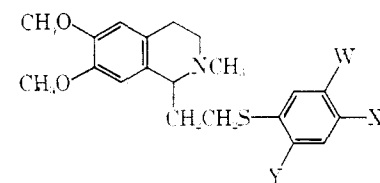
(7) W. M. Whaley and T. R. Govindachari, *ibid.*, **6**, 151 (1951).



factory for the oxygen analogs and did not lead to easy variation of the aromatic substituents, another synthetic approach was developed. The key intermediate in this scheme, 7,8-dimethoxy-3-methyl-3,4,5,9b-tetrahydroazetidino[2,1-a]isoquinolinium *p*-bromobenzenesulfonate (VIII), was synthesized as shown in Chart III. LAH reduction of the tetrahydroisoquinoline-acetic acid ester VII afforded the tetrahydroisoquinoline-ethanol VII. Treatment of VII with *p*-bromobenzenesulfonyl chloride and Na₂CO₃ in chloroform at 25° gave a good yield of the azetidinium compound VIII.⁸

(8) The piperidinium analog, 1-methyl-1-azoniabicyclo[4.2.0]octane chloride, has been reported; see (a) A. Ebnöther and E. Jucker, *Helv. Chim. Acta*, **47**, 745 (1964); (b) E. R. Lavagnino, R. R. Chauvette, W. N. Cannon, and E. C. Kornfeld, *J. Am. Chem. Soc.*, **82**, 2609 (1960).

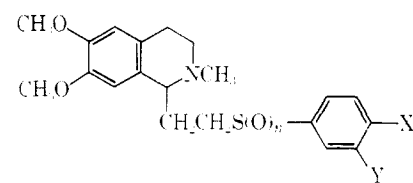
TABLE I: 6,7-DIMETHOXY-2-METHYL-1-THIOPHENOXYETHYL-TETRAHYDROISOQUINOLINES



No.	W	X	Y	Method ^a	Yield, %	Mp, °C	Crystn solvent ^b	Formula ^c
1	H	H	H	A	42	144-144.5	A	C ₂₀ H ₂₃ NO ₂ S·HCl
2	H	Cl	H	A, B	80, 70	197-199 dec	B	C ₂₀ H ₂₄ ClNO ₂ S·HCl
3	Cl	H	H	B	58	156-158	C-D	C ₂₀ H ₂₄ ClNO ₂ S·HCl
4	Cl	Cl	H	B	95	167.5-170.5	E	C ₂₀ H ₂₃ Cl ₂ NO ₂ S·HCl
5	Cl	Cl	Cl	B	46	100-101	C-F	C ₂₀ H ₂₂ Cl ₃ NO ₂ S
6	H	F	H	A	85	<i>d</i>	G	C ₂₀ H ₂₄ FNO ₂ S·HCl
7	H	Br	H	B	76	192-200 dec	B	C ₂₀ H ₂₄ BrNO ₂ S·HCl
8	H	CF ₃	H	A	80	198-212 dec	B	C ₂₁ H ₂₄ F ₃ NO ₂ S·HCl
9	H	NO ₂	H	B	61	129-131	C	C ₂₀ H ₂₄ N ₂ O ₄ S
10	H	CH ₃	H	B	89	190-194	H-I	C ₂₁ H ₂₇ NO ₂ S·HBr
11	H	OCH ₃	H	B	94	142-142.5	B	C ₂₁ H ₂₇ NO ₃ S·C ₂ H ₂ O ₄ ^e

^a Method refers to Experimental Section. ^b A = 95% EtOH, B = MeOH, C = EtOAc, D = EtOH, E = *n*-PrOH, F = Skellysolve B, G = MeCN, H = Me₂CO, I = H₂O. ^c All compounds were analyzed for C, H, N, and the analytical results obtained were within $\pm 0.4\%$ of the theoretical values. ^d Material melts at 130 and 160° with neither melting point well defined. ^e C₂H₂O₄ = oxalate.

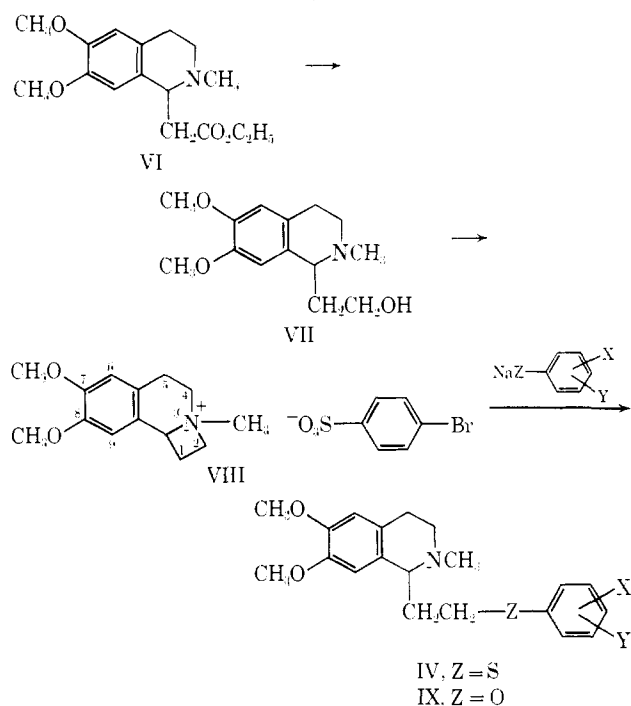
TABLE II: 6,7-DIMETHOXY-2-METHYL-1-THIOPHENOXYETHYL-TETRAHYDROISOQUINOLINE SULFOXIDES AND SULFONES



No.	X	Y	Yield, %	Mp, °C	Crystn solvent ^a	Formula ^b
12	Cl	H	51	115-127 dec	A	C ₂₀ H ₂₄ ClNO ₃ S·C ₄ H ₄ O ₄ ^c
13 ^d	Cl	Cl	61	170.5-173.5	B	C ₂₀ H ₂₃ Cl ₂ NO ₃ S·HCl
14 ^d	Cl	Cl	29	152.5-155	A-C	C ₂₀ H ₂₃ Cl ₂ NO ₃ S·HCl
15	OCH ₃	H	20	160-164 dec	A-D	C ₂₁ H ₂₇ NO ₄ S·HCl
16	Cl	H	67	147-151	A-C	C ₂₀ H ₂₄ ClNO ₄ S·HCl
17	Cl	Cl	38	188.5-193.5 dec	B	C ₂₀ H ₂₃ Cl ₂ NO ₄ S·HCl

^a A = EtOH, B = *n*-PrOH, C = EtOAc, D = Me₂CO. ^b All compounds were analyzed for C, H, N, and the analytical results obtained were within $\pm 0.4\%$ of the theoretical values. ^c C₄H₄O₄ = fumarate. ^d Diastereomers.

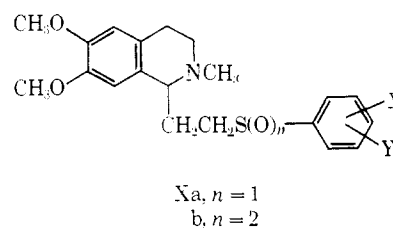
CHART III



The reaction of this compound with the Na salts of substituted phenols and thiophenols gave the desired tetrahydroisoquinolines (IV and IX) in good yields.⁹

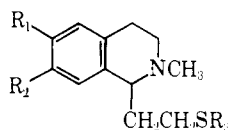
1-*p*-Chlorothiophenoxyethyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (2) was prepared both by the cyclization of the homoveratrylamide with POCl₃ and by the reaction of *p*-chlorothiophenol with VIII, thus confirming the position of the ring opening on the azetidinium ring and the structural assignment of the products.

The sulfoxides Xa and sulfones Xb were prepared by



(9) Azetidinium compounds have only recently been shown to have good alkylating properties; see (a) G. Fodor, *J. Am. Chem. Soc.*, **88**, 1040 (1966); O. E. Edwards, G. Fodor, and L. Marion, *Can. J. Chem.*, **44**, 13 (1966); (b) V. R. Gaertner, *Tetrahedron Lett.*, 343 (1967); V. R. Gaertner, *J. Org. Chem.*, **33**, 523 (1968).

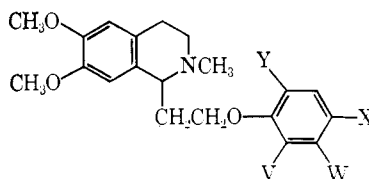
TABLE III
2-METHYL-1-SUBSTITUTED THIOETHYLTETRAHYDROISOQUINOLINES



No.	R ₁	R ₂	R ₃	Method ^a	Yield, %	Mp, °C	Crystn solvent ^b	Formula ^c
18	OCH ₃	OCH ₃		B	40	98-98.5	A	C ₂₁ H ₂₆ ClNO ₂ S
19	OCH ₃	OCH ₃		B	85	156.5-157.5	B-C	C ₁₉ H ₂₄ N ₂ O ₃ S
20	OCH ₃	OCH ₃		C	95	95-96.5	C-D	C ₁₉ H ₂₄ N ₂ O ₂ S ^d
21	OCH ₃	OCH ₃		B	71	110-135 dec	E	C ₁₉ H ₂₄ N ₂ O ₃ S · 2HCl · C ₂ H ₅ OH ^e
22	OCH ₃	OCH ₃		C	40	118-135 dec	E	C ₁₉ H ₂₄ N ₂ O ₂ S · 2HCl · C ₂ H ₅ OH ^e
23	OCH ₃	OCH ₃		A	57	180-184 dec	F-G	C ₁₉ H ₂₆ N ₂ O ₂ S ₂ · HCl
24	OH	OH		D	25	100-104	B-G	C ₁₈ H ₂₀ ClNO ₂ S · HBr · H ₂ O ^f
25	OCH ₃	H		B ^g	57	151-155	C-E	C ₁₉ H ₂₁ Cl ₂ NOS · HCl
26	H	H		B ^h	45	152-155	C-E	C ₁₈ H ₂₀ ClNS · HCl
27	H	H		B ^h	83	165-167	C-E	C ₁₈ H ₁₉ Cl ₂ NS · HCl

^a Method refers to Experimental Section. ^b A = 95% EtOH, B = MeOH, C = EtOAc, D = Skellysolve B, E = EtOH, F = Me₂CO, G = H₂O. ^c All compounds were analyzed for C, H, N, and unless otherwise indicated the analytical results obtained were within ±0.4% of the theoretical values. ^d C: calcd, 66.24; found, 65.74. ^e One mole of EtOH shows in nmr. ^f H₂O: calcd, 4.02; found, 4.38. ^g 7-Methoxy-3-methyl-3,4,5,9b-tetrahydroazetidino[2,1-a]isoquinolinium *p*-bromobenzenesulfonate (66) was used as starting material. ^h 3-Methyl-3,4,5,9b-tetrahydroazetidino[2,1-a]isoquinolinium bromide (65) was used as starting material.

TABLE IV
6,7-DIMETHOXY-2-METHYL-1-PHENOXYETHYLTETRAHYDROISOQUINOLINES



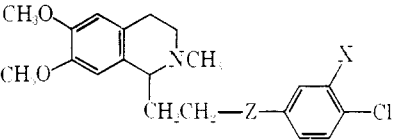
No.	V	W	X	Y	Yield, %	Mp, °C	Crystn solvent ^a	Formula ^b
28	H	H	H	H	52	181-184	A	C ₂₀ H ₂₅ NO ₃ · HCl
29	H	H	Cl	H	60	190-194	B	C ₂₀ H ₂₄ ClNO ₃ · HCl
30	H	Cl	H	H	57	177-182	C	C ₂₀ H ₂₄ ClNO ₃ · HCl
31	Cl	H	H	H	67	116.5-119.5	C	C ₂₀ H ₂₄ ClNO ₃ · HCl
32	H	Cl	Cl	H	82	171.5-174	A	C ₂₀ H ₂₃ Cl ₂ NO ₃ · HCl
33	Cl	H	H	Cl	82	185-188	C	C ₂₀ H ₂₃ Cl ₂ NO ₃ · HCl
34	Cl	H	Cl	H	61	146-149	C	C ₂₀ H ₂₃ Cl ₂ NO ₃ · HCl · 0.5H ₂ O ^c
35	Cl	Cl	H	H	85	127-129	B	C ₂₀ H ₂₃ Cl ₂ NO ₃ · HCl
36	H	H	Br	H	59	179-189	C	C ₂₀ H ₂₄ BrNO ₃ · HCl
37	H	H	F	H	62	177.5-187.5	C	C ₂₀ H ₂₄ FNO ₃ · HCl · 0.5C ₂ H ₅ OH ^d
38	H	H	NO ₂	H	58	179-189	C	C ₂₀ H ₂₄ N ₂ O ₅ · HCl
39	NO ₂	H	H	H	22	150-152	B	C ₂₀ H ₂₄ N ₂ O ₅ · HCl · 0.5H ₂ O
40	H	H	CF ₃	H	74	199-206	C	C ₂₁ H ₂₄ F ₃ NO ₃ · HCl
41	H	H	OCH ₃	H	70	178-181.5	B	C ₂₁ H ₂₇ NO ₄ · HCl

^a A = *i*-PrOH, B = EtOH, C = 95% EtOH. ^b All compounds were analyzed for C, H, N, and the analytical results obtained were within ±0.4% of the theoretical values. ^c H₂O: calcd, 2.04; found, 2.41. ^d 0.5 mole of EtOH shows in nmr.

H₂O₂ oxidation of the corresponding thio compounds IV in AcOH (see Table II).

Pharmacology.—The compounds were evaluated for analgetic activity by the mouse hot plate test.¹⁰ The average per cent increase in response time was determined at 15, 30, and 60 min after the administration of the test drug. The dose which produced a 50% increase in reaction time in 50% of the treated animals was calculated from a plot of the average proportion of animals responding (>50%) against the logarithm of the dose. The ED₅₀ was computed by the method of Litchfield and Wilcoxon.¹¹ Table V lists the most

TABLE V
ACTIVITIES AND TOXICITIES



No.	X	Z	ED ₅₀ , mg/kg sc	LD ₅₀ , mg/kg sc
2	H	S	25 ^a	975
4	Cl	S	50	>1000
12	H	SO	2	226
13	Cl	SO	0.3	160
14	Cl	SO	0.3	
16	H	SO ₂	50 ^a	
17	Cl	SO ₂	2.5	508
Codeine			15	140 ^b
<i>d</i> -Propoxyphene			16	120

^a Approximate value. ^b Reference 2.

active compounds and their LD₅₀ values. Codeine and *d*-propoxyphene are included for comparison.

The oxygen series (IX) was inactive except for minimal analgetic activity in compounds **32** and **36**. The thio compounds IV with a 4-chloro (**2**) or 3,4-dichloro (**4**) substituents showed significant activity which was generally enhanced by sulfoxide or sulfone formation. Demethylation of the 6,7-methoxyls (**24**) or removal of either the 7-methoxyl (**25**) or both methoxyls (**26** and **27**) destroyed the activity. The structural requirements for analgetic activity in this series appear quite inflexible and do not correspond to the methopholine series.^{2,3} The 4-nitro and 4-fluoro compounds in the methopholine series are very active while these analogs in our series are inactive.

Experimental Section

All melting points were determined on a Fisher-Johns melting point apparatus and are corrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Nmr and ir spectra were recorded for all compounds and are consistent with assigned structures.

Substituted β-thiophenoxypropionic acids (Table VI) were prepared by the method of Stewart and Mathes¹² using 2 equiv of NaOH and β-bromopropionic acid in place of β-propiolactone.

Substituted Thiophenoxypropionic Acid Homoveratrylamides (Table VII).—A mixture of substituted thiophenoxypropionic acid (0.5 mole) and homoveratrylamine (90 g, 0.5 mole) in 1 l. of PhMe was heated under reflux using a Dean-Stark trap to remove H₂O. When the theoretical amount of H₂O (9 ml) had

been collected, the solvent was removed at reduced pressure, and the residue was crystallized from the appropriate solvent.

6,7-Dimethoxy-1-thiophenoxyethyl-3,4-dihydroisoquinolines (Table VIII) were prepared by the cyclization¹³ of the substituted thiophenoxypropionic acid homoveratrylamides in either refluxing POCl₃-PhMe (1 hr) or in refluxing POCl₃-CHCl₃ (1.5 hr).

6,7-Dimethoxy-1-thiophenoxyethyl-1,2,3,4-tetrahydroisoquinolines (Table IX). **Method A.**—The dihydroisoquinolines were reduced to the tetrahydroisoquinolines with NaBH₄ in EtOH.

Method B.—A solution of β-thiophenoxypropionaldehyde¹³ (9.0 g, 0.054 mole) and homoveratrylamine (11.0 g, 0.61 mole) in *i*-PrOH was heated for 1 hr, then concentrated to dryness. The residue was treated with 75 ml of 24% HCl and heated for 1.5 hr on a steam bath. The warm mixture was diluted with *i*-PrOH, treated with Norit, filtered, and concentrated to dryness to leave a crystalline residue which was recrystallized twice from aqueous EtOH.

2-Methyl-1,2,3,4-tetrahydroisoquinolineacetic acid esters (Table X) were prepared from the substituted 1,2,3,4-tetrahydroisoquinolineacetic acid esters¹⁴ by methylation (CH₂O-HCO₂H).¹⁵

2-Methyl-1,2,3,4-tetrahydroisoquinolineethanols (Table XI) were prepared by LAH (THF) reduction of the esters. The hydrochlorides were formed and recrystallized from EtOH or EtOH-EtOAc.

3-Methyl-3,4,5,9b-tetrahydroazetidino[2,1-*a*]isoquinolinium Compounds (Table XII).—A stirred solution of 2-methyl-1,2,3,4-tetrahydroisoquinolineethanol (0.02 mole) in CHCl₃ (100 ml) was treated with *p*-bromobenzenesulfonyl chloride (0.022 mole). After stirring for 4 hr, anhydrous Na₂CO₃ (11.2 g) was added and the mixture was stirred for an additional 16 hr. The solids were removed by filtration and the filtrate was concentrated. The residue was either purified by crystallization from *i*-PrOH or by conversion to a bromide salt with NaBr and crystallized from EtOH-EtOAc.

2-Methyl-1-arylthioethyl-1,2,3,4-tetrahydroisoquinolines (Tables I and III). **Method A.**—The 6,7-dimethoxy-1-arylthioethyl-1,2,3,4-tetrahydroisoquinolines were methylated with CH₂O-HCO₂H.¹⁵

Method B.—A solution of arylthiol (0.01 mole) and NaOH (0.4 g, 0.01 mole) in 50 ml of EtOH was treated with 7,8-dimethoxy-3-methyl-3,4,5,9b-tetrahydroazetidino[2,1-*a*]isoquinolinium *p*-bromobenzenesulfonate (0.01 mole) and heated for 1 hr on a steam bath. After the mixture was concentrated to dryness, the residue was treated with H₂O and extracted with CHCl₃. Drying (MgSO₄) and concentration of these extracts gave the crude product which was purified by crystallization of either the free base or an acid addition salt from a suitable solvent.

Method C.—A solution of 6,7-dimethoxy-2-methyl-1-[β-(or 4)-*N*-oxyppyridylmercaptoethyl]-1,2,3,4-tetrahydroisoquinoline (4 g, 0.011 mole) in 30 ml of CHCl₃ was treated with 2.2 ml of POCl₃ and heated at reflux for 1.5 hr. The resultant solution was washed with dilute Na₂CO₃, dried (MgSO₄), and concentrated to dryness. The residue was purified by crystallization of either the free base or hydrochloride.

Method D.—A mixture of pyridine hydrochloride (20 g) and 1-(β-*p*-chlorothiophenoxyethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (3.5 g, 0.0084 mole) was heated in an oil bath at 200–220° for 25 min under N₂. The cooled mixture was taken up in 50 ml of H₂O and treated with 5 g of NaBr. The crystals were collected and recrystallized several times from MeOH-H₂O containing a trace of HBr.

Sulfoxides of 6,7-Dimethoxy-2-methyl-1-arylthioethyl-1,2,3,4-tetrahydroisoquinolines (Table II).—A suspension of 6,7-dimethoxy-2-methyl-1-arylthioethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.013 mole) in 50 ml of glacial HOAc was treated with 30% H₂O₂ (1.5 ml, 0.013 mole) and stirred for 65 hr. The HOAc was removed at reduced pressure. The residue was purified by crystallization from the appropriate solvent.

(13) K. Sirovanovic, M. Bajlon-Rocen, and D. Galovic, *Glasnik Hem. Društva, Beograd*, **25**, 26, 509 (1960–1961); *Chem. Abstr.*, **59**, 8635e (1963).

(14) (a) S. G. Agbalyan, A. O. Nshanyan, and L. A. Nersisyan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauki*, **16**, 77 (1963); *Chem. Abstr.*, **59**, 5132 (1963); (b) N. A. Nelson, K. O. Gelotte, Y. Tamura, H. B. Snelcher, J. M. Schleck, V. J. Baizer, and R. W. White, *J. Org. Chem.*, **26**, 2599 (1961); (c) A. Brossi, H. Lindlar, M. Walter, and O. Schnider, *Helv. Chim. Acta*, **41**, 419 (1958); (d) W. J. Gensler and A. L. Bluhm, *J. Org. Chem.*, **21**, 336 (1956).

(15) H. T. Clarke, H. B. Gillespie, and S. Z. Weissblau, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

(10) N. B. Eddy and D. Leimback, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953).

(11) J. T. Litchfield and F. Wilcoxon, *ibid.*, **96**, 99 (1949).

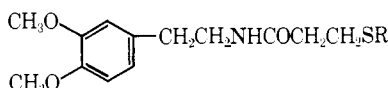
(12) F. D. Stewart and R. A. Mathes, *J. Org. Chem.*, **14**, 1111 (1949).

TABLE VI
 RSCH₂CH₂CO₂H

No.	R	Crystn solvent	Yield, %	Mp, °C	Formula	Analyses
42	4-ClC ₆ H ₄	H ₂ O-EtOH	90	87-90 ^a	C ₉ H ₉ ClO ₂ S	
43	4-CF ₃ C ₆ H ₄	<i>n</i> -Hexane	89	63-64	C ₁₀ H ₉ F ₃ O ₂ S	C, H
44	4-FC ₆ H ₄	EtOAc	95	70-72	C ₉ H ₉ FO ₂ S	C, H
45	2-C ₃ H ₆ NS ^b	C ₆ H ₆	85	66-69 ^c	C ₈ H ₁₁ NO ₂ S	

^a F. Krollpfeiffer, H. Schultze, E. Schulmbohm, and E. Sommermeyer, *Ber.*, **58**, 1654 (1925), reported mp 90-91°. ^b C₃H₆NS = 4,5-dimethylthiazolyl. ^c Lit.¹² mp 66-67°.

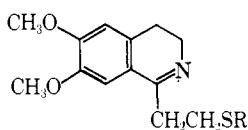
TABLE VII



No.	R	Crystn solvent	Yield, %	Mp, °C	Formula	Analyses
46	4-ClC ₆ H ₄	Me ₂ CO-H ₂ O	80	82-84	C ₁₉ H ₂₂ ClNO ₃ S	C, H, N
47	4-CF ₃ C ₆ H ₄	EtOAc-hexane	54	81-83	C ₂₀ H ₂₂ F ₃ NO ₃ S	C, H, N
48	4-FC ₆ H ₄	EtOAc-hexane	61	76-77	C ₁₉ H ₂₂ FNO ₃ S	C, H, N
49	2-C ₃ H ₆ NS ^a	Me ₂ CO-H ₂ O	26	113.5-115	C ₁₈ H ₂₄ N ₂ O ₃ S ₂	H, N; C ^b

^a C₃H₆NS = 4,5-dimethylthiazolyl. ^b C: calcd, 56.83; found, 57.32.

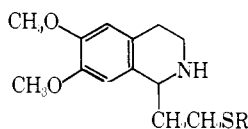
TABLE VIII



No.	R	Method	Crystn solvent	Yield, %	Mp, °C	Formula	Analyses
50	4-ClC ₆ H ₄	POCl ₃	Me ₂ CO	80	110-111	C ₁₉ H ₂₀ ClNO ₂ S	C, H, N
51	4-CF ₃ C ₆ H ₄	POCl ₃	Me ₂ CO-EtOH	65	152.5-154	C ₂₀ H ₂₀ F ₃ NO ₂ S·HCl	C, H, N
52	4-FC ₆ H ₄	PCl ₅	<i>a</i>			C ₁₉ H ₂₀ FNO ₂ S	
53	2-C ₃ H ₆ NS ^b	PCl ₅	MeOH-EtOAc	67	145-148 dec	C ₁₈ H ₂₂ N ₂ O ₂ S ₂	C, H, N

^a Material did not recrystallize well and was carried on to the next reaction without purification. ^b C₃H₆NS = 4,5-dimethylthiazolyl.

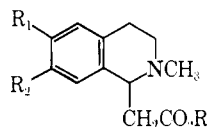
TABLE IX



No.	R	Method	Crystn solvent	Yield, %	Mp, °C	Formula	Analyses
54	C ₆ H ₅	B	EtOH-H ₂ O	23	214-216	C ₁₉ H ₂₃ NO ₂ S·HCl	C, H, N
55	4-ClC ₆ H ₄	A	MeOH	45	81-82	C ₁₉ H ₂₂ ClNO ₂ S·HCl	C, H, N
56	4-CF ₃ C ₆ H ₄	A	EtOAc	60	110-165	C ₂₀ H ₂₂ F ₃ NO ₂ S·HCl	C, H, N
57	4-FC ₆ H ₄	A	EtOAc-hexane	26	95.5-97.5	C ₁₉ H ₂₂ FNO ₂ S	C, H, N
58	2-C ₃ H ₆ NS ^a	A	Me ₂ CO-H ₂ O	50	>220	C ₁₈ H ₂₄ N ₂ O ₂ S ₂ ·HCl	C, H, N

^a C₃H₆NS = 4,5-dimethylthiazolyl.

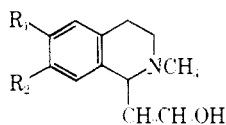
TABLE X



No.	R	R ₁	R ₂	Yield, %	Mp, °C	Formula	Analyses
59	CH ₃	H	H	90	142.5-144	C ₁₃ H ₁₇ NO ₂ ·HCl	C, H, N
60	C ₂ H ₅	OCH ₃	H	90	<i>a</i>	C ₁₅ H ₂₁ NO ₃	
61	C ₂ H ₅	OCH ₃	OCH ₃	95	179-183 ^b	C ₁₆ H ₂₃ NO ₄ ·HCl	C, H, N

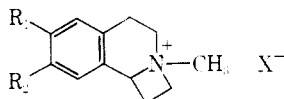
^a Material did not crystallize and was used crude in the next reaction. ^b A. Brossi, L. H. Chopard-dit-Jean, J. Würsch, and O. Schnider, *Helv. Chim. Acta*, **43**, 583 (1960), reported the HBr salt.

TABLE XI



No.	R ₁	R ₂	Yield, %	Mp, °C	Formula	Analyses
62	H	H	95	146-147	C ₁₂ H ₁₇ NO · HCl	C, H, N
63	OCH ₃	H	60	179.5-180	C ₁₃ H ₁₉ NO ₂ · HCl	C, H, N
64	OCH ₃	OCH ₃	75	179-182	C ₁₄ H ₂₁ NO ₃ · HCl	C, H, N

TABLE XII



No.	R ₁	R ₂	X	Yield, %	Mp, °C	Formula	Analyses
65	H	H	Br ^a	79	182-185	C ₁₂ H ₁₆ BrN	C, H, N
66	OCH ₃	H	C ₆ H ₄ BrO ₃ S ^a	78	141-146	C ₁₃ H ₂₀ BrNO ₃ S	C, H, N
67	OCH ₃	OCH ₃	C ₆ H ₄ BrO ₃ S ^a	72	182-184.5	C ₂₆ H ₂₄ BrNO ₃ S	C, H, N

^a C₆H₄BrO₃S = *p*-bromobenzenesulfonate.

Sulfones of 6,7-Dimethoxy-2-methyl-1-arylthioethyl-1,2,3,4-tetrahydroisoquinolines (Table II).—A suspension of 6,7-dimethoxy-2-methyl-1-arylthioethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.02 mole) in 60 ml of glacial HOAc was treated with 30% H₂O₂ (10 ml, 0.1 mole) and stirred for 7 days. After the excess AcO₂H was destroyed with aqueous Na₂S₂O₃ the mixture was concentrated to dryness under reduced pressure. The residue was treated with 10% Na₂CO₃ and extracted with CH₂Cl₂. The extracts were treated with 20 ml of 6 *N* HCl and concentrated to dryness to leave a crystalline residue which was recrystallized from the appropriate solvent.

6,7-Dimethoxy-2-methyl-1-β-phenoxyethyl-1,2,3,4-tetrahydroisoquinolines (Table IV).—A solution of substituted phenol (0.0084 mole) in 25 ml of dry DMF was treated with 0.38 g (0.0092 mole) of 58% NaH in mineral oil dispersion under N₂. After 15 min, 3.6 g (0.0076 mole) of 7,8-dimethoxy-3-methyl-

3,4,5,9b-tetrahydroazetidino[2,1-*a*]isoquinolinium-*p*-bromobenzenesulfonate was added and the mixture was stirred under N₂ for 20 hr. The DMF was removed under reduced pressure. The residue was treated with H₂O and extracted with EtOAc. The extracts were dried (MgSO₄) and concentrated to leave a residue which was taken up in MeCN, washed with pentane to remove the mineral oil, and concentrated to dryness. The resultant oil was converted to an HCl salt and crystallized from the appropriate solvent.

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Analgetic Activity of Cyclized Basic Anilides

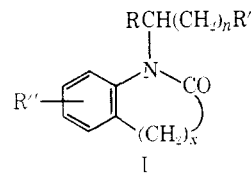
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A series of cyclized basic anilides with potential analgetic activity was synthesized. Structure-activity relationships are discussed.

In our search for new potent analgetics, we have synthesized a group of cyclized basic anilides which are structurally related to the *N*-substituted propionanilides.² It was our intention to compare the analgetic activity of the cyclic basic anilides of varying ring sizes to that of the propionanilides. The compounds reported here are listed in Tables I-IV and may be represented by the general formula I.



1,3,4,5-Tetrahydro-2H-1-benzazepin-2-one and 3,4,5,6-tetrahydro-1-benzazocin-2(1H)-one were prepared by the Schmidt reaction on α -tetralone and 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one, respectively.³ The sodium salts of the cyclic amides, prepared by treatment of the amide with NaH in xylene, were treated with the appropriate aminoalkyl halide to give the desired derivatives (*cf.* Tables III and IV).

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