Tetrahydroisoquinolines. I. The Preparation and Analgetic Activity of Some 1-Thiophenoxyethyltetrahydroisoquinolines and 1-Phenoxyethyltetrahydroisoquinolines[1]

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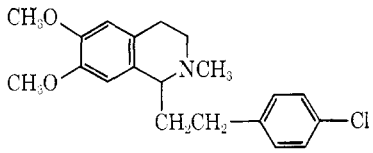
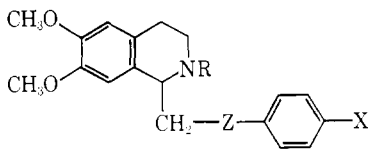
A series of substituted 1-thiophenoxyethyltetrahydroisoquinolines (IV), their sulfoxide and sulfone analogs, and several substituted 1-phenoxyethyltetrahydroisoquinolines (IX) were synthesized and evaluated for analgetic activity. Some of these compounds demonstrated good analgetic activity when tested 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-phenoxymethyltetrahydroisoquinolines and 1-thiophenoxymethyltetrahydroisoquinolines (II) have been reported.[4,5] These compounds show little if any analgetic activity. We have prepared several substituted 1-thiophenoxyethyltetrahydroisoquinolines,



I



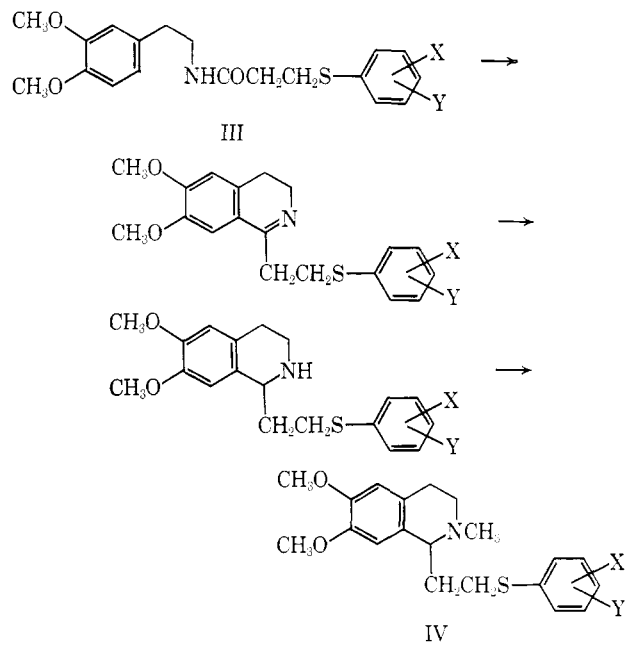
II, Z = O, S; X = Br, Cl; R = H, CH_3

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–Napieralski[6] cyclization of several homoveratrylamides (III) with $POCl_3$ or PCl_5 followed by $NaBH_4$ reduction and formaldehyde–formic acid methylation worked for several of the thio compounds (IV) as shown in Chart I. The Pictet–Spengler procedure[7] was used for the preparation of V but was generally an unsatisfactory procedure (Chart II).

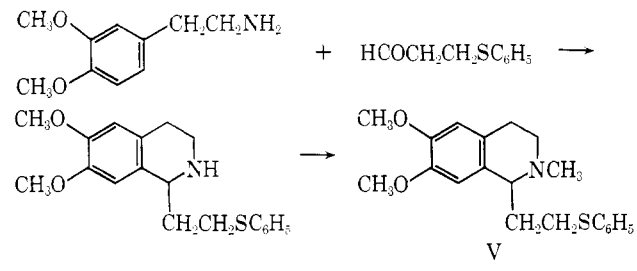
Since these two synthetic methods were not satisfactory for the oxygen analogs and did not lead to easy variation of the aromatic substituents, another synthetic approach was developed. The key intermediate in this scheme, 7,8-dimethoxy-3-methyl-3,4,5,9b-tetrahydroazetidino[2,1-*a*]isoquinolinium *p*-bromobenzenesulfonate (VIII), was synthesized as shown in Chart III. LAH reduction of the tetrahydroisoquinolineacetic acid ester VI afforded the tetrahydroisoquinolineethanol VII. Treatment of VII with *p*-bromobenzenesulfonyl chloride and Na_2CO_3 in chloroform at 25° gave a good yield of the azetidinium compound VIII.[8]

CHART I



III IV

CHART II



V

(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. Peilmont, M. Walter, and O. Schider, *Helv. Chim. Acta*, **43**, 1459 (1960); (b) M. Walter, H. Besendorf, and O. Schnider, *ibid.*, **46**, 1127 (1963).

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

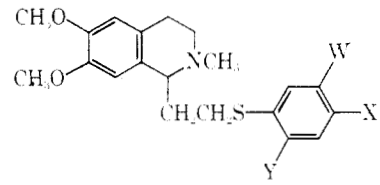
(5) R. Dorme, P. Rumpf, C. Viel, R. Morin, D. Vigier, and C. Menillet, *Bull. Soc. Chim. Fr.*, 2582 (1965).

(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).

(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).

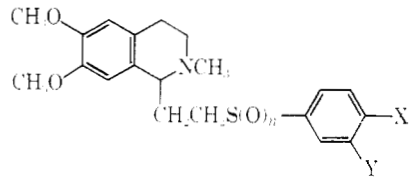
TABLE I: 6,7-DIMETHOXY-2-METHYL-1-THIOPHENOXYETHYLTETRAHYDROISOQUINOLINES



No.	W	X	Y	Method[a]	Yield, %	Mp, °C	Crystn solvent[b]	Formula[c]
1	H	H	H	A	42	144–144.5	A	$C_{20}H_{27}NO_2S \cdot HI$
2	H	Cl	H	A, B	80, 70	197–199 dec	B	$C_{20}H_{24}ClNO_2S \cdot HCl$
3	Cl	H	H	B	58	156–158	C–D	$C_{20}H_{24}ClNO_2S \cdot HCl$
4	Cl	Cl	H	B	95	167.5–170.5	E	$C_{20}H_{23}Cl_2NO_2S \cdot HCl$
5	Cl	Cl	Cl	B	46	100–101	C–F	$C_{20}H_{22}Cl_3NO_2S$
6	H	F	H	A	85	*d*	G	$C_{20}H_{24}FNO_2S \cdot HCl$
7	H	Br	H	B	76	192–200 dec	B	$C_{20}H_{24}BrNO_2S \cdot HCl$
8	H	CF_3	H	A	80	198–212 dec	B	$C_{21}H_{24}F_3NO_2S \cdot HCl$
9	H	NO_2	H	B	61	129–131	C	$C_{20}H_{24}N_2O_4S$
10	H	CH_3	H	B	89	190–194	H–I	$C_{21}H_{27}NO_2S \cdot HBr$
11	H	OCH_3	H	B	94	142–142.5	B	$C_{21}H_{27}NO_3S \cdot C_2H_2O_4$[e]

[a] Method refers to Experimental Section. [b] A = 95% EtOH, B = MeOH, C = EtOAc, D = EtOH, E = *i*-PrOH, F = Skellysolve B, G = MeCN, H = Me_2CO, I = H_2O. [c] All compounds were analyzed for C, H, N, and the analytical results obtained were within ±0.4% of the theoretical values. [d] Material melts at 130 and 160° with neither melting point well defined. [e] $C_2H_2O_4$ = oxalate.

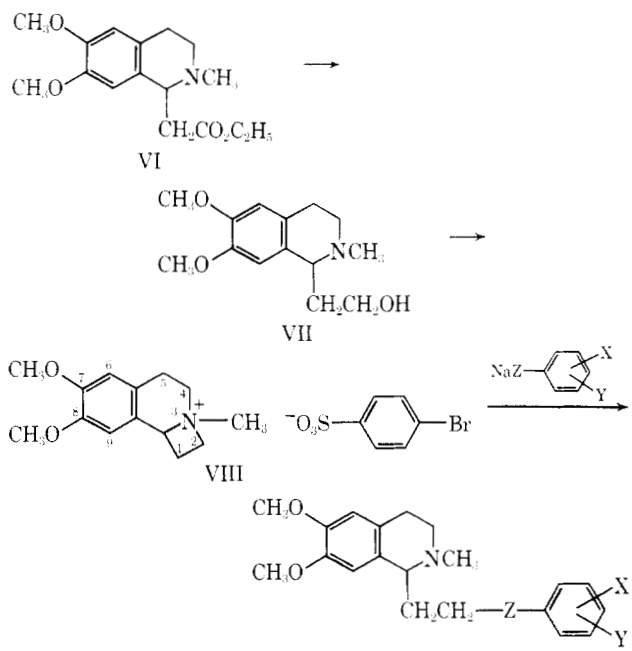
TABLE II: 6,7-DIMETHOXY-2-METHYL-1-THIOPHENOXYETHYLTETRAHYDROISOQUINOLINE SULFOXIDES AND SULFONES



No.	*n*	X	Y	Yield, %	Mp, °C	Crystn solvent[a]	Formula[b]
12	1	Cl	H	51	115–127 dec	A	$C_{20}H_{24}ClNO_3S \cdot C_4H_4O_4$[c]
13[d]	1	Cl	Cl	61	170.5–173.5	B	$C_{20}H_{23}Cl_2NO_3S \cdot HCl$
14[d]	1	Cl	Cl	29	152.5–155	A–C	$C_{20}H_{23}Cl_2NO_3S \cdot HCl$
15	1	OCH_3	H	20	160–164 dec	A–D	$C_{21}H_{27}NO_4S \cdot HCl$
16	2	Cl	H	67	147–151	A–C	$C_{20}H_{24}ClNO_4S \cdot HCl$
17	2	Cl	Cl	38	188.5–193.5 dec	B	$C_{20}H_{23}Cl_2NO_4S \cdot HCl$

[a] A = EtOH, B = *n*-PrOH, C = EtOAc, D = Me_2CO. [b] All compounds were analyzed for C, H, N, and the analytical results obtained were within ±0.4% of the theoretical values. [c] $C_4H_4O_4$ = fumarate. [d] Diastereomers.

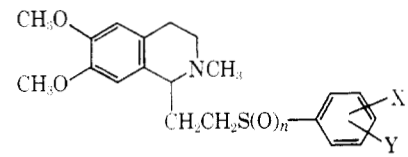
CHART III



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 $POCl_3$ 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

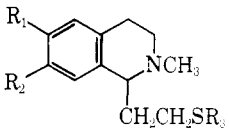


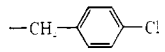
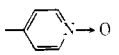
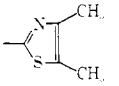
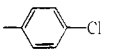
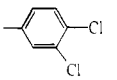
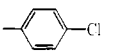
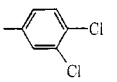
Xa, $n = 1$
b, $n = 2$

(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

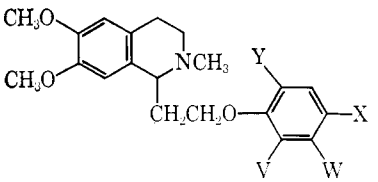


No.	R_1	R_2	R_3	Method[a]	Yield, %	Mp, °C	Crystn solvent[b]	Formula[c]
18	OCH_3	OCH_3		B	40	98–98.5	A	$C_{21}H_{26}ClNO_2S$
19	OCH_3	OCH_3		B	85	156.5–157.5	B–C	$C_{19}H_{24}N_2O_3S$
20	OCH_3	OCH_3		C	95	95–96.5	C–D	$C_{19}H_{24}N_2O_2S$[d]
21	OCH_3	OCH_3		B	71	110–135 dec	E	$C_{19}H_{24}N_2O_3S \cdot 2HCl \cdot C_2H_5OH$[e]
22	OCH_3	OCH_3		C	40	118–135 dec	E	$C_{19}H_{24}N_2O_2S \cdot 2HCl \cdot C_2H_5OH$[e]
23	OCH_3	OCH_3		A	57	180–184 dec	F–G	$C_{19}H_{26}N_2O_2S_2 \cdot HCl$
24	OH	OH		D	25	100–104	B–G	$C_{18}H_{20}ClNO_2S \cdot HBr \cdot H_2O$[f]
25	OCH_3	H		B[g]	57	151–155	C–E	$C_{19}H_{21}Cl_2NOS \cdot HCl$
26	H	H		B[h]	45	152–155	C–E	$C_{18}H_{20}ClNS \cdot HCl$
27	H	H		B[h]	83	165–167	C–E	$C_{18}H_{19}Cl_2NS \cdot HCl$

[a] Method refers to Experimental Section. [b] A = 95% EtOH, B = MeOH, C = EtOAc, D = Skellysolve B, E = EtOH, F = Me_2CO, G = H_2O. [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] H_2O: 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	$C_{20}H_{25}NO_3 \cdot HCl$
29	H	H	Cl	H	60	190–194	B	$C_{20}H_{24}ClNO_3 \cdot HCl$
30	H	Cl	H	H	57	177–182	C	$C_{20}H_{24}ClNO_3 \cdot HCl$
31	Cl	H	H	H	67	116.5–119.5	C	$C_{20}H_{24}ClNO_3 \cdot HCl$
32	H	Cl	Cl	H	82	171.5–174	A	$C_{20}H_{23}Cl_2NO_3 \cdot HCl$
33	Cl	H	H	Cl	82	185–188	C	$C_{20}H_{23}Cl_2NO_3 \cdot HCl$
34	Cl	H	Cl	H	61	146–149	C	$C_{20}H_{23}Cl_2NO_3 \cdot HCl \cdot 0.5H_2O$[c]
35	Cl	Cl	H	H	85	127–129	B	$C_{20}H_{23}Cl_2NO_3 \cdot HCl$
36	H	H	Br	H	59	179–189	C	$C_{20}H_{24}BrNO_3 \cdot HCl$
37	H	H	F	H	62	177.5–187.5	C	$C_{20}H_{24}FNO_3 \cdot HCl \cdot 0.5C_2H_5OH$[d]
38	H	H	NO_2	H	58	179–189	C	$C_{20}H_{24}N_2O_5 \cdot HCl$
39	NO_2	H	H	H	22	150–152	B	$C_{20}H_{24}N_2O_5 \cdot HCl \cdot 0.5H_2O$
40	H	H	CF_3	H	74	199–206	C	$C_{21}H_{24}F_3NO_3 \cdot HCl$
41	H	H	OCH_3	H	70	178–181.5	B	$C_{21}H_{27}NO_4 \cdot HCl$

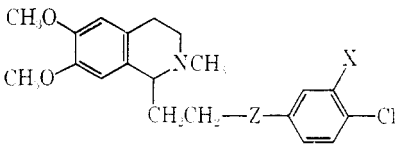
[a] A = *i*-PrOH, B = EtOH, C = 95% EtOH. [b] All compounds were analyzed for C, H, N, and the analytical results obtained were within ±0.4% of the theoretical values. [c] H_2O: calcd, 2.04; found, 2.41. [d] 0.5 mole of EtOH shows in nmr.

H_2O_2 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 ED_{50} 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	80	>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]
d-Propoxyphene			16	120

[a] Approximate value. [b] Reference 2.

active compounds and their LD_{50} 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%. 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 Mathes[12] 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 H_2O. When the theoretical amount of H_2O (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 cyclization[6] of the substituted thiophenoxypropionic acid homoveratrylamides in either refluxing $POCl_3$–PhMe (1 hr) or in refluxing PCl_5–$CHCl_3$ (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 $NaBH_4$ in EtOH.

Method B.—A solution of β-thiophenoxypropionaldehyde[13] (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 esters[14] by methylation (CH_2O–HCO_2H).[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 $CHCl_3$ (100 ml) was treated with *p*-bromobenzenesulfonyl chloride (0.022 mole). After stirring for 4 hr, anhydrous Na_2CO_3 (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 CH_2O–HCO_2H.[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 H_2O and extracted with $CHCl_3$. Drying ($MgSO_4$) 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-2(or 4)-N-oxypyridylmercaptoethyl]-1,2,3,4-tetrahydroisoquinoline (4 g, 0.011 mole) in 30 ml of $CHCl_3$ was treated with 2.2 ml of PCl_3 and heated at reflux for 1.5 hr. The resultant solution was washed with dilute Na_2CO_3, dried ($MgSO_4$), 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 N_2. The cooled mixture was taken up in 50 ml of H_2O and treated with 5 g of NaBr. The crystals were collected and recrystallized several times from MeOH–H_2O 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% H_2O_2 (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.

(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).

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

(14) (a) S. G. Agbalyan, A. O. Nshanyan, and L. A. Nersesyan, *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. Sinclair, J. M. Schuck, V. J. Bauer, and R. W. White, *J. Org. Chem.*, **26**, 2599 (1961); (c) A. Brossi, H. Lindlar, M. Walter, and O. Schnider, *Helv. Chim. Acta*, **41**, 119 (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. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

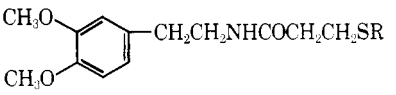
TABLE VI

$RSCH_2CH_2CO_2H$

No.	R	Crystn solvent	Yield, %	Mp, °C	Formula	Analyses
42	$4\text{-}ClC_6H_4$	H_2O–EtOH	90	87–90[a]	$C_9H_9ClO_2S$	
43	$4\text{-}CF_3C_6H_4$	*n*-Hexane	89	63–64	$C_{10}H_9F_3O_2S$	C, H
44	$4\text{-}FC_6H_4$	EtOAc	95	70–72	$C_9H_9FO_2S$	C, H
45	$2\text{-}C_5H_6NS$[b]	C_6H_6	85	66–69[c]	$C_8H_{11}NO_2S$	

[a] F. Krollpfeiffer, H. Schultze, E. Schulmbohm, and E. Sommermeyer, *Ber.*, **58**, 1654 (1925), reported mp 90–91°. [b] C_5H_6NS = 4,5-dimethylthiazolyl. [c] Lit.[12] mp 66–67°.

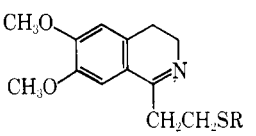
TABLE VII



No.	R	Crystn solvent	Yield, %	Mp, °C	Formula	Analyses
46	$4\text{-}ClC_6H_4$	Me_2CO–H_2O	80	82–84	$C_{19}H_{22}ClNO_3S$	C, H, N
47	$4\text{-}CF_3C_6H_4$	EtOAc–hexane	54	81–83	$C_{20}H_{22}F_3NO_3S$	C, H, N
48	$4\text{-}FC_6H_4$	EtOAc–hexane	61	76–77	$C_{19}H_{22}FNO_3S$	C, H, N
49	$2\text{-}C_5H_6NS$[a]	Me_2CO–H_2O	26	113.5–115	$C_{18}H_{24}N_2O_3S_2$	H, N; C[b]

[a] C_5H_6NS = 4,5-dimethylthiazolyl. [b] C: calcd, 56.83; found, 57.32.

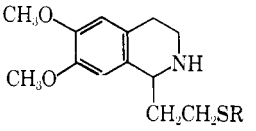
TABLE VIII



No.	R	Method	Crystn solvent	Yield, %	Mp, °C	Formula	Analyses
50	$4\text{-}ClC_6H_4$	$POCl_3$	Me_2CO	80	110–111	$C_{19}H_{20}ClNO_2S$	C, H, N
51	$4\text{-}CF_3C_6H_4$	$POCl_3$	Me_2CO–EtOH	65	152.5–154	$C_{20}H_{20}F_3NO_2S\cdot HCl$	C, H, N
52	$4\text{-}FC_6H_4$	PCl_5	*a*			$C_{19}H_{20}FNO_2S$	
53	$2\text{-}C_5H_6NS$[b]	PCl_5	MeOH–EtOAc	67	145–148 dec	$C_{18}H_{22}N_2O_2S_2$	C, H, N

[a] Material did not recrystallize well and was carried on to the next reaction without purification. [b] C_5H_6NS = 4,5-dimethylthiazolyl.

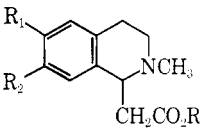
TABLE IX



No.	R	Method	Crystn solvent	Yield, %	Mp, °C	Formula	Analyses
54	C_6H_5	B	EtOH–H_2O	23	214–216	$C_{19}H_{23}NO_2S\cdot HCl$	C, H, N
55	$4\text{-}ClC_6H_4$	A	MeOH	45	81–82	$C_{19}H_{22}ClNO_2S\cdot HCl$	C, H, N
56	$4\text{-}CF_3C_6H_4$	A	EtOAc	60	110–165	$C_{20}H_{22}F_3NO_2S\cdot HCl$	C, H, N
57	$4\text{-}FC_6H_4$	A	EtOAc–hexane	26	95.5–97.5	$C_{19}H_{22}FNO_2S$	C, H, N
58	$2\text{-}C_5H_6NS$[a]	A	Me_2CO–H_2O	50	>220	$C_{18}H_{24}N_2O_2S_2\cdot HCl$	C, H, N

[a] C_5H_6NS = 4,5-dimethylthiazolyl.

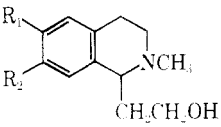
TABLE X



No.	R	R_1	R_2	Yield, %	Mp, °C	Formula	Analyses
59	CH_3	H	H	90	142.5–144	$C_{13}H_{17}NO_2\cdot HCl$	C, H, N
60	C_2H_5	OCH_3	H	90	*a*	$C_{15}H_{21}NO_3$	
61	C_2H_5	OCH_3	OCH_3	95	179–183[b]	$C_{16}H_{23}NO_4\cdot HCl$	C, H, N

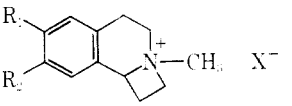
[a] Material did not crystallize and was used crude in the next reaction. [b] A. Brossi, L. H. Chopard-dit-Jean, J. Würsch, and O. Schnider, *Helv. Chim. Acta*, **43**, 583 (1960), reported the HBr salt.

TABLE XI



No.	R_1	R_2	Yield, %	Mp, °C	Formula	Analyses
62	H	H	95	146–147	$C_{12}H_{17}NO \cdot HCl$	C, H, N
63	OCH_3	H	60	179.5–180	$C_{13}H_{19}NO_2 \cdot HCl$	C, H, N
64	OCH_3	OCH_3	75	179–182	$C_{14}H_{21}NO_3 \cdot HCl$	C, H, N

TABLE XII



No.	R_1	R_2	X	Yield, %	Mp, °C	Formula	Analyses
65	H	H	Br	79	182–185	$C_{12}H_{16}BrN$	C, H, N
66	OCH_3	H	$C_6H_4BrO_3S^a$	78	141–146	$C_{19}H_{22}BrNO_4S$	C, H, N
67	OCH_3	OCH_3	$C_6H_4BrO_3S^a$	72	182–184.5	$C_{20}H_{24}BrNO_5S$	C, H, N

[a] $C_6H_4BrO_3S$ = *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% H_2O_2 (10 ml, 0.1 mole) and stirred for 7 days. After the excess AcO_2H was destroyed with aqueous $Na_2S_2O_3$ the mixture was concentrated to dryness under reduced pressure. The residue was treated with 10% Na_2CO_3 and extracted with CH_2Cl_2. 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 N_2. 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 N_2 for 20 hr. The DMF was removed under reduced pressure. The residue was treated with H_2O and extracted with EtOAc. The extracts were dried ($MgSO_4$) 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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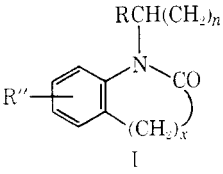
A series of cyclized basic anilides with potential analgetic activity was synthesized. Structure–activity relationships are discussed.

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.



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).

(1) To whom communications should be directed.

(2) (a) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **81**, 1518 (1959); *J. Org. Chem.*, **26**, 476,485 (1961); (b) W. B. Wright, Jr., *ibid.*, **25**, 1033 (1960); (c) N. Shigematsu, *Yakugaku Zasshi*, **81**, 423, 815 (1961); (d) N. Sugimoto, K. Okumara, N. Shigematsu, and G. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **10**, 1061 (1962); (e) G. Hyashi, N. Shigematsu, and Y. Kowa, *Yakugaku Zasshi*, **81**, 62 (1963); (f) P. M. Carabateas, W. F. Wetterau, and L. Grumbach, *J. Med. Chem.*, **6**, 355 (1963); (g) O. E. Fancher, S. Hayao, W. G. Strycker, and L. F. Sancilio, *ibid.*, **7**, 721 (1964).

(3) N. S. Hjelte and T. Agback, *Acta Chem. Scand.*, **18**, 191 (1964).