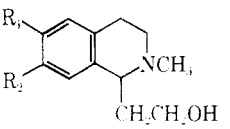
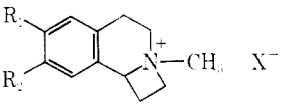
TABLE XI



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.

Acknowledgment.—The authors wish to express their appreciation to Drs. Max E. Bierwagen and Anthony W. Pircio and their staffs for the pharmacological data and to the analytical and spectroscopic departments for their services.

Analgetic Activity of Cyclized Basic Anilides

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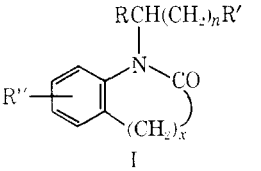
A series of cyclized basic anilides with potential analgetic activity was synthesized. Structure–activity relationships are discussed.

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).

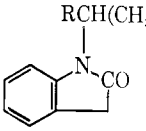
(1) To whom communications should be directed.

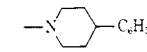
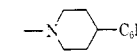
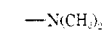
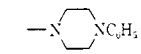
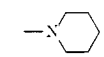
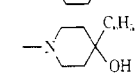
(2) (a) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **81**, 1518 (1959); *J. Org. Chem.*, **26**, 476,485 (1961); (b) W. B. Wright, Jr., *ibid.*, **25**, 1033 (1960); (c) N. Shigematsu, *Yakugaku Zasshi*, **81**, 423, 815 (1961); (d) N. Sugimoto, K. Okumara, N. Shigematsu, 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).

TABLE I

BASIC 1-SUBSTITUTED 2-INDOLINONE SALTS

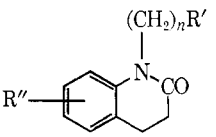


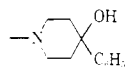
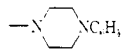
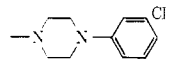
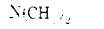
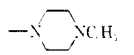
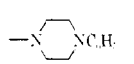
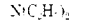
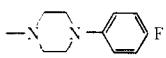
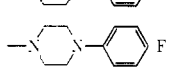
No.	R	R′	n	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses
1	H		1	32.5	200–201	MeOH–*i*-PrOH–Et_2O	$C_{21}H_{24}N_2O \cdot C_2H_2O_4$	H, N; C[a]
2	H		2	23	136–138	MeOH–EtOAc–Et_2O	$C_{22}H_{26}N_2O \cdot C_2H_2O_4$	N(total), N(basic)
3	H		2	38	183–185	*i*-PrOH–EtOAc	$C_{13}H_{18}N_2O \cdot HCl$	N, Cl
4	H		2	27	148–150	*i*-PrOH–Et_2O	$C_{21}H_{25}N_3O \cdot C_4H_4O_4$	N(total), N(basic)
5	CH_3		1	39.5	190–192	MeOH–EtOAc	$C_{16}H_{22}N_2O \cdot C_2H_2O_4$	H, N; C[b]
6	H		1	53.5	234–236	*i*-PrOH	$C_{21}H_{24}N_2O_2 \cdot HCl$	C, H, N

[a] C: calcd, 67.29; found, 66.54. [b] C: calcd, 62.05; found, 61.54.

TABLE II

SALTS OF BASIC 3,4-DIHYDROCARBOSTYRIL DERIVATIVES



No.	R′	R″	n	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses
7		H	2	10	237–238	MeOH–H_2O–DMF	$C_{22}H_{26}N_2O_2 \cdot 0.5C_2H_2O_4$	C, H, N
8		H	3	40	210–211	*i*-PrOH–H_2O–Et_2O	$C_{22}H_{27}N_3O \cdot C_2H_2O_4$	C, H, N
9		H	3	50	137–139	*i*-PrOH–EtOAc–Et_2O	$C_{22}H_{26}ClN_3O \cdot C_4H_4O_4$	H, N; C[a]
10		H	3	50	178–179	MeOH–Et_2O	$C_{14}H_{20}N_2O \cdot C_2H_2O_4$[b]	
11		6-$OCH_2C_6H_5$	3	40	185–186	MeOH–Et_2O	$C_{29}H_{33}N_3O_2 \cdot C_2H_2O_4$	C, H, N
12		6-OH	3	40	245–246	MeOH–DMF–H_2O	$C_{22}H_{27}N_3O_2 \cdot C_2H_2O_4$	C, H, N
13		H	2	15	164–165	MeOH–DMF–H_2O	$C_{15}H_{22}N_2O \cdot C_2H_2O_4$[b]	
14		7-$OCH_2C_6H_5$	3	18	163–164	MeOH–Et_2O	$C_{29}H_{32}FN_3O_2 \cdot C_2H_2O_4$	C, H, N
15		7-OH	3	11	209–210	MeOH–Et_2O	$C_{22}H_{26}FN_3O_2 \cdot 0.5C_2H_2O_4$	C, H, N

[a] C: calcd, 62.58; found, 61.92. [b] Reference 4.

3,4-Dihydrocarbostyril, 6-benzyloxy-3,4-dihydrocarbostyril, and 7-benzyloxy-3,4-dihydrocarbostyril were prepared according to the procedure of Shigematsu.[4] The desired derivatives of 3,4-dihydrocarbostyril (Table II) were prepared by the same method as the other ring systems. The hydroxyl derivatives were obtained by debenzylation of the benzyloxy derivatives with 10% Pd–C and H_2.

The 1-substituted derivatives of 2-indolinone (Table I) were prepared by treatment of the sodium salt of 2-indolinone with the appropriate aminoalkyl halide in an autoclave.

Pharmacology.—Analgetic activity of the cyclized basic anilides was determined by the subcutaneous or intraperitoneal routes by the method of Bianchi and Franceschini.[5] At 30 min following the subcutaneous administration or 5, 15, and 30 min following the intraperitoneal administration of the test compound, an artery clip (serrefine clamp) was placed at the base of the tail. Analgesia was considered present if the animal failed to bite the clip within 30 sec. Twenty animals were used at each dose level, and the median analgetic dose (AD_{50}) was determined by the Litchfield–Wilcoxon method[6] using a minimum of three doses.

Compounds **17** and **21** demonstrated analgetic activity which was comparable to meperidine (Table V). Carabateas, *et al.*, report the analgetic potency of

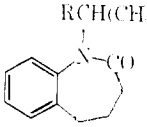
(4) N. Shigematsu, *Chem. Pharm. Bull.* (Tokyo), **9**, 970 (1961).

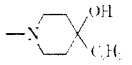
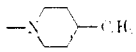
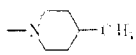
(5) C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954).

(6) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).

TABLE III

BASIC 1-SUBSTITUTED 1,3,4,5-TETRAHYDRO-2H-1-BENZAZEPIN-2-ONES

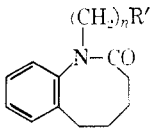


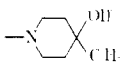
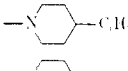
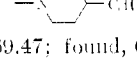
No.	R	R'	n	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses
16	H		1	20	117–119	MeOH–H_2O	$C_{23}H_{28}N_2O_2 \cdot C_2H_2O_4 \cdot H_2O$	C, H, N
17	H		2	80	220–222[a]		$C_{24}H_{30}N_2O$	C, H, N
18	H	$N(CH_3)_2$	2	24	165–166.5	MeOH–Et_2O	$C_{15}H_{22}N_2O \cdot C_2H_2O_4$	H, N; C[b]
19	H		1	25	228–229	MeOH–Et_2O	$C_{23}H_{28}N_2O \cdot HCl$	C, H, N
20	$-CH_3$		1	24	197–199	MeOH–Et_2O	$C_{18}H_{20}N_2O \cdot C_2H_2O_4$	H, N; C[c]

[a] Boiling point (0.3 mm). [b] C: calcd, 60.70; found, 60.17. [c] C: calcd, 63.80; found, 63.15.

TABLE IV

BASIC 1-SUBSTITUTED 3,4,5,6-TETRAHYDRO-1-BENZAZOCIN-2(1H)-ONES



No.	R'	n	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses
21		2	12	237–238	MeOH–Et_2O	$C_{24}H_{30}N_2O_2 \cdot HCl$	H, N; C[a]
22		2	18	225–227	MeOH–Et_2O	$C_{23}H_{30}N_2O \cdot HCl$	C, H, N
23		3	70	229–230[b]		$C_{25}H_{32}N_2O$	N(total), N(basic)

[a] C: calcd, 69.47; found, 68.98. [b] Boiling point (0.1 mm).

TABLE V

THE ANALGETIC ACTIVITY OF CYCLIZED BASIC ANILIDES IN THE ARTERY CLIP ASSAY IN MICE

No.	AD_{50},[a] mg/kg[b]
1	>50 ip
2	>25 sc
3	>42.8 sc
4	>54.7 sc
5	>50 ip
6	>10[c] ip
7	>90 ip
8	>39.8 sc
9	>50 sc
10	>100 sc
11	>50 sc
12	>27.3 sc
13	>75 sc
14	~100 sc
15	>100 sc
16	~20[d]
17	12.0 (8.8–16.5) sc
18	>53.8 sc
19	>16 ip
20	>50 ip
21	12.7 (9.3–17.4) ip
22	23.8 (20.6–34.8) ip
23	>50 ip
Meperidine HCl	16.2 (12.2–21.6) sc
	8.6 (6.0–12.3) ip

[a] Median analgetic dose (95% confidence limits). [b] Base. [c] At 100 mg/kg, 100% death. [d] Higher doses produce toxic effects.

1-(2-N-phenylpropionamidoethyl)-4-phenyl-4-piperidinol to be 50 times that of meperidine.[2f] The analgetic activity of **21** decreased by one-half upon removing the 4-hydroxy group on the 4-phenylpiperidine moiety. Reduction of the size of the ring to seven-, six-, and five-membered structures (**16**, **7**, and **6**, respectively) further decreased the analgetic properties. With respect to **17**, analgesia was decreased upon increasing the ring size to eight members (**23**) or decreasing it to five members (**2**).

Experimental Section[7]

The following detailed procedures are representative of the preparation of compounds with varied ring sizes.

1-[2-(4-Hydroxy-4-phenyl-1-piperidyl)ethyl]-2-indolinone Hydrochloride (6).—A mixture of 2-indolinone (7.4 g, 0.056 mole), 1-(2-chloroethyl)-4-hydroxy-4-phenylpiperidine hydrobromide (18 g, 0.056 mole), and 6.1 g (0.113 mole) of NaOMe was suspended in 50 ml of C_6H_6 and the mixture was heated in a steel autoclave at 110–120° for 3 hr. The mixture was filtered and the red filtrate was concentrated. The residual red oil was treated with HCl. The nonbasic material was extracted with $CHCl_3$. The hydrochloride, which was insoluble in both H_2O and $CHCl_3$, was recrystallized from *i*-PrOH; yield 10 g. For further purification, the material was sublimed (160°, 0.5 mm) and again recrystallized from *i*-PrOH; yield 2.5 g, mp 234–236°.

(7) All melting points are uncorrected and were determined with a Büchi capillary melting point apparatus (W. Büchi, Glasapparatefabrik, Flawil, Switzerland). Ir spectra were determined with a Perkin-Elmer Model 237 grating spectrophotometer. Titrations were carried out with a Sargent Model D recording titrator. Where analyses are indicated by symbols, the elements or functions were within ±0.4% of the calculated values.

3,4,5,6-Tetrahydro-1-[2-(4-hydroxy-4-phenyl-1-piperidyl)-ethyl]-1-benzazocin-2(1H)-one Hydrochloride (21).—To 10.0 g (0.057 mole) of 3,4,5,6-tetrahydrobenzazocin-2(1H)-one in 100 ml of xylene was carefully added 3.0 g of NaH with stirring. The reaction mixture was then refluxed with stirring for 2 hr. To the mixture was added 3.0 g of NaH and 19.2 g (0.06 mole) of 1-(2-chlorethyl)-4-hydroxy-4-phenylpiperidine hydrobromide. The reaction mixture was stirred under reflux for 8 hr, then treated with H_2O and $CHCl_3$. The organic solvents were concentrated *in vacuo* leaving an oily residue. The starting amide was removed by vacuum distillation; the remaining residue weighed 17.0 g. The hydrochloride was prepared by adding excess HCl in *i*-PrOH to a solution of the base in MeOH. Upon addition of Et_2O, a solid formed which was recrystallized three times from MeOH–Et_2O; yield 3.5 g, mp 237–238°.

1-[3-(4-*p*-Fluorophenyl-1-piperazyl)propyl]-3,4-dihydro-7-hydroxycarbostyril Hemioxalate (15).—To 15.0 g (0.032 mole) of 7-benzyloxy-1-[3-(4-*p*-fluorophenyl-1-piperazyl)propyl]-3,4-dihydrocarbostyril in 200 ml of absolute EtOH was added 2.5 g of 10% Pd–C and the mixture was hydrogenated at 3.5 kg/cm² for 2 hr. The solution was filtered to remove the catalyst and the filtrate was concentrated *in vacuo* leaving an oil. The oxalate was prepared by adding 3.0 g (0.034 mole) of oxalic acid in Et_2O to 13.0 g (0.034 mole) of the free base. A solid material was obtained which was recrystallized from MeOH–Et_2O; yield 5.0 g, mp 209–210°.

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Synthesis and Analgetic Activity of Some 1-Substituted 3-Pyrrolidinylanilides and Dihydrobenzoxazinones

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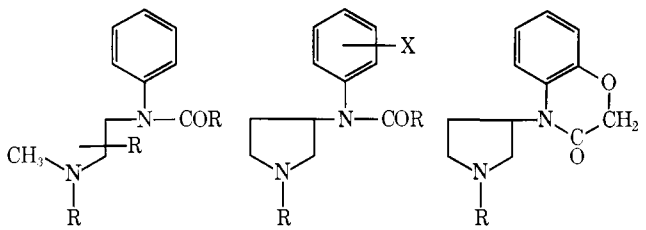
Some 1-substituted 3-pyrrolidinylanilides and 1-substituted 3-pyrrolidinyl-2H-1,4-benzoxazin-3(4H)-ones have been prepared and tested for analgetic activity. Several of the compounds show moderate to potent activity.

Anilides of the structural type I have been shown to be strong analgetics.[1] In this paper the preparation and analgetic properties of a series of 1-substituted 3-pyrrolidinylanilides (II) and dihydrobenzoxazinones (III) are described. These structures can be viewed as cyclized versions of I.



I II III

Chemistry.—The synthetic routes used to obtain these compounds are shown in Chart I. The anilinopyrrolidines (V) were prepared by the nucleophilic displacement of the toluenesulfonate ester of a 3-pyrrolidinol or a 3-bromopyrrolidine (IV) by an aniline derivative. This tosylate displacement reaction has been previously reported.[2] The properties of new compounds are given in Table I. The N-substituent was varied by starting with the appropriate 1-substituted pyrrolidine (IV) or by catalytically hydrogenating the 1-benzylpyrrolidine (V, R = benzyl) to the corresponding secondary amine and alkylating with the appropriate alkyl halide. Treatment of the anilinopyrrolidines with an acid chloride or anhydride gave the anilides (VI) in good yield. The hydroxyanilides (VI, X = OH) were prepared by the reaction of the hydroxyanilinopyrrolidines and 2 equiv of propionic anhydride or propionyl chloride and subsequent hydrolysis of the ester with dilute NaOH. The first equivalent of anhydride or acid chloride gave a mixture of ester and amide as shown by ir and nmr spectra.

The dihydrobenzoxazinones (IX) were prepared by the reaction of the 2-hydroxyanilinopyrrolidines (VII) with chloroacetyl chloride and treatment of the resulting amide (VIII) with base.

The experimental details are given in Tables I–III and in the Experimental Section.

The ir and nmr spectra of the compounds described are consistent with the proposed structures. It is interesting to note, however, that the aromatic hydrogen at position 8 (*ortho* to N) in **21**, **22**, **24**, and **25** are at unusually low-field positions (τ 2.3–1.9) for compounds of this type. Molecular models suggest that the *o*-hydrogen of these compounds is crowded into close proximity with the nitrogen of the pyrrolidine ring, thereby experiencing a deshielding influence from the unshared electrons on the N. Related proximity effects have been described.[3]

Pharmacology.—Compounds were tested for analgetic activity in female mice (ICR strain) using a modification of the method of Nilsen[4] as previously described.[5]

Toxicity was estimated in female mice of the same strain, using two animals per dose level. The results of these tests are summarized in Table IV. Some of the compounds were also investigated for analgetic activity using the method of Randall and Selitto.[6] In

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