added to a solution of 7.1 g. of sodium in 150 ml. of ethanol. To the mixture was added a solution of 60 g. of 2-bromo-2-ethylbutyramide[8] in 100 ml. of ethanol and the reaction mixture refluxed for 16 hr. under nitrogen. The precipitated sodium bromide was filtered off and the solvent removed *in vacuo*. The residue was dissolved in 300 ml. of acetone, filtered from additional sodium bromide, and the filtrate evaporated to dryness. The residue was recrystallized from petroleum ether, yielding 27 g. (54%) of 2-ethyl-2-ethylmercaptobutyramide, melting at 54–55°.

Sulfones (Table IV).—The preparation of 2-ethyl-2-ethylsulfonylbutyramide (4) is described as a representative example. 2-Ethyl-2-ethylmercaptobutyramide (27 g.) was dissolved in 100 ml. of a mixture of acetic acid–acetic anhydride (5:1). To the ice-cooled solution was added, in portions, 40 ml. of 30% hydrogen peroxide. After the addition was completed, the mixture was kept in the cooling bath for 3 hr. and then at room temperature for 3 days. The solvent was removed *in vacuo*, and the residue treated repeatedly by dissolving in benzene and removing the solvent *in vacuo*. Recrystallization from benzene–petroleum ether yielded 20.4 g. (64%) of 2-ethyl-2-ethylsulfonylbutyramide, melting at 99–100°.

(8) G. Fuchs, *Angew. Chem.*, **17**, 1505 (1904).

Acknowledgments.—We are indebted to Dr. A. Steyermark and his staff for the microanalyses, to Mr. S. Karlan and Mr. F. Jenkins for assistance in the synthetic work, to Dr. E. Keith for the anticonvulsant tests, to Dr. W. Benson for the hypnotic tests, and to Dr. W. Schallek for the observations in dogs.

Strong Analgesics: Some N-(Piperidinoalkyl)-anilides

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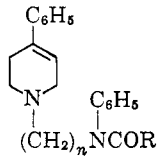
A number of N-(piperidinoalkyl) anilides have been prepared and tested for analgesic activity. One of these compounds, 1-[2-(N-phenylpropionamidoethyl)]-4-phenyl-4-piperidinol, was approximately fifty times as potent as meperidine. Several others also possessed strong analgesic activity.

One of the unsuccessful methods tried for the synthesis of 1-(2-anilinoethyl)-4-phenyl-4-propionoxypiperidine, a potent analgesic,[1] was a preferential O-acylation of 1-(2-anilinoethyl)-4-phenyl-4-piperidinol dihydrochloride using propionic anhydride as the acylating agent. The crystalline product, isolated in low yield, was found to be a mixture of N-[2-(4-phenyl-1,2,3,6-tetrahydropyridino)ethyl]-propionanilide (I, n = 2, R = C_2H_5) and N-[2-(4-hydroxy-4-phenylpiperidino)-ethyl]-propionanilide (II, n = 2, R = C_2H_5). Pure samples of each of these compounds were prepared and tested for analgesic activity, but only II (n = 2, R = C_2H_5) proved to be a potent analgesic, having about 50 times the activity of meperidine.



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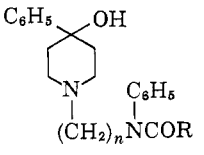


II

On the basis of these observations, it seemed desirable to prepare additional compounds based on structures I and II in which n and R were varied, and saturated analogs of I, quaternaries, O-acyl derivatives, 3-methyl derivatives, and compounds in which the anilide benzene ring was substituted. Melting points and analytical data for the compounds prepared are listed in Table I.

Most of the compounds of series I and II were prepared by N-alkylation of either 4-phenyl-1,2,3,6-tetrahydropyridine, 4-phenyl-4-piperidinol, or 3-methyl-4-phenyl-4-piperidinol[1] with the appropriate anilinoalkyl bromide followed by acylation with the appropriate acid chloride or anhydride. A *m*-hydroxyanilide, 1-[2-N-(3-hydroxyphenyl)propionamidoethyl]-4-phenyl-4-piperidinol, was prepared from *m*-benzyloxyaniline as described in the Experimental section.

All modifications of structure II (n = 2, R = C_2H_5) decreased activity. Saturation of the Δ^3 double bond was the only modification which appreciably increased activity in structure I (n = 2, R = C_2H_5).

It is of interest to note that N(1-methyl-2-piperidinoethyl)propionanilide, reported[2] while this work was in progress, possessed about $^1/_{50}$ of the activity of II (n = 2, R = C_2H_5).

Experimental[3]

1-(2-Anilinoethyl)-4-phenyl-4-piperidinol.—A mixture of 4-phenyl-4-piperidinol[4] (26.6 g., 0.15 mole), 2-anilinoethyl bromide hydrobromide[5] (47.8 g., 0.17 mole), 60 ml. of triethylamine, and 300 ml. of chloroform was refluxed for 24 hr., cooled and washed well with water. The chloroform solution was dried over sodium sulfate and concentrated to a red oil which completely crystallized after standing for 1 week. It was recrystallized from cyclohexane using decolorizing charcoal; m.p. 101–103°, 26 g. (58.5%).

A small portion was converted to the **dihydrochloride** and recrystallized from ethanol–ether; m.p. 158.6–160.4°.

Anal. Calcd. for $C_{19}H_{24}N_2O \cdot 2HCl$: Cl, 19.2; O, 4.33. Found: Cl, 19.15; O, 4.37.

1-(3-Anilinopropyl)-4-phenyl-4-piperidinol.—This compound was prepared by the procedure described for 1-(2-anilinoethyl)-4-phenyl-4-piperidinol, using 3-anilinopropylbromide hydrobromide,[6] m.p. 91–93°, yield 65%.

(1) P. M. Carabateas and L. Grumbach, *J. Med. Pharm. Chem.*, **5**, 913 (1962).

(2) W. B. Wright, H. A. Brabander, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **81**, 1518 (1959).

(3) All melting points were taken in a modified Hershberg apparatus and are corrected.

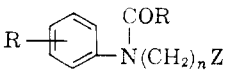
(4) C. J. Schmidle and R. C. Mansfield, *J. Am. Chem. Soc.*, **78**, 1702 (1956).

(5) W. M. Pearlman, *ibid.*, **70**, 871 (1948).

(6) B. Elpern, P. M. Carabateas, and L. Grumbach, *J. Org. Chem* **26**, 4728 (1961).

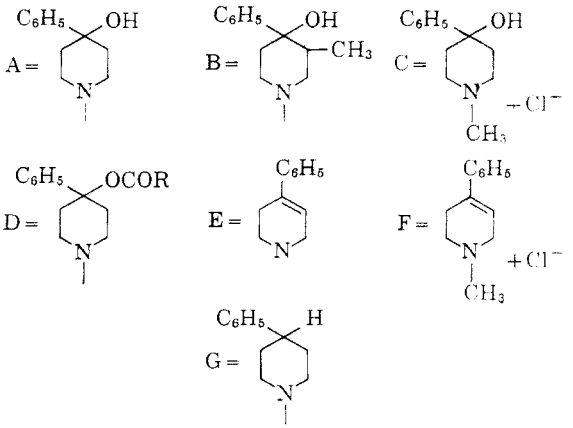
TABLE I

STRONG ANALGESICS: SOME N-(PIPERIDINOALKYL)-ANILIDES



R	R'	Z	n	M.p., °C.	Yield, %	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found	Potency relative to meperidine[a]
CH_3	H	A	2	172.2–176.6	66	$C_{21}H_{26}N_2O_2 \cdot HCl$			N, 7.47	N, 7.17	9.46	9.30	5.77
C_2H_5	H	A	2	166.9–172.6	93	$C_{22}H_{28}N_2O_2 \cdot HCl$			N, 7.21	N, 6.96	O, 8.23	O, 8.25	49.5
C_3H_7	H	A	2	156.6–162.8	67	$C_{23}H_{30}N_2O_2 \cdot HCl$	68.55	68.79	7.76	8.03	8.80	8.95	32.2
C_2H_5	H	A	3	135.2–136.4	52	$C_{23}H_{30}N_2O_2 \cdot HCl$			N, 6.95	N, 6.87	8.80	8.74	3.0
C_3H_7	H	A	3	118.8–120.2	43	$C_{24}H_{32}N_2O_2 \cdot HCl$	69.14	69.06	7.98	8.06	8.50	8.70	[b]
C_2H_5	*m*-OH	A	2	215.8–217.8	25	$C_{22}H_{28}N_2O_3 \cdot HCl$	65.26	65.12	7.22	6.97	8.76	8.97	[b]
C_2H_5	H	B	2	180.2–181.4	20	$C_{23}H_{30}N_2O_2 \cdot C_7H_8O_3S$	66.86	67.16	7.14	6.79	S, 5.96	S, 6.15	12.4
C_2H_5	H	C	2	231.8–234.5	47	$C_{23}H_{31}ClN_2O_2$	68.55	68.39	7.76	7.61	8.80	8.81	[b]
CH_3	H	D	2	177.4–185.8	41	$C_{23}H_{28}N_2O_3 \cdot HCl$			N, 6.72	N, 6.65	8.51	8.37	5.44
C_2H_5	H	D	2	184.2–187.2	23	$C_{25}H_{32}N_2O_3 \cdot HCl$			O, 10.78	O, 11.00	7.97	7.80	2.66
CH_3	H	E	2	188.4–189.6	11	$C_{21}H_{24}N_2O \cdot HCl$	70.69	70.76	7.06	7.01	9.94	10.12	[b]
C_2H_5	H	E	2	183.2–185.6	18	$C_{22}H_{26}N_2O \cdot HCl$	71.21	71.39	7.34	7.46	9.56	9.39	[b]
C_3H_7	H	E	2	182.4–183.6	11	$C_{23}H_{28}N_2O \cdot HCl$	71.78	71.77	7.60	7.79	9.21	8.96	[b]
C_2H_5	H	E	3	188.5–193.0	14	$C_{23}H_{28}N_2O \cdot HCl$	71.78	72.09	7.69	7.52	9.21	9.24	0.7
C_2H_5	H	F	2	198.0–199.2	76	$C_{28}H_{29}ClN_2O$			N, 7.28	N, 7.42	9.21	9.36	[b]
C_2H_5	H	G	2	220.0–221.2	60	$C_{22}H_{28}N_2O \cdot HCl$			N, 7.52	N, 7.67	9.51	9.62	11.3
Meperidine													1

[a] Analgesic potency was determined by the Bass, Vanderbrook modification[c] of the D'Amour, Smith[d] rat thermal stimulus method. [b] No response at threshold levels tested. [c] W. B. Bass and M. J. Vanderbrook, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 569 (1952). [d] F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1941).



Anal. Calcd. for $C_{20}H_{26}N_2O$: N, 9.03. Found: N, 8.92.

1-[2-(N-Phenylbutyramidoethyl)]-4-phenyl-4-piperidinol Hydrochloride.—A solution of butyryl chloride (1.06 g., 0.02 mole) in 5 ml. of chloroform was added during 5 min. to a solution of 1-(2-anilinoethyl)-4-phenyl-4-piperidinol (2.96 g., 0.01 mole) in 10 ml. of chloroform. After standing for 1 hr., the solution was concentrated to an oil. Trituration with ether produced a white solid which was recrystallized from methanol–ethyl acetate several times to yield 2.7 g. of product. The other N-acyl derivatives were similarly prepared.

1-[2-(N-Phenylpropionamidoethyl)]-4-phenyl-4-piperidinol Methochloride.—A solution of 1-[2-(N-phenylpropionamidoethyl)]-4-phenyl-4-piperidinol (8.9 g., 0.03 mole) in 25 ml. of hot acetonitrile was treated with 4 ml. of methyl iodide. After standing overnight, the solution was concentrated to an oil. The oil was dissolved in methanol and passed through a column of IRA-400 ion exchange resin. The eluate was concentrated to a semisolid which, on trituration with acetone, gave a white solid. This was recrystallized from isopropyl alcohol–ether to give 3.9 g. of product.

1-[2-(N-Phenylacetamidoethyl)]-4-phenyl-4-acetoxypiperidine hydrochloride.—Crude 1-(2-anilinoethyl-4-phenyl-4-piperidinol (from 17.7 g., 0.1 mole, of 4-phenyl-4-piperidinol and 28.1 g., [0.1 mole] of 2-anilinoethyl bromide hydrobromide) was treated with 50 ml. of acetic anhydride, warmed on the steam bath for 5 hr. and allowed to stand overnight. The red solution was concentrated to an oil *in vacuo*, dissolved in ether and filtered to remove cloudiness. Ethereal hydrogen chloride was added and the resulting gum triturated with ether to produce a white solid which was recrystallized several times from methanol–ethyl acetate to give 17.2 g. of product.

The N,O-dipropionyl compound was prepared in the same way.

***m*-Benzyloxy α-chloroacetanilide.**—A solution of *m*-benzyloxyaniline[7] (99.6 g., 0.5 mole) in 300 ml. of ethylene dichloride was cooled to 0° in an ice–salt bath and a solution of chloroacetyl chloride (67.6 g., 0.6 mole) in 100 ml. ethylene dichloride added over 0.5 hr. with vigorous stirring at less than 10°. A solution of 10% sodium hydroxide was added as necessary to keep the mixture basic. The mixture turned to a white semisolid which was collected, washed with water and dissolved in 1500 ml. of hot benzene. The water layer was separated and the benzene layer concentrated to a volume of about 750 ml. The solution was filtered and diluted with hexane. The white solid which crystallized had m.p. 123–123.5°, yield 124.0 g. (90.5%).

Anal. Calcd. for $C_{15}H_{14}ClNO_2$: Cl, 12.83. Found: Cl, 13.20.

N-(4-Hydroxy-4-phenylpiperidinoacetyl)-*m*-benzyloxyaniline.—A mixture of 4-phenyl-4-piperidinol (26.6 g., 0.15 mole), *m*-benzyloxy-α-chloroacetanilide (41.6 g., 0.15 mole), sodium carbonate (20 g., 0.188 mole), and 200 ml. of toluene was stirred and refluxed for 24 hr. The mixture was filtered hot and the filtrate allowed to cool. The product was recrystallized from toluene–hexane; m.p. 152–153°, yield 58.5 g. (94.3%).

Anal. Calcd. for $C_{26}H_{28}N_2O_3$: C, 74.96; H, 6.78; N, 6.73. Found: C, 75.08; H, 6.59; N, 6.47.

1-[2-(3-Benzyloxyphenylamino)ethyl]-4-phenyl-4-piperidinol.—Solid N-(4-hydroxy-4-phenylpiperidinoacetyl)-*m*-benzyloxyaniline (53.2 g., 0.128 mole) was added in portions to a slurry of lithium aluminum hydride (12.1 g., 0.32 mole) in 500 ml. of tetrahydrofuran. The mixture was stirred at reflux for 18 hr. After cooling, it was decomposed by cautious addition of 12 ml. of

(7) A. A. Morton and W. R. Slaunwhite, *J. Biol. Chem.*, **179**, 264 (1949).

water, followed by 150 ml. of a saturated solution of potassium sodium tartarate. The slurry was filtered and the filtrate concentrated to an oil which was dried by azeotropic distillation with benzene. The crude product weighed 51.4 g. (100%) and was used without further purification in the following step.

1-[2-N-(3-Benzyloxyphenyl)propionamidoethyl]-4-phenyl-4-piperidinol.—A solution of crude 1-[2-(3-benzyloxyphenylamino)-ethyl]-4-phenyl-4-piperidinol (51.4 g., 0.128 mole) in 100 ml. of chloroform was treated with propionyl chloride (11.9 g., 0.128 mole). After standing for 3 hr., the solution was concentrated to an oil (56.2 g., 95.7%) which could not be obtained crystalline, either as the free base or as a salt. It was used directly in the next step.

1-[2-N-(3-Hydroxyphenyl)propionamidoethyl]-4-phenyl-4-piperidinol Hydrochloride.–A solution of crude 1-[2-N-(3-benzyloxyphenyl)propionamidoethyl]-4-phenyl-4-piperidinol (56.2 g., 0.123 mole) in 700 ml. of absolute ethanol was hydrogenated at 111 kg./cm.^{2} and 27°, using 6 g. of 10% palladium–charcoal. After 6.75 hr., 80% of the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate concentrated to about 100 ml. The solution was made strongly basic with 35% sodium hydroxide and extracted with ether to remove non-phenolic material. The aqueous solution was brought to about pH 8 by the slow addition of acetic acid and the precipitated oil was extracted with ether. The ether extracts deposited a crystalline solid after standing for 1 hr. The solid was converted to the hydrochloride by stirring with ethereal hydrogen chloride. Recrystallization from methanol–ethyl acetate gave 12.4 g. (24.9%) of product, m.p. 215.8–217.8°.

4-Phenyl-1-[2-(N-phenylpropionamidoethyl)]-1,2,3,6-tetrahydropyridine Hydrochloride.—A mixture of 4-phenyl-1,2,3,6-tetrahydropyridine[4] (63.6 g., 0.4 mole), 2-anilinoethyl bromide hydrobromide (112 g., 0.4 mole), 500 ml. of chloroform, and 60 ml. of triethylamine was refluxed for 24 hr. Propionic anhydride (150 ml.) was added and the mixture allowed to stand overnight. Methanol (150 ml.) was added and the solution concentrated to an oil which was made basic with 35% sodium hydroxide. The oil was extracted with benzene, washed with water, and concentrated. The oil was dissolved in ether, filtered to remove some insoluble material, and concentrated again to an oil which was distilled through a short path column. The fraction boiling at 190–200° (0.3 mm.) was collected, dissolved in ether, and treated with ethereal hydrogen chloride. The resulting gum yielded a solid on trituration with ether. The solid was recrystallized from methanol–ethyl acetate to give 27 g. of product. The methochloride of this compound was prepared as described for the methochloride of the analogous piperidinol.

4-Phenyl-1-[2-(N-phenylpropionamidoethyl)]piperidine Hydrochloride.—A solution of 4-phenyl-1-[2-(N-phenylpropionamidoethyl)]-1,2,3,6-tetrahydropyridine hydrochloride (4.7 g., 0.0126 mole) in 100 ml. of ethanol was hydrogenated at 3.5 kg./cm.^{2} in a Parr apparatus using 150 mg. of platinum oxide as catalyst. The theoretical amount of hydrogen was absorbed in 15 min. The catalyst was removed by filtration and the filtrate concentrated to about 25 ml. Crystals were deposited on standing for a short time. After recrystallization from ethanol–ether, 2.9 g. of product was obtained.

Acknowledgments.—We are greatly indebted to Messrs. M. E. Auerbach, K. D. Fleischer, and staff for the chemical analyses, to Dr. F. C. Nachod and staff for spectral data, and to Mrs. A. Pierson and Mrs. H. Lawyer for technical assistance in the pharmacological evaluations.

Investigations in Heterocycles. XIII. Structure-Activity Relationships of Heterocyclic Compounds with Potent Analgetic Effects

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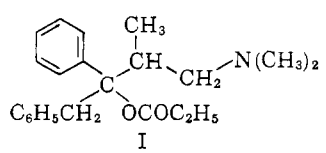
A variety of tetralin, chromane, and thiachromane compounds structurally related to propoxyphene have been prepared, and the structure–activity relationship has been discussed. It has been observed that the 2-picolyl moiety markedly enhances the analgetic activity in this group of compounds. Some stereochemical considerations have been deduced by means of chemical and spectral data.

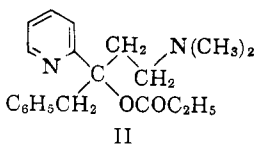
As part of a continuing program directed toward the preparation of clinically effective analgetic agents, we wish to outline a phase of work carried out in our Laboratories which has led to some highly active compounds.

Since *d*-propoxyphene[1] (I) was reported to be a clinically useful analgetic without possessing appreciable addiction liability, it was of interest to prepare some heterocyclic analogs of I, as well as cyclic analogs containing hetero atoms. This could be done in two ways; namely, replacing at least one of the phenyl groups with a heterocycle (*e.g.*, pyridyl) or preparing cyclic analogs of I in the chromane and thiachromane series. It is also conceivable that a compound incorporating a combination of these ideas could also be prepared.

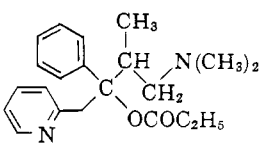


I

The initial phase of the study involved the preparation of a pyridyl analog (II) of I. Thus, 3-dimethylamino-1-(2-pyridyl)-1-propanone was allowed to react with benzylmagnesium chloride to form a tertiary alcohol which was esterified with propionic anhydride



II



III

(1) A. Pohland, H. R. Sullivan, and R. E. McMahon, *J. Am. Chem. Soc.*, **79**, 1442 (1957).