Cooper.[19] A 5% palladium-on-activated-charcoal was used as a catalyst. In all cases the quantity of reagents used was approximately a 0.1-g. sample, 0.12 g. of 5% palladium-on-charcoal and 10 ml. of anhydrous alcohol. Reactions were carried out at room temperature and atmospheric pressure.

Solid VI, m.p. 295.4–296.2°, 0.0945 g., was hydrogenated in 10 ml. of ethanol in the presence of 0.12 g. of 5% palladium-on-charcoal catalyst. No uptake of hydrogen was noted over a period of one hour. After standing in the hydrogenator overnight, the solution was filtered free of catalyst and evaporated to dryness. The solid residue weighed 0.086 g., m.p. 285–290°.

A mixture melting point with pure VI gave m.p. 290.8–293.5°. Hence, VI contains no carbon–carbon unsaturation.

Solid XII, linear diamide, 0.0967 g., was hydrogenated in 10 ml. of ethanol over 0.12 g. of palladium-on-charcoal. The hydrogen uptake amounted to 11.14 ml. (in 15 minutes) and corresponded to 101.8% of the theoretical linear diamide. Filtration of the catalyst, and evaporation of solvent left behind 0.09 g. of solid residue. Recrystallization from 5 ml. of methanol gave 0.055 g. of white crystalline solid, m.p. 220–224°. The infrared absorption spectrum showed bands at 2.98, 3.15, 6.0, 6.07 and 7.05 μ.

Solid XIII, m.p. 76.8–77.6°, 0.871 g., was hydrogenated in 10 ml. of anhydrous ethanol over 0.12 g. of 5% palladium-on-charcoal. The hydrogen uptake amounted to 10.98 ml. (in 15 minutes) and corresponded to 101.3% of the theoretical linear monoamide. The filtered and evaporated solution yielded 0.088 g. of white solid residue of wide melting point range, m.p. 109–120°. The infrared spectrum was examined particularly for the position of the nitrile frequency as compared to the unhydrogenated XIII. The infrared absorption showed bands at 2.96, 3.13, 4.45, 6.01, 6.1 and 7.05 μ. The shift in the nitrile frequency on hydrogenation from 2210 (4.52 μ) to 2245 cm.$^{-1}$ (4.45 μ) supports the presence of an α,β-unsaturated cyano grouping in the linear unsaturated monoamide, solid XIII.

(19) C. L. Ogg and E. J. Cooper, *Anal. Chem.*, **21**, 1400 (1949).

BROOKLYN 1, N. Y.

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Strong Analgesics. The Preparation of Some Ethyl 1-Anilinoalkyl-4-Phenylpiperidine-4-Carboxylates

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A series of ethyl 1-(ω-arylaminoalkyl)-4-phenylpiperidine-4-carboxylates has been prepared and evaluated for analgesic activity by the rat thermal stimulus method. The most effective groups were the 2-aminoanilinoethyl and the unsubstituted anilinoethyl.

In an earlier paper[2] we reported that the N-methyl group of meperidine, ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride, could be replaced by an N-cinnamyl group to give a compound having enhanced analgesic activity. When the cinnamyl group bore an amino substituent in the 4-position the activity fell to about one-third of the unsubstituted compound. This is in contrast to the 4-aminophenethyl derivative which was more active than the unsubstituted phenethyl derivative. It was of interest to us to investigate the effect of inserting the amino group between the aryl and alkyl portions of the aralkyl substituent on the meperidine nitrogen. The resulting substituted anilinoalkyl derivatives of nor-meperidine are the subject of this paper.

In the preparation of the ethyl 1-anilinoalkyl-4-phenylpiperidine-4-carboxylates it was found that several methods could be used. When the appropriate anilinoalkyl bromide could be readily obtained it was condensed with ethyl 4-phenylpiperidine-4-carboxylate (method A). It was found that ethyl 1-(ω-chloroalkyl)-4-phenylpiperidine-4-carboxylate hydrochloride could be condensed with various substituted anilines in the presence of aqueous sodium carbonate (method B), sodamide in dry toluene (method C) or in Cellosolve (method D). Method D is generally the easiest to carry out and gives the best yields.

The ethyl 1-(ω-chloralkyl)-4-phenylpiperidine-4-carboxylates were obtained by refluxing the corresponding hydroxyalkyl compounds with thionyl chloride. The hydroxyalkyl compounds were obtained by treating ethyl 4-phenylpiperidine-4-carboxylate with ethylene oxide or trimethylene chlorohydrin to give ethyl 1-(2-hydroxyethyl)-4-phenylpiperidine-4-carboxylate or ethyl 1-(3-hydroxypropyl)-4-phenylpiperidine-4-carboxylate, respectively.

The anilinoalkyl bromides were obtained by treating the corresponding alcohols with hydrobromic acid using the procedure of Pearlman,[3] or by adding phosphorus tribromide to the corresponding alcohol.

The nitro compounds were reduced following the procedure of Furst and Balcom.[4]

The pharmacological evaluation of these compounds for analgesic potency was done by the Bass, Vander Brook[5a] modification of the D'Amour, Smith[5b] rat thermal stimulus method. The results are given in Table I and will be discussed in detail elsewhere.

Experimental[6]

The following intermediates were prepared by methods reported in the literature: 2-(4-methylanilino)-ethanol, 3-(2-nitroanilino)-1-propanol, 2-(2-nitroanilino)-ethanol, 2-(2-nitroanilino)-ethyl chloride.

3-(2,6-Dimethylanilino)-propanol Hydrobromide.—2,6-Dimethylaniline (12.1 g., 0.1 mole) and trimethylene bromohydrin (13.9 g., 0.1 mole) were heated on a steam-bath 4 hours. After cooling and standing, the oil crystallized. It was recrystallized from absolute alcohol and washed with ether; yield 23.4 g. (90%), m.p. 195–197°.

Anal. Calcd. for $C_{11}H_{18}BrNO$: Br, 30.71. Found: Br, 30.58.

(1) Cutter Laboratories, Berkeley, Calif.

(2) B. Elpern, L. Gardner and L. Grumbach, THIS JOURNAL, **79**, 1951 (1957).

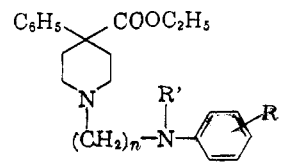
(3) W. M. Pearlman, *ibid.*, **70**, 871 (1948).

(4) D. Balcom and A. Furst, *ibid.*, **75**, 4334 (1953).

(5) (a) W. B. Bass and M. J. Vander Brook, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 569 (1952); (b) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1941).

(6) All melting points corrected.

TABLE I



R	n	R'	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Method	Activity
H	2	H	153.4–157.2	$C_{22}H_{28}N_2O_2 \cdot NH_2SO_3H$	58.67	58.60	6.92	6.85	9.32[c]	8.96	B	101
H	2	CH_3	204.6–208.0	$C_{23}H_{30}N_2O_2 \cdot 2HCl$	62.83	63.07	7.34	7.04	16.13	15.95	B	4.0
4-OCH_3	2	H	181.4–189.2	$C_{23}H_{30}N_2O_3 \cdot 2HCl$	60.65	60.54	6.63	7.13	15.57	15.40	C	18.8
4-CH_3	2	H	218 dec.	$C_{23}H_{30}N_2O_2 \cdot 2HCl$	62.86	62.98	7.34	7.16	16.14	16.01	A	24.3
4-Cl	2	H	200.0–202.0	$C_{22}H_{27}ClN_2O_2 \cdot HCl$	6.82[c]	6.53			16.75	16.81	D	4.8
2-NO_2	2	H	183.0–185.6	$C_{27}H_{27}N_3O_4 \cdot HCl$	60.89	60.83	6.50	6.36	8.17	8.32	A	2.5
2-NH_2	2	H	185.4–186.8	$C_{22}H_{29}N_3O_2 \cdot HCl$	65.41	65.70	7.21	7.26	8.77	8.76	..	113.7
3-NO_2	2	H	166.8–168.6	$C_{27}H_{27}N_3O_4 \cdot HCl$	60.89	60.94	6.50	6.77	8.17	8.19	D	21.4
4-NO_2	2	H	195.8–199.8	$C_{27}H_{27}N_3O_4 \cdot HCl$	60.89	60.70	6.50	6.51	8.17	8.19	D	Sl. act.
4-$N(Et)_2$	2	H	227 dec.	$C_{26}H_{37}N_3O_2 \cdot 2HCl$	62.89	63.15	7.91	7.28	14.28	14.33	B	Sl. act.
H	3	H	219.4–222.2	$C_{23}H_{30}N_2O_2 \cdot 2HCl$	62.86	62.98	7.34	7.37	7.28[a]	7.00	B	30.5
H	3	Et	170.4–174.0	$C_{25}H_{34}N_2O_2 \cdot 2HBr$	53.98	53.72	6.52	6.27	28.73[b]	28.46	B	2.7
4-OCH_3	3	H	180.4–184.0	$C_{24}H_{32}N_2O_3 \cdot HCl$	6.47[c]	6.40			8.19	8.27	C	Sl. act.
2,6-$DiCH_3$	3	H	124.8–128.0	$C_{25}H_{34}N_2O_2 \cdot HCl$	6.50[c]	6.48			8.23	8.06	A	1.5
5-Cl-2-CH_3	3	H	80.4– 82.8	$C_{24}H_{31}ClN_2O_2$	6.75[c]	6.51			8.53	8.52	B	Sl. act.
4-$COOC_2H_5$	3	H	179.0–183.4	$C_{26}H_{34}N_2O_4 \cdot HCl$	5.90[c]	5.92			7.46	7.74	C	Sl. act.
2-NO_2	3	H	152.6–154.8	$C_{23}H_{29}N_3O_4 \cdot HCl$	61.67	61.15	6.75	7.03	7.91	7.73	A	1.3
2-NH_2	3	H	216.7–219.0	$C_{23}H_{31}N_3O_2 \cdot HCl$	66.09	65.80	7.72	7.63	10.05[c]	9.88	..	14.9
3-NO_2	3	H	199.4–204.6	$C_{23}H_{29}N_3O_4 \cdot HCl$	9.38[c]	9.61			7.91	7.91	C	1
3-NH_2	3	H	100.4–109.8	$C_{23}H_{31}N_3O_2 \cdot H_2O$	69.14	69.14	8.33	8.40	10.6[c]	10.82	..	12.6
4-NO_2	3	H	108.6–109.8	$C_{23}H_{29}N_3O_4$	67.13	67.39	7.10	7.38	10.21[c]	10.02	A	Sl. act.
4-NH_2	3	H	237.6–239.6	$C_{23}H_{31}N_3O_2 \cdot 2HCl$	9.25[c]	8.97			15.61	15.41	..	1.63
Meperidine												1.0

[a] Analyzed for oxygen. [b] Analyzed for bromine. [c] Analyzed for nitrogen.

3-(2,6-Dimethylanilino)-propyl bromide hydrobromide was prepared from 3-(2,6-dimethylanilino)-propanol.HBr (11.7 g., 0.045 mole) and 12 cc. of 48% hydrobromic acid by the procedure of Pearlman[3]; yield 13.0 g. (89.6%), m.p. 191–192°.

Anal. Calcd. for $C_{11}H_{17}Br_2N$: Br, 49.4. Found: Br, 49.05.

2-(4-Methylanilino)-ethyl Bromide Hydrobromide.—The procedure of Pearlman was used for the preparation of this compound also; yield 25.5%; m.p. 178–179°.

Anal. Calcd. for $C_9H_{13}Br_2N$: C, 36.64; H, 4.44. Found: C, 36.34; H, 4.26.

3-(2-Nitroanilino)-1-bromopropane.—Phosphorus tribromide (10.6 g., 0.039 mole) in 50 ml. of benzene was added dropwise with stirring to 3-(2-nitroanilino)-1-propanol (19 g., 0.1 mole) in 150 ml. of benzene at about 5°. Stirring was continued after the addition was completed for 30 minutes in the ice-bath and then 30 minutes at room temperature. The mixture was heated to 60–70° for 5 hours on the water-bath and then poured into ice-water. The layers were separated, the aqueous layer extracted with benzene, the combined benzene solutions washed with dilute sodium hydroxide and then with water. The benzene solution was concentrated *in vacuo* on the steam-bath to a gum. On trituration with ether, the gum solidified. Recrystallization from Skelly C gave 19.1 g. (81%) of material melting at 40–41°.

Anal. Calcd. for $C_9H_{11}BrN_2O_2$: Br, 31.4. Found: Br, 30.76.

Ethyl 1-(2-Hydroxyethyl)-4-phenylpiperidine-4-carboxylate.[7]—Ethyl 4-phenylpiperidine-4-carboxylate hydrochloride (675 g., 2.5 moles) was dissolved in 1 liter of water. Excess 35% sodium hydroxide was added to liberate the free base. The oily base was separated and dissolved in 2 liters of methanol in a 5-liter flask fitted with a Dry Ice condenser and a Dry Ice cooled dropping funnel containing 150 g. (3.4 moles) of ethylene oxide. The ethylene oxide was added at such a rate as to keep the reaction mixture refluxing. After the addition was completed, the solution was gently refluxed on the steam-bath for 2.5 hr. The solution was then concentrated *in vacuo* on the steam-bath to a viscous oil which solidified on cooling. It was recrystallized by dissolving in hot methanol and adding an equal amount of water; yield 486 g. (71%), m.p. 89–93°.

Anal. Calcd. for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.36; O, 17.31. Found: C, 69.60; H, 8.01; O, 17.30.

Ethyl 1-(2-Chloroethyl)-4-phenylpiperidine-4-carboxylate Hydrochloride.—Ethyl 1-(2-hydroxyethyl)-4-phenylpiperidine-4-carboxylate (486 g., 1.76 moles) in 3 liters of dry benzene was added with stirring to a mixture of 238 g. (2.0 moles) of thionyl chloride. 500 ml. of benzene and 1 ml. of pyridine at a rate sufficient to keep the solution refluxing. The addition required 1.25 hr., during which time a white solid formed in the solution. The mixture was refluxed an additional hour. After cooling, the white crystalline product was collected and washed repeatedly with ether, giving 540 g. (92%), m.p. 218–220° dec.

Anal. Calcd. for $C_{16}H_{22}ClNO_2 \cdot HCl$: C, 57.84; H, 6.98; Cl, 10.69. Found: C, 57.67; H, 6.82; Cl, 10.58.

Ethyl 1-(3-Hydroxypropyl)-4-phenylpiperidine-4-carboxylate Hydrochloride.—A mixture of ethyl 4-phenylpiperidine-4-carboxylate hydrochloride (330 g., 1.22 moles), trimethylene chlorohydrin (129 g., 1.35 moles), 250 g. of anhydrous sodium carbonate and 2 liters of dry butanol was refluxed for 18 hr. with stirring. The cooled reaction mixture was filtered to remove inorganic salts. The filtrate was concentrated *in vacuo* on the steam-bath to a viscous oil. The oil was taken up in ether and the ether solution saturated with hydrogen chloride. An amorphous solid precipitated which crystallized on standing. On recrystallization from ethanol–ether there was obtained 295 g. (74%) of product, m.p. 139–141°.

Anal. Calcd. for $C_{17}H_{25}NO_3 \cdot HCl$: C, 62.27; H, 8.00; O, 14.64. Found: C, 62.43; H, 8.05; O, 14.80.

Ethyl 1-(3-Chloropropyl)-4-phenylpiperidine-4-carboxylate Hydrochloride.—Ethyl 1-(3-hydroxypropyl)-4-phenyl-

(7) Named but not characterized by Schaumann, *Arch. Exper. Path. Pharmak.*, **196**, 109 (1940).

piperidine-4-carboxylate hydrochloride (295 g., 0.9 mole) was added portionwise during 0.5 hr. to a vigorously stirred mixture of 120 g. (1.0 mole) of thionyl chloride, 1 ml. of pyridine and 2 liters of benzene. After the addition was completed, the mixture was stirred 0.5 hr. at room temperature, and then refluxed for 2 hr. After cooling, the crystalline product was collected and washed with ether; yield 307 g. (98%), m.p. 189–192°.

Anal. Calcd. for $C_{17}H_{24}ClNO_2 \cdot HCl$: C, 58.96; H, 7.28; Cl, 20.47. Found: C, 59.00; H, 7.01; Cl, 20.18.

Method A: Reaction between Ethyl 4-Phenylpiperidine-4-carboxylate and Arylaminoalkyl Halides. Preparation of Ethyl 1-[2-(4-Methylphenylamino)-ethyl]-4-phenylpiperidine-4-carboxylate Dihydrochloride.—A mixture of ethyl 4-phenylpiperidine-4-carboxylate hydrochloride (13.5 g., 0.05 mole), 2-(4-methylanilino)-ethyl bromide hydrobromide (14.7 g., 0.05 mole), 20 g. of anhydrous sodium carbonate and 100 ml. of butanol was refluxed for 24 hr. with vigorous stirring. The cooled solution was filtered to remove inorganic salts and concentrated *in vacuo* on the steam-bath to a light yellow oil. The oil was taken up in 100 ml. of ether and several small pieces of Dry Ice added. A small quantity of the carbamate of ethyl 4-phenylpiperidine-4-carboxylate was filtered off and the filtrate treated with a solution of hydrogen chloride in ether. A white gum precipitated which turned solid on standing. Crystallization from ethanol–ethyl acetate gave 5.4 g. (25%) of product, m.p. 212–218° dec.

Anal. Calcd. for $C_{25}H_{30}N_2O_2 \cdot 2HCl$: C, 62.86; H, 7.34; Cl, 16.14. Found: C, 62.98; H, 7.16; Cl, 16.01.

Method B: Reaction between Ethyl 1-(ω-Chloroalkyl)-4-phenylpiperidine-4-carboxylate and Aromatic Amines. Preparation of Ethyl 1-(2-Phenylaminoethyl)-4-phenylpiperidine-4-carboxylate Sulfamate.—Ethyl 1-(2-chloroethyl)-4-phenylpiperidine-4-carboxylate hydrochloride (100 g., 0.3 mole) in 500 ml. of water was added in a steady stream to a well stirred mixture of aniline (112 g., 1.2 moles), 100 g. of anhydrous sodium carbonate and 500 ml. of water heated to 90°. After the addition was completed the mixture was stirred on the steam-bath for 3 hr. After cooling, the organic layer was separated and the aqueous layer extracted three times with benzene. The extracts and the organic layer were combined and the benzene removed on the steam-bath under reduced pressure. The excess aniline was removed by distillation at 78° (18 mm.). The residual oil weighed 104 g. The crude free base (38 g., 0.117 mole) was dissolved in 100 ml. of ethanol and a solution of 11.3 g. (0.117 mole) of sulfamic acid in 60 ml. of 50% ethanol was added. On cooling and scratching, a heavy precipitate formed which was collected and washed with ether. On recrystallization from ethanol there was obtained 30 g. (60%) of product, m.p. 153.4–157.2°.

Anal. Calcd. for $C_{22}H_{28}N_2O_2 \cdot NH_2SO_3H$: C, 58.67; H, 6.92; N, 9.32. Found: C, 58.60; H, 6.85; N, 8.96.

Method C: Reaction between Ethyl 1-(ω-Chloroalkyl)-4-phenylpiperidine-4-carboxylate with Aromatic Amines in the Presence of Sodamide. Preparation of Ethyl 1-[2-(4-Methoxyphenylamino)-ethyl]-4-phenylpiperidine-4-carboxylate Dihydrochloride.—To a stirred, refluxing suspension of sodamide (11.7 g., 0.3 mole) in 200 ml. of dry toluene was added 12.3 g. (0.1 mole) of *p*-anisidine. The mixture was refluxed 1.5 hr. and then cooled. Ethyl 1-(2-chloroethyl)-4-phenylpiperidine-4-carboxylate hydrochloride (33.2 g., 0.1 mole) was added all at once and the mixture stirred and refluxed for 3.5 hr. After cooling, the mixture was hydrolyzed with 500 ml. of water. The toluene layer was separated, the aqueous layer extracted with ether, the organic layers combined and concentrated *in vacuo* on the steam-bath. The residue was dissolved in isopropyl alcohol, filtered to remove some insoluble salts and the solution was saturated with HCl gas. On cooling and scratching the product precipitated out. After recrystallization from isopropyl alcohol there was obtained 9.7 g. (21%) of product melting at 181–189°.

Anal. Calcd. for $C_{23}H_{30}N_2O_3 \cdot HCl$: C, 60.65; H, 6.63; Cl, 15.57. Found: C, 60.54; H, 7.13; Cl, 15.40.

Method D: Reaction between Ethyl 1-(ω-Chloroalkyl)-4-phenylpiperidine-4-carboxylate and Aromatic Amines in Cellosolve. Preparation of Ethyl 1-[2-(4-Chlorophenylamino)-ethyl]-4-phenylpiperidine-4-carboxylate Dihydrochloride.—A mixture of ethyl 1-(2-chloroethyl)-4-phenylpiperidine-4-carboxylate hydrochloride (16.6 g., 0.05 mole), *p*-chloroaniline (25.2 g., 0.2 mole) and 110 ml. of Cellosolve was refluxed 16 hr. The red-orange solution was concentrated *in vacuo* on the steam-bath to a red oil which solidified on cooling. Crystallization first from 25 ml. of Cellosolve, then from ethanol, gave 12.0 g. (56.6%) of product, m.p. 200–202°.

Anal. Calcd. for $C_{22}H_{26}N_2O_2 \cdot 2HCl$: Cl, 16.75; N, 6.82. Found: Cl, 16.81; N, 6.53.

Reduction of Ethyl 1-[3-(3-Nitrophenylamino)-propyl]-4-phenylpiperidine-4-carboxylate.—Ethyl 1-[3-(3-nitrophenylamino)-propyl]-4-phenylpiperidine-4-carboxylate hydrochloride (35 g., 0.079 mole) was suspended in 300 ml. of ethanol. Hydrazine hydrate (100%, 16 g., 0.316 mole) was added and the mixture heated to 50° on the steam-bath. Small portions of Raney nickel catalyst were then added over about 30 minutes, until the color change from yellow to colorless indicated reduction was complete. The solution was heated to boiling to remove any gases, filtered hot and then cooled in an ice-bath. The crystalline product was collected and dried at 50°. There was obtained 23 g. (72%) of product melting 100–108°, and requiring no further purification.

Anal. Calcd. for $C_{23}H_{31}N_3O_2 \cdot H_2O$: C, 69.14; H, 8.33; N, 10.6; H_2O, 4.50. Found: C, 69.14; H, 8.40; N, 10.82; H_2O, 4.55.

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[CONTRIBUTION FROM THE PHYSIOLOGY DEPARTMENT, TUFTS UNIVERSITY SCHOOL OF MEDICINE]

Chemistry of Pyrimidines. II. The Conversion of 5-Bromo- to 5-Hydroxyuracils[1,2]

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Neither silver oxide nor lead oxide causes a conversion of 5-bromopyrimidines to the corresponding 5-hydroxy derivatives. Sodium bicarbonate, however, brings about such a conversion quite successfully. 5-Bromo-6-hydroxy-5,6-dihydropyrimidines can also be used for this preparation. The mechanism of this reaction is discussed and a general method of preparation is presented.

Introduction

Although, in 1912, Levene and LaForge[3] reported the preparation of 5-hydroxy-uridine by the bromine and lead oxide method, subsequent workers have found it difficult to use their method.[4] In

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(2) The author wishes to thank L. A. Johnson and R. Weintraub for their able assistance.

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(4) M. Roberts and D. W. Visser, THIS JOURNAL, **74**, 668 (1952).