Strong Analgesics. Some 1-Substituted 4-Phenyl-4-Propionoxypiperidines

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Several 1-substituted-4-phenyl-4-propionoxypiperidines have been prepared and evaluated for analgesic activity. The compounds in which the substituent was 1-(2-anilinoethyl), 1-(3-oxo-3-phenylpropyl) or 1-(3-hydroxy-3-phenypropyl) proved to be very potent analgesics.

In continuation of our work on strong analgesics, we thought it of interest to prepare some 1-substituted 4-phenyl-4-propionoxypiperidines (I) wherein the nitrogen substituents were the 2-anilinoethyl, 3-oxo-3-phenylpropyl, 2-phenylsulfinylethyl and 3-hydroxy-3-phenylpropyl moieties, in the hope that these structures might afford high analgesic activity.[1-3]

The synthesis of I (R = $CH_2CH_2COC_6H_5$) was accomplished by alkylation of 4-phenyl-4-piperidinol with 3-oxo-3-phenylpropyltrimethylammonium iodide, using the method of Fry and May[1] to give 1-(3-oxo-3-phenylpropyl)-4-phenyl-4-piperidinol. This product was also prepared from 4-phenyl-4-piperidinol hydrochloride, paraformaldehyde and acetophenone, *via* the Mannich reaction. The piperidinol was then acylated with propionic anhydride or, preferably, propionyl chloride.

The 3-methyl analog [3-methyl-1-(3-oxo-3-phenylpropyl)-4-phenyl-4-propionoxypiperidine] was prepared in similar fashion. In this case, the required starting material, 3-methyl-4-phenyl-4-piperidinol, was obtained by the condensation of benzylamine with methyl methacrylate to give methyl 3-benzylamino-2-methylpropionate, which was then treated with methyl acrylate. The resulting diester was cyclized with sodium hydride and the keto ester was hydrolyzed and decarboxylated to give 1-benzyl-3-methyl-4-piperidone. The latter was converted to 1-benzyl-3-methyl-4-phenyl-4-piperidinol with phenyllithium and the benzyl group was removed by catalytic hydrogenation to give 3-methyl-4-phenyl-4-piperidinol. Two diastereoisomeric

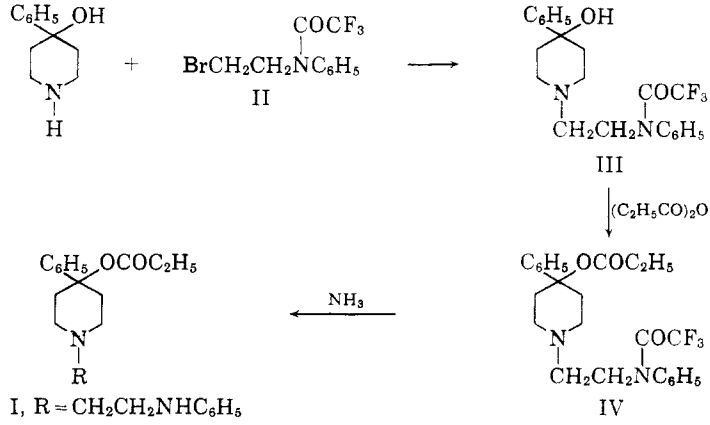
(1) E. M. Fry and E. L. May, *J. Org. Chem.*, **24**, 116 (1959).
(2) B. Elpern, P. Carabateas, A. E. Soria, L. N. Gardner, and L. Grumbach, *J. Am. Chem. Soc.*, **81**, 3784 (1959).
(3) A. Ziering, L. Berger, S. D. Heineman and J. Lee, *J. Org. Chem.*, **12**, 894 (1947).

alcohols probably were produced[4] when phenyllithium was added to 1-benzyl-3-methyl-4-piperidone, but no attempt was made to separate the isomers.

The ketone group of I was readily converted to the oxime (I, R = $CH_2CH_2C(=NOH)C_6H_5$) with hydroxylamine hydrochloride and also reduced to the corresponding alcohol (I, R = $CH_2CH_2CHOHC_6H_5$) with sodium borohydride.

Alkylation of 4-phenyl-4-piperidinol with 2-phenylmercaptoethyl chloride and acylation with propionic anhydride gave I, R = $CH_2CH_2SC_6H_5$. Oxidation with peracetic acid yielded the corresponding sulfoxide (I, R = $CH_2CH_2SOC_6H_5$).

Various attempts to prepare I, R = $CH_2CH_2NHC_6H_5$, by selective acylation of 1-(2-anilinoethyl)-4-phenyl-4-piperidinol or by selective deacylation of O,N-bisacyl derivatives were unsuccessful. The desired product finally was synthesized by the sequence

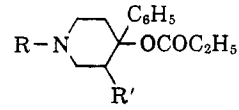


Alkylation of 4-phenyl-4-piperidinol with N-(2-bromoethyl)-trifluoroacetanilide gave 1-[2-(N-phenyl-N-trifluoroacetamido)-ethyl]-4-phenyl-4-piperidinol (III), an oil which could not be obtained solid. The infrared spectra of this compound showed a strong band at 5.89 μ which was assigned to the N-trifluoroacetamido group.[5] Acylation of this product gave 1-[2-(N-phenyl-N-trifluoroacetomido)-ethyl]-4-phenyl-4-propionoxypiperidine (IV). This product was also an oil, which showed strong bands at 5.72 and 5.89 μ. Attempts to prepare a crystalline hydrochloride were unsuccessful. The crude N-trifluoroacetamide (IV) was treated with aqueous-methanolic

(4) A. H. Beckett, A. F. Casy, and P. M. Phillips, *J. Med. Pharm. Chem.*, **2**, 249 (1960).

(5) H. Letaw and A. H. Gropp, *J. Chem. Phys.*, **21**, 1621 (1953), found a band at 5.91 μ for N,N-dibutyltrifluoroacetamide.

TABLE I



Analgesic potency was determined by the Bass, Vanderbrook modification[c] of the D'Amour, Smith[d] rat thermal stimulus method.

	R	R′	M.p., °C.	Yield, %	Formula
1	$(CH_2)_2COC_6H_5$	−H	157.4–159.0	87.0	$C_{23}H_{27}NO_3 \cdot HCl$
2	$(CH_2)_2C(=NOH)C_6H_5$	−H	180.0–181.2	36.8	$C_{23}H_{28}N_2O_3$
3	$(CH_2)_2CHOHC_6H_5$	−H	174.0–175.4	36.1	$C_{23}H_{29}NO_3 \cdot HCl$
4	$(CH_2)_2COC_6H_5$	$-CH_3$	152.4–156.2	17.5	$C_{24}H_{29}NO_3 \cdot HCl \cdot H_2O$
5	$(CH_2)_2SC_6H_5$	−H	146.2–147.8	63.0	$C_{22}H_{27}NO_2S \cdot C_7H_8O_3S$
6	$(CH_2)_2SOC_6H_5$	−H	156.4–157.8	65.0	$C_{22}H_{27}NO_3S \cdot C_7H_8O_3S$
7	$(CH_2)_2NHC_6H_5$	−H	173.8–175.0	5.0	$C_{22}H_{28}N_2O_2 \cdot 2HCl$
8	Meperidine				

	Carbon		Hydrogen		Chlorine		Sulfur		Potency, relative to meperidine
	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	
1	68.73	68.39	7.02	7.14	8.82	9.10			1346
2	72.56	72.60	7.41	7.23			7.36[a]	7.76	313.6
3	68.39	68.67	7.49	7.37	8.78	8.82			3219
4	66.40	66.39	7.43	7.13	8.17	8.18	4.14[b]	4.15	893
5	64.29	64.37	6.51	6.33			11.84	11.62	2.72
6	62.44	62.10	6.33	6.03			11.50	11.22	42.9
7	62.11	62.11	7.11	6.93	16.67	16.54			1301
8									1

[a] Analyzed for nitrogen. [b] Analyzed for water. [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).

ammonia and then ethereal hydrogen chloride to give the dihydrochloride of I, R = $CH_2CH_2NHC_6H_5$, which was obtained as a crystalline solid. This product showed a strong ester carbonyl band at 5.73 μ whereas the tertiary amide band at 5.89 μ had disappeared.

The analgesic potencies as well as the analytical data are listed in Table I. Of particular interest is the fact that reduction of the ketone group in I, R = $CH_2CH_2COC_6H_5$, gave a compound 3219 times as potent as meperidine. Such extremely high analgesic activity in piperidine analgesics is rare; only one other example, which was reported while this work was in progress, is known.[6]

Experimental

Methyl 3-Benzylamino-2-methylpropionate.—A mixture of benzylamine (214 g., 2.0 moles) methyl methacrylate (300.3 g., 3.0 moles) and 200 ml. of methanol

(6) P. Janssen and N. B. Eddy, *J. Med. Pharm. Chem.*, **2**, 31 (1960), reported that 1-(3-phenyl-3-propionoxypropyl)-4-phenyl-4-propionoxypiperidine (I, R = $CH_2CH_2CH(OCOC_2H_5)C_6H_5$) had an activity equal to 3040 times meperidine.

was refluxed for 4 hr. and allowed to stand for 2 days. After concentration *in vacuo*, the residue was fractionated. The product boiled at 150–155° (17 mm.), $n^{26}D$ 1.5034, lit.[7] 142–144° (17 mm.); yield, 78%, based on recovered benzylamine.

Anal. Calcd. for $C_{12}H_{17}NO_2$: N, 6.76. Found: N, 6.69.

N-Benzyl-N-(2-carbomethoxyethyl)-N-(2-carbomethoxypropyl)-amine.—A mixture of methyl-3-benzylamino-2-methylpropionate (219 g., 1.05 moles) and methyl acrylate (138 g., 1.6 moles) was refluxed for 24 hr. Distillation gave two fractions: (a) 79 g. of recovered starting material, 100–105° (0.3 mm.), $n^{26}D$ 1.5032; and (b) 179 g. of product 140–145° (0.3 mm.), $n^{27}D$ 1.4946; yield, 90.5% based on recovered starting material.

Anal. Calcd. for $C_{16}H_{23}NO_4$: N, 4.77. Found: N, 4.81.

1-Benzyl-3-methyl-4-piperidone.—A 52.9% dispersion of sodium hydride in mineral oil (55 g., 1.23 mole) was suspended in 2 l. of dry benzene by vigorous stirring and heated to reflux. Absolute ethanol (2 ml.) was added and then N-benzyl-N-(2-carbomethoxyethyl)-N-(2-carbomethoxypropyl)-amine (179 g., 0.61 mole) over 1.5 hr. It is essential that hydrogen evolution is proceeding vigorously before much ester is added. After the addition was completed, the mixture was stirred and refluxed for an additional 2.5 hr. After cooling, the mixture was hydrolyzed by cautious addition of 250 ml. of water, then 200 ml. of concd. hydrochloric acid. The aqueous layer was separated and refluxed for 6 hr. After cooling, it was made basic with solid potassium carbonate and extracted with benzene. The benzene extracts were washed with water and concentrated *in vacuo* to an oil. Distillation of the oil gave 107.9 g. of product, b.p. 110–115° (0.3 mm.), $n^{26}D$ 1.5283; yield, 86.4%.

Anal. Calcd. for $C_{13}H_{17}NO$: N, 6.89. Found: N, 6.78.

1-Benzyl-3-methyl-4-phenyl-4-piperidinol.—To a stirred phenyllithium solution prepared from lithium wire (14.7 g., 2.1 g./atom), bromobenzene (163 g., 1.05 moles) and 1 l. of ether was added a solution of 1-benzyl-3-methyl-4-piperidone (107.5 g., 0.53 mole) in 1 l. of ether. After addition was completed, the solution was refluxed for 2 hr., and then poured onto a mixture of ammonium chloride and ice. The ether layer was separated and concentrated to an oil weighing 133 g. (89.2% yield). This product could not be obtained crystalline and was used directly in the next step.

3-Methyl-4-phenyl-4-piperidinol.—A solution of crude 1-benzyl-3-methyl-4-phenyl-4-piperidinol (133 g., 0.474 mole) in 1500 ml. of ethanol was hydrogenated at 42 kg./cm.^{2} and 60°, using 14 g. of 10% palladium charcoal as a catalyst. The theoretical amount of hydrogen was absorbed in 2.75 hr. The catalyst was removed by filtration and the filtrate concentrated *in vacuo* to a white solid. Recrystallization from cyclohexane gave 82.2 g. of product, m.p. 126.5–127.5°; yield, 90.8%.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.34; H, 8.96; N, 7.32. Found: C, 75.27; H, 8.75; N, 7.24.

4-Phenyl-4-piperidinol was prepared by the procedure of Schmidle and Mansfield.[8]

1-(3-Oxo-3-phenylpropyl)-4-phenyl-4-piperidinol was prepared using the method of Fry and May.[1] Crystallization from cyclohexane gave 79.3% yield of product, m.p. 133–134°.

(7) R. C. Smith and S. B. Binkley, *J. Org. Chem.*, **24**, 249 (1959).
(8) C. J. Schmidle and R. C. Mansfield, *J. Am. Chem. Soc.*, **78**, 1702 (1956).

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.61; H, 7.49; N, 4.53. Found: C, 77.36; H, 7.25; N, 4.52.

The hydrochloride had m.p. 187–189° (from ethanol).

Anal. Calcd. for $C_{20}H_{23}NO_2 \cdot HCl$: C, 69.45; H, 6.99; Cl, 10.25. Found: C, 69.13; H, 7.19; Cl, 10.55.

The hydrochloride could also be prepared in one step in 30.6% yield by refluxing for 4 hr. a solution of 4-phenyl-4-piperidinol hydrochloride (21.4 g., 0.1 mole), paraformaldehyde (6.0 g., 0.2 mole) and acetophenone (12.1 g., 0.11 mole) in 20 ml. of ethanol. The product crystallized on cooling and was recrystallized from ethanol; m.p. 187–189°.

1-(3-Oxo-3-phenylpropyl)-3-methyl-4-phenyl-4-piperidinol was also prepared by the method of Fry and May,[1] m.p. 143–145° from cyclohexane; yield, 86.7%.

Anal. Calcd. for $C_{21}H_{25}NO_2$: N, 4.33. Found: N, 4.28.

1-(3-Oxo-3-phenylpropyl)-4-phenyl-4-propionoxypiperidine Hydrochloride.—A. Propionic Anhydride Method.—A solution of 1-(3-oxo-3-phenylpropyl-4-phenyl-4-piperidinol hydrochloride (6.0 g., 0.0173 mole) in 50 ml. of propionic anhydride was heated overnight on the steam-bath. The solution was concentrated to an oil *in vacuo*. The oil was poured into 300 ml. of absolute ether and allowed to stand. The ether was decanted and the solid residue recrystallized from ethyl acetate and then acetone; yield, 1.7 g. (24.4%), m.p. 147.6–152.8°.

Anal. Calcd. for $C_{23}H_{27}NO_3 \cdot HCl$: C, 68.73; H, 7.02; Cl, 8.82. Found: C, 68.39; H, 7.14; Cl, 9.10.

B. Propionyl Chloride Method.—Propionyl chloride (41 g., 0.44 mole) was added to a solution of 1-(3-oxo-3-phenylpropyl)-4-phenyl-4-piperidinol (135 g., 0.435 mole) in 700 ml. of dry chloroform. A mildly exothermic reaction occurred. After the reaction had subsided, the solution was allowed to stand for 2 hr. The chloroform was evaporated and ether was added. After standing overnight in the refrigerator, the ether was decanted and the semi-solid residue boiled with 1 l. of ethyl acetate until the product solidified. After cooling, the product was filtered and washed with fresh ethyl acetate, then dry ether. The product weighed 151 g. (87%) and had m.p. 157.4–159°.

Anal. Calcd. for $C_{23}H_{27}NO_3 \cdot HCl$: Cl, 8.85; O, 12.00. Found: Cl, 8.77; O, 12.05.

The 3-methyl analog was prepared by method A.

1-(3-Oximino-3-phenylpropyl)-4-phenyl-4-propionoxypiperidine. A stirred suspension of 1-(3-oxo-3-phenylpropyl)-4-phenyl-4-propionoxypiperidine hydrochloride (4.02 g., 0.01 mole) in 15 ml. of water was treated with excess 35% sodium hydroxide solution and then with a solution of hydroxylamine hydrochloride (1.00 g., 0.0144 mole) in 10 ml. of water and 10 ml. of ethanol. The mixture was warmed gently until a clear solution was obtained. After cooling, the product was collected and crystallized first from methanol, and then from ethyl acetate; yield, 1.4 g.

1-(3-Hydroxy-3-phenylpropyl)-4-phenyl-4-propionoxypiperidine Hydrochloride.—One gram of sodium borohydride was added to a solution of 1-(3-oxo-3-phenylpropyl)-4-phenyl-4-propionoxypiperidine (8.5 g., 0.0233 mole) in 100 ml. of methanol. The solution was stirred for 2 hr., then concentrated to an oil. The oil was extracted with chloroform, the chloroform evaporated and the residue dried by azeotropic distillation with benzene. The residual oil was taken up in ether and ethereal hydrogen chloride was added. The resulting gum was boiled

with ethyl acetate until it turned solid. The solid was recrystallized from acetone; yield, 3.4 g.

1-(2-Phenylmercaptoethyl)-4-phenyl-4-propionoxypiperidine *p*-Toluenesulfonate.—A mixture of 4-phenyl-4-piperidinol (5.3 g., 0.03 mole), 2-chloroethyl phenyl sulfide[9] (5.2 g., 0.03 mole), 6 g. of sodium carbonate and 50 ml. of *n*-butyl alcohol was refluxed for 24 hr., cooled and diluted with 100 ml. of acetone. The solution was filtered and the filtrate concentrated to an oil which crystallized on cooling. A mixture of 40 ml. of propionic anhydride and 10 ml. of pyridine was added and the solution heated overnight on the steam-bath. The solution was concentrated to an oil *in vacuo*, and the residue was made basic with 10% sodium hydroxide. The resulting oil was extracted with ether, washed with water and dried over sodium sulfate. The ether solution was concentrated to a dark oil which was taken up in 15 ml. of absolute ethanol. A solution of 5.6 g. of *p*-toluenesulfonic acid·H_2O in 20 ml. of ethanol was added. On cooling and scratching, a crystalline solid precipitated. Recrystallization from isopropyl alcohol gave 10.1 g. of product.

1-(2-Phenylsulfinylethyl)-4-phenyl-4-propionoxypiperidine *p*-Toluenesulfonate.—A 40% solution of peracetic acid (2.1 g., 0.011 mole) was added all at once to a stirred suspension of 1-(2-phenylmercaptoethyl)-4-phenyl-4-propionoxypiperidine *p*-toluenesulfonate (6.0 g., 0.011 mole) in 100 ml. of ethyl acetate. The temperature rose to 36° and all the solid dissolved. After stirring for 1 hr., the solution was concentrated to a gum which solidified on trituration with ether. Recrystallization from isopropyl alcohol gave 4.0 g. of product.

N-2-Bromoethyltrifluoracetanilide.—Trifluoroacetic anhydride (25.0 g., 0.119 mole) was added to 2-anilinoethyl bromide hydrobromide (28.1 g., 0.1 mole).[10] Hydrogen bromide was evolved. The mixture was refluxed gently for 1 hr., and allowed to stand overnight. The solution was taken up in chloroform and washed successively with water, 5% sodium bicarbonate, dilute hydrochloric acid and water. After drying over sodium sulfate, the chloroform solution was concentrated to a dark oil. Distillation gave 17.5 g. of colorless liquid, b.p. 89–95° (0.55 mm.), $n^{30}D$ 1.5058; yield, 59%.

Anal. Calcd. for $C_{10}H_9BrF_3NO$: Br, 27.00. Found: Br, 27.61.

1-(2-Anilinoethyl)-4-phenyl-4-propionoxypiperidine Dihydrochloride.—A mixture of 4-phenyl-4-piperidinol (10.0 g., 0.0564 mole), N-(2-bromoethyl)-trifluoroacetanilide (16.7 g., 0.0564 mole), 15 ml. of triethylamine and 100 ml. of chloroform was refluxed for 22 hr. The solution was concentrated *in vacuo* to a semi-solid, which was taken up in ethyl acetate. A white solid was removed by filtration. The precipitate was washed with acetone and the filtrate and washings were concentrated to a red oil. The oil was heated on the steam-bath for 6 hr. with 40 ml. of propionic anhydride and 0.5 ml. of pyridine and then poured into 500 ml. of methanol. After concentration *in vacuo* to a small volume, the residue was taken up in ether, washed with 10% sodium carbonate solution and then with water. The ether was evaporated and the residue dissolved in 250 ml. of methanol. A 28% ammonia solution (75 ml.) was added and the mixture allowed to stand for 1 hr. The solution was concentrated to about 75 ml. and diluted with 200 ml. of water. The aqueous solution was extracted with ether and the extract washed with water. The ether extract was concentrated to an oil which was dried by azeo-

(9) A. H. Ford-Moore, R. A. Peters, and R. W. Wakelin, *J. Chem. Soc.*, 1754 (1949).
(10) W. M. Pearlman, *J. Am. Chem. Soc.*, **70**, 871 (1948).

tropic distillation with benzene. Addition of ethereal hydrogen chloride gave a white solid which was recrystallized several times from ethanol; yield, 1.2 g.

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Dicarbamates and Thiolcarbamates

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A number of thiolcarbamates structurally related to monocarbamates known to elicit muscle-relaxant and tranquilizing effects were synthesized for biological evaluation. One compound, phenoxypropylthiolcarbamate (compound 10, Table I), showed good taming effect in experimental animals. However, the thiolcarbamates in general possessed an offensive odor and consequently further work in this series was of limited value. Some dicarbamates were prepared but these were devoid of significant biological activity.

Several years ago we initiated a project in our Laboratory which had as its goal the synthesis and evaluation of substances for analgetic effects. A wide variety of thiazolin-2-ones[1,2] were prepared by the condensation of an α-halo ketone with ethyl xanthamidate. One of the compounds, 4-piperidinomethyl-2,3,4,5,6,7-hexahydrothiazolin-2-one,[3] exhibited good analgetic effects with rapid onset of action when tested in humans. However, a drug side effect (*i.e.*, reversible inflammation of the optic nerve) curtailed further investigations with this class of compounds.

In the course of the synthetic work in this series, it was observed that α-chlorocyclohexanone condensed with ethyl xanthamidate under relatively mild conditions to afford the corresponding thiazolin-2-one,

(1) G. deStevens, H. A. Luts, and J. A. Schneider, *J. Am. Chem. Soc.*, **79**, 1516 (1957).
(2) G. deStevens, A. Frutchey, A. Halamandaris, and H. A. Luts, *ibid.*, **79**, 5263 (1957).
(3) G. deStevens, A. L. Hopkinson, M. A. Connelly, P. Oke, and D. C. Schroeder, *ibid.*, **80**, 2201 (1958).