Strong Analgesics. Some 1-Substituted 4-Acyl-4-phenylpiperidines

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Received May 1, 1961

In a continuation of our work on strong analgesics,[3] it was of interest to prepare compounds related to meperidine in which the carbethoxy group of meperidine was replaced by acyl and the methyl group replaced by some of the large moieties found to enhance analgesic activity in the meperidine series.[3]

Accordingly, 1-benzyl-4-phenyl-4-cyanopiperidine was treated with alkylmagnesium bromide to form 4-acyl-1-benzyl-4-phenylpiperidine which was then catalytically debenzylated. The resulting amino ketone was then *N*-substituted either by treating with the desired halide in the presence of sodium carbonate, or in the cases of two of the substituted phenylaminoethyl groups, the piperidine ketone was hydroxyethylated, the hydroxyl replaced by halogen and this finally treated with the substituted aniline.

The pharmacological evaluation of these compounds for analgesic potency by the Bass-VanderBrook modification[4] of the D'Amour-Smith rat thermal stimulus method[5] will be reported more fully elsewhere, but a brief summary can be given here. It is clear that when the *N*-substituent is 2-phenylaminoethyl and the alkyl portion of the ketone is varied, maximum activity is found with the propyl group. It is of interest to note that when the alkyl group is ethyl the compound is a potent general anesthetic, and the analgesic potency is masked in this screening procedure. If the alkylene chain between the nitrogens is lengthened or if a *para* methyl group is placed on the phenyl, the potency is increased.

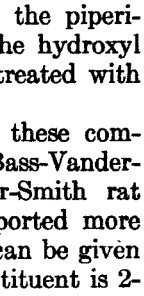
EXPERIMENTAL[6]

Perrine[7] has described 1-benzyl-4-phenyl-4-acetylpiperidine and Eisleb[8] has described the corresponding propionyl compound. The butyryl and valeroyl compounds were prepared by Eisleb's method.

1-Benzyl-4-phenyl-4-butyrylpiperidine hydrochloride was prepared in 85.3% yield; m.p., 227.0–230.0°.

TABLE I

1-SUBSTITUTED 4-ACYL-4-PHENYLPIPERIDINES



R	R′	M.P.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Potency Relative to Meperidine (1)	Method
CH_3—	$C_6H_5NHCH_2CH_2$—	235.0–236.4	42.5	$C_{21}H_{26}N_2O\cdot HCl$					9.88	10.03	7.81	7.80	0.37	A
C_2H_5—	$C_6H_5CH{=}CHCH_2$—	188.0–191.2	51.0	$C_{23}H_{27}NO\cdot HCl$	74.69	74.74	7.63	7.73	9.58	9.40			4.0	A
C_3H_7—	$C_6H_5NHCH_2CH_2$—	209.0–211.2	56.7	$C_{23}H_{28}NO\cdot HBr$	63.31	63.46	7.00	6.95	19.15	19.12			—	A
C_3H_7—	$HOCH_2CH_2$—	187.0–190.0	71.7	$C_{17}H_{23}NO_2\cdot HCl$	64.51	64.53	8.12	8.20	11.90	11.89			0	A
C_3H_7—	$ClCH_2CH_2$—	231.0–232.4	91.9	$C_{17}H_{22}ClNO\cdot HCl$					22.42	22.20	4.43	4.42	0	—
C_3H_7—	p-$O_2NC_6H_4NHCH_2CH_2$—	219.6–221.6	28.8	$C_{28}H_{27}N_3O_3\cdot HCl$					8.49	8.48	10.06	9.93	Sl. Act.	B
C_3H_7—	p-$ClC_6H_4NHCH_2CH_2$—	229.2–230.8	71.3	$C_{28}H_{27}ClN_2O\cdot HCl$					17.41	17.61	6.88	6.82	0.71	B
C_3H_7—	p-$CH_3C_6H_4NHCH_2CH_2$—	198.4–200.2	19.8	$C_{29}H_{30}N_2O\cdot 2HCl$	65.26	65.00	7.62	7.49	16.75	16.75			3.55	A
C_3H_7—	$C_6H_5NHCH_2CH_2CH_2$—	206.6–212.8 dec.	32.0	$C_{29}H_{30}N_2O\cdot 2HCl$	65.26	65.03	7.62	7.77	16.75	16.55			5.92	A
C_4H_9—	$C_6H_5NHCH_2CH_2$—	209.0–210.8	35.5	$C_{22}H_{30}N_2O\cdot HCl$					9.16	9.05	7.24	7.23	9.14	A
C_4H_9—	$C_6H_5NHCH_2CH_2$—	180.4–188.0	5.5	$C_{24}H_{32}N_2O\cdot 2HCl$	65.90	65.66	7.83	7.83	16.21	16.00			0.76	A

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Anal. Calcd. for $C_{22}H_{27}NO \cdot HCl$: C, 73.82; H, 7.89; Cl, 9.91. Found: C, 74.18; H, 7.65; Cl, 9.98.

1-Benzyl-4-phenyl-4-valeroylpiperidine hydrochloride was prepared in 48% yield; m.p., 200.0–203.0°.

Anal. Calcd. for $C_{23}H_{30}NO \cdot HCl$: Cl, 9.54. Found: Cl, 9.90.

4-Phenyl-4-acetylpiperidine. 1-Benzyl-4-phenyl-4-acetylpiperidine (86.1 g., 0.294 mole) was dissolved in 200 ml. of glacial acetic acid and 500 ml. of ethanol. Ten grams of 10% palladium-charcoal was added and the mixture hydrogenated at 560 lb. and 55°. The theoretical amount of hydrogen was taken up in 4 hr. The catalyst was removed by filtration, the filtrate concentrated to an oil and the oil made basic with 10% sodium hydroxide. The resulting oil was extracted with benzene, washed with water, concentrated to an oil, and distilled; b.p., 90–96°; 0.1 mm.; 4.43 g. of colorless oil (74.4%). A small portion of the base was converted to the hydrochloride and crystallized from methanol–ethyl acetate, m.p. 241–242°.

Anal. Calcd. for $C_{13}H_{17}NO$: N, 6.91. Found: N, 6.93.

The propionyl, butyryl, and valeroyl analogs were similarly prepared.

4-Phenyl-4-propionylpiperidine was prepared in 38.8% yield; hydrochloride, m.p. 206–207°.

Anal. Calcd. for $C_{14}H_{19}NO \cdot HCl$: C, 66.24; H, 7.94; Cl, 13.97. Found: C, 65.96; H, 7.79; Cl, 13.72.

4-Phenyl-4-butyrylpiperidine was prepared in 70.6% yield; b.p. 90–100°, 0.1 mm., hydrochloride, m.p. 165.6°.

Anal. Calcd. for $C_{15}H_{21}NO$: N, 6.06. Found: N, 6.13.

4-Phenyl-4-valeroylpiperidine was prepared in 73.2% yield; hydrochloride, m.p. 113–115°.

Anal. Calcd. for $C_{15}H_{23}NO \cdot HCl$: Cl, 12.58. Found: Cl, 12.80.

1-(2-Chloroethyl)-4-phenyl-4-propionylpiperidine. 1-(2-Hydroxyethyl) - 4 - phenyl- 4 - propionylpiperidine (32.5 g., 0.109 mole) was suspended in 400 ml. of benzene and 2 drops of pyridine. The solution was heated to reflux and a solution of thionyl chloride (13.1 g., 0.11 mole) in 50 ml. of benzene was added over 15 min. Reflux was continued for 1.5 hr. After standing for 2 days, the white solid was filtered and recrystallized from ethanol; m.p., 220–223° dec.; 31.7 g., yield 91.9%.

2-Phenylaminoethylbromide hydrobromide. This compound was prepared by Pearlman's method,[9] as were 3-phenylaminopropylbromide hydrobromide and 2-(4-methylphenylamino)ethyl bromide hydrobromide.

3-Phenylaminopropylbromide hydrobromide was prepared from *N*-3-hydroxypropyl aniline;[10] m.p., 128.5–129.5° (from ethanol), yield 63.5%.

Anal. Calcd. for $C_9H_{12}BrN \cdot HBr$: Br, 54.19. Found: Br, 53.95.

2-(4-Methylphenylamino)ethylbromide hydrobromide was prepared from 2-(4-methylanilino)ethanol; m.p., 178.9° (from acetone–ether), yield 54.2%.

Anal. Calcd. for $C_9H_{12}BrN \cdot HBr$: C, 36.64; H, 4.44. Found: C, 36.34; H, 4.26.

2-(4-Methylphenylamino)ethanol. This compound was prepared by the general method of Adams and Segur,[11] b.p., 95–97°/0.1 mm.; n_D^{25} 1.5616; yield, 76.4%.

Anal. Calcd. for $C_9H_{13}NO$: N, 9.26. Found: N, 9.23.

1-(2-Hydroxyethyl)-4-phenyl-4-propionylpiperidine hydrochloride. Method A. A mixture of 4-phenyl-4-propionylpiperidine, (36 g., 0.166 mole), ethylene chlorohydrin (22 g., 0.25 mole), sodium carbonate (32 g., 0.3 mole), and 150 ml. of *n*-butyl alcohol was refluxed for 24 hr. with stirring. The mixture was cooled, inorganic salts filtered and the filtrate concentrated to an oil. The oil was taken up in ether and a few small pieces of solid carbon dioxide added to precipitate any unchanged secondary amine. The ether solution was filtered and ethereal hydrogen chloride was added. The resulting white gum solidified on standing. Recrystallization from ethanol–ethyl acetate gave 35.5 g. of product (71.7%), m.p., 184–185°.

1-[2-(4-Chlorophenylamino)ethyl]-4-phenyl-4-propionylpiperidine hydrochloride. Method B. A mixture of 1-(2-chloroethyl)-4-phenyl-4-propionylpiperidine hydrochloride (6.32 g., 0.02 mole), 4-chloroaniline (10.2 g., 0.08 mole), and 50 ml. of Methyl Cellosolve (R) solvent was refluxed for 16 hr. The solution was chilled for several hours and the resulting solid recrystallized from ethanol; m.p., 216–218°, 5.8 g., yield, 71.3%.

Acknowledgment. We are greatly indebted to Messrs. M. E. Auerbach, K. D. Fleischer, and staff for the chemical analyses, and to Mrs. H. Lawyer and Mrs. A. Pierson for technical assistance in the pharmacological evaluations.

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gem-Dinitroalkyl Acrylates

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Received May 2, 1961

The preparation of a number of nitroalkyl acrylates, crotonates, and methacrylates has been reported.[1] The synthesis of a series of *gem*-dinitroalkyl acrylates is described in this paper. The acrylates were prepared in 47–75% yield by refluxing a benzene solution of acrylic acid or methacrylic acid with the appropriate *gem*-dinitro alcohol in the presence of sulfuric acid catalyst, until the theoretical amount of water was evolved. The properties of the compounds which were prepared are summarized in Table I.

The majority of the *gem*-dinitro alcohols were prepared by the Henry reaction of the *gem*-dinitroalkane and formaldehyde.[2] The only exceptions were 3,3-dinitro-1-butanol, which was prepared from 3,3-dinitro-1-butylamine,[3] and *N*-(2,2-dinitropropyl)-*N*-nitroethanolamine (IV), which was synthesized as shown in Chart I.

The Mannich condensation of 2,2-dinitropropanol and ethanolamine[4] gave *N*-(2,2-dinitropropyl)-ethanolamine, (I), which was nitrated directly to give *N*-(2,2-dinitropropyl)-*N*-nitroethanolamine nitrate (II). Using a procedure similar to that de-

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