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PIPERIDINE DERIVATIVES. IV. 4-ALKYL-, 4-CYCLOALKYL-, AND 4-HETEROCYCLYL-PIPERIDINES[1]

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In a previous paper of this series it was shown that certain members of the series of 1-alkyl-4-phenyl-4-acyloxypiperidines possess extremely high analgesic activity in rats when tested by a modification of the Hardy-Wolff-Goodell technique (1). Considerable variation of the alkyl and acyl substituents and of substitution in the phenyl nucleus was made, the optimum activity being found in compounds having an unsubstituted phenyl group at the 4-position. It was therefore thought desirable to find out whether the phenyl group could be replaced by other groups with the retention of analgesic activity. In this paper the synthesis of 4-heterocyclylpiperidines derived from pyridine, thiophene, and furan, the 4-heterocyclylalkylpiperidines derived from α-picoline and $\alpha\alpha'$-lutidine and the 4-methyl-, butyl-, and *n*-hexyl-piperidines and 4-cyclohexyl-piperidines is reported.

The synthesis of the 1,4-dialkyl-4-hydroxypiperidines offered no difficulties. 1-Alkyl-4-piperidones I react with lithiumalkyls to yield the 1,4-dialkyl-4-hydroxy-piperidines (VII, R^1 = alkyl). Similarly, the heterocyclyllithium and heterocyclylalkyllithium compounds yielded the corresponding 4-piperidinols (VII, R^1 = 2-pyridyl, 3-pyridyl, 2-furyl, 2-picolyl, 2-lutidyl, and 2-thienyl). 1-Alkyl-4-piperidones with cycloalkylmagnesium halides gave no isolable yield of the desired 4-cyclohexyl derivative. The Grignard reagent in the reaction apparently catalyzes an aldol condensation of the 1-alkyl-4-piperidone to a compound of the type II. In the reaction of cyclohexylmagnesium chloride and 1-butyl-4-piperidone, a compound which analyzes correctly for 1-butyl-4-hydroxy-4 (1′-butyl-4′-keto-3′-piperidyl)piperidone hydrochloride (II, R = C_4H_9) was obtained. A similar reaction had already been noted in the corresponding reaction with 1-alkyl-2-piperidones (2). It was found that 4-phenyl-4-hydroxypiperidine salts III could be hydrogenated to the corresponding cyclohexyl compounds IV. The free bases could not be hydrogenated in this manner, neutral or acid conditions being required. The corresponding piperidinol esters V could not be hydrogenated to the 1-alkyl-4-cyclohexyl-4-piperidinol esters, in this case reduction occurs with removal of a molecule of acid and the formation of 1-alkyl-4-cycloalkylpiperidines VI.

Pharmacological results. The replacement of the phenyl group in 1-alkyl-4-phenyl-4-acyloxypiperidines as described here leads invariably to compounds of lowered activity. Replacing phenyl with a methyl or hexyl group gave compounds of practically no activity. The butyl group showed some slight activity.

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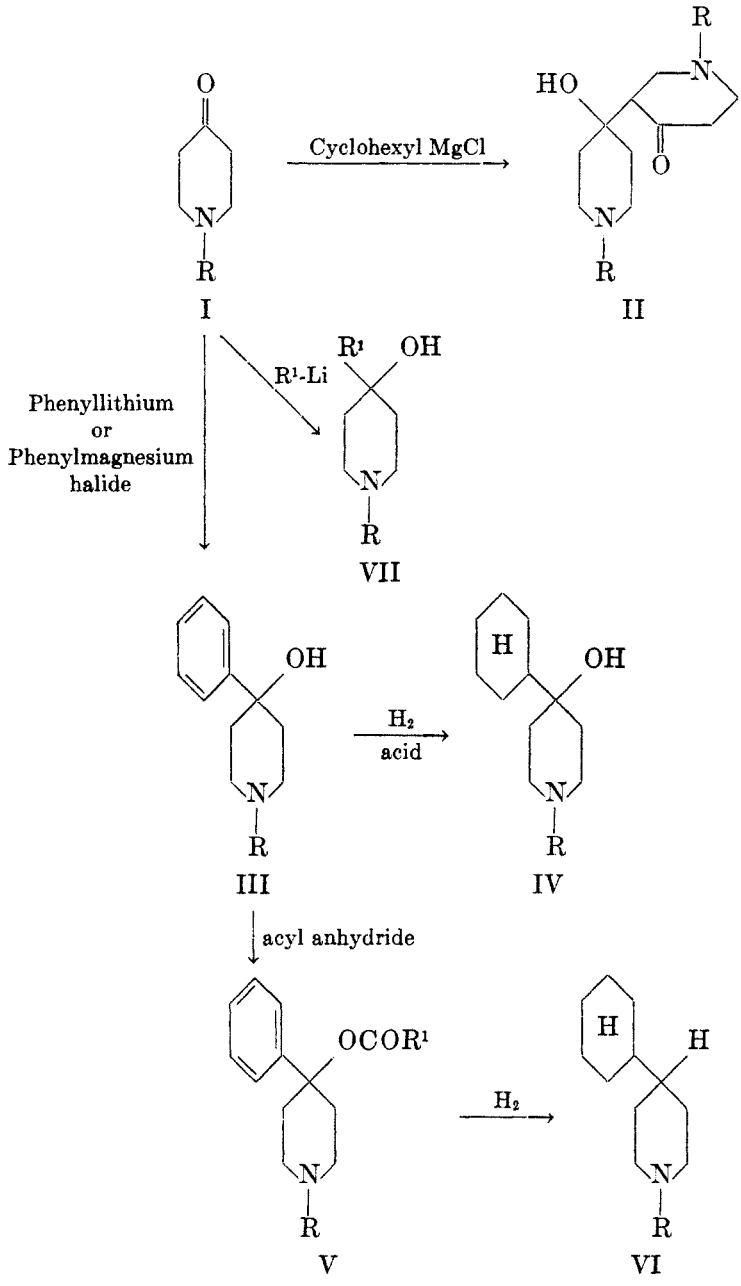
The acetate of 1,4-dibutyl-4-piperidinol was slightly active, the propionate and butyrate being of greater and about equal activity. This contrasts with the



4-phenyl series VI, where there is a pronounced peak of activity with the propionic ester. Replacing the phenyl residue in V with hydrogen as in the case

of 1-butyl-4-propionoxypiperidine gives a compound which still has activity at higher dose levels.

The substitution of the phenyl in V with heterocyclyl or heterocyclylalkyl residues has a definite dystherapeutic effect. The best compound of this series is the β-pyridyl derivative. This compound has about half of the activity of Demerol and about half of the toxicity of the latter, but this activity is only about one-thirtieth of that of the corresponding phenyl compound. The substitution of phenyl by cyclohexyl in V, yielding the esters of IV, gives compounds which are also less active than the phenyl compounds. 1-Methyl-4-cyclohexyl-4-propionoxypiperidine has about one-third of the activity of 1-methyl-4-phenyl-4-propionoxypiperidine. It is, however, less toxic, and contrary to the latter, forms aqueous solutions which are stable under practical conditions. The compounds prepared are shown in Table I. Typical methods of preparation are given in the experimental part.

Acknowledgment. The analysis of the compounds recorded here was performed in the Microanalytical Division of these Laboratories by Dr. Al Steyermark and his co-workers and the pharmacological results are due to Drs. R. H. K. Foster, G. Lehmann, and their co-workers of the Pharmacological Laboratory. We wish to express our appreciation of their co-operation.

EXPERIMENTAL

4-(3-Pyridyl)-4-hydroxyl-1-butylpiperidine. Thirty-nine grams of butyl chloride in 250 cc. of dry ether was refluxed with 6 g. of lithium wire. The butyllithium solution which formed was cooled to −40° and 50 g. of 3-bromopyridine in 50 cc. of dry ether was added dropwise (3). An instantaneous reaction occurred, forming a brown complex, which was stirred at −40° for 15 minutes. Fifteen and one-half grams of 1-butyl-4-piperidone in 25 cc. of dry ether was slowly added at this temperature and on completion of the addition, the temperature was allowed to rise to −15°. After stirring for 45 minutes at this temperature the reaction mixture was decomposed by pouring it onto a mixture of ice and hydrochloric acid. The ethereal solution was separated, extracted with a little dilute hydrochloric acid and the acid solution returned to the reaction mixture. This was basified with cold 10% NaOH solution to *p*H 10 and extracted with ether. After drying the ether extract and removal of the solvent, 9 g. of a viscous yellow syrup remained which distilled at 156–158° at 0.5 mm. The product crystallized spontaneously and was recrystallized from hexane yielding 4-(3-pyridyl)-4-hydroxy-1-butylpiperidine, m.p. 80–81°.

The *acetate* was prepared by heating with acetic anhydride in the presence of a trace of sulfuric acid. The hydrochloride, when recrystallized from ethyl acetate-methanol, melted at 215–216°. The *propionate* hydrochloride prepared under the same conditions melts 198–199°.

4-(2-Picolyl)-4-hydroxy-1-butylpiperidine. Picolyllithium was prepared from 28 g. of bromobenzene, 2.5 g. of lithium, and 12.4 g. of α-picoline as described by Bergmann and Rosenthal (4). The resultant picolyllithium was reacted with 15.5 g. of 1-butylpiperidone-4 under the conditions described above. On working up the reaction in the usual manner, 18.4 g. (75% yield) of a light thin syrup was obtained which boiled at 148–150°/0.9 mm.

The *acetate* prepared under the usual conditions is a hygroscopic amorphous glass. The *propionate* has similar characteristics.

4-Hydroxy-4-(6'-methyl-2'-pyridylmethyl)-1-butylpiperidine dihydrochloride. Phenyllithium was prepared in the usual manner from 5.0 g. of lithium and 49 g. of bromobenzene in 200 cc. of ether. To this, at 0°, 13.4 g. of 2,6-lutidine in ether was added in 20 minutes. The purplish-colored solution was cooled to −30° and 31 g. of 1-butyl-4-piperidone in 50

cc. of ether was added slowly. The color changed from purple to deep Burgundy-red and became clear. After a further ½ hour at −20° the reaction mixture was decomposed with a mixture of equal parts of concentrated hydrochloric acid and ice. The aqueous solution was separated and alkalinized, and extracted with ether. The ether solution was dried over potassium carbonate for 24 hours, filtered, and the solvent removed. The residue, fractionated at 1 mm., yielded 14.4 g. of material boiling at 141–142° and analyzed correctly for the above-mentioned structure.

The *dihydrochloride* is a light yellow hygroscopic amorphous compound containing 3 molecules of water of crystallization. The *acetate* and *propionate* are hygroscopic glasses.

4-Methyl-4-hydroxy-1-butylpiperidine. Twenty-eight grams of freshly distilled methyl iodide and 2.8 g. of freshly cut lithium metal were stirred in 200 cc. of ether. The reaction was complete in two hours. The mixture was cooled to −15° and 15.5 g. of 1-butylpiperidone-4 in ether was added dropwise. After stirring for one hour at this temperature, the mixture was decomposed with ice and hydrochloric acid and worked up in the usual manner. The reaction product, fractionated at 1.0 mm., yielded 12 g. of an oil boiling at 75–76°. The product is the desired 4-methyl-4-hydroxy-1-butylpiperidine.

4-Cyclohexyl-4-hydroxy-1-butylpiperidine hydrochloride. Eight grams of 1-butyl-4-phenyl-4-hydroxypiperidine hydrochloride was dissolved in 100 cc. of absolute alcohol and hydrogenated in the presence of Adams' platinum oxide catalyst at 85° and at a hydrogen pressure of 1100 lb./per sq. inch. The absorption of the theoretical amount of H_2 required four hours. The alcoholic solution was filtered, evaporated to dryness and the residue recrystallized from acetone. The hydrochloride melts at 223.5–225.5°. The *base* on crystallization from *n*-hexane melts at 96–98°. The acyloxy compounds were prepared by heating the bases with the respective acyl anhydrides in the presence of a drop of conc'd H_2SO_4 on a steam-bath. They were converted to the hydrochlorides and crystallized from ethyl acetate-methanol.

The *acetate hydrochloride* melts at 229–230°

The *propionate hydrochloride* melts at 224–225°

The *butyrate hydrochloride* melts at 202.5°.

1-Butyl-4-hydroxy-4-(1′-butyl-4′-keto-3′-piperidyl)piperidine dihydrochloride. To a suspension of 3.3 g. of magnesium in 50 cc. of dry ether was added 16 g. of freshly distilled cyclohexyl chloride. Upon completion of the reaction the Grignard complex was heated for two hours more at reflux temperature. The reaction mixture was cooled to 0° and 15.5 g. of 1-butylpiperidone-4 in 25 cc. of dry ether was added. Upon completion of the addition, a white insoluble complex precipitated out. The reaction mixture was refluxed for 3 hours more and left to stand overnight. Decomposed and worked up in the usual manner, the basic fractions were collected in ether, the ether solution dried over Na_2SO_4, the solvent removed and the residual oil fractionated. Two fractions were obtained. At 9 mm., 5 g. of the starting piperidone boiling at 85–90° was recovered. The main fraction (8.5 g.) boiled at 140° at 0.25 mm. The higher-boiling fraction was converted to the hydrochloride and the crude hydrochloride was recrystallized from ethyl acetate and methanol with some ethyl ether. A colorless crystalline salt was obtained melting at 195–196°. It analyzed correctly for the piperidone aldol condensation product.

4-(2-Thienyl)-4-hydroxy-1-butylpiperidine. Fifty-two and one-half grams of dry bromobenzene was treated with 5 g. of lithium in 500 cc. of dry ether. Upon completion of the reaction the solution of phenyllithium was cooled to room temperature and 21 g. of dry freshly distilled thiophene in 25 cc. of dry ether was added rapidly, and the reaction mixture was refluxed for 2–3 hours. The solution was cooled to −20° and 15.5 g. of 1-butylpiperidone-4 was added. The solution was stirred at 25° for 1 hour and left to stand overnight. The reaction mixture was decomposed with ice and conc'd HCl and worked up in the usual manner. There was obtained a crystalline base which melted at 82–83° when recrystallized twice from Skellysolve B. The base was dissolved in dry ether and converted to the hydrochloride with dry HCl gas. The crystalline product obtained was recrystallized from a mixture of acetone and methanol to yield a colorless crystalline product melting at 168–

TABLE I

4,4-DISUBSTITUTED 1-BUTYLPIPERIDINES

1-BUTYLPIPERIDINE·HCl	M.P.* °C. AND SOLVENT OF CRYST.	FORMULA	ANALYSES					
			Calculated			Found		
			C	H	N	C	H	N
4-Butyl-4-hydroxy	147–148 (EtAc-MeOH)	$C_{13}H_{27}NO \cdot HCl$ (249.5)	62.55	11.21	5.62	62.58	11.16	5.52
4-Butyl-4-acetoxy	229–230 (EtAc-MeOH)	$C_{15}H_{29}NO_2 \cdot HCl$ (291.5)	61.75	10.30		61.42	10.27	
4-Butyl-4-propionoxy	218–219 (EtAc-MeOH)	$C_{16}H_{31}NO_2 \cdot HCl \cdot 1\ H_2O$ (323.5)	59.35	10.50		59.08	10.67	
4-Butyl-4-butyroxy	214–215 (EtAc-MeOH)	$C_{17}H_{33}NO_2 \cdot HCl$(319.5)	63.85	10.64		64.04	10.74	
4-(3-Pyridyl)-4-acetoxy HCl	215–216 (EtAc-MeOH)	$C_{16}H_{24}N_2O_2 \cdot 2HCl \cdot 0.5H_2O$ (358)	53.62	7.54		53.76	7.26	
4-(3-Pyridyl)-4-propionoxy HCl	198–199 (EtAc-MeOH)	$C_{17}H_{26}N_2O_2 \cdot 2HCl \cdot 0.3H_2O$	55.25	7.78		55.49	8.03	
4-(3-Pyridyl)-4-butyroxy HCl	154–155 (EtAc-MeOH)	$C_{18}H_{28}N_2O_2 \cdot 2HCl$ (377)			7.43			7.10
4-(2-Picolyl)-4-hydroxy HCl	glass	$C_{15}H_{24}N_2O \cdot 2HCl \cdot 0.5H_2O$ (330)	54.75	8.18		54.66	8.45	
4-(2-Picolyl)-4-acetoxy HCl	glass	$C_{17}H_{26}N_2O_2 \cdot 2HCl \cdot 1.5H_2O$ (390)	52.30	7.95	7.18	52.40	7.91	6.69
4-(2-Picolyl)-4-propionoxy·HCl	glass	$C_{18}H_{28}N_2O_2 \cdot 2HCl$ (377)	57.30	7.96		57.46	8.33	
4-Hydroxy-4-(1′-butyl-4′-keto-3′-piperidyl) HCl	195–196 (EtAc-MeOH-Et_2O)	$C_{18}H_{34}N_2O_2 \cdot 2HCl$ (383)	56.40	9.40	7.31	56.72	9.29	7.28
4-Propionoxy-4-(1′-butyl-4′-keto-3′-piperidyl)·HCl	syrup	$C_{21}H_{38}N_2O_3 \cdot 2HCl \cdot 3H_2O$ (493)	51.10	9.34	5.68	51.26	8.97	5.79
4-Hydroxy-4-(6′-methyl-2′-picolyl) HCl	amorphous powder	$C_{16}H_{26}N_2O \cdot 2HCl \cdot 3H_2O$ (389)			7.20			7.35
4-Acetoxy-4-(6′-methyl 2′-picolyl) HCl	glass	$C_{18}H_{28}N_2O_2 \cdot 2HCl \cdot 0.9H_2O$ (393.2)	54.95	8.08		55.06	8.05	
4-Propionoxy-4-(6′-methyl 2′-picolyl) HCl	glass	$C_{19}H_{30}N_2O_2 \cdot 2HCl \cdot 1.3H_2O$ (415)	54.95	8.34		55.01	8.58	
4-(2-Furyl)-4-hydroxy	glass	$C_{13}H_{21}NO_2 \cdot HCl$ (259.5)	60.15	8.48	5.40	60.04	8.78	5.44
4-(2-Furyl)-4-propionoxy	glass	$C_{16}H_{25}NO_3 \cdot HCl$ (315.5)			4.44			4.50
4-Cyclohexyl-4-hydroxy	223–225 (acetone)	$C_{15}H_{29}NO \cdot HCl$ (275.5)	62.25	10.89	5.08	65.45	10.81	4.99
4-Cyclohexyl-4-acetoxy	229–230 (EtAc-MeOH)	$C_{17}H_{31}NO_2 \cdot HCl$ (317.5)	64.25	10.06		64.31	9.54	
4-Cyclohexyl-4-propionoxy	224–225 (EtAc-MeOH)	$C_{18}H_{33}NO_2 \cdot HCl$ (331.5)	65.18	10.25	4.22	64.98	9.88	4.04

4-(2-Pyridyl)-4-hydroxy base	145–147/1 mm.	$C_{14}H_{22}N_2O$ (234)	71.81	9.40		71.94	9.07	
4-(2-Pyridyl)-4-propionoxy HCl	170–172 (EtAc-MeOH)	$C_{17}H_{26}N_2O_2 \cdot 2HCl$			7.71			8.02
4-Methyl-4-hydroxy base	75–75/1 mm.	$C_{10}H_{21}NO \cdot 0.5H_2O$ (180)	66.70	12.20		66.64	11.99	
4-Methyl-4-propionoxy	226–228 (EtAc-MeOH)	$C_{13}H_{25}NO_2 \cdot HCl$ (263.5)	59.20	9.87		59.10	9.68	
4-(2-Pyridylmethyl)-4-hydroxy dimethiodide	95–97 (alcohol)	$C_{17}H_{30}I_2N_2O \cdot 0.5\ H_2O$ (541)	37.70	5.73	5.18	37.59	5.79	4.87
4-Hexyl-4-propionoxy	210–211 (EtAc-MeOH)	$C_{18}H_{35}NO_2 \cdot HCl \cdot 0.3H_2O$ (339.5)	63.60	10.78	4.12	63.67	10.57	3.88
4-Cyclohexyl-4-butyroxy	202.5 (EtAc)	$C_{19}H_{35}NO_2 \cdot HCl$ (345.5)			4.10			4.60
4-(2-Thienyl)-4-hydroxy	168–169.5 (Acetone MeOH)	$C_{13}H_{21}NOS \cdot HCl$ (275.5)	56.62	7.90		56.72	7.81	
4-(2-Thienyl)-4-propionoxy	151–153 (EtAc-MeOH)	$C_{16}H_{25}NO_2S \cdot HCl$ (331.5)	57.95	7.82		57.90	7.92	

* All melting points uncorrected.

169.5°. The product was the desired 4-(2-thienyl)-4-hydroxy-1-butylpiperidine hydrochloride.

The *propionate* of the above thienyl compound was prepared from the base with propionic anhydride and a catalytic amount of conc'd H_2SO_4 on the steam-bath. The product obtained was recrystallized from a mixture of ethyl acetate and methanol to yield colorless crystals of the desired propionate melting at 151–153°.

SUMMARY

1. A series of 4-alkyl-, 4-cycloalkyl-, 4-heterocyclyl-, and 4-heterocyclylalkyl-4-acyloxy-1-alkylpiperidines were prepared and tested for morphine-like analgesic activity.

2. Most of the members of the 4-alkyl-, 4-heterocyclyl- and 4-heterocyclylalkyl-piperidinol esters were inactive or slightly active at best. The most potent member of this series was one-half as active as Demerol.

3. The 4-cyclohexyl-4-piperidinol esters were the most active compounds in this series. Some members of this series are several times as active as Demerol.

4. Replacement of the phenyl group in 1-alkyl-4-phenyl-4-acyloxypiperidines with alkyl, heterocyclyl, heterocyclylalkyl, or cycloalkyl residues has a dystherapeutic effect.

NUTLEY, N. J.

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