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PIPERIDINE DERIVATIVES. PART II. 2-PHENYL- AND 2-PHENYLALKYL-PIPERIDINES[1]

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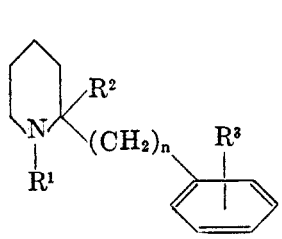
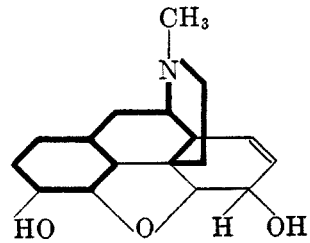
1-Methyl-2-benzylpiperidine (I, $R^1 = CH_3$, R^2, $R^3 = H$, $n = 0$) can be considered as an integral part of the structure of the morphine skeleton II, as indibycated the thickened lines.



I



II

It might be thefefore considered that a suitable substitution of this compound as in I ($R^1 = CH_3$, $R^2 = H$, $R^3 = OH$, $n = 0$) would give substances which, due to their spatial similarity to morphine and on account of a possible similarity of physico-chemical characteristics due to the presence of the basic nitrogen and phenolic hydroxyl group, might be expected to have morphine-like analgesic activity.

Compounds of the structure I as shown in Tables II and III have been prepared.

The method of synthesis of the structure of the compounds I where $n = 0$ is shown in the reaction scheme of Figure 1. Aryl- or aralkyl-magnesium halides were reacted with 1-methyl-2-piperidone. When the Grignard complex was decomposed in the normal manner, dehydration resulted, with formation of the 2-substituted-1,4,5,6-tetrahydro-1-methylpyridines. Similar experience is reported in the literature in the reaction of alkylmagnesium halides with the same piperidone (1). The tetrahydropyridines are unstable in air, oxidizing rapidly. Hydrogenation of the 1-methyl-4-phenyl-1,4,5,6-tetrahydropyridines at atmospheric or elevated pressure occurs with ease using Raney nickel or noble metal catalysts. When an alkoxyl substituent was present in the phenyl ring, dealkylation to the corresponding phenol and acylation of the hydroxyl group so formed proceeds normally. In order to obtain the 1-methyl-2-phenyl-2-piperidinol

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esters V, the Grignard complex was directly acylated with an acyl chloride or anhydride.

The reaction scheme can also be carried out using benzylmagnesium halide to obtain compounds of the type I (n = 1). When, however, a substituent is desired in the benzyl nucleus this method is not satisfactory on account of the tendency of substituted benzyl magnesium halides to form α,β-diphenylethane derivatives in the Grignard reaction. A *p*-hydroxyl group was introduced into the phenyl ring of 2-benzylpiperidine by nitration, reduction and diazotization of the *p*-amino group.

In attempting to react 1-methyl-2-piperidone with cyclohexylmagnesium chloride, the desired product was not obtained, and the reaction mixture on

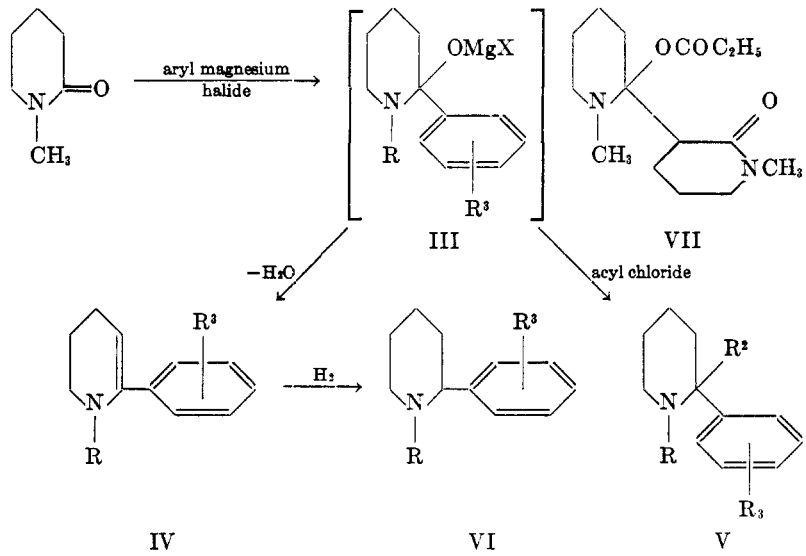

FIG. 1

R = alkyl
R^2 = acyloxy
R^3 = hydrogen, alkoxy

working up yielding no identifiable material. However, when the Grignard complex was directly acylated with propionic anhydride, a monopropionyl product was obtained which apparently has the structure VII, and was isolated in the form of its dihydrochloride.

Since the phenyl group of N-benzylpiperidines could be considered to occupy relatively the same position as the phenyl ring in 2-phenylpiperidine, 1-*p*-methoxyphenylpiperidine and 1-*p*-dimethylcarbamoxyphenylpiperidine were made in order to determine whether the analgesic activity displayed in the 2-phenyl series was retained.

The physical characteristics and the analyses of the compounds prepared are given in Tables I to IV.

TABLE I

1-METHYL 2-SUBSTITUTED 1,4,5,6-TETRAHYDROPYRIDINES (IV)

SUBSTANCE: 1,4,5,6-TETRAHYDROPYRIDINE	B.P.°,C (UNCORR)	FORMULA	M.W.	ANALYSIS					
				Calculated			Found		
				C	H	N	C	H	N
1-Methyl-2-*o*-methoxyphenyl-	oil 118–124/3 mm.	$C_{13}H_{17}NO$	203.2	76.8	8.4		75.7	8.2	
1-Methyl-2-*m*-methoxyphenyl-	oil 142/6 mm.	$C_{13}H_{17}NO$	203.2	76.8	8.4		76.2	7.8	
1-Methyl-2-*p*-methoxyphenyl-	oil 125/3 mm.	$C_{13}H_{17}NO$	203.2	76.8	8.4		*		
1-Methyl-2-*p*-methoxyphenyl- HCl	170 (m.p.)	$C_{13}H_{18}ClNO$	239.7			5.80			5.52
1-Methyl-2-[6′-methoxynaphthyl-(2′)]-	oil 175/2 mm.	$C_{13}H_{19}NO$	262.3	80.63	7.50	5.53	80.00	7.37	5.50
1-Methyl-2-benzyl-	120/2 mm.	$C_{13}H_{17}N$	187.2	83.4	9.1		82.1	8.95	

* The material was unstable and used directly for further syntheses.

TABLE II

1-METHYL 2-SUBSTITUTED PIPERIDINES

SUBSTANCE: PIPERIDINE		M.P.°,C (UNCORR)	FORMULA	M.W.	ANALYSIS					
					Calculated			Found		
					C	H	N	C	H	N
1-Methyl-2-*o*-methoxyphenyl-	HCl	147	$C_{13}H_{20}ClNO$	241.7			5.79			5.19
1-Methyl-2-*o*-hydroxyphenyl-	HCl	—	$C_{12}H_{18}ClNO$	227.7	63.1	7.91	6.15			
1-Methyl-2-*m*-methoxyphenyl-	HCl	—	$C_{13}H_{20}ClNO$	241.7	63.7	8.28	5.79	64.56	8.37	
1-Methyl-2-*m*-hydroxyphenyl-	HBr	~60	$C_{12}H_{18}BrNO$ $\frac{1}{2}$ H_2O	281.1	51.2	6.76		52.9	6.76	
1-Methyl-2-*p*-methoxyphenyl-	HCl	170 ether-acetone	$C_{13}H_{19}ClNO$	240.8	64.0	8.28	5.79			5.52
1-Methyl-2-*p*-hydroxyphenyl-	HBr	231 ether-acetone	$C_{12}H_{18}BrNO$	272.2	53.2	6.64		52.9	6.62	
1-Methyl-2-*p*-acetoxyphenyl-	HCl	189 ether-acetone	$C_{14}H_{20}ClNO_2$	269.7			5.18			5.03
1-Methyl-2-*p*-dimethylcarbamoxyphenyl-	HCl	145 ether-acetone	$C_{15}H_{23}ClN_2O_2$	298.7			9.38			9.18
1-Methyl-2-*p*-phenylmethylcarbamoxyphenyl-	HCl	140 ether-acetone	$C_{15}H_{25}ClN_2O_2$	360.7			7.76			7.56
1-Methyl-2-*p*-diethylcarbamoxyphenyl-	HCl	—	$C_{17}H_{27}ClN_2O_2$	330.7			8.47			8.50
1-Methyl-2-benzyl-	HCl	158–160	$C_{13}H_{20}ClN$	225.7	69.2	8.8		68.0	8.7	

1-Methyl-2-*p*-hydroxybenzyl-		153 benzene	$C_{13}H_{19}NO$	205.2	76.09	9.26	6.83	76.23	9.42	7.03
1-Methyl-2-*p*-dimethylcarbamoxybenzyl-	HCl	166 EtOAc	$C_{16}H_{25}ClN_2O_2$	312.7			8.96			9.02
1-Methyl-2-[6′-methoxynaphthyl-(2′)]-	HCl	235 acetone-methanol	$C_{17}H_{22}ClNO$	291.7	70.00	7.54	4.87	69.97	7.67	4.80
1-Methyl-2-[6′-hydroxynaphthyl-(2′)]-	HCl	235 acetone-MeOH	$C_{16}H_{20}ClNO$	277.7	69.7	7.21		69.11	6.89	
1-Methyl-2-[6′-dimethylcarbamoxy-naphthyl-(2′)]-	HCl	220 acetone	$C_{19}H_{25}ClN_2O_6$	384.7	65.40	7.22	8.02	65.36	7.33	7.88

TABLE III

2-PIPERIDINOL ESTERS (I, R_2 = ACYLOXY)

SUBSTANCE: PIPERIDINE		DESCRIPTION	M.P., °C.	FORMULA	M.W.	ANALYSIS					
						Calculated			Found		
						C	H	N	C	H	N
1-Methyl-2-benzyl-2-propionoxy-	HCl	syrup*	—	$C_{16}H_{24}ClNO_2$	251.8	65.3**	7.77**		64.98	8.0	
1-Methyl-2-phenyl-2-acetoxy-	HCl	syrup	—	$C_{14}H_{20}ClNO_2$	269.5	62.3	7.32	5.19	61.95	7.67	5.66
1-Methyl-2-phenyl-2-propionoxy-	HCl	colorless prisms	119–120 (corr) acetone	$C_{15}H_{22}ClNO_2$	283.5	63.50	7.76	4.94	63.11	7.40	5.56
1-Methyl-2-(1′-methyl-2′-oxo-3′-piperidyl)-2-propionoxy di-	HCl	hygroscopic colorless crystals	80	$C_{15}H_{26}N_2O_3$ 2 HCl·H_2O	373.3	48.28	8.04	7.51	48.10	7.86	7.32

* A mixture with dehydration product.

** Calculated for 90% ester and 10% 1-methyl-2-benzyl-1,4,5,6-tetrahydropyridine HCl.

Pharmacological results. The detailed pharmacological results will be reported elsewhere. The following general observations were made.

When a phenyl group is attached directly to the piperidine nucleus in the 2 position (compounds I, $R^1 = CH_3$, $R^2 = H$, $R^3 = H$, $n = 0$), the compound was inactive. A low analgesic activity was noted with substitution of the methoxyl groups in the phenyl nucleus. Little or no activity was found with free hydroxyl groups (I, $R^1 = CH_3$, $R^2 = H$, $R^3 = OH$, $n = 0$), and the acetylation of the hydroxyl groups also gave materials of only slight activity. However, on acylating the phenolic hydroxyl with a group more resistant to hydrolysis, as for example the dimethylcarbamyl group, increased activity was obtained the best compounds being those with *p*-substituents. The activity was not sufficient to be of practical interest. Replacing the phenyl with a β-naphthyl group reduced the activity. When the phenyl group was linked to the piperidine nucleus by a CH_2 group (I, $R^1 = CH_3$, $R^2 = H$, $R^3 = H$, $n = 1$), thus conforming more closely to the type I structure, it was found that the compound was inactive, and substitution in the ring of hydroxyl, methoxyl, or acyloxyl groups in the *p*-position did not change this. It would appear from this that strict adherence in this series to the relationship of the individual atoms in the morphine skeleton does not give the highest analgesic activity; in fact, here the compounds more closely related to morphine are less active than those more remote in structure.

1-Methyl-2-substituted piperidinol esters (I, R^2 = acyloxy, $R^3 = H$, $n = 0$ or 1) were without significant activity.

Increasing the length of the side chain to 2 carbon atoms yielding 2-phenethyl derivatives (I, R = alkyl, $R^2 = H$, R^3 = alkoxy, $n = 2$) gives compounds with low analgesic activity. These compounds were described in the previous paper of this series (2). The 1-*p*-acyloxybenzyl piperidines were inactive.

Acknowledgment. Most of the analyses of the compounds described in this paper were performed in the Microanalytical Division of these laboratories under the direction of Dr. A. Steyermark. The pharmacological results are due to Drs. N. Ercoli, R. H. K. Foster, and G. Lehman. We wish to express our thanks to these workers for their co-operation.

EXPERIMENTAL

1-Methyl-2-(p-methoxyphenyl)-1,4,5,6-tetrahydropyridine. Two-tenths mole of magnesium and 50 cc. of dry ether were placed in a three-necked flask provided with a ground sealed stirrer, dropping-funnel, and reflux condenser. To this was added 0.2 mole of *p*-bromoanisole in 50 cc. of ether. After the complete addition of the *p*-bromoanisole the ether solution was refluxed for one hour to complete the reaction. The flask was then cooled in an ice-bath and 0.2 mole of 1-methyl-2-piperidone in 100 cc. of ether was added. After the complete addition the mixture was refluxed with stirring for eight hours, during which the gummy complex became solid. This was decomposed with dilute hydrochloric acid, the ether layer separated, the aqueous layer saturated with sodium carbonate, extracted with ether and the ether solutions combined. The ether solution was dried, and the ether removed by distillation. On fractionation in vacuum, 1-methyl-2-(*p*-methoxyphenyl)-1,4,5,6-tetrahydropyridine was obtained having the b.p. 125° at 3 mm. By passing dry hydrochloric acid gas into a dry ether solution of the base, the hydrochloride, m.p. 175°, was obtained.

1-Methyl-2-(p-methoxyphenyl)piperidine hydrochloride. Twenty grams of 1-methyl-2-(*p*-methoxyphenyl)-1,4,5,6-tetrahydropyridine was dissolved in 100 cc. of absolute alcohol, 5 g. of Raney nickel added, and the reduction carried out under pressure of 50 pounds at room temperature. The pressure and the temperature are not critical and may vary up to 4000 pounds and 100°. The quantitative amount of hydrogen was adsorbed rapidly and when complete, the catalyst was filtered off and the alcohol removed from the filtrate. The crude 1-methyl-2-(*p*-methoxyphenyl)piperidine was dissolved in ether and dry hydrochloric acid gas passed in. The hydrochloride separated out as white crystals, m.p. 170°.

1-Methyl-2-(p-hydroxyphenyl)piperidine hydrobromide. Twenty grams of 1-methyl-2-(*p*-methoxyphenyl)piperidine base was dissolved in 50 cc. of acetic acid and 60 cc. of 30% hydrobromic acid in acetic acid was added. The solution was refluxed for four hours and then distilled in a vacuum to remove the acetic acid and excess hydrobromic acid. The residue was crystallized from alcohol, m.p. 231°.

1-Methyl-2-(p-dimethylcarbamoxyphenyl)piperidine hydrochloride. Twenty grams of 1-methyl-2-(*p*-hydroxyphenyl)piperidine hydrobromide was dissolved in 100 cc. of water and the solution saturated with potassium carbonate. The separated piperidine base was extracted with ether, the ether solution dried, and the ether removed by distillation. The free phenolic base was dissolved in 50 cc. of dry pyridine and 9 g. of dimethylcarbamyl chloride added. The solution was heated on a water-bath for three hours, when a further 9 g. of dimethylcarbamyl chloride was added and the solution heated for another hour. The solvent was removed in a vacuum, the residue dissolved in water, and the solution made alkaline with sodium hydroxide. The dimethylcarbamyl ester was extracted with ether, and after drying over potassium carbonate the solution was filtered and hydrogen chloride passed in. The product, 1-methyl-2-(*p*-dimethylcarbamoxyphenyl)piperidine hydrochloride melted at 145°.

1-Methyl-2-acetoxy-2-phenylpiperidine hydrochloride. The Grignard reagent prepared from 23.5 g. of freshly distilled bromobenzene (0.15 mole) and 3.6 g. of magnesium (0.15 mole) was reacted with 11.3 g. of 1-methyl-2-piperidone (0.1 mole) in the usual manner. The gum that formed soon hardened after addition of dry benzene. After refluxing for one hour the reaction was cooled and 20.4 g. (0.2 mole) of acetic anhydride in dry benzene added. The reaction was refluxed for several minutes, then left to stand overnight. It was decomposed with ice cold 6 *N* HCl and the product isolated in the usual manner.

Four grams of a thick oil, boiling at 185–198° at 5 mm. was obtained. This was converted to the hydrochloride, which was also a thick syrup (hygroscopic) and which could not be crystallized. It was submitted for analysis as such.

In a like manner 2-phenyl-2-propionoxy-1-methylpiperidine hydrochloride was prepared. This product was a white solid which crystallized from acetone in small prisms. Recrystallized twice, it melted at 119–120°.

1-Methyl-2-[6′-methoxynaphthyl-(2′)]-1,4,5,6-tetrahydropyridine. Eight grams of magnesium in a Grignard reaction apparatus was covered with 150 cc. of dry ether, a crystal of iodine was added, and a solution of 50 g. of 2-bromo-6-methoxynaphthalene in 150 cc. of dry benzene was added. It was refluxed on a water-bath; two cc. of ethyl bromide was added every hour until a total of 10 cc. had been added. At this time most of the magnesium had disappeared and the flask was cooled in an ice-bath, and a solution of 37 g. of 1-methyl-2-piperidone in 100 cc. of ether was added dropwise. The mixture was then refluxed for three hours and after cooling, it was decomposed with dilute hydrochloric acid. The hydrochloride of the tetrahydropyridine base separated out and was filtered off. This was converted to the free base by suspension in warm sodium hydroxide solution, extracted with ether, dried, and fractionated, b.p. 175°/2 mm.; yield 11 g.

1-Methyl-2-benzylpiperidine. A Grignard reaction was carried out in the usual manner using 34.2 g. of benzyl bromide, 4.8 g. of magnesium, and 22.6 g. of 1-methyl-2-piperidone. The product, 1-methyl-2-benzyl-1,4,5,6-tetrahydropyridine boiled at 120°/2 mm.; yield, 9 g.

The product of the above reaction was dissolved in 100 cc. of alcohol and hydrogenated at room temperature and atmospheric pressure in the presence of Adams' catalyst. 1-Methyl-2-benzylpiperidine was obtained as an oil, boiling at 105°/3 mm. A picrate, m.p. 181°, corr., obtained from this base corresponded in melting point to that of the same compound obtained by Bryans and Pyman (3) by the reduction of 2-benzylpyridine methosalts.

1-Methyl-2-(p-hydroxybenzyl)piperidine. Four grams of 1-methyl-2-benzylpiperidine was dissolved in 12 g. of concentrated sulfuric acid, cooled to −10°, and a mixture of 2.5 cc. of concentrated nitric acid dissolved in 6 g. of concentrated sulfuric acid was added dropwise to the solution with stirring. After standing for one hour at −10°, it was poured onto ice, basified, and the oil which separated was extracted with ether. After drying the ether, the solvent was removed and 4.7 g. of crude 1-methyl-2-(*p*-nitrobenzyl)piperidine was obtained. This was dissolved in 50 cc. of absolute alcohol and hydrogenated at room temperature and atmospheric pressure in the presence of Adams' platinum catalyst. This yielded 3 g. of 1-methyl-2-(*p*-aminobenzyl)piperidine boiling at 145°/4 mm.

Three grams of 1-methyl-2-(*p*-aminobenzyl)piperidine was dissolved in a mixture of 5 g. of concentrated sulfuric acid in 50 cc. of water. The solution was cooled to 2° and a solution of 1 g. of sodium nitrite in 10 cc. of water was added dropwise with stirring to the amine solution. It was then warmed on the steam-bath in the presence of copper until the evolution of nitrogen ceased. It was cooled, basified with sodium carbonate, and extracted with ether. After drying, the ether was removed and the residue crystallized from benzene. This yielded 1.8 g. of 1-methyl-2-(*p*-hydroxybenzyl)piperidine, melting at 153°.

1-Methyl-2-(p-dimethylcarbamoxybenzyl)piperidine hydrochloride. One and five-tenths gram of 1-methyl-2-(*p*-hydroxybenzyl)piperidine and 1 g. of dimethylcarbamyl chloride were dissolved in 10 cc. of dry pyridine and the solution heated on a steam-bath for three hours. The pyridine was then removed in vacuum, dilute alkali added to the residue, and the liberated base extracted with ether. This, on transformation to the hydrochloride in the usual manner and recrystallization from ethyl acetate, gave the dimethylcarbamyl ester, melting at 166°.

1-(p-Dimethylcarbamoxybenzyl)piperidine hydrochloride. *p*-Hydroxybenzylpiperidine was prepared according to the method of Königs and Bernhart (4). Four grams of N-*p*-hydroxybenzylpiperidine was dissolved in 12 cc. of pyridine and 3 g. of dimethylcarbamyl chloride added. The mixture was heated on the steam-bath for 4 hours and then the pyridine was distilled off in a vacuum, and the residue alkalized with dilute sodium hydroxide solution. The oil was extracted with ether and the ether distilled off. The residue was crystallized from Skellysolve B. The material was dissolved in ether and HCl gas bubbled in. The hydrochloride was crystallized from acetone, m.p. 205°; yield 3.8 g.

Anal. Calc'd for $C_{15}H_{22}N_2O_2 \cdot HCl$: N, 9.38. Found: N, 9.18.

SUMMARY

1. A series of 1-alkyl-2-arylpiperidines was prepared and some members were found to have a slight analgesic activity.

2. A series of 1-alkyl-2-benzyl piperidine derivatives was found to be without analgesic activity.

3. In both the above series the introduction of a 2-acyloxyl group resulted in compounds of no activity.

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