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Weakly Basic Analogues of Potent Analgesics

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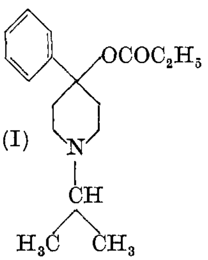
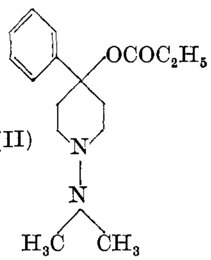
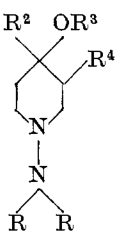
Introduction

The piperidine derivative (I) is a more powerful analgesic than morphine in animals.[1]

(I) 

(II) 

(III) 

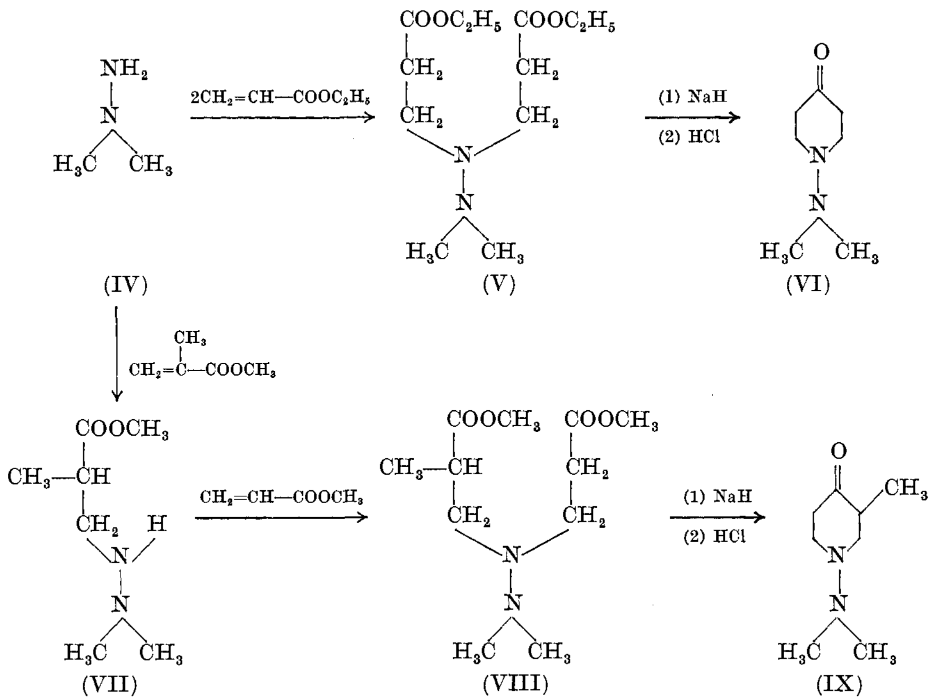
Alkyl hydrazines are known to be much weaker bases than the corresponding amines.[2] The *N*-dimethylaminopiperidine (II) would have the same geometry as (I) but would probably be very little ionized at physiological pH. Thus the effect of change in the strength of the basic group on analgesic potency could be investigated by comparing the activities of compounds of type (I) with those of type (III) which represent weakly basic counterparts of active analgesics. Many hydrazines also possess anti-depressant properties, so compounds of type (III) are also of interest in this respect.

N-Dimethylamino-4-Aryl-4-piperidinols

The *N*-dimethylamino-4-piperidones (VI and IX) were prepared by routes essentially similar to those of Beckett, Casy and Kirk,[3] as outlined in Flow Sheet I. Treatment of the 4-piperidinols with lithium-aryls led to the required 4-aryl-4-piperidinols.

The addition of lithium-aryl compounds to 3-alkyl-4-piperidones can give two diastereoisomeric alcohols. The *trans* alkyl-aryl isomer should be formed in the major amount[3] and its propor-

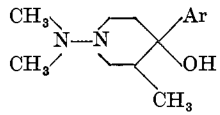
Flow Sheet I

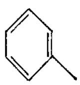
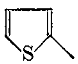
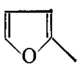


tion should increase with increasing size of the aryl addendum in the vicinity of the reaction centre. The reaction of 2-thienyl-lithium with *N*-dimethylamino-3-methyl-4-piperidone gave isomers which were isolated in a 5:1 ratio. A sulphur atom is intermediate in size between the >CH group of phenyl-lithium, which yielded a 3:1 isomeric mixture, and the >C–CH_3 group of *o*-tolyl-lithium, which gave a high yield of one pure isomer with the corresponding *N*-methyl-piperidone. Phenyl-lithium and 2-furanyl-lithium were also added to *N*-dimethylamino-3-methyl-4-piperidone but it was not possible to achieve quantitative separations of the isomers obtained from these reactions.

Infrared characteristics of these compounds are listed in Table I.

Table I. Infrared details of some piperidinols

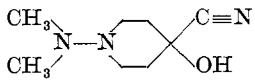


Ar	Isomer	% Theoretical obtained	Absorption peaks of characteristic frequency: 990–1010 cm^{-1}	Absorption peaks of characteristic frequency: 1350–1385 cm^{-1}
	A	50·3	No pronounced peak	1342 1379
	B	4·1	998 1005	1339 1372 1379
	A	42·3	994	1344 1372
	B	8·0	No peak	1351 1368
			1010	1376
α-Prodine alcohol			1000	1355 1383
β-Prodine alcohol			No peak	1372 1380

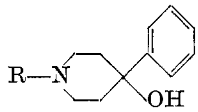
Esterification

In several series of 4-piperidinols, much higher activity is found in the acetoxy and propionoxy esters than in the parent alcohols.[3,4] Esters of some of the above alcohols were, therefore, required. Similar piperidinols have been esterified by refluxing with pyridine and acid anhydrides.[3] In some compounds this treatment caused elimination to an olefin,[5] but only when the hydroxyl group was very highly hindered was unchanged starting material recovered.[6]

The present piperidinols were much more difficult to esterify than those previously described. *N*-Dimethylamino-4-cyano-4-piperidinol (X), which presents by far the smallest steric hinderance to the hydroxyl group in the present series, was the only one which could be esterified by heating with pyridine and acetic anhydride.



(X)



(XI)

The acetoxy ester of *N*-dimethylamino-4-phenyl-4-piperidinol (XI; R = $(CH_3)_2N$—) was prepared by reaction with phenyllithium to give the OLi salt followed by refluxing with acetic anhydride in ether. The corresponding propionoxy ester was successfully prepared only when the OLi salt and propionic anhydride were refluxed in the higher-boiling benzene. The acetoxy ester of *N*-isopropyl-4-phenyl-4-piperidinol (XI; R = $(CH_3)_2CH$—), on the other hand, was readily prepared in good yield by heating with pyridine and acetic anhydride.

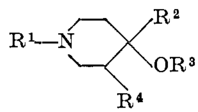
4-Phenyl-4-piperidinol may conveniently be prepared by *N*-debenzylation of *N*-benzyl-4-phenyl-4-piperidinol.[7] Treatment of the secondary base with sodium nitrite and dilute acid yielded the *N*-nitroso derivative as a colourless solid. Reduction of the nitrosamine using zinc and acetic acid gave the required *N*-amino-4-phenyl-4-piperidinol (XI; R = —NH_2).

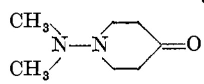
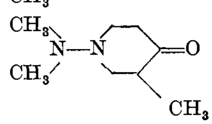
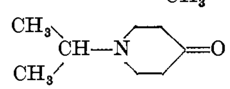
Dissociation Constants and Theoretical Considerations

The dissociation constants the hydrazino compounds described in this paper are given in Table II; replacement of *N*-isopropyl by *N*-dimethylamino results in a lowering of the basic strength by about 4 pK_a units.

A consideration of the dissociation constants of simple amines and hydrazines (Table III) helps to clarify the effect of various factors on these constants. In hydrazines, the nitrogen bearing the most alkyl groups is accepted as being the most basic of the two nitrogen atoms; further substitution of mono-alkyl hydrazines occurs on the atom bearing the alkyl groups and such alkylation (and alkylation of hydrazine itself) is accompanied by a fall in basic strength.[8, 9]

Table II. pK_a Values of compounds prepared during the present work

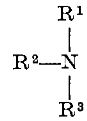


No.	R^1	R^2	R^3	R^4	Isomer	pK_a
1	H_2N	C_6H_5	H	H		6·59
2	$(CH_3)_2N$	C_6H_5	H	H		5·98
3	$(CH_3)_2N$	C_6H_5	COC_2H_5	H		5·66
4	$(CH_3)_2N$	C_6H_5	H	CH_3	A	6·62
5	$(CH_3)_2N$	C_6H_5	H	CH_3	B	6·01
6	$(CH_3)_2CH$	C_6H_5	H	H		9·80
7	$(CH_3)_2N$	$2,6(CH_3)_2C_6H_3$	H	H		6·44
8	$(CH_3)_2N$	$C_6H_5C{\equiv}C$	H	H		5·60
9	$(CH_3)_2N$	2-thienyl	H	H		5·85
10	$(CH_3)_2N$	2-thienyl	H	CH_3	A	6·32
11	$(CH_3)_2N$	2-thienyl	H	CH_3	B	6·29
12	$(CH_3)_2N$	$C{\equiv}N$	H	H		5·35
13	$(CH_3)_2N$	$C{\equiv}N$	$COCH_3$	H		5·12
14						5·48
15						5·39
16						9·40

The increase in basic strength from ammonia (17) to methylamine (18), and to a lesser extent dimethylamine (19), is explained as being due to the $+I$ effect of the methyl groups. That trimethylamine (20) is more weakly basic is attributed to the B strain in the protonated form being greater than that in the non-protonated form, this effect outweighing the $+I$ contribution of the methyl groups.[10]

If it is assumed that the lone electron pair of only one of the nitrogen atoms of a hydrazine is involved in salt formation, then

Table III. pK_a Values of simple amines and hydrazines



No.	R^1	R^2	R^3	pK_a
Amines[10]				
17	H	H	H	9·25
18	CH_3	H	H	10·63
19	CH_3	CH_3	H	10·78
20	CH_3	CH_5	CH_3	9·80
Hydrazines[1]				
21	NH_2	H	H	8·07
22	NH_2	CH_3	H	7·87
23	NH_2	CH_3	CH_3	7·21
24	$NHCH_3$	CH_3	H	7·52
25	$NHCH_3$	CH_3	CH_3	6·56
26	$N(CH_3)_2$	CH_3	CH_3	6·30
27	NH_2	C_2H_5	H	7·99
28	NH_2	C_2H_5	C_2H_5	7·71
29	NHC_2H_5	C_2H_5	H	7·78

hydrazine may be regarded as *N*-amino ammonia and its lower basic strength relative to ammonia explained as a result of the $-I$ effect of the 'non-basic' $-NH_2$ group. The radius of an $-NH_2$ group is similar to that of a CH_3 group.[11] Monomethylhydrazine (22) may therefore be regarded as having the *B*-strain of dimethylamine with the $-I$ effect of the $-NH_2$ group replacing the $+I$ effect of a CH_3 group. Its more weakly basic properties as compared with dimethylamine (19) or hydrazine (21) are therefore explained. Substitution on the second nitrogen atom of methylhydrazine (22) to give symmetrical dimethylhydrazine (24) slightly increases the steric effects without significantly changing the electronic state of the first nitrogen atom so that a weaker base is obtained. Unsymmetrical dimethylhydrazine (23) has more *B*-strain than symmetrical dimethylhydrazine (24), the base-weakening effect of the extra CH_3 group simulating the effect of the third CH_3 group of trimethylamine (20).

The change from methyl to ethyl in amines increases basic properties[12] and a similar result is obtained in substituted hydrazines (cf. Compds. 27 and 22, 28 and 23, 29 and 24). These results are due to the greater $+I$ effect of a C_2H_5 group as compared with that of a CH_3 group being more important than the relatively small increase in steric size in the vicinity of the nitrogen atom.

Tetramethylhydrazine (26) is the weakest base of the series presented in Table III and other tetrasubstituted hydrazines would be expected to show approximately the same basic strength. Reference to Table II shows that most of the new *N*-disubstituted amino piperidines are somewhat weaker than the simple hydrazines. This must be due to the strong $-I$ effects of the aryl, hydroxy and acycloxy groups in the 4-position. For example, the compound having 4-phenyl and 4-hydroxy groups (2) is weaker than tetramethylhydrazine by $0 \cdot 3$ pK units. Replacement of the 4-phenyl by the 4-phenylethinyl group (8) or the 4-hydroxy by the 4-propionoxy group (3) increases the $-I$ effect of the ring substituents and produces still weaker bases. On the other hand, the change from 4-phenyl to 4-(2,6-dimethyl)phenyl (7) decreases the $-I$ effect of the substituents and produces a stronger base. The pair of stereoisomers (10 and 11) show an increased pK_a over the parent compound with an unsubstituted 3 position (9). This is due, presumably, to the $+I$ effect of the 3-methyl group. Of the other pair of stereoisomers examined, only one isomer (4) shows a comparable increase in pK_a while the other (5) has virtually the same basic strength as the parent compound (2). It is not possible to explain this difference at present but further investigations are proceeding.

Pharmacological Results

A number of the compounds prepared during the present work were tested for analgesic and mydriatic activity. Compounds were administered to mice by subcutaneous injection and the analgesic activity was determined by the hot-plate method.[14] The mydriatic activity was determined by the method of Janssen *et al.*[15] None of the hydrazines tested produced any analgesia or mydriasis up to a dose level of 40 mg/kg. *N*-Isopropyl-4-phenyl-4-acetoxypiperidine, tested in the same laboratory, had an ED_{50}

of 15 mg/kg. *N*-Dimethylamino-4-phenyl-4-propionoxypiperidine showed no analgesic effect in doses of 100 mg/kg when tested by the Randall–Selitto method in rats. The corresponding *N*-isopropyl compound was shown to be more powerful as an analgesic than morphine in rats.[1] Thus a change from the *N*-isopropyl to the *N*-dimethylamino group is accompanied by loss of activity, although the two groups have the same size and shape.

All powerful morphine-type analgesics exist largely in the ionized form at physiological pH.[13] *N*-Dimethylamino-4-phenyl-4-propionoxypiperidine has pK_a 5·66 and is about 2·0 per cent ionized at physiological pH. Since none of the hydrazines tested showed significant analgesic activity, it appears that, for activity, ionization of structures of analgesic type is necessary to give strong binding with the analgesic receptor-sites.

Most of the compounds were also tested in mice for central nervous system activity, but no significant activity was demonstrated.

Experimental

N′-*Di*-(*β-ethoxycarbonylethyl*)-N²-*dimethylhydrazine*

Method (*1*). A mixture of unsymmetrical dimethylhydrazine (100 g) and ethyl acrylate (420 g) was refluxed for 48 h. Excess ethyl acrylate was removed at the water pump. Fractional distillation of the residue yielded:

(*a*) N′-*β-Ethoxycarbonylethyl*-N²-*dimethylhydrazine* (5 g) b.p. 60°/0·5 mm. Calcd. for $C_7H_{16}N_2O_2$: equiv. wt., 160. Found: equiv. wt., 171. It gave a picrate as yellow needles from ethanol, m.p. 71–71·5°.

Anal. Calcd. for $C_{13}H_{19}N_5O_9$: C, 40·0; H, 4·90; N, 18·0; equiv. wt. 389. Found: C, 40·5; H, 4·90; N, 17·2; equiv. wt., 391.

(*b*) N′-*Di*-(*β-ethoxycarbonylethyl*)-N²-*dimethylhydrazine* (404 g, 93 per cent) b.p. 138–142°/1·0 mm, n_D^{19} 1·4771. Calcd. for $C_{12}H_{24}N_2O_4$: equiv. wt., 260. Found: equiv. wt., 260. It gave a picrate, yellow needles from ethanol, m.p. 114·5°.

Anal. Calcd. for $C_{18}H_{27}N_5O_{11}$: C, 44·2; H, 5·53; N, 14·3; equiv. wt., 489. Found: C, 44·4; H, 5·52; N, 14·8; equiv. wt., 490.

Method (2). A mixture of unsymmetrical dimethylhydrazine (100 g) and ethyl acrylate (420 g) was allowed to stand for 6 weeks. Excess ethyl acrylate was removed at the water pump. Fractional distillation of the residue yielded *N*′-β-ethoxycarbonylethyl-*N*²-dimethylhydrazine (23 g) and *N*′-di-(β-ethoxycarbonylethyl)-*N*²-dimethylhydrazine (320 g, 74 per cent).

N - *Dimethylamino - 4 - piperidone.* *N*′-Di-(β-ethoxycarbonyl-ethyl)-*N*²-dimethylhydrazine (50 g) was added to a stirred suspension of sodium hydride (56·8 g) in xylene (3·5 l.) and the mixture warmed on an oil bath at 80° to start the reaction. The bath was then removed and a further 450 g of the diester added at a rate sufficient to maintain gentle refluxing. The mixture was then further refluxed for 1 h. The product was allowed to cool and poured onto ice (1500 g). The aqueous layer was separated and sufficient concentrated hydrochloric acid added to give a 10 per cent solution with regard to HCl. This solution was refluxed until no purple colour was obtained with a solution of ferric chloride (1 h). After cooling, the solution was made alkaline with 50 per cent w/v sodium hydroxide solution. During the addition of the alkali, the temperature was not allowed to rise above 30°. The alkaline solution was extracted with chloroform (6 × 100 ml quantities). The chloroform solution was dried, filtered and the solvent evaporated at the water pump. Distillation of the residue yielded N-*dimethylamino-4-piperidone* (140 g, 51 per cent) b.p. 58–60°/1·0 mm, n_D^{20} 1·4771.

Anal. Calcd. for $C_7H_{14}N_2O$: C, 59·1; H, 9·9; N, 19·7; equiv. wt., 142. Found: C, 59·4; H, 10·5; N, 19·4; equiv. wt., 145. It gave a hydriodide, pale yellow prisms, m.p. 167·5–168°, from alcohol-free chloroform.

Anal. Calcd. for $C_7H_{14}N_2O \cdot HI$: C, 31·2; H, 5·56; N, 10·04; equiv. wt., 270. Found: C, 31·4; H, 5·61; N, 9·60; equiv. wt., 271.

N′-β-*Methoxycarbonylpropyl*-N²-*dimethylhydrazine.* A mixture of dimethylhydrazine (100 g) and methyl methacrylate (420 g) was allowed to stand for 6 weeks. Fractional distillation of the product yielded N′-β-*methoxycarbonylpropyl*-N²-*dimethylhydrazine* (113 g, 43 per cent), b.p. 70°/10 mm, n_D^{20} 1·4410. Calcd. for $C_7H_{16}N_2O_2$: equiv. wt., 160. Found: equiv. wt., 165. It gave a picrate, yellow needles, m.p. 94·5°, from ethanol.

Anal. Calcd. for $C_{13}H_{19}N_5O_9$: C, 40·1; H, 4·90; N, 18·0; equiv. wt., 389. Found: C, 40·1; H, 5·00; N, 18·2; equiv. wt., 384.

N′-β-*Methoxycarbonylpropyl*-N′-β-*methoxycarbonylethyl*-N^2-*dimethylhydrazine.* A mixture of *N*′-β-methoxycarbonylpropyl-N^2-dimethylhydrazine (570 g) and methyl acrylate (520 g) was refluxed for 48 h. Excess methyl acrylate was removed at the water pump. Distillation of the residue yielded N′-β-*methoxycarbonylpropyl*-N′-β-*methoxycarbonylethyl*-N^2-*dimethylhydrazine* (776 g, 89 per cent), b.p. 109–111°/0·5 mm, n_D^{20} 1·4477. Calcd. for $C_{11}H_{22}N_2O_4$: equiv. wt., 246. Found: equiv. wt., 256. It gave a picrate, yellow microcrystals, m.p. 76·5–77·5°, from ethanol.

Anal. Calcd for $C_{17}H_{25}N_5O_{11}$: C, 43·0; H, 5·26; N, 14·7; equiv. wt., 475. Found: C, 42·9; H, 5·07; N, 14·9; equiv. wt., 476.

N-*Dimethylamino-3-methyl-4-piperidone.* *N*′-β-Methoxycarbonylpropyl-*N*-β-methoxycarbonylethyl-N^2-dimethylhydrazine (80 g) was cyclized using sodium hydride (7·5 g) in xylene (250 ml) by the method previously described. Decarboxylation of the resulting β-ketonic ester in refluxing 10 per cent hydrochloric acid was complete within 30 min yielding N-*dimethylamino-3-methyl-4-piperidone* (30 g, 60 per cent), b.p. 59°/0·3 mm, n_D^{19} 1·4733.

Anal. Calcd. for $C_8H_{16}N_2O$: C, 61·5; H, 10·2; N, 17·9; equiv. wt., 156. Found: C, 62·4; H, 10·2; N, 17·7; equiv. wt., 153. It gave a hydriodide, pale yellow prisms, m.p. 163·5–164·5°, from alcohol-free chloroform–ether.

Anal. Calcd. for $C_8H_{16}N_2O \cdot HI$: C, 33·8; H, 5·99; N, 9·85; equiv. wt., 284. Found: C, 33·9; H, 6·06; N, 9·60; equiv. wt., 285.

General Method for the Preparation of 4-Aryl-4-piperidinols

The piperidone (1 mole) was added dropwise to a stirred, cooled solution of the aryl-lithium in ether prepared from lithium (2·4 atoms) and an aryl bromide (1·2 mole). (2-Furyl-lithium, 2-thienyl-lithium and 2-pyridyl-lithium were prepared according to the methods of Beckett, Casy and Phillips[5]). The mixture was refluxed for 1 h, cooled, poured onto ice and acidified with glacial acetic acid. The aqueous layer was separated, made alkaline with ammonium hydroxide and extracted with chloroform. The chloroform solution was washed with water, dried ($MgSO_4$ anhyd.), filtered and the solvent evaporated. The residue was recrystallized from benzene or mixtures of benzene and petroleum ether, b.p. 40–60°.

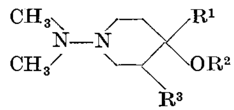
Preparation of Acetoxy Esters of Tertiary Alcohols

A solution of the suspension of the tertiary alcohol (1·0 mole) in ether was added slowly to a stirred ethereal solution of phenyllithium prepared from lithium (2·4 atoms) and bromobenzene (1·2 mole). The mixture was cooled and a solution of acetic anhydride (1·1 mole) in an equal volume of ether was added dropwise. After stirring for 30 min, the mixture was warmed, refluxed for 8 h and allowed to stand overnight. Extraction was carried out by the method described above and the residue converted to its hydrochloride which was recrystallized from ethanol. Only the acetoxy esters listed in Table IV could be obtained by this method. In all other cases only starting material was recovered from the reaction mixture.

N-*Dimethylamino-4-phenylethinyl-4-piperidinol.* Liquid ammonia (0·75 l.) containing a crystal of ferric nitrate was stirred until it became red (5 min). Sodium (4·6 g) was then added slowly in small portions. When the addition was complete, phenylacetylene (24 g) in ether (20 ml) was added slowly and the solution stirred for a further 2 h. *N*-Dimethylamino-4-piperidone (14·2 g) in ether (15 ml) was then added slowly and stirring continued for 3 h. The product was diluted with dry ether and treated with ammonium chloride (7·5 g), ammonium hydroxide (50 ml) and crushed ice (100 g). The reaction mixture was left to stand overnight and then extracted with chloroform. The combined extracts were dried ($MgSO_4$ anhyd.), filtered and the solvent evaporated to yield a viscous oil (14 g). Crystallization from benzene gave colourless needles of N-*dimethylamino-4-phenylethinyl-4-piperidinol,* m.p. 111·5° (see Table IV).

*4-Cyano-*N*-dimethylamino-4-piperidinol.* A saturated solution of sodium cyanide (25 g) in water was added dropwise over 0·75 h to a cooled solution of *N*-dimethylamino-4-piperidone (35 g) in 15 per cent hydrochloric acid (90 ml). The mixture was stirred on the ice bath for 1 h further. The solid was then collected,

Table IV



R^1	R^2	R^3	Isomer	Form	m.p., °C	Analysis, % Calcd. C	H	N	Equiv. wt.	Found C	H	N	Equiv. wt.
C_6H_5	H	H	—	Base	137–138	70·9	9·09	12·7	220	71·0	9·15	12·7	220
C_6H_5	H	H	—	HCl	211	61·1	7·86	11·0	256	61·3	8·16	11·0	256
C_6H_5	$COCH_3$	H	—	HCl	179	60·4	7·72	9·40	298	60·3	7·73	9·16	296
o-$CH_3C_6H_4$	H	H	—	Base	177·5–178·5	71·8	9·40	12·0	234	72·8	9·22	11·8	232
2,6-$(CH_3)_2C_6H_3$	H	H	—	HCl	194	63·4	8·80	9·86	284	63·2	8·63	9·85	284
C_6H_5	H	CH_3	A	Base	147·8–148	71·8	9·40	12·0	234	72·2	9·39	12·2	235
C_6H_5	H	CH_3	A	HCl	186	62·2	8·51	10·4	270	63·5	8·60	10·8	271
C_6H_5	H	CH_3	B	Base	106–107	71·8	9·40	12·0	234	72·5	9·21	11·5	235
C_6H_5	H	CH_3	B	HCl	195–195·5	62·2	8·51	10·4	270	62·1	8·63	10·8	271
2-Thienyl	H	H	—	Base	135	58·5	7·96	12·4	226	60·2	7·93	11·9	228
2-Furyl	H	H	—	Base	92–93	62·9	8·56	13·3	210	62·8	8·53	13·2	210
2-Pyridyl	H	H	—	$\frac{1}{2}H_2O$ 2HCl	210	47·6	7·30	13·9	151	47·7	7·85	14·0	151
2-Pyridyl	$COCH_3$	H	—	$2HCl \cdot H_2O$	176–177 (d.)	47·6	7·08	11·9	177	49·4	7·43	12·1	177
2-Thienyl	H	CH_3	A	Base	117–117·5	60·0	8·35	11·7	240	60·0	8·31	11·9	238
2-Thienyl	H	CH_3	B	Base	126·5–127	60·0	8·35	11·7	240	60·1	8·44	11·9	237
2-Furyl	H	CH_3	—	Base	80	64·3	8·93	12·5	224	64·7	9·23	12·3	224
2-Furyl	H	CH_3	—	HCl	168·5–169	55·4	8·07	10·8	260	55·6	8·26	11·1	262
C_6H_5—C≡C	H	H	—	Base	111·5	73·8	8·19	11·5	244	74·0	7·95	11·4	244
C_6H_5—C≡C	H	H	—	HCl	194–195	64·3	7·50	10·0	280	64·0	7·43	10·3	279
C_6H_5—C≡C	$COCH_3$	H	—	$HCl \cdot H_2O$	109	60·0	7·35		240	59·7	7·41		240

dissolved in ethanol and acidified by addition of ice-cold ethanolic hydrochloric acid. Addition of ether yielded a precipitate (19·5 g, 38·5 per cent) which was recrystallized from ethanol as colourless prisms of *4-cyano-*N*-dimethylamino-4-piperidinol hydrochloride*, m.p. 176–177°.

Anal. Calcd. for $C_8H_{15}N_3O \cdot HCl$: C, 46·9; H, 7·8; N, 20·5; equiv. wt., 205. Found: C, 47·0; H, 7·9; N, 20·3; equiv. wt., 201.

*4-Acetoxy-4-cyano-*N*-dimethylaminopiperidine.* A solution of 4-cyano-*N*-dimethylamino-4-piperidinol hydrochloride (2 g) in acetic anhydride (3 ml) and pyridine (4 ml) was refluxed gently for 1·5 h. Excess pyridine and acetic anhydride were removed by evaporation at the water pump followed by azeotropic distillation with ethanol. The residue was dissolved in ethanol and acidified with ethanolic hydrochloric acid. Addition of ether yielded a solid (2·0 g, 83 per cent). Recrystallization from ethanol–ether yielded *4-acetoxy-4-cyano-*N*-dimethylaminopiperidine hydrochloride*, m.p. 240–240·5°.

Anal. Calcd. for $C_{10}H_{17}N_3O_2 \cdot HCl$: C, 48·6; H, 7·30; N, 17·0; equiv. wt., 247. Found: C, 48·5; H, 7·57; N, 17·4; equiv. wt., 246.

N*-Nitroso-4-phenyl-4-piperidinol.* A solution of sodium nitrite (12 g) in water (20 ml) was added dropwise to an ice-cold stirred solution of 4-phenyl-4-piperidinol (10·7 g) in two equivalents of dilute hydrochloric acid. Stirring was continued for a further 2 h and the product collected. Recrystallization from ethanol yielded 11·5 g (92 per cent) of N*-nitroso-4-phenyl-4-piperidinol*, m.p. 161·5–162°.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64·1; H, 6·79; N, 13·6. Found: C, 63·8; H, 6·86; N, 13·3.

N*-Amino-4-phenyl-4-piperidinol.* Acetic acid (50 per cent, 60 ml) was added dropwise to a stirred, cooled suspension of zinc dust (20 g) and *N*-nitroso-4-phenyl-4-piperidinol (4·1 g) in 90 per cent alcohol (45 ml). When the addition was complete, the mixture was warmed on a water bath which was maintained at 50° for 1 h. The warm solution was filtered free from excess zinc, the filtrate refrigerated and again filtered to remove zinc acetate. Evaporation of the solvent yielded a viscous oil which was shaken with 50 per cent potassium hydroxide solution and extracted with chloroform (4×50 ml quantities). The combined chloroform extracts were dried ($MgSO_4$ anhyd.), filtered and the solvent removed to yield a solid. Recrystallization from benzene gave colourless needles of N-*amino-4-phenyl-4-piperidinol* (1·2 g, 32 per cent), m.p. 188°.

Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 68·7; H, 8·34; N, 14·6; equiv. wt., 192. Found: C, 68·6; H, 8·31; N, 14·6; equiv. wt., 194.

Summary. The novelty of the pethidine reversed esters described in this paper lies in their possession of a hydrazino rather than an amino group. The pK_a values for the compounds are discussed in relation to those of simple amines and hydrazines. No analgesic activity could be demonstrated in any of the new compounds and this is attributed to the fact that they would be substantially unionized at physiological pH.

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