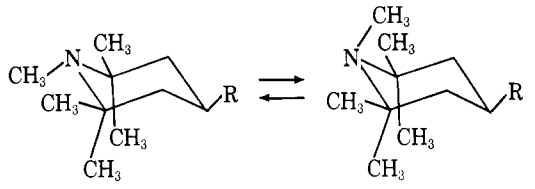
the electron pair of conformer XXIII four 1,3-diaxial nonbonded interactions due to the hydrogens on C-3 and C-5 and the methyl substituents in the 2- and 6-positions. Since there are only three such interactions which are due to the methyl groups for XXIV, interaction with an electrophilic center may occur primarily in this somewhat less hindered conformational form.

Finally, the glycolate esters of 1,2,2,6,6-pentamethyl-4-piperidinol (VII), which are virtually devoid of psychotogenic activity, can be seen to have a highly hindered amino nitrogen. An approaching electrophilic center would be subjected to four 1,3-diaxial nonbonded interactions in each of the two possible



XXV XXVI

conformers (XXV and XXVI). As corroboration for the inaccessibility of the amino group of VII, it should be noted that 2,2,6,6-tetramethylpiperidine is alkylated in a very low yield even after prolonged heating with an excess of ethyl *p*-toluenesulfonate.[15] Quaternization can be expected to be even more difficult.

Although further refinements could be made regarding the nucleophilicities of these drugs, they would be unwarranted in view of the semiquantitative nature of the pharmacological assays. As an addendum, however, substituent groups on nitrogen larger than methyl will decrease nucleophilicity and should, therefore, decrease potency, as has been verified.[1] Replacement of the N-methyl group by hydrogen will promote rapid destruction of the drug *via* transfer of the acyl group to nitrogen to form an amide. It must be emphasized that although the drugs were differentiated by their degree of nucleophilicity, it remains to be demonstrated whether an alkylation step is essential for their pharmacological action.

(15) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5444 (1957).

Compounds Affecting the Central Nervous System. I. 4-Piperidones and Related Compounds

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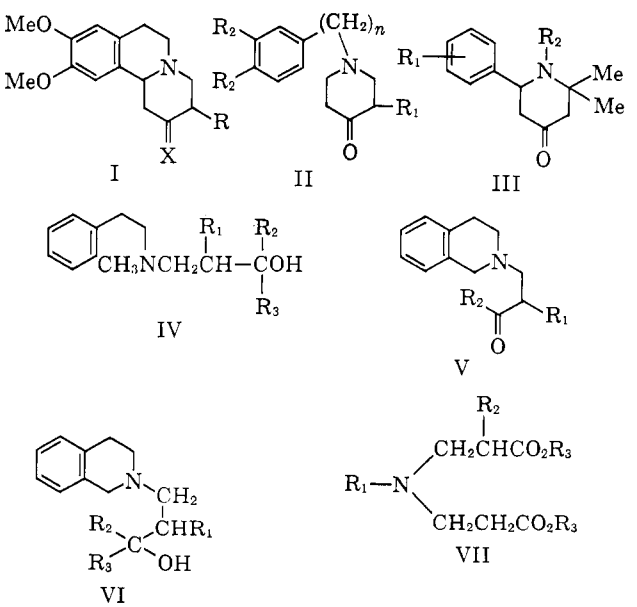
1-Arylalkyl-3-alkyl-4-piperidones, the corresponding secondary alcohols and their esters, and 2,2-dimethyl-6-aryl-4-piperidones (III) were prepared as modifications of 9,10-dimethoxy-3-isobutyl-2-oxo-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine for pharmacological testing. Other related structures, IV–VI, were also synthesized. None of these compounds possessed reserpine-like activity, but structures III and IV had a combination of stimulant and depressant effects on the central nervous system.

Reserpine possesses therapeutically useful sedative and antihypertensive properties,[1] but major modifications of the pentacyclic nucleus of the alkaloid destroys this biological activity.[2] Kralt, *et al.*,[3] suggested that the pharmacological properties of reserpine are determined by three chemical groups in the molecule: (1) the β-indolylethylamine group, (2) the tertiary nitrogen atom, and (3) the alcohol group esterified by trimethoxybenzoic acid. Other investigators have shown that activity does not reside specifically in the trimethoxybenzoyl ester group and that trimethoxybenzoic acid may be replaced by other acids[4] or even by alkyl.[5] Brossi, *et al.*,[6,7] during synthetic studies in the emetine field, discovered reserpine-like activity in the benzoquinolizines I (X = =O, or H and OH), thus indicating that the β-indolylethylamine



I II III

IV V

VI VII

residue can be replaced by arylethylamine. The noteworthy features common to both structures appear to be an oxygen-containing function, a basic tertiary nitrogen atom which is sterically shielded, and an aromatic ring system. Tetrabenazine® (I, R =

(1) R. E. Woodson, Jr., H. W. Yangken, E. Schittler, and J. A. Schneider, "*Rauwolfia:* Botany, Pharmacognosy, Chemistry and Pharmacology," Little, Brown and Co., Boston, Mass., 1957.

(2) M. A. Karim, *Pakistan J. Sci.*, **12**, 119 (1960).

(3) T. Kralt, W. J. Asma, H. H. Haeck, and D. H. Moed, *Rec. trav. chim.*, **80**, 313 (1961).

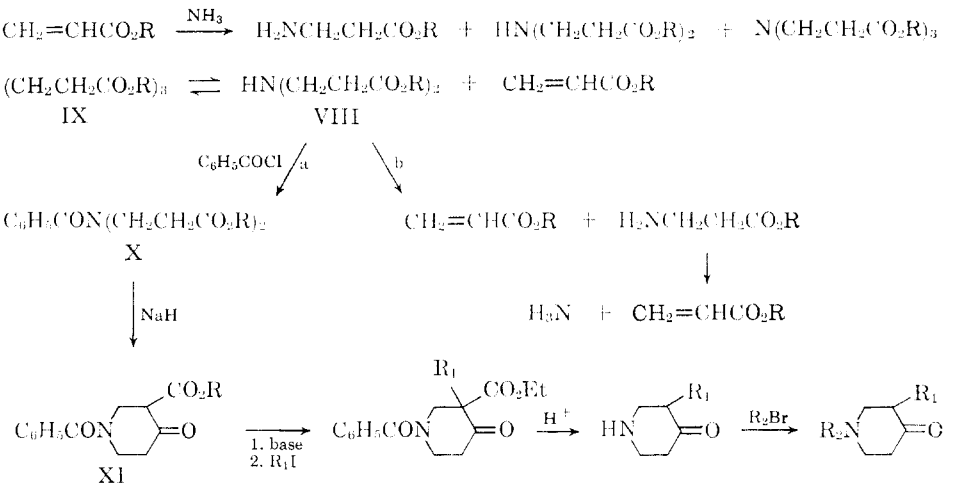
(4) R. A. Lucas, M. E. Kuehne, M. J. Ceglowksi, R. L. Dziemian, and H. B. MacPhillamy, *J. Am. Chem. Soc.*, **81**, 1928 (1959).

(5) M. M. Robison, R. A. Lucas, H. B. MacPhillamy, W. Barrett, and A. J. Plummer, *Experientia*, **17**, 14 (1961).

(6) A. Brossi, H. Lindlar, M. Walter, and O. Schnider, *Helv. Chim. Acta*, **41**, 119 (1958).

(7) A. Brossi, L. H. Chopard-dit-Jean, and O. Schnider, *ibid.*, **41**, 1793 (1958).

CHART I



isobutyl; X = O) which has been the most extensively investigated compound of the benzoquinolizines is a tranquilizing sedative and, like reserpine, causes release of serotonin and norepinephrine[8-10]; it is not, however, a hypotensive agent.[11,12]

This article is concerned with structural modifications of the benzoquinolizine molecule. The structures II–IV can be regarded formally as fragments of I. The most important difference is that in benzoquinolizine the tertiary nitrogen atom is firmly attached to the aromatic nucleus, where as the modifications II–IV allow free rotation.

The piperidones (II, R_1 = H or CH_3; R_2 = H or OCH_3; n = 1 or 2) were prepared by cyclization of the appropriate diesters VII (R_1 = arylalkyl; R_2 = H or CH_3; R_3 = Me).[13-15] Methyl β-benzylaminoisobutyrate, required for the preparation of II (R_1 = CH_3; R_2 = H; n = 1), was obtained from benzylamine and methyl methacrylate in boiling methanol.[15] In boiling ethanol, however, the only product isolated was N-benzyl-β-benzylaminoisobutyramide, and we investigated this reaction further. We found that, although addition to the double bond occurs slowly at room temperature and is accelerated by an increase in temperature, above 70° substitution at the carbonyl group also occurs.

1-Arylalkyl-3-ethyl-4-piperidones (II, R_1 = Et; R_2 = H; n = 2 and 3) were prepared from 3-ethyl-4-piperidone and the latter was obtained according to the procedure established by Stork and McElvain,[16] as outlined in Chart I.

Although McElvain and Stork employed ethyl acrylate in this synthesis we reinvestigated the use of the more readily available methyl ester. Morsh[17] had obtained the secondary amino ester (VIII, R = CH_3) from the addition of methyl acrylate to ammonia in ethanol but McElvain and Stork[18] reported that they were unable to reproduce this result. Since Morsh also obtained this ester, together with the tertiary amino ester, from methyl acrylate and liquid ammonia we investigated a modification of his procedure. The reaction of liquid ammonia with methyl acrylate in ethanol at −60° gave reproducible yields of the amino esters and, furthermore, similar results were obtained with ethyl acrylate.

When the amino esters (VIII and IX, R = CH_3) were heated with benzoyl chloride, we found that, although the secondary amino ester was smoothly converted into the benzamide X (R = CH_3), the tertiary amino ester in hot xylene containing tributylamine afforded a mixture from which a pure product could not be isolated.

McElvain and Stork have commented on the series of equilibria which are involved in these reactions. The tertiary amino ester dissociates initially into acrylate and the secondary amino ester, and the latter can either react with benzoyl chloride to form the stable benzamide or decompose further, eventually yielding acrylate and ammonia. It appears that the secondary amino methyl ester is sufficiently stable in boiling benzene to allow benzoylation, but that, at the higher temperature required for its formation from the tertiary amino ester, it undergoes pyrolytic decomposition in competition with benzoylation. No such complication arose with the corresponding ethyl esters and these were used for the synthetic program outlined in Chart I.

Alkylation of 1-benzoyl-3-carboethoxy-4-piperidone with ethyl or isobutyl iodide was conveniently effected with sodium hydride in toluene, and acidic hydrolysis afforded the corresponding 3-alkyl-4-piperidone. Reaction of these norpiperidones with a phenylalkyl bromide was attended by considerable decomposition under the usual conditions (the thermal instability of norpiperidones has been noted by Stork and McElvain[16]) but 3-ethyl-4-piperidone could be stabilized as its bicarbonate[19] to afford the required products (II, R = C_2H_5; n = 2 or 3) in 75% yield. On the other hand the decomposition of 3-isobutyl-4-piperidone

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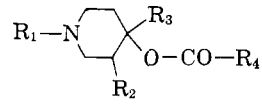
Table I

Esters of Substituted 4-Piperidinols



R_1	R_2	R_3	R_4	Salt	Solvent[a]	B.p. (mm.) or m.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
$C_6H_5(CH_2)_2$	H	H	TMB[b]		B	92.5–93.5	$C_{23}H_{29}NO_5$	69.2	7.3	3.5	69.1	7.05	3.8
				HCl	A	222.5–224	$C_{23}H_{29}NO_5\cdot HCl$	63.4	6.9	3.2	63.4	6.7	3.6
$C_6H_5(CH_2)_2$	H	H	C[c]		B	85.5–86.5	$C_{22}H_{25}NO_2$	78.8	7.5	4.1	78.6	7.5	4.2
				HCl	A	221–222	$C_{22}H_{25}NO_2\cdot HCl$	71.1	7.05	3.8	71.0	7.0	3.6
$C_6H_5(CH_2)_2$	CH_3	H	TMB		D	87.5–89.5	$C_{24}H_{31}NO_5$	69.7	7.6	3.4	70.1	7.65	3.5
				HCl	C	224.5–226	$C_{24}H_{31}NO_5\cdot HCl$	64.0	7.2	3.1	63.8	7.0	3.1
$C_6H_5(CH_2)_2$	H	H	DPA[d]		C	83–85	$C_{27}H_{29}NO_2$	81.2	7.3	3.5	81.3	7.3	3.5
				HCl	A	226–227	$C_{27}H_{29}NO_2\cdot HCl$	74.4	6.9	3.2	74.2	6.95	3.3
$C_6H_5(CH_2)_2$	CH_3	H	C		B	82–83	$C_{23}H_{27}NO_2$	79.1	7.8	4.0	79.0	7.85	4.2
				HCl	C	270–272	$C_{23}H_{27}NO_2\cdot HCl$	71.6	7.3	3.6	71.8	7.3	3.7
C_2H_5	CH_3	H	DPA		Oil	148–150 (0.05)	$C_{22}H_{27}NO_2$	78.3	8.1	4.2	78.3	8.3	4.1
C_2H_5	CH_3	H	C		Oil	137 (0.05)	$C_{17}H_{23}NO_2$	64.7	8.5	5.1	64.6	8.4	5.1
				HCl	A	192–202	$C_{17}H_{23}NO_2\cdot HCl$	65.9	7.8	4.5	65.9	7.8	4.6
C_2H_5	H	H	TMB	HCl	A	217.5–218.5	$C_{17}H_{25}NO_5\cdot HCl$	56.7	7.3	3.9	56.8	7.4	3.9
CH_3	CH_3	H	TMB	HCl	C	234.5–237.5	$C_{17}H_{25}NO_5\cdot HCl$	56.7	7.3	3.9	56.7	7.2	3.9
CH_3	CH_3	H	C	HCl	A	218–228	$C_{16}H_{21}NO_2\cdot HCl$	65.0	7.5	4.7	64.9	7.5	4.7
C_2H_5	H	H	C		Oil	144 (0.05)	$C_{16}H_{21}NO_2$	74.1	8.2	5.4	74.3	8.1	5.3
				HCl	A	187–188	$C_{16}H_{21}NO_2\cdot HCl$	65.0	7.5	4.7	65.0	7.7	4.7
CH_3	H	H	C	HCl	A	168–169	$C_{15}H_{19}NO_2\cdot HCl$	63.9	7.2	5.0	62.2	7.2	5.0
CH_3	H	H	TMB	HCl	A	234–235	$C_{16}H_{23}NO_5\cdot HCl$	55.6	7.0	4.1	55.5	7.2	4.2
$C_6H_5(CH_2)_2$	CH_3	H	DPA	HCl	C	225–226	$C_{28}H_{31}NO_2\cdot HCl$	74.7	7.2	3.1	74.7	7.2	3.4
$C_6H_5(CH_2)_2$	CH_3	C_6H_5	TMB	HCl	C	194.5–195	$C_{19}H_{33}NO_5\cdot HCl$	68.0	6.7	2.7	68.3	6.7	2.7

[a] Solvents used for recrystallization: A, ethanol–ether; B, ethanol–water; C, ethanol; D, petroleum ether. [b] TMB, 3,4,5-trimethoxybenzoyl. [c] C, cinnamoyl. [d] DPA, diphenylacetyl.

could not be suppressed and we were unable to isolate a pure product.

Substituted piperidinols were prepared from the ketones by reduction with aluminum isopropoxide in 2-propanol. Although this method may give an equilibrium mixture of the epimers,[20] we did not attempt to isolate both isomers. The trimethoxybenzoate, cinnamate, and diphenylacetate esters of these piperidinols (Table I) were prepared by a standard procedure.

The ketone (V, R_1 = H; R_2 = CH_3) was prepared by the addition of tetrahydroisoquinoline to either vinyl methyl ketone or β-chloroethyl methyl ketone.

The carbinols (IV, R_1 = R_2 = R_3 = CH_3 and R_1 = CH_3; R_2 = R_3 = C_6H_5) were obtained from methyl (N-phenethyl-N-methyl)aminoisobutyrate by reaction with the appropriate Grignard reagent.[21]

N-Phenethylpiperidine and N-phenethyl-3-methylpiperidine were synthesized for pharmacological comparison; the former by Clemmenson reduction of the corresponding ketone and the latter by reduction of phenethyl-3-picolinium bromide with formic acid–triethylamine.[22]

6-Aryl- and -alkyl-2,2-dimethyl-4-piperidones (III) were conveniently prepared from diacetonamine oxalate and the appropriate aldehyde.[23]

Biological Activity.—The following pharmacological tests were employed (administration *per os*): dose range in mice, blockade of conditioned avoidance response in rats,[24] protection against amphetamine toxicity in aggregated mice,[25] prevention of reserpine-induced ptosis in rats,[26] prevention of maximal electro-

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shock[27] and pentylenetetrazole[28] induced seizures in mice, analgesic activity in mice (hot plate method),[29] diuretic activity in rats,[30] potentiation of tryptamine convulsions in mice,[31] and potentiation of picrotoxin convulsions in rats.[32]

1-Alkyl-, -benzyl-, and -phenylpropyl-4-piperidones were inactive in the pharmacological tests employed. On the other hand the 1-phenylethyl compounds were weakly active (ED_{50} 40–140 mg./kg., LD_{50} 350–650 mg./kg.) in blocking the conditioned avoidance response in rats. The corresponding secondary alcohols showed a similar order of activity but their esters (acetates, trimethoxybenzoates, cinnamates, and diphenylacetates) were inactive. 1-Phenethylpiperidine and its 3-methyl derivative were also inactive. Thus optimum conditioned response blocking activity in this series was obtained with the 1-phenethyl-3-alkyl-4-piperidones or -piperidinols.

The diphenylpropanolamine IV (R_1 = CH_3; R_2 = R_3 = C_6H_5) possessed a combination of stimulant and depressant actions on the central nervous system and was also twice as active as chlorthiazide in causing diuresis in rats. The related isoquinoline VI was considerably less active. The properties of these and related compounds will be reported more fully at a later date.

Thus reserpine-like activity is absent in the open-chain analogs of the benzoquinolizines I and in the isoquinolines V and VI where, although rotation between the tertiary nitrogen atom and the aromatic portion of the nucleus is restricted, the oxygen-containing function is allowed more freedom than in the benzoquinolizine derivatives.

2,2-Dimethyl-6-*p*-chlorophenyl-4-piperidone (III, R_1 = *p*-Cl; R_2 = H) possessed both stimulant and depressant properties. As a stimulant it increased spontaneous motor activity (rats and cats) and potentiated the convulsant effects of picrotoxin and pentylenetetrazole (mice), but not of strychnine (mice) or tryptamine (rats). As a depressant it suppressed the toxic effect of amphetamine in aggregated mice, specifically blocked the conditioned avoidance response in rats, and potentiated hexobarbital sleeping time in mice. Of the related aryl derivatives (Table II) we found that halogen substitution gave the most active compounds with ED_{50} values in the range 15–75 mg./kg. (anti-amphetamine) and 50–150 mg./kg. (block of conditioned response), and LD_{50} values in the range 400–1000 mg./kg. The activity of chlorpromazine under similar experimental conditions was 2, 10, and 200 mg./kg., respectively. Greater structural changes such as replacement of the 6-aryl group by alkyl or arylalkyl, or replacement of the 2,2-dimethyl group by a chlorophenyl group led to inactive compounds. The open-chain analogs, 1-dimethylamino-5-phenyl-4-penten-3-one and its 2-methyl derivative were also inactive.

Since this work was completed, a similar series of 1,2,2-trimethyl-6-aryl-4-piperidones has been described[33] with "action on the central nervous system that brings about a psychological harmonizing *via* normalization."

2,2-Dimethyl-6-*p*-chlorophenyl-4-piperidone has been investigated in man in doses up to 600 mg./day and has been found to possess a good therapeutic index and to be free of toxic reactions even after prolonged administration. It is relatively free of side effects and when they do occur they are easily controlled. Probably the most interesting action exhibited by the compound is the increase in purposeful activity and manageability of schizophrenic patients, many of whom had been hospitalized for periods ranging from 10–25 years.[34]

Experimental

Melting points were recorded using an electrothermal melting point apparatus comprising a gas-heated block and thermometer calibrated for exposed stem. Microanalyses are by Mr. M. Graham (Analytical Laboratories, Smith Kline and French Laboratories Ltd.). The infrared spectrum of all of the products was recorded.

Substituted 4-Piperidones. 1-Phenylethyl-3-methyl-4-piperidone was prepared by the method of Beckett, *et al.*[14]; b.p. 126° (0.4 mm.) [lit.[14] b.p. 123–125° (0.3 mm.)]; **hydrochloride,** m.p. 173–176°.

1-(3,4-Dimethoxyphenethyl)-4-piperidone was prepared in a similar manner and crystallized as colorless prisms from petroleum ether (b.p. 40–60°); m.p. 76–78.5°.

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.4; H, 8.0; N, 5.3. Found: C, 68.3; H, 8.0; N, 5.4.

1-(3,4-Dimethoxyphenethyl)-3-methyl-4-piperidone was prepared similarly and crystallized as colorless needles from benzene–petroleum ether: m.p. 48–49°.

Anal. Calcd. for $C_{16}H_{23}NO_3$: C, 69.3; H, 8.5; N, 5.1. Found: C, 69.3; H, 8.4; N, 5.1.

1-Ethyl-3-methyl-4-piperidone was synthesized similarly and was isolated as a colorless oil, b.p. 69–72° (9 mm.).

Anal. Calcd. for $C_8H_{15}NO$: C, 68.1; H, 10.6; N, 9.9. Found: C, 67.9; H, 10.3; N, 10.0.

Picrate, yellow needles from ethanol, had m.p. 155.5–156.5°.

Anal. Calcd. for $C_8H_{15}NO{\cdot}C_6H_3N_3O_7$: C, 45.4; H, 4.9; N, 15.1. Found: C, 45.4; H, 4.7; N, 14.9.

The following substituted 4-piperidones required for biological comparison were synthesized by published procedures: **1-phenethyl-4-piperidone,** m.p. 60–60.5°, lit.[14] m.p. 60.5–61.5°; **1,3-dimethylpiperidone,** b.p. 74–76° (20 mm.), lit.[35] b.p. 43–44° (5.5 mm.), **picrate** m.p. 190°, lit.[35] m.p. 191.9–192.2°; **1-ethyl-4-piperidone,** b.p. 75° (15 mm.), lit.[36] b.p. 46–48° (1 mm.), **picrate** m.p. 160–161° (*Anal.* Calcd. for $C_7H_{13}NO{\cdot}C_6H_3N_3O_7$: C, 43.8; H, 4.5; N, 15.7. Found: C, 43.4; H, 4.8; N, 15.5.); **1-benzyl-4-piperidone,**[37] b.p. 118–120° (1 mm.) (*Anal.* Calcd. for $C_{12}H_{15}NO$: C, 76.2; H, 8.0; N, 7.4. Found: C, 76.2; H, 7.9; N, 7.4.); **1,2-dimethylipiperidone,** b.p. 84° (20 mm.), lit.[38] b.p. 52.5° (4.5 mm.), **picrate** m.p. 175.5–176.5°, lit.[38] m.p. 152–153.5° (*Anal.* Calcd. for $C_7H_{13}NO{\cdot}C_6H_3NO_7$: C, 43.8; H, 4.5; N, 15.7. Found: C, 43.7; H, 4.7; N, 16.1.); **1-ethyl-2-methyl-4-piperidone,** b.p. 94–98° (22 mm.), lit.[39] b.p. 67–68° (3 mm.), **picrate** m.p. 149°, lit.[39] m.p. 149–150°; **1-benzyl-3-methyl-4-piperidone,** b.p. 111° (0.2 mm.), lit.[15] b.p. 110–115° (0.3 mm.).

Reaction of Benzylamine and Methyl Methacrylate. A. A mixture of methyl methacrylate (1.36 kg., 13.6 moles), benzylamine (2.46 kg., 23 moles), and ethanol (2.72 l.) was heated under reflux for 96 hr. (internal temperature initially 90°) and then con-

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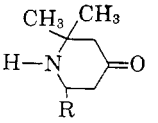
Table II

6-Substituted 2,2-Dimethyl-4-piperidones



R	Salt	Solvent[a]	B.p. (mm.) or m.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Calcd., % Equiv. wt. or Cl⁻	Found, % C	Found, % H	Found, % N	Found, % Equiv. wt. or Cl⁻
2-ClC_6H_4		A	65.5–66.5	$C_{13}H_{16}ClNO$	65.7	6.8	5.9	238	65.4	6.9	5.9	238
	HCl	D	180–180.5 dec.	$C_{13}H_{16}ClNO\cdot HCl$	56.9	6.3	5.1	12.9	56.9	6.5	5.3	12.3
3-ClC_6H_4		Oil	135 (0.2)	$C_{13}H_{16}ClNO$	65.7	6.8	5.9	238	65.5	6.7	5.6	234
	HCl	D	167.5–168.5 dec.	$C_{13}H_{16}ClNO\cdot HCl$				12.9				12.7
4-ClC_6H_4[b]		A	69.5–70	$C_{13}H_{16}ClNO$	65.7	6.8	5.9	238	65.8	6.9	5.9	238
	HCl	D	181.5–182 dec.	$C_{13}H_{16}ClNO\cdot HCl$				12.9				12.9
4-FC_6H_4		A	48–48.5	$C_{13}H_{16}FNO$	70.6	7.3	6.3	221	70.6	7.5	6.6	222
	HCl	B	170.5 dec.	$C_{13}H_{16}FNO\cdot HCl$				13.8				13.8
4-BrC_6H_4		A	70–71	$C_{13}H_{16}BrNO$	55.3	5.7	5.0	282	55.3	5.7	4.9	284
	HCl	D	170–170.5 dec.	$C_{13}H_{16}BrNO\cdot HCl$				11.1				11.1
4-$CH_3OC_6H_4$[c,d]		Oil	120 (0.03)	$C_{14}H_{19}NO_2$	72.1	8.2	6.0	233	72.1	8.1	5.8	237
	HCl	D	166.5–167 dec.	$C_{14}H_{19}NO_2\cdot HCl$				13.1				13.0
2,3-$(CH_3O)_2C_6H_3$	HCl	D	189–191 dec.	$C_{15}H_{21}NO_3\cdot HCl$	60.1	7.4	4.7	11.8	59.4	7.4	4.9	11.9
3,4-$(CH_3O)_2C_6H_3$[b]		C	72–74	$C_{15}H_{21}NO_3$	68.4	8.0	5.3	263	68.2	8.2	5.4	265
	HCl	D	172–173 dec.	$C_{15}H_{21}NO_3\cdot HCl$				11.8				11.9
4-$C_2H_5OC_6H_4$		C	99–101	$C_{15}H_{21}NO_2$	72.8	8.6	5.7	247	72.7	8.4	5.7	249
	HCl	D	161–161.5 dec.	$C_{15}H_{21}NO_2\cdot HCl$				12.5				12.5
4-$CH_3C_6H_4$[b,d]		Oil	110 (0.2)	$C_{14}H_{19}NO$	77.4	8.8	6.5	217	77.2	8.8	6.7	220
	HCl	E	97–100	$C_{14}H_{19}NO\cdot HCl\cdot C_4H_8O$	66.3	8.6	4.3	10.9	66.3	8.4	4.1	10.9
3-$CF_3C_6H_4$	HCl	E	182.5–183.5 dec.	$C_{14}H_{16}F_3NO\cdot HCl$	54.6	5.6	4.6	11.5	54.4	5.4	4.7	11.6
4-$CF_3C_6H_4$	HCl	D	220–221	$C_{14}H_{16}F_3NO\cdot HCl$	54.6	5.6	4.55	11.5	54.9	5.8	4.7	11.7
n-C_3H_7[d,e]		Oil	75 (0.9)	$C_{10}H_{19}NO$	71.0	11.3	8.3	169	71.0	11.2	8.2	171
	HCl	D	177–177.5 dec.	$C_{10}H_{19}NO\cdot HCl$				17.2				17.2
i-C_3H_7[d,f]			70 (1.5)	$C_{10}H_{19}NO$				169				171
	HCl	D	166–167 dec.	$C_{10}H_{19}NO\cdot HCl$	58.4	9.8	6.8	17.2	58.5	10.0	7.0	17.2
$(CH_2)_2C_6H_5$		Oil	128 (0.2)	$C_{15}H_{21}NO$	77.9	9.2	6.1	231	77.2	9.2	6.1	231
$CH{=}CHC_6H_5$[c,d]		Oil	148 (0.4)	$C_{15}H_{19}NO$				229				238
	HCl	D	162–162.5	$C_{15}H_{19}NO\cdot HCl$	68.0	7.2	5.3	13.4	67.7	7.4	5.4	13.4

[a] Solvents used for crystallization: A, petroleum ether; B, water; C, petroleum ether–benzene; D, ethanol–ether; E, methyl ethyl ketone–ether. [b] Bases and oxalates reported in ref. 33. [c] Bases and oxalates reported by ref. 44. [d] Oxalates reported by E. D. Evens, E. C. Gifford, and W. E. L. Griffiths, *J. Chem. Soc.*, **107,** 1675 (1915). [e] Oxalates reported by F. Francis, F. H. Geake, and J. W. Rloche, *ibid.*, **107,** 1662 (1915). [f] Base, b.p. 115° (22 mm.), reported by M. Kohn and F. Wenzel, *Monaish.*, **27,** 981 (1906).

centrated when a mass of crystals separated. These were collected, washed with ethanol, and dried (1.21 kg., 38% conversion based on benzylamine); m.p. 76–77°. Pure N-benzyl-β-benzylaminoisobutyramide crystallized from benzene–petroleum ether as colorless needles, m.p. 88–89°.

Anal. Calcd. for $C_{18}H_{22}N_2O$: C, 76.6; H, 7.85; N, 9.9. Found: C, 76.7; H, 8.1; N, 10.0.

B.—A mixture of benzylamine (535 g., 5 moles), methyl methacrylate (500 g., 5 moles), and ethanol (500 ml.) was heated on a steam bath for 6 hr. and then distilled *in vacuo*. Methyl β-benzylaminoisobutyrate was obtained as a colorless oil, b.p. 96–98° (0.3 mm.), lit.[40] b.p. 97–100° (0.3 mm.) (392 g., 66% yield based on benzylamine consumed).

When the reactants were heated in methanol at 60–65° for 24 hr. and then stood at room temperature for 3 days, 83% of the benzylamine was converted to the required methyl ester.

1-Substituted 4-Piperidinols. A.—The secondary alcohols were prepared by boiling the appropriate ketone (0.25 mole) with aluminum isopropoxide (0.25 mole) in 2-propanol (400 ml.), in a flask fitted with a fractionating column. When the reaction was complete (distillate contained no more acetone) the solvent was distilled under reduced pressure, and the residue was made alkaline with NH_4OH. The secondary alcohols were extracted with ether.

1-Phenethyl-4-piperidinol, m.p. 93–94°, lit.[41] 95.5–98.5°.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.5; H, 8.9; N, 6.9. Found: C, 76.2; H, 9.0; N, 7.2.

Picrate, m.p. 123–124°.

Anal. Calcd. for $C_{13}H_{19}NO\cdot C_6H_3N_3O_7$: C, 52.7; H, 4.9; N, 12.9. Found: C, 52.5; H, 5.0; N, 12.9.

1-Phenethyl-3-methyl-4-piperidinol, colorless oil, b.p. 134–137° (0.6 mm.).

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.6; H, 9.6; N, 6.4. Found: C, 76.2; H, 9.5; N, 6.7.

Picrate, yellow needles from 60% methanol, m.p. 127–134°.

Anal. Calcd. for $C_{14}H_{21}NO\cdot C_6H_3N_3O_7$: C, 53.7; H, 5.2; N, 12.5. Found: C, 53.6; H, 5.3; N, 12.6.

1,3-Dimethyl-4-piperidinol, colorless oil, b.p. 64° (0.25 mm.).

Anal. Calcd. for $C_{17}H_{15}NO$: C, 65.1; H, 11.6; N, 10.9. Found: C, 65.0; H, 11.7; N, 11.2.

Picrate, yellow needles from ethanol, m.p. 183–185°.

Anal. Calcd. for $C_7H_{15}NO\cdot C_6H_3N_3O_7$: C, 43.7; H, 4.8; N, 15.7. Found: C, 43.8; H, 4.9; N, 15.6.

1-Ethyl-3-methyl-4-piperidinol, colorless oil, b.p. 92° (6 mm.); **picrate,** yellow needles from ethanol–ether, m.p. 105–107°.

Anal. Calcd. for $C_8H_{17}NO\cdot C_6H_3N_3O_7$: C, 45.2; H, 5.4; N, 15.05. Found: C, 45.0; H, 5.3; N, 15.05.

1-Ethyl-4-piperidinol, colorless oil, b.p. 100° (10 mm.).

Anal. Calcd. for $C_7H_{15}NO$: C, 65.1; H, 11.7; N, 10.85. Found: C, 65.3; H, 11.45; N, 10.6.

B.—The tertiary alcohols were prepared by treating the corresponding piperidone with phenyllithium in ether.[42]

(40) F. F. Blicke and W. A. Gould, *J. Org. Chem.*, **23,** 1102 (1958).

(41) R. P. Holysz, Upjohn Co., U. S. Patent 3,014,913 (1961); *Chem. Abstr.*, **56,** 10112 (1961); U. S. Patent 3,031,355 (1962); *Chem. Abstr.*, **57,** 13742 (1962).

(42) A. H. Beckett, A. F. Casy, G. Kirk, and J. Walker, *J. Pharm. Pharmacol.*, **9,** 939 (1957).

1,3-Dimethyl-4-phenylpiperidinol, m.p. 100.5°, lit.[42] m.p. 101–102° (for α-isomer); 1-phenylethyl-4-phenyl-4-piperidinol, m.p. 93–94°, lit.[14] m.p. 101–103°; 1-phenethyl-3-methyl-4-piperidinol, m.p. 102–103°, lit.[14] m.p. 105–106°.

Esters of 1-Substituted 4-Piperidinols.—1-Phenethyl-3-methyl-4-piperidyl acetate was prepared in the usual manner from the alcohol and acetic anhydride; b.p. 124–126° (0.2 mm.); **hydrochloride,** m.p. 234–237°, colorless crystals from ethanol–ether.

Anal. Calcd. for $C_{16}H_{22}NO_2 \cdot HCl$: C, 64.5; H, 8.1; N, 4.7. Found: C, 64.1; H, 8.1; N, 5.0.

Esters of 3,4,5-trimethoxybenzoic, cinnamic, and diphenylacetic acids were prepared by heating equimolar amounts of the alcohol and acid chloride on a steam bath for 1 hr. The hydrochlorides were isolated by addition of an ethanol–ether mixture. These compounds are listed in Table I.

2,2-Dimethyl-6-aryl- (alkyl- or arylalkyl-) 4-piperidones.—Diacetonamine hydrogen oxalate was prepared according to Haeseler.[43] A minor modification, whereby the quantity of ethanol used during neutralization of diacetonamine was reduced to its minimum and the product was crystallized from water, permitted a convenient scale-up (to 20 *M*).

The piperidones of Table II were prepared by heating diacetonamine hydrogen oxalate (0.3 mole) with an equimolar quantity of the requisite aldehyde in boiling ethanol (300 ml.) according to the directions of Heintz.[23] They were purified by distillation *in vacuo* or crystallization and were then converted into their hydrochlorides by precipitation from ether with ethereal HCl. The hydrochlorides were subsequently crystallized to constant melting point.

The following compounds, previously reported in the literature, were prepared for pharmacological comparison: 2,2-dimethyl-6-phenyl-4-piperidone, m.p. 62–64°, lit.[23] m.p. 62–63°; 2,2-dimethyl-6-*p*-nitrophenyl-4-piperidone, m.p. 142.5–143.5°, lit.[44] m.p. 142.5°; 1,2,2-trimethyl-6-phenyl-4-piperidone, m.p. 74.5–76.5°, lit.[45] m.p. 77–88°; and 1,2,2-trimethyl-6-*p*-chlorophenyl-4-piperidone, m.p. 116.5–117.5°, lit.[33] m.p. 116–118°.

1-Methyl-2,6-di(*p*-chlorophenyl)-4-piperidone was prepared by addition of methylamine to di(*p*-chlorobenzal)acetone in methanol according to the method published for 1-methyl-2,6-diphenyl-4-piperidone.[46] It was obtained as colorless prisms, m.p. 140.5–144°, from petroleum ether (60–80°).

Anal. Calcd. for $C_{18}H_{17}Cl_2NO$: C, 64.7; H, 5.1; Cl, 21.2; N, 4.2. Found: C, 64.5; H, 5.1; Cl, 21.4; N, 3.9.

1-Benzoyl-3-carbomethoxy-4-piperidone (XI, R = CH_3).—Methyl acrylate (344 g., 4 moles) was added to a mixture of liquid ammonia (500 ml.) and ethanol (500 ml.) in a 2-l. flask fitted with a KOH drying tube, left overnight at −60°, and then slowly brought to room temperature. Most of the excess NH_3 had evaporated, and the ethanol and β-alanine methyl ester were removed on a steam bath under reduced pressure. The residue (360 g.) was fractionally distilled *in vacuo* to give di(β-carbomethoxyethyl)amine (VIII, R = CH_3), b.p. 75° (0.05 mm.), basic equiv. 191 (calcd. 189), yield 76 g. (20%); and tri(β-carbomethoxyethyl)amine (IX, R = CH_3), b.p. 132° (0.1 mm.), basic equiv. 285 (calcd. 275), yield 205 g. (56%).

The above secondary amino ester (90 g., 0.48 mole) and benzoyl chloride (81 g., 0.58 mole) were heated in dry benzene (200 ml.) under reflux for 16 hr. N,N-Di(β-carbomethoxyethyl)benzamide (X, R = CH_3) was isolated as described[18] for the corresponding ethyl ester, b.p. 188° (0.8 mm.), yield 120 g. (85%).

Cyclization of the above benzamide (120 g., 0.41 mole) was effected by sodium hydride (73 g., 27% suspension in paraffin, 0.82 mole) in dry benzene (550 ml.) to afford 1-benzoyl-3-carbomethoxy-4-piperidone as a pale orange viscous oil which solidified after several months; m.p. 50–60°, yield 82 g. (76%).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.3; H, 5.8. Found: C, 64.1; H, 5.8.

1-Benzoyl-3-carboethoxy-4-piperidone (XI, R = C_2H_5).—Ethyl acrylate was treated with NH_3 in ethanol at −60°, as described above for methyl acrylate, and afforded 90 g. (21%) of di(β-carboethoxyethyl)amine (VIII, R = Et), b.p. 80° (0.07 mm.), basic equiv. 216 (calcd. 217); and 243 g. (58%) of tri(β-carboethoxyethyl)amine (IX, R = Et), b.p. 136° (0.06 mm.), basic equiv. 336 (calcd. 317). These amines, either separately or as a crude mixture, were converted into di(β-carboethoxyethyl)-benzamide by the described procedure.[18]

Cyclization of the latter was effected by adding it slowly to sodium hydride (27% suspension in paraffin) in dry benzene containing 2 ml. of ethanol, since rapid addition, in contrast to the reported use of sodium hydride powder,[47] resulted in a violent reaction.

1-Benzoyl-3-carboethoxy-4-piperidone was isolated by the reported procedure[47] and obtained as a viscous oil which shortly solidified. Two crystallizations from petroleum ether (40–60°) afforded colorless needles, m.p. 68–70°, lit.[47] m.p. 56–59°.

1-Phenethyl-3-ethyl-4-piperidone.—3-Ethyl-4-piperidone hydrochloride (prepared from 1-benzoyl-3-carboethoxy-4-piperidone as reported[16]) (7.7 g., 0.047 mole) in ethanol (100 ml.) was neutralized with sodium methoxide (2.5 g., 0.046 mole) and filtered from the precipitated NaCl. To the filtrate were added water (0.8 ml.), a few small pieces of solid CO_2, 1-bromo-2-phenylethane (9.25 g., 0.05 mole), and $NaHCO_3$ (10.7 g.), and the mixture was heated under reflux for 40 hr. until the evolution of CO_2 had ceased. The mixture was cooled, filtered from inorganic salts, diluted with water (30 ml.), evaporated under reduced pressure to *ca.* 40 ml., acidified with HCl, and washed with ether to remove neutral material. Basification then liberated 1-phenethyl-3-ethyl-4-piperidone which, after distillation *in vacuo*, was obtained as a colorless mobile oil, b.p. 110° (0.02 mm.), $n^{20}D$ 1.5230, yield 7.8 g. (75%); lit.[14] b.p. 138° (0.25 mm.), $n^{18}D$ 1.5248.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.9; H, 9.2; N, 6.1; basic equiv., 231. Found: C, 77.7; H, 9.2; N, 6.2; basic equiv., 231.

Hydrochloride, colorless plates from ethyl methyl ketone–diethyl ether mixture, m.p. 119–120°.

Anal. Calcd. for $C_{15}H_{22}ClNO$: C, 67.3; H, 8.3; Cl^-, 13.2; N, 5.2. Found: C, 66.9; H, 8.1; Cl^-, 13.1; N, 5.4.

Picrate, m.p. 176.5° dec., lit.[14] m.p. 176–178°.

1-(3-Phenylpropyl)-3-ethyl-4-piperidone was prepared in a similar manner from 3-ethyl-4-piperidone and 1-bromo-3-phenylpropane, yield 75%, b.p. 100° (0.01 mm.), $n^{20}D$ 1.5201.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.3; H, 9.5; N, 5.7; basic equiv., 245. Found: C, 77.6; H, 9.5; N, 6.0; basic equiv., 246.

Hydrochloride, colorless plates from ethyl methyl ketone–diethyl ether mixture, m.p. 128–129°.

Anal. Calcd. for $C_{16}H_{24}ClNO$: C, 68.2; H, 8.6; N, 5.0; Cl^-, 12.6. Found: C, 68.0; H, 8.4; N, 5.1; Cl^-, 12.5.

1-Benzoyl-3-isobutyl-3-carboethoxy-4-piperidone.—1-Benzoyl-3-carbethoxy-4-piperidone (130 g., 0.47 mole) was converted into its sodium enolate by reaction with sodium hydride (21.1 g. of 54% dispersion in paraffin, 0.47 mole) in dry toluene (500 ml.) under reflux. The sodium enolate separated as a yellow granular solid and after 2.5 hr. isobutyl iodide (136 g., 0.74 mole) was added. The mixture was heated under reflux for 72 hr. in an atmosphere of nitrogen, then cooled, and decanted. The toluene solution, after successive washings with 5% NaOH, 5% HCl, water, and 10% $NaHCO_3$, was evaporated under reduced pressure to yield 88 g. of a mixture of 1-benzoyl-3-isobutyl-3-carboethoxy-4-piperidone and paraffin (from the sodium hydride reagent). After allowing for the paraffin the yield of piperidone was 78 g. (50%).

Semicarbazone, colorless prisms from methanol containing a few drops of water, m.p. 204.5–205.5°.

Anal. Calcd. for $C_{20}H_{28}N_4O_4$: C, 61.8; H, 7.3; N, 14.4. Found: C, 61.9; H, 7.35; N, 14.65.

The hydrolysis of the above piperidone in 5 *N* HCl (75 ml.) under reflux for 12 hr. gave, after work-up according to the method used for 3-ethyl-4-piperidone hydrochloride, a crude hydrochloride as a glass (45 g.). We were unable to crystallize this directly but neutralization with saturated K_2CO_3 solution followed by repreparation of the hydrochloride in ether furnished a solid which crystallized from ethanol-diethyl ether mixture as colorless microprisms, m.p. 161–163°. The analysis was, however, in poor agreement with 3-isobutyl-4-piperidone hydrochloride.

Anal. Calcd. for $C_9H_{18}ClNO$: C, 56.4; H, 9.5; Cl, 18.5; N, 7.3. Found: C, 55.3; H, 9.2; Cl, 18.9; N, 8.1.

Alkylation of this piperidone (bicarbonate method) with 1-bromo-2-phenylethane afforded a hydrochloride, m.p. 134–138°, whose analysis was in poor agreement with the anticipated product.

(43) P. R. Haeseler, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 196.

(44) O. Antrick, *Ann.*, **227**, 365 (1885).

(45) P. W. Neber, A. Burgard, and W. Their, *ibid.*, **526**, 277 (1936).

(46) R. E. Lyle and G. G. Lyle, *J. Org. Chem.*, **24**, 1679 (1959).

(47) S. M. McElvain and R. E. McMahon, *J. Am. Chem. Soc.*, **71**, 901 (1949).

Methyl β-(N-Phenethyl-N-methyl)aminoisobutyrate.—A mixture of methyl β-(phenethylamino)isobutyrate (22.1 g., 0.1 mole), paraformaldehyde (3.2 g., 1.07 moles), and formic acid (98%, 40 ml.) was slowly heated on a steam bath. A vigorous evolution of gas occurred at first and the paraformaldehyde dissolved. The mixture was heated for a further 15 min. and excess formic acid was distilled under reduced pressure. The residue was made alkaline with 40% NaOH and the oil was extracted with ether. The product (20 g., 85% yield) was recovered as a colorless oil, b.p. 88–90° (0.08 mm.).

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.0; N, 5.95. Found: C, 71.4; H, 9.2; N, 5.9.

Methyl β-[2-(1,2,3,4-Tetrahydro)isoquinolyl]isobutyrate.—A mixture of 1,2,3,4-tetrahydroisoquinoline (33.8 g., 0.25 mole) and methyl methacrylate (25.8 g., 0.3 mole) was heated in ethanol (100 ml.) for 20 hr. The product was isolated by distillation as a colorless oil, b.p. 95° (0.05 mm.), yield 23.3 g. (39.6%).

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.2; N, 6.0. Found: C, 71.8; H, 8.1; N, 6.1.

1,1-Diphenyl-2-methyl-3-(N-phenethyl-N-methyl)aminopropan-1-ol.—To the Grignard reagent prepared from magnesium (4.85 g., 0.2 g.-atom) and bromobenzene (31.4 g., 0.2 mole) in dry ether (100 ml.) was added with stirring and cooling a solution of methyl β-(N-phenethyl-N-methyl)aminoisobutyrate (23.5 g., 0.1 mole). After the mixture had stood at room temperature for 2 days, crushed ice was added followed by dilute HCl. The resulting white solid was collected and ground with dilute ammonia and the oil which separated out was extracted into ether. Distillation *in vacuo* gave the **base** (24.4 g., 68%), b.p. 200° (0.1 mm.).

Anal. Calcd. for $C_{25}H_{29}NO$: C, 83.5; H, 8.1; N, 3.9. Found: C, 83.1; H, 8.2; N, 3.95.

Hydrochloride, colorless prisms from 2-propanol, m.p. 191–193°.

Anal. Calcd. for $C_{25}H_{29}NO\cdot HCl$: C, 75.8; H, 7.6; Cl, 9.0; N, 3.5. Found: C, 75.5; H, 7.7; Cl, 8.9; N, 3.4.

Hydrobromide, colorless needles from ethanol–ether, m.p. 179–180°.

Anal. Calcd. for $C_{25}H_{29}NO\cdot HBr$: Br^-, 18.15; N, 3.2. Found: Br^-, 18.0; N, 3.4.

1,1-Diphenyl-3,2′-(1,2,3,4-tetrahydroisoquinolyl)propan-1-ol was prepared in a similar manner from methyl β-[2-(1,2,3,4-tetrahydro)isoquinolyl]propionate[48] and phenylmagnesium bromide.

The **base** crystallized from benzene–petroleum ether, m.p. 138–139°.

Anal. Calcd. for $C_{24}H_{25}NO$: C, 83.9; H, 7.3; N, 4.1. Found: C, 83.6; H, 7.3; N, 4.1.

The mother liquor from the crystallization of the **base** was treated with a saturated solution of HCl in ether until acid (pH 3.5) and the resulting solid was crystallized from 2-propanol to give **2-β-benzoylethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride** (1.2 g.), m.p. 183–185°, lit.[49] m.p. 188°.

1,1-Diphenyl-2-methyl-3-[2-(1,2,3,4-tetrahydroisoquinolyl)]-propan-1-ol was prepared by treating methyl β-[2-(1,2,3,4-tetrahydroisoquinolyl)]isobutyrate with phenyllithium in ether. The **base** crystallized from benzene–petroleum ether as colorless prisms, m.p. 135–136.5°.

Anal. Calcd. for $C_{25}H_{27}NO$: C, 84.0; H, 7.6; N, 3.9. Found: C, 84.2; H, 7.9; N, 4.0.

1,1-Diphenyl(3-N-phenylethyl-N-methyl)aminopropan-1-ol was prepared in a similar manner from methyl-β-(N-phenethyl-N-methyl)aminopropionate and phenyllithium. The **base** crystallized from benzene–petroleum ether as colorless prisms, m.p. 109–110°.

Anal. Calcd. for $C_{24}H_{27}NO$: C, 83.4; H, 7.9; N, 4.1. Found: C, 83.5; H, 8.05; N, 4.3.

1,1,2-Trimethyl-3-(N-methyl-N-β-phenylethyl)aminopropan-1-ol.—To the Grignard reagent prepared from magnesium (4.86 g., 0.2 g.-atom) and methyl iodide (28.4 g., 0.2 mole) in ether (1.50 ml.) was added methyl β-(N-methyl-N-phenethyl)aminoisobutyrate (23.5 g., 0.1 mole) with stirring and cooling (0–10°). After standing at room temperature for 4 hr. the complex was decomposed with a mixture of ice (100 g.) and concentrated HCl (25 ml.). The aqueous layer was separated, made alkalline with 40% NaOH, and then extracted with ether. Distillation *in vacuo* gave the **base** (16.6 g., 70.5%) as a colorless oil, b.p. 114° (0.7 mm.).

Anal. Calcd. for $C_{15}H_{25}NO$: C, 76.5; H, 10.7; N, 5.95. Found: C, 76.6; H, 10.55; N, 6.1.

1-Methyl-3-[2-(1,2,3,4-tetrahydroisoquinolyl)]propan-1-one. A.—2-Chloroethyl methyl ketone (3.3 g.) was mixed with 1,2,3,4-tetrahydroisoquinoline (4.12 g.) when a spontaneous reaction occurred and the mass became warm. The mixture was left at room temperature for 1 hr., when it solidified. After making alkaline and extracting with ether the same base was isolated as that obtained below from vinylacetone and tetrahydroisoquinoline.

B.—Vinylacetone (10 g., 0.15 mole) was slowly added to 1,2,3,4-tetrahydroisoquinoline (13.3 g., 0.1 mole) with cooling. The mixture was refluxed for several hours. Distillation *in vacuo* gave tetrahydroisoquinoline (7.4 g.) and a fraction, b.p. 75–120° (1 mm.). The latter was dissolved in dilute HCl, the acidic layer was washed with ether, then basified, and the resulting oil was extracted into ether. Distillation gave the required ketone as a colorless oil, b.p. 100–102° (0.01 mm.), yield 3.4 g. (38% yield based on tetrahydroisoquinoline consumed).

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.8; H, 8.4; N, 6.9. Found: C, 76.4; H, 8.5; N, 7.0.

Semicarbazone, m.p. 145–147° (from water).

Anal. Calcd. for $C_{14}H_{20}N_4O$: C, 64.6; H, 7.7; N, 21.5. Found: C, 64.9; H, 7.8; N, 21.4.

1-Dimethylamino-5-phenyl-4-penten-3-one.—Reaction of benzalacetone with dimethylamine hydrochloride and formaldehyde in ethanol[50] gave the base as a yellow oil which decomposed on attempted distillation.

Maleate, m.p. 129–130° from 2-propanol.

Anal. Calcd. for $C_{13}H_{17}NO\cdot C_4H_4O_4$: C, 63.9; H, 6.8; N, 4.4. Found: C, 63.8; H, 6.8; N, 4.4.

1-Dimethylamino-2-methyl-5-phenyl-4-penten-3-one.—Reaction of 1-phenyl-1-penten-3-one with paraformaldehyde and dimethylamine hydrochloride in ethanol[51] gave the base as a light brown mobile oil which decomposed on attempted distillation.

Maleate, m.p. 115–117° from 2-propanol–petroleum ether.

Anal. Calcd. for $C_{14}H_{19}NO\cdot C_4H_4O_4$: C, 64.95; H, 6.95; N, 4.2. Found: C, 64.9; H, 7.0; N, 4.3.

1-Phenethylpiperidine.—1-Phenethyl-4-piperidone (50.1 g., 0.25 mole) was added in four portions to amalgamated zinc wool (prepared from 120 g. zinc wool and 9 g. of mercuric chloride) in HCl (250 ml. of concentrated HCl and 75 ml. of water).[52] After the initial vigorous reaction had subsided, the mixture was boiled under reflux for 24 hr., then made alkaline and extracted several times with chloroform. The combined extracts were dried and concentrated, and the residue was distilled *in vacuo* to give 1-phenethylpiperidine, b.p. 90° (0.5 mm.), 33.5 g., 71%.

Picrate, m.p. 142.5–144.5°, lit.[53] m.p. 144–145°.

1-Phenethyl-3-methylpiperidine.—A mixture of 3-picoline (18.6 g., 0.2 mole) and phenethyl bromide (37.1 g., 0.2 mole) was heated in an oil bath at 130–140° for 30 min. Formic acid (46 g., 98–100%) and triethylamine (40 g.) were added and the mixture refluxed for 4 hr. After dilution with water the solution was made alkaline with 40% NaOH, and the oil was extracted with ether. Distillation gave 30 g. (70%) of product, b.p. 122° (2 mm.).

Anal. Calcd. for $C_{14}H_{21}N$: N, 6.9. Found: N, 6.85.

Picrate, m.p. 143.5–145.5° from ethanol.

Anal. Calcd. for $C_{14}H_{21}N\cdot C_6H_3N_3O_7$: C, 55.55; H, 5.6; N, 13.0. Found: C, 55.4; H, 5.6; N, 13.1.

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