459. Δ^1-*Piperideines.*

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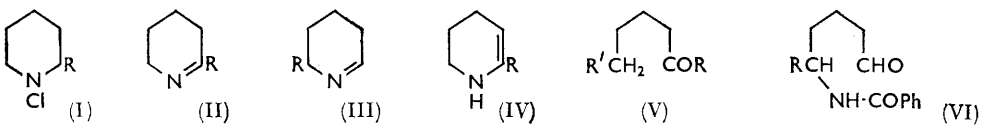
A series of 2-alkylpiperidines has been converted by way of 1-chloropiperidines and by reaction with mercuric acetate into 2-alkyl-Δ^1-piperideines; 3- and 4-methylpiperidines afford polymers. The structures of some compounds, previously described as Δ^2-piperideines, have been revised.

Interest in piperideines stems from the investigations of the hemlock alkaloid γ-coniceine, which was assigned[1] the Δ^2-piperideine structure (IV; R = Pr^n). The position of the double bond was not established, and the syntheses of the alkaloid by way of the amino-ketone (V; R = Pr^n, R′ = NH_2)[2] or by reaction of 2-piperidone with propylmagnesium bromide[3] do not distinguish between the Δ^1-structure (II; R = Pr^n) and the Δ^2-structure (IV; R = Pr^n). Other alkylpiperideines were also formulated as Δ^2-derivatives,[4] but again without sufficient justification. In fact, the alternative structures (II) now seem more likely,[5–7] by analogy with the Δ^1-structures established for some related pyrrolines.[7–9a] The purpose of this work has been to develop a synthesis of piperideines from readily accessible piperidines, and to study the structures of the products.



Lellmann reported,[10] without giving experimental details, that γ-coniceine was formed by the action of alkali on 1-chloro-2-n-propylpiperidine, and we have explored this method further. Reaction of a series of substituted piperidines with *N*-chlorosuccinimide in ether at 20° gave the 1-chloropiperidines in good yield. Treatment of the chloro-compounds (I; R = Me, Pr^n, Bu^n, or Bu^t) and 1-chloro-2,6-dimethylpiperidine with potassium hydroxide in ethanol then gave the corresponding alkyl piperideines. Vapour-phase

[1] Lellmann and Müller, *Ber.*, 1890, **23**, 680.
[2] Gabriel, *Ber.*, 1909, **42**, 4059.
[3] Lukeš, Šorm, and Arnold, *Coll. Czech. Chem. Comm.*, 1947, **12**, 641.
[4] For references see Barnes in "Pyridine and Derivatives," Part I, ed. Klingsberg, Interscience, New York, 1960, p. 90.
[5] Cf. Hancox, *Austral. J. Chem.*, 1953, **6**, 143; Sury and Hoffmann, *Helv. Chim. Acta*, 1955, **38**, 728.
[6] Červinka, *Coll. Czech. Chem. Comm.*, 1959, **24**, 1146.
[7] Witkop, *J. Amer. Chem. Soc.*, 1954, **76**, 5597.
[8] Evans, *J. Amer. Chem. Soc.*, 1951, **73**, 5230; Eddy and Eisner, *Analyt. Chem.*, 1954, **26**, 1428.
[9] (*a*) Bonnett, Clark, Giddey, and Todd, *J.*, 1959, 2087; (*b*) Grundon and McGarvey, *J.*, 1960, 2739.
[10] Lellmann, *Ber.*, 1889, **22**, 1000.

chromatography indicated that a single isomer was obtained in each case. Since some of the piperideines darkened on exposure to air, and good analyses were not always obtained, each compound was characterised as its benzoyl derivative and as its picrolonate.

The 2-n-butyl- and the 2-t-butyl-piperideine in hexane do not absorb in the NH region of the infrared, but strong bands appear at 1665—1655 cm.$^{-1}$ (C:N); these compounds are therefore Δ^1- rather than Δ^2-derivatives. The picrolonates possess infrared bands at 1690—1680 cm.$^{-1}$ (C=NH$^+$), which are absent from the spectra of the corresponding piperidine picrolonates. Protonation of the C:N bond thus produces the expected hypsochromic shift of 20—25 cm.$^{-1}$,[7,9] but this observation alone does not distinguish between the isomers because protonation of a Δ^2-piperideine (>C=C–NH– ⟶ H–C–C=NH$^+$–) should result in a similar shift.[11] The 2-methyl-, 2,6-dimethyl-, and 2-n-propyl-piperideine, and their picrolonates, absorb similarly in the 1690—1655 cm.$^{-1}$ region (Table 1),

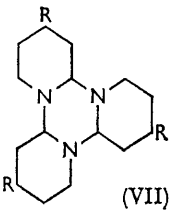
TABLE 1.

Infrared absorption bands (cm.$^{-1}$) of C:N in Δ^1-piperideines (in hexane) and of C=NH$^+$ in Δ^1-piperideine picrolonates (KBr disc.).

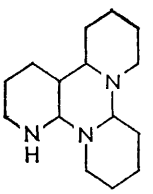
	2-Me	2,6-Me$_2$	2-Pr^n	2-Bu^n	2-Bu^t
Δ^1-Piperideine	1660	1655	1660	1665	1660
Δ^1-Piperideine picrolonate	1690	1690	1685	1690	1680

and are probably also Δ^1-compounds. However, the infrared evidence is less conclusive in these cases, because the bases show peaks at *ca.* 3400 cm.$^{-1}$, which could indicate the presence of an NH group as in structure (IV). Since these bands are weak and broad, and increase in intensity when the compounds are exposed to air, we prefer to attribute this absorption to the presence of water, resulting perhaps in partial conversion of the piperideines into carbinolamines.

Elimination of hydrogen chloride from 2-alkyl-1-chloropiperidines could lead to either 6-alkyl-Δ^1-piperideines (III) or 2-alkyl-Δ^1-piperideines (II). The latter formulation is supported by the following evidence. (*a*) The syntheses of 2-methyl-[12] and 2-n-propyl-piperideine[2] by way of the amino-ketones (V; R = Me, R′ = NH_2) and (V; R = Pr^n, R′ = NH_2) were repeated. The products were obtained in low yields, but were shown by comparison of derivatives to be identical with the piperideines obtained from 1-chloropiperidines. The amino-ketone route cannot give the 6-alkyl-Δ^1-piperideines (III). (*b*) Schöpf and his co-workers[13] showed that treatment of 1-chloropiperidine with alkali gave



(VII)



(VIII)

polymers [*e.g.*, (VII; R = H) and (VIII)] which were derived presumably from the initial product, Δ^1-piperideine. We find that 1-chloro-3-methylpiperidine and its 4-methyl-isomer behave similarly, and do not afford monomeric piperideines. One of the products from 1-chloro-4-methylpiperidine was shown by mass spectrometry to be a trimer of 4-methyl-piperideine; it probably has structure (VII; R = Me), analogous to the tripiperideines (VII; R = H) rather than to isotripiperideine (VIII), because it does not absorb in the NH region of the infrared. It appears, therefore, that Δ^1-piperideines unsubstituted at the 2-position, cf. (III), are too unstable to be isolated, at least under the preparative

[11] Cf. Leonard and Gash, *J. Amer. Chem. Soc.*, 1954, **76**, 2781.
[12] Gabriel, *Ber.*, 1909, **42**, 1238.
[13] Schöpf, Komzak, Braun, Jacobi, Bormuth, Bullnheimer, and Hagel, *Annalen*, 1948, **559**, 1.

conditions employed here. This accords with their cyclic aldimine structure. (*c*) Benzoylation of Δ^1-piperideines (II) and (III) would be expected to furnish benzamido-ketones (V; R′ = NH·COPh) and benzamido-aldehydes (VI), respectively. The products from the reaction of the 2-methyl-, 2-n-propyl-, and 2-n-butyl-piperideine with benzoyl chloride and aqueous sodium hydroxide were apparently benzamido-ketones, since they absorbed at 1720—1710 (ketone CO) and 1645—1640 (amide CO), but not at 2850—2700 cm.$^{-1}$ (CHO). The derivative from 2,6-dimethyl-Δ^1-piperideine, which cannot be a benzamido-aldehyde, had a similar spectrum.

These results suggest that, except when the nitrogen is alkylated, compounds described formerly as Δ^2-piperideines [4] should now be regarded as Δ^1-derivatives. During this work, Beyerman and his associates,[14] and later Büchel and Korte,[15] also established the new structure (II; R = Pr^n) for γ-coniceine.

The reaction of tertiary amines with mercuric acetate has been studied intensively,[16] and under more strenuous conditions certain pyrrolidines containing secondary amino-groups have been converted into Δ^1-pyrrolines.[9a] We have investigated the behaviour of piperidines with mercuric acetate. When 2-methyl-, 2,6-dimethyl-, 2-n-propyl-, and 2-n-butyl-piperidine were refluxed with an excess of mercuric acetate in 10% aqueous acetic acid, a mixture of two compounds was obtained in each case. Vapour-phase chromatography and separation of the picrolonates by fractional crystallisation showed that the components were the starting piperidines and the same Δ^1-piperideines (II) that were obtained previously. The crude dehydrogenation products formed under standard conditions were shown by vapour-phase chromatography to contain 64—86% of the piperideines (Table 2). Since the total basic products were recovered in rather low yields (48—63%), it is unprofitable to attempt to relate these figures to the nature of the 2-alkyl substituents. In contrast, the dehydrogenation of 2-t-butylpiperidine gave the piperideine (II; R = Bu^t) in 75% yield, and unchanged piperidine was not detected; this is, therefore, a convenient procedure for the preparation of the t-butyl-derivative. As in the reactions of 1-chloropiperidines with alkali, dehydrogenation of piperidine and its 3- and 4-methyl derivatives with mercuric acetate did not give monomeric products. Isotripiperideine (VIII) was isolated from the piperidine reaction.

Since the same products were obtained by dehydrogenation of 2-alkylpiperidines and by dehydrohalogenation of 1-chloro-2-alkylpiperidines, it is likely that both processes involve preferential attack of bases (OAc^- and OH^-, respectively) at a 2-methine hydrogen. By analogy with the dehydrogenation of tertiary amines,[17] reaction of 2-alkylpiperidines with mercuric acetate may proceed by elimination from a mercurated intermediate, but formulation of such a mechanism should await comparative rate data and further knowledge of the mercurated complexes formed by secondary amines.

Experimental

2-t-Butylpiperidine.—Sodium (24 g.) was added in portions to 2-t-butylpyridine (11·5 g.) in dry ethanol (240 c.c.), and the solution was refluxed for 4 hr. and then evaporated. After the addition of water, the solution was extracted with ether (6 × 100 c.c.). The ether solution was saturated with hydrogen chloride and the resultant precipitate was extracted continuously with acetone. Evaporation of the acetone solution, treatment of the residue with aqueous potassium hydroxide, and extraction of the solution with ether gave *2-t-butylpiperidine*, which was obtained by distillation as an oil (7·8 g., 68%), b. p. 173—174°, n_D^{18} 1·4572 (Found: C, 77·1; H, 13·6. $C_9H_{19}N$ requires C, 76·5; H, 13·6%). Vapour-phase chromatography (silicone on Celite; 99°) gave a single peak. The *hydrochloride* separated from acetone in needles, m. p. 229—232° (Found: C, 60·8; H, 11·6; N, 8·0. $C_9H_{20}ClN$ requires C, 60·8; H, 11·3; N, 7·9%).

[14] Beyerman, van Leeuwen, Smidt, and van Veen, *Rec. Trav. chim.*, 1961, **80**, 513.
[15] Büchel and Korte, *Chem. Ber.*, 1962, **95**, 2460.
[16] Leonard and Hauck, *J. Amer. Chem. Soc.*, 1957, **79**, 5279.
[17] Leonard, Hay, Fulmer, and Gash, *J. Amer. Chem. Soc.*, 1955, **77**, 439; Leonard and Morrow, *ibid.*, 1958, **80**, 371.

Picrolonates of Substituted Piperidines.—The following derivatives separated from ethanol or methanol: 2-methylpiperidine picrolonate, m. p. 225—227° (decomp.) (Found: C, 53·0; H, 6·0. $C_{16}H_{21}N_5O_5$ requires C, 52·9; H, 5·9%); *3-methylpiperidine picrolonate*, m. p. 229—232° (decomp.) (Found: C, 53·1; H, 5·8. $C_{16}H_{21}N_5O_5$ requires C, 52·9; H, 5·9%); *4-methylpiperidine picrolonate*, m. p. 246—247° (decomp.) (Found: C, 53·1; H, 5·9%); 2,6-dimethylpiperidine picrolonate, m. p. 262—265° (decomp.) (lit.,[18] m. p. 262—268°); *2-n-propylpiperidine picrolonate*, m. p. 205—207° (Found: C, 55·3; H, 6·5. $C_{18}H_{25}N_5O_5$ requires C, 55·2; H, 6·4%); 2-n-butylpiperidine picrolonate, m. p. 186—188° (lit.,[19] m. p. 182°); *2-t-butylpiperidine picrolonate*, m. p. 243—245° (decomp.) (Found: C, 56·1; H, 6·5. $C_{19}H_{27}N_5O_5$ requires C, 56·3; N, 6·7%).

1-Chloropiperidines.—The following 1-chloropiperidines were prepared by the method described [20] for 2-n-butyl-1-chloropiperidine: 1-chloropiperidine (53%), b. p. 56°/31 mm. (lit.,[13] 50—60°/40—50 mm.), n_D^{18} 1·4734 (Found: C, 50·7; H, 8·4; N, 11·5. Calc. for $C_5H_{10}ClN$: C, 50·2; H, 8·4; N, 11·7%); *1-chloro-2-methylpiperidine* (57%), b. p. 58°/36 mm., n_D^{18} 1·4730 (Found: C, 54·7; H, 8·9; N, 10·3. $C_6H_{12}ClN$ requires C, 53·9; H, 9·0; N, 10·5%); *1-chloro-3-methylpiperidine* (70%), b. p. 68—70°/57 mm., n_D^{18} 1·4675 (Found: C, 53·6; H, 8·6%); *1-chloro-4-methylpiperidine* (64%), b. p. 82—84°/71 mm., n_D^{18} 1·4669 (Found: C, 53·8; H, 8·9%); *1-chloro-2,6-dimethylpiperidine* (58%), b. p. 36—40°/20 mm., n_D^{18} 1·4671 (Found: C, 57·3; H, 9·1. $C_7H_{14}ClN$ requires C, 56·9; H, 9·6%); *1-chloro-2-n-propylpiperidine* (60%), b. p. 54°/2 mm., 1·4749 (Found: C, 59·5; H, 9·5; N, 8·8. $C_8H_{16}ClN$ requires C, 59·4; H, 9·9; N, 8·7%). Since 1-chloro-2-methylpiperidine and 1-chloro-2,6-dimethylpiperidine were unstable, good analyses could not be obtained.

Δ^1-Piperideines.—(*a*) 1-Chloro-2-methylpiperidine (7·42 g.) was added to a solution of potassium hydroxide (30 g.) in methanol (250 c.c.). A precipitate of potassium chloride soon appeared, and after 2 hr. at room temperature the mixture was acidified with hydrochloric acid, and filtered. The filtrate was evaporated, and the residue in aqueous potassium hydroxide was extracted continuously with ether for 16 hr. Evaporation of the ether solution and distillation of the residue gave 2-methyl-Δ^1-piperideine as a yellow oil (2·88 g., 54%), b. p. 78°/222 mm., n_D^{16} 1·4657 (Found: C. 72·3; H, 10·5; N, 13·9. Calc. for $C_6H_{11}N$: C, 74·3; H, 11·3; N, 14·4%). The *picrolonate* separated from ethanol in yellow prisms, m. p. 206—208° (decomp.) (Found: C, 53·0; H, 5·5. $C_{16}H_{19}N_5O_5$ requires C, 53·2; H, 5·3%). Reaction of 2-methyl-Δ^1-piperideine with benzoyl chloride and aqueous sodium hydroxide gave the benzoyl derivative, crystallising from ether–light petroleum (b. p. 40—60°) in needles, m. p. 74—76° (lit.,[21] 75—76°).

2-Methyl-Δ^1-piperideine (1·06 g., 14%) was obtained from ethyl acetoacetate (10·5 g.) by the method of Gabriel,[12] and gave a picrolonate, m. p. 204—206°, and a benzoyl derivative, m. p. 74—75°. Both m. p.s were undepressed on admixture with authentic samples.

(*b*) Reaction of 1-chloro-2,6-dimethylpiperidine (9·0 g.) with alkali as described in (*a*) gave *2,6-dimethyl-Δ^1-piperideine* as a yellow oil (3·6 g., 54%), b. p. 38—42°/66 mm., n_D^{19} 1·4570 (Found: C, 73·0; H, 11·1. $C_7H_{13}N$ requires C, 75·7; H, 11·7%). The *picrolonate* separated from ethanol in yellow plates, m. p. 179—181° (Found: C, 54·4; H, 5·5. $C_{17}H_{21}N_5O_5$ requires C, 54·4; H, 5·6%). The *benzoyl derivative* crystallised from ether–light petroleum (b. p. 40—60°) in needles, m. p. 85—87° (Found: C, 72·4; H, 8·1; N, 6·1. $C_{14}H_{19}NO_2$ requires C, 72·1; H, 8·2; N, 6·0%).

(*c*) 2-n-Propyl-Δ^1-piperideine (86%), b. p. 84—85°/36 mm., n_D^{18} 1·4610 (lit.,[6] b. p. 54—64°/18 mm., n_D^{16} 1·4661) (Found: C, 76·1; H, 12·4; N, 11·1. Calc. for $C_8H_{15}N$: C, 76·7; H, 12·1; N, 11·2%), was prepared from 1-chloro-2-n-propylpiperidine as described for the 2-methyl analogue. The picrolonate had m. p. 141° (lit.,[6] 141°) and the benzoyl derivative had m. p. 58—59°. The latter had been prepared and characterised previously,[22] but the m. p. was not reported. The piperidine was prepared by Gabriel's method [2] in 6% yield, and gave a picrolonate, m. p. and mixed m. p. 141°, and a benzoyl derivative, m. p. and mixed m. p. 57—59°.

(*d*) Reaction of 2-n-butyl-1-chloropiperidine [20] (3·38 g.) with alkali as described in (*a*) gave *2-n-butyl-Δ^1-piperideine* as a yellow oil (1·71 g., 64%), b. p. 50°/3·5 mm., n_D^{20} 1·4618 (Found: C, 76·7; H, 11·2. $C_9H_{17}N$ requires C, 77·6; H, 12·2%). The *picrolonate* crystallised from

[18] Thomas and Baker, *J. Pharm. Pharmacol.*, 1960, **12**, 466.
[19] Clemo, Ramage, and Raper, *J.*, 1932, 2959.
[20] Grundon and Reynolds, *J.*, 1963, 3898.
[21] Lipp, *Annalen*, 1896, **289**, 173.
[22] von Braun and Steindorff, *Ber.*, 1905, 3094.

ethanol in yellow needles, m. p. 122—123° (Found: C, 56·6; H, 6·1. $C_{19}H_{25}N_5O_5$ requires C, 56·6; H, 6·3%). The *benzoyl derivative* separated from ether in needles, m. p. 55—56° (Found: C, 73·2; H, 8·7; N, 5·2. $C_{16}H_{23}NO_2$ requires C, 73·5; H, 8·9; N, 5·4%).

(*e*) By the method described previously,[20] 2-t-butylpiperidine (4·03 g.) was converted into the crude 1-chloro-derivative, b. p. 40—42°/0·1 mm. Reaction of the latter with alkali as described in (*a*) furnished 2-*t-butyl*-Δ^1-*piperideine* (2·04 g., 51%), b. p. 22°/1·4 mm., n_D^{19} 1·4632 (Found: C, 77·6; H, 12·3. $C_9H_{17}N$ requires C, 77·7; H, 12·2%). The *picrolonate* crystallised from ethanol in yellow plates, m. p. 199—201° (Found: C, 56·7; H, 6·3. $C_{19}H_{25}N_5O_5$ requires C, 56·6; H, 6·3%).

(*f*) Treatment of 1-chloro-3-methylpiperidine and of 1-chloro-4-methylpiperidine with alkali gave no product with b. p. <70°/4 mm. The 4-methyl-derivative furnished a *trimer*, b. p. 70—80°/4 mm., n_D^{19} 1·5018 (Found: C, 74·1; H, 11·3; *M* (mass spectroscopy), 291. $C_{18}H_{33}N_3$ requires C, 74·2; H, 11·3%; *M*, 291).

Reaction of Piperidines with Mercuric Acetate.—A solution of the piperidine (4—5 g.) and mercuric acetate (4 mol.) in 10% aqueous acetic acid (200 c.c.) was refluxed for 20 hr. After removal of mercurous acetate by filtration, the filtrate was saturated with hydrogen sulphide and filtered. The filtrate was acidified with hydrochloric acid, concentrated to 50 c.c., made basic with potassium hydroxide, and extracted continuously with ether for 12 hr. The ether was evaporated and a small portion of the residue was analysed by vapour-phase chromatography (see below). The bulk of the product, in ethanol, was treated with an excess of picrolonic acid, and the resultant precipitate was fractionally crystallised from methanol or water. The products from 2-methyl-, 2,6-dimethyl-, 2-n-propyl-, and 2-n-butyl-piperidine gave the picrolonates of the piperidines and of the corresponding Δ^1-piperideines, identical (mixed m. p.) with authentic samples; in each case the piperidine picrolonate was less soluble than the Δ^1-piperideine picrolonate. The products from 3- and 4-methylpiperidine gave single picrolonates identical with those of the starting materials. The product (75%) from 2-t-butylpiperidine was identical (infrared) with an authentic sample of 2-t-butylpiperideine, and gave a high yield of a picrolonate, m. p. 199—202°, undepressed on admixture with 2-t-butyl-Δ^1-piperideine picrolonate.

The crude products were submitted to vapour-phase chromatography [6 ft. column; 12% silicone oil on Celite (80—120 mesh); carrier gas N_2 (2 l. per hr.)]. The products from 2-methyl-, 2,6-dimethyl-, 2-n-propyl-, and 2-n-butyl-piperidine gave two peaks having the retention times of the piperidine and the Δ^1-piperideine, respectively. The products from 3- and 4-methylpiperidine contained polymers, and at the temperature of the chromatograms gave single peaks having the retention times of the starting materials. Other evidence (see above) suggested that the product from 2-t-butylpiperidine was homogeneous, but this could not be confirmed by vapour-phase chromatography because a mixture of authentic 2-t-butylpiperidine and the corresponding piperideine gave a single peak.

The compositions of the products were estimated by integration of the piperidine peak in relation to an internal standard giving a similar peak shape. The error was *ca.* ±2% (Table 2).

Reaction of piperidine with mercuric acetate, and distillation of the product gave first

TABLE 2.

Vapour-phase chromatography of the products of the reaction of piperidines with mercuric acetate.

Piperidine	Total recovery (%)	Internal standard	Temp.	Retention times (min.) Piperidine	Piperideine	Piperidine (%)	Piperideine (%)
2-Methyl-	48	Toluene	64°	8	16	36	64
3-Methyl-	51	,,	64	11	—	31	—
4-Methyl-	64	,,	60	14	—	47	—
2,6-Dimethyl-	63	,,	64	11	18	27	73
2-n-Propyl- ...	49	2-Ethylpiperidine	86	18	23	14	86
2-n-Butyl-	48	,,	86	27	32	34	66

piperidine, b. p. 40°/50 mm. [picrolonate, m. p. and mixed m. p. 243—245° (lit.,[13] 243°)], and then a fraction, b. p. 140—148°/8·5 mm., which solidified. Crystallisation from acetone–light petroleum (b. p. 40—60°) gave needles, m. p. 98—100°, $\nu_{max.}$ 3250 cm.$^{-1}$ (NH) (Found: C, 72·2; H, 10·9; N, 17·3. Calc. for $C_{15}H_{27}N_3$: C, 72·2; H, 10·9; N, 16·9%). This was identical

(mixed m. p. and infrared) with a sample of isotripiperideine, m. p. 98—100° (lit.,[13] 97—98°), prepared from 1-chloropiperidine.

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