450. *Stereochemical Investigations of Cyclic Bases. Part II.* Hofmann Degradation of Some Cyclic Quaternary Ammonium Salts.*

By K. JEWERS and J. McKENNA.

The factors are reviewed which influence Hofmann degradation of quaternary ammonium salts, particularly in cyclic systems. An examination of the degradation of piperidinium-1-*spiro*-1′-pyrrolidinium hydroxide indicates that the olefin-forming elimination can involve either ring with about equal ease, but that the alternative nucleophilic replacement preferentially opens the pyrrolidine ring. Hofmann elimination of 2 : 2′-dimethylpiperidinium-1-*spiro*-1′-pyrrolidinium hydroxide, *cyclo*hexyldimethyl*cyclo*pentylammonium hydroxide, and (*cyclo*hexylmethyl)dimethyl(*cyclo*pentylmethyl)ammonium hydroxide proceeds mainly in one direction in each case, yielding respectively 2-methyl-1-pent-4′-enylpiperidine, *cyclo*pentene (with *N*-*cyclo*hexyldimethylamine), and methylene*cyclo*hexane [with dimethyl(*cyclo*pentylmethyl)amine].

HOFMANN degradation of quaternary ammonium hydroxides has been extensively investigated, particularly by Ingold and his collaborators[1] who concluded that in a bimolecular Hofmann elimination the tendency, because of hyperconjugation, for the most highly alkylated olefin to be formed (Saytzeff rule) is effectively opposed by the reduction in acidity of hydrogen atoms caused by increasing alkylation at the carbon atoms carrying them, owing to electron repulsion by the alkyl groups in the electrical field of the quaternary ammonium pole. Degradation of the ammonium hydroxide (I; R, R′, R″, and R‴ = alkyl), for example, would lead to preferential anion-attack at a methyl rather than at a methylene or methine hydrogen atom. This theory would in general predict formation of the " least substituted olefin " (Hofmann rule †) on degradation of quaternary ammonium salts, but a " least substituted olefin " does not always arise from anion-attack on a hydrogen atom attached to the least alkylated carbon β to the quaternary nitrogen atom; furthermore, it would be illogical to interpret, for example, the observed[2] degradation of *cis*- and *trans*-decahydro-1-methylquinoline methohydroxides

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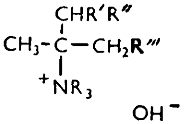
* Part I, *J.*, 1956, 573. A preliminary note on Hofmann fission of heterocyclic bases was published in *Chem. and Ind.*, 1954, 406. Dr. F. E. King's statement made in *J.*, 1954, 3798, footnote, does not accord with my recollection of events or with my interpretation of the facts. J. McK.

† The Hofmann rule in the strictest sense applies to quaternary ammonium salts containing only primary alkyl groups.

[1] For summary see the chapter on " Olefin-forming Eliminations " in Ingold, " Structure and Mechanism in Organic Chemistry," Bell, London, 1953.

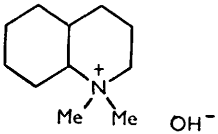
[2] Bailey, Haworth, and McKenna, *J.*, 1954, 967.

(II) to the corresponding 2-allyl*cyclo*hexyldimethylamines (III) by reference to the fact that the unsaturated amines are the " least substituted olefins."



$CH_3-\overset{CHR'R''}{\underset{+NR_3}{C}}-CH_2R'''$ OH^-

(I)



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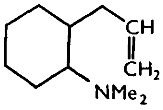
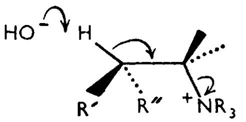


(III)

Ingold's interpretation of the departure from Saytzeff elimination observed with quaternary ammonium salts is not accepted by H. C. Brown and his collaborators,[3] who have suggested that steric interaction between the bulky $^+NR_3$ group and groups R′, R″ in the intermediate complex (IV; R, R′, R″ = alkyl) explains the observed direction of elimination, since the steric interaction is smaller if R′ or R″ (or both) is hydrogen. Whatever the relative merits of Ingold's and Brown's interpretation of the results summarised by the Hofmann rule in the acyclic series, a detailed conformational approach is in general required for discussion of the reaction in alicyclic and reduced heterocyclic systems. Relevant well-recognised factors are the normal preference in the transition state for a coplanar *trans*-arrangement of the groups being eliminated and the intervening carbon atoms (as in IV, for example) and the normal greater difficulty of introducing a double bond in a position *endo* or *exo* in relation to a six- rather than a five-membered ring.[4] Double bonds in different positions in the same ring (or in different rings of the same size) in polycyclic systems may also vary considerably in stability.[5] A minor point is that the statistical probabilities of elimination of a methyl, methylene, or methine hydrogen in (I) are altered if the methylene and methine carbon atoms are included in a small ring system, owing to diminished possibilities of free rotation. A further factor of potential importance in Hofmann degradation of some cyclic quaternary salts is the possibility of formation of a thermodynamically more stable methine, irrespective of opposing kinetic factors which may control the primary reaction, by repeated recyclisation [6] of the primary methine followed by further ring fission or by other secondary changes.[7] This particular aspect is not considered further in the present paper, where the methines derived by pyrolysis of four selected quaternary ammonium hydroxides in all cases appear to be the primary products.



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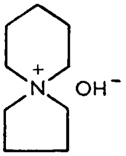

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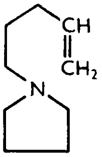

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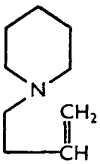

(VII)

The pyrolysis of piperidinium-1-*spiro*-1′-pyrrolidinium hydroxide (V) was described by von Braun,[8] who obtained a monounsaturated product, $C_9H_{17}N$, b. p. 176—180°, together with a higher-boiling fraction identified as 1-4′-hydroxybutylpiperidine (IX). The unsaturated fraction was thought to be a mixture of 1-pent-4′-enylpyrrolidine (VI) and 1-but-3′-enylpiperidine (VII), and hydrogenation followed by fractional distillation yielded some 1-pentylpyrrolidine. Repetition of this pyrolysis yielded lower- and higher-boiling products analysing respectively as $C_9H_{17}N$ and $C_{18}H_{36}ON_2$. Of these the first

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[3] Brown and Moritani, *J. Amer. Chem. Soc.*, 1956, **78**, 2203, and immediately preceding papers by Brown and his collaborators.

[4] Weinstock, Pearson, and Bordwell, *ibid.*, 1956, **78**, 3468; cf. ref. 17.

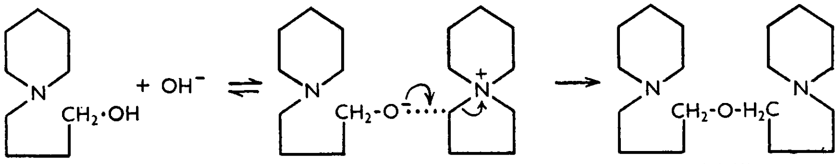
[5] Cf. Turner, Meador, and Winkler, *ibid.*, 1957, **79**, 4122.

[6] Favre, Haworth, McKenna, Powell, and Whitfield, *J.*, 1953, 1115.

[7] *Inter al.*, Weinstock, *J. Org. Chem.*, 1956, **21**, 540.

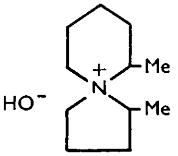
[8] von Braun, *Ber.*, 1916, **49**, 2629.

evidently corresponds to von Braun's mixture of unsaturated amines, but the second appeared to be the basic ether (VIII) rather than the alcohol (IX). Such ethers have often been encountered in Hofmann pyrolysis mixtures, and (VIII) could arise from (IX) by further reaction as shown. The constitution of the ether (VIII) was confirmed by fission with hydrobromic acid to 1-4'-bromobutylpiperidine hydrobromide. No isomeric hydrobromide was isolated, and this result, together with von Braun's (and, less specifically, with the numerous examples in the literature of similar pyrrolidine ring fission), indicates that the pyrrolidine is more easily opened than the piperidine ring in this type of displacement reaction. In the strongly alkaline medium the reaction is probably synchronous, involving the anion in the rate-determining step, but, irrespective of mechanism, the readier fission of the five-membered ring appears (as in many similar cases) to be related to the ease with which the energetically unfavourable bond oppositions in pyrrolidine can be disturbed; piperidine, like *cyclo*hexane, can be written in a chair conformation with a fully staggered arrangement of carbon–hydrogen bonds.

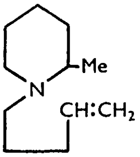


(IX) (VIII)

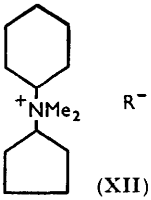
The unsaturated basic mixture, $C_9H_{17}N$, from the pyrolysis did not appear to undergo cyclisation in hot glacial acetic acid as do[2] other methines, *e.g.*, (III), stereochemically more suitable for such cyclisation. For determination of the ratio of (VI) to (VII), the methine fraction was converted by hydrogenation and methylation into a mixture of 1-pentylpyrrolidine and 1-butylpiperidine methiodides, chromatographic examination of which indicated that the salts were present in equal proportion. The equal ease of fission of the piperidine and the pyrrolidine rings in the olefin-forming decomposition of the *spiro*-quaternary ammonium salt appears to be related to the considerations that the *trans*-coplanar type of intermediate complex (*i.e.*, H–C–C–N^+ coplanar, with H and N^+ *trans*) is possible for the piperidine, but not for the pyrrolidine ring fission, but that, contrariwise, the five-membered pyrrolidine ring with its unfavourable bond oppositions has a greater inherent tendency towards intermediate complex formation if conformational strain is thereby reduced. These two factors are also considered by Weinstock *et al.* in their discussion[4] of the relative ease of *trans*-elimination from *cyclo*pentane and *cyclo*hexane ring systems, with formation of the cyclic olefins; in these eliminations (where the rings are *not* simultaneously broken in the reactions), the two factors do not appear to balance and *cyclo*pentenes are more readily formed.



(X)



(XI)



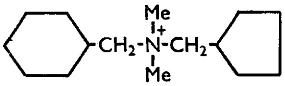
(XII)

The next base pyrolysed was (X), the 2 : 2'-dimethyl homologue of (V); this structure corresponds to four racemic forms (with varying degrees of internal strain) but the product obtained by condensation of 2-methylpiperidine with 1 : 4-dibromopentane appeared homogeneous; the actual stereochemical structure or homogeneity of our spiran is of little consequence, however, in considerations of its Hofmann fission. When the quaternary hydroxide was pyrolysed no basic alcohol or ether was formed, but an unsaturated base

$C_{11}H_{21}N$ was obtained, identified as 2-methyl-1-pent-4′-enylpiperidine (XI) by (*a*) hydrogenation to 2-methyl-1-pentylpiperidine (the methiodide of which, like that of the unsaturated base, was chromatographically homogeneous), (*b*) the infrared spectrum, with bands at 905 and 992 cm.$^{-1}$ ($-CH=CH_2$),[9] and (*c*) analogy with the pyrolysis of 1 : 2-dimethylpyrrolidinium methohydroxide, which yields dimethylpent-4′-enylamine.[10] The greater ease of fission of the pyrrolidine ring is illustrated by this pyrolysis; in this case the favoured *trans*-coplanar type of intermediate complex can arise by anion-attack on a hydrogen atom forming part of the pyrrolidine methyl (or of the piperidine methyl or appropriate methylene) but not of a pyrrolidine methylene group. The observed fission should therefore occur more readily than *either* olefin-forming fission observed with the quaternary hydroxide (V). The lack of formation of a basic alcohol or ether on pyrolysis of the hydroxide (X) is in agreement with this reasoning, since hydroxyl attack on the β-methylene carbon atom in the pyrrolidine ring of (X) should take place with about the same ease as the reaction leading ultimately to the basic ether (VIII).

Preliminary attempts to synthesise *cyclo*hexyldimethyl*cyclo*pentylammonium bromide (XII; R = Br) by reaction of *cyclo*pentyl bromide with *cyclo*hexyldimethylamine resulted only in elimination of hydrogen bromide from the *cyclo*pentyl bromide, which has been shown, however, to undergo condensation as well as elimination with aniline and piperidine.[11] *cyclo*Hexyl bromide reacted in a similar manner. *cyclo*Hexylmethyl*cyclo*pentylamine was synthesised by a method analogous to that used for related amines by Norton and his collaborators:[12] the ketimine derived from *cyclo*pentylamine and *cyclo*hexanone was reduced with hydrogen in presence of Raney nickel, and the resultant secondary base methylated with formaldehyde and formic acid. Pyrolysis of the related quaternary ammonium hydroxide (XII; R = OH) yielded almost exclusively *cyclo*pentene and *cyclo*hexyldimethylamine (the base from the reaction mixture was shown by vapour-phase chromatography to contain about 5% of dimethyl*cyclo*pentylamine). The bulky quaternary ammonium group is clearly attached to the *cyclo*hexane ring by an equatorial link, so that the geometry of the molecule does not favour formation of *cyclo*hexene by *trans*-elimination.[13]

We also examined the pyrolysis of (*cyclo*hexylmethyl)dimethyl(*cyclo*pentylmethyl)-ammonium hydroxide (XIII; R = OH). Methyl*cyclo*pentylamine was prepared by a modification of a previous method;[14] in addition, generous supplies of the amine and its *N*-benzoyl derivative were kindly given to us by Imperial Chemical Industries Limited, Dyestuffs Division, Blackley, Manchester, whom we thank also for helpful advice on the preparation and characterisation of the amine. Condensation of the base with *cyclo*hexanecarbonyl chloride, and reduction of the resulting amide with lithium aluminium hydride gave (*cyclo*hexylmethyl)(*cyclo*pentylmethyl)amine, from which the ammonium salt (XIII; R = I) was prepared by methylation with formaldehyde and formic acid followed by reaction of the product with methyl iodide.



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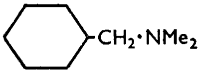
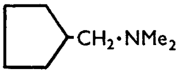


(XIV)



(XV)

Pyrolysis of the quaternary hydroxide gave basic and neutral products. Fractional distillation of the former yielded (*cyclo*hexylmethyl)methyl(*cyclo*pentylmethyl)amine and a smaller lower-boiling fraction from which pure samples of only dimethyl(*cyclo*pentylmethyl)amine picrate or methiodide were obtained on fractional crystallisation of

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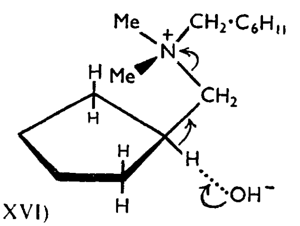
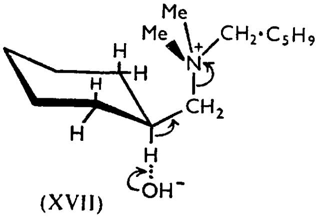
[9] Bellamy, " The Infra-Red Spectra of Complex Molecules," Methuen, London, 1954, p. 31.
[10] Ladenburg, Mugdan, and Brzostovicz, *Annalen*, 1893, **279**, 344.
[11] Loevenich, Utsch, Moldrickx, and Schaefer, *Ber.*, 1929, **62**, 3084.
[12] Norton, Haury, Davis, Mitchell, and Ballard, *J. Org. Chem.*, 1954, **19**, 1054.
[13] Cf. Haworth, McKenna, and Powell, *J.*, 1953, 1110; Gent and McKenna, *J.*, 1956, 573.
[14] von Braun and Anton, *Ber.*, 1933, **66**, 1374.

the crude salts. Vapour-phase chromatography of the unfractionated basic product from the Hofmann decomposition showed, however (by comparison of the results with those obtained with synthetic mixtures), that (*cyclo*hexylmethyl)dimethylamine (XIV) was present along with the dimethyl(*cyclo*pentylmethyl)amine (XV) in the molar ratio of *ca.* 1 : 2. After ozonolysis of the hydrocarbon fraction from the degradation, only *cyclo*hexanone was identified (as 2 : 4-dinitrophenylhydrazone); this is clearly derived from methylene*cyclo*hexane, but vapour-phase chromatography showed the presence in the hydrocarbon fraction of a smaller proportion of a more easily eluted (probably more volatile) component, in agreement with the complementary results of the analysis of the basic fraction. We did not have samples of methylene*cyclo*pentane and methylene*cyclo*hexane for comparative chromatograms, but the more volatile component is obviously mainly the former hydrocarbon, although the recent work of Cope and his collaborators [15] on Hofmann degradation of the methohydroxides of (XIV), (XV), and related compounds suggests that the hydrocarbon mixture may have contained also a little 1-methyl*cyclo*pentene. It is clear, however, that the most important mode of olefin-forming decomposition of the quaternary hydroxide (XIII; R = OH) is fission between the quaternary nitrogen atom and the *cyclo*hexylmethyl group, and this result accords with the American authors' work which shows that degradation of the methohydroxide of (XIV) to methylene-*cyclo*hexane is smoother than the analogous decomposition of the methohydroxide of (XV).

It is of interest to consider the observed pyrolysis of (*cyclo*hexylmethyl)dimethyl-(*cyclo*pentylmethyl)ammonium hydroxide from the standpoint of a generalisation proposed in 1954 by H. C. Brown and his collaborators [16] regarding the relative ease of introduction of a double bond into a position *exo* to a six- or a five-membered reduced ring; after some criticism and misunderstanding the following revised statement was recently [17] given by Brown. " Double bonds which are *exo* to a 5-ring are less reactive and more stable (relative to the saturated derivatives) than related double bonds which are *exo* to a 6-ring. Reactions which involve the formation or retention of an *exo* double bond in a 5-ring derivative will be favoured over corresponding reactions which involve the formation or retention of an *exo* double bond in a 6-ring derivative. Reactions which involve the loss of an *exo* double bond will be favoured in the 6-ring as compared to the corresponding 5-ring derivative." This generalisation correlates a wide range of observations, and is in accord with the recently determined [18] heats of hydrogenation of methylene*cyclo*pentane and methylene*cyclo*hexane. Since methylene*cyclo*hexane, however, is preferentially formed on pyrolysis of (*cyclo*hexylmethyl)dimethyl(*cyclo*pentylmethyl)ammonium hydroxide, the second sentence in Brown's statement must be regarded only as one factor which can affect the course of a reaction but which may be offset by others. The observed preferential course of the pyrolysis is probably due to the hindrance arising between the quaternary ammonium group and the *cis*-hydrogen atoms attached to adjacent *cyclo*pentane carbon atoms in the intermediate complex (XVI) if the usual *trans*-coplanarity requirement of H–C–C–N$^+$ is met; the hindrance is less in the intermediate complex



(XVI)



(XVII)

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[15] Cope, Bumgardner, and Schweizer, *J. Amer. Chem. Soc.*, 1957, **79**, 4729.
[16] Brown, Brewster, and Shechter, *ibid.*, 1954, **76**, 467.
[17] Brown, *J. Org. Chem.*, 1957, **22**, 439.
[18] Turner and Garner, *J. Amer. Chem. Soc.*, 1957, **79**, 253.

(XVII) leading to methylene*cyclo*hexane formation, since the bulky group which includes the quaternary nitrogen is expected to be equatorial. The transition states are here pictured with geometries resembling those of the reactants[3] (as also in formula IV), but the moderate proportion of fission products formed in accordance with Brown's rule [*i.e.*, methylene*cyclo*pentane and (*cyclo*hexylmethyl)dimethylamine] affords an indication of the degrees to which the double bonds have developed.[19] The formation of 2-methyl-1-pent-4′-enylpiperidine (XI) rather than 1-hex-5′-enyl-2-methylpyrrolidine on pyrolysis of the ammonium hydroxide (X) may be regarded as an example of the Brown rule, the incipient double bond being formed *exo* to the partly opened 5-ring rather than the partly opened 6-ring.

Degradation of some fused polycyclic quaternary ammonium hydroxides will be considered in later publications.

EXPERIMENTAL

Degradation of Piperidinium-1-spiro-1′-*pyrrolidinium Hydroxide*.—The appropriate quaternary bromide[20] (7·9 g.) was converted into the hydroxide by the silver oxide method, and this was heated at 140° (bath) for 0·5 hr. during which decomposition occurred and some volatile base distilled. Distillation was completed by raising the temperature. The distillate and still-residue, on extraction with ether, yielded a product (3·8 g.) from which by fractional distillation were obtained a fraction (1·8 g.), b. p. 170—180° (bath), unsaturated to acid permanganate (Found: C, 77·3; H, 11·7; N, 9·7. Calc. for $C_9H_{17}N$: C, 77·7; H, 12·2; N, 10·1%), and *di*-(4-*piperidinobutyl*) *ether* (VIII) (0·9 g.), b. p. 80—100° (bath)/0·6 mm. (Found: N, 9·7. $C_{18}H_{36}ON_2$ requires N, 9·5%), characterised as the *picrate*, yellow needles (from ethanol), m. p. 188° (Found: C, 48·1; H, 5·9; N, 14·9. $C_{30}H_{42}O_{15}N_8$ requires C, 47·7; H, 5·6; N, 14·9%). The still-residue contained some undecomposed quaternary hydroxide, isolated as picrate[21] (230 mg.), m. p. 232°.

Examination of the Basic Fraction, $C_9H_{17}N$.—When the base (128 mg.) was refluxed in acetic acid (10 c.c.) for 2·5 hr. no quaternary salt was isolated but the original base (116 mg.) was recovered. Attempted fractional crystallisation of the mixed picrates, m. p. 102—107° (Found: C, 49·0; H, 5·3; N, 15·0. Calc. for $C_{15}H_{20}O_7N_4$: C, 48·9; H, 5·5; N, 15·2%), was unsuccessful. Hydrogenation of the base (527 mg.) in ethanol (10 c.c.) in presence of 10% palladium-charcoal (460 mg.) was complete in 1 hr.; the mixture of saturated bases, b. p. 170—180° (bath) (Found: C, 76·6; H, 13·8; N, 9·7. Calc. for $C_9H_{19}N$: C, 76·6; H, 13·5; N, 9·9%), yielded a mixture of methiodides, m. p. 164—166°.

Analysis of the Methiodide Mixture, m. p. 164—166°.—From 1-*n*-butylpiperidine,[22, 23] b. p. 176°, were obtained samples of methiodide, m. p. 198° (von Braun[23] gives m. p. 199°), *picrolonate*, yellow needles (from ethanol), m. p. 161° (Found: C, 56·2; H, 6·9; N, 17·1. $C_{19}H_{27}O_5N_5$ requires C, 56·3; H, 6·7; N, 17·3%), and p-*azobenzenebenzylobromide*, orange solid, m. p. 188—190° (Found: N, 9·8; Br, 19·4. $C_{22}H_{30}N_3Br$ requires N, 10·1; Br, 19·2%). 1-*n*-Pentylpyrrolidine, b. p. 176°, yielded a methiodide, m. p. 173° (von Braun[8] gives m. p. 169—170°), a *picrolonate*, yellow needles (from ethanol), m. p. 140° (Found: C, 56·2; H, 6·7; N, 17·1. $C_{19}H_{27}O_5N_5$ requires C, 56·3; H, 6·7; N, 17·3%), and an orange p-*azobenzenebenzylobromide*, m. p. 140° (Found: N, 9·9; Br, 19·3. $C_{22}H_{30}N_3Br$ requires N, 10·1; Br, 19·2%).

The observed variation of melting range with composition for mixtures of the methiodides of 1-*n*-butylpiperidine and 1-*n*-pentylpyrrolidine was:

1-*n*-Pentylpyrrolidine methiodide (%)	90	75	60	50	40	30
Melting range	166—173°	166—171°	166—170°	164—166°	165—175°	165—180°

Methanol solutions (6 mg./c.c.) were prepared of the methiodide mixture, m. p. 164—166°, from the degradation, and of "synthetic" mixtures of 1-*n*-butylpiperidine and 1-*n*-pentylpyrrolidine methiodides in ratios 1 : 1, 1 : 2, and 2 : 1. Spots of these solutions were placed

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[19] Cf. Cram, Greene, and Depuy, *J. Amer. Chem. Soc.*, 1956, **78**, 790.
[20] von Braun, *Ber.*, 1916, **49**, 966.
[21] Albert, *Ber.*, 1909, **42**, 545.
[22] von Braun, *Ber.*, 1907, **40**, 3914.
[23] *Idem, Ber.*, 1909, **42**, 2532.

on sheets of Whatman's No. 1 filter paper, and the chromatogram developed (upward flow) for 24 hr. with butan-1-ol saturated with water. After being dried, the paper was sprayed with a silver nitrate–dichlorofluorescein solution to mark the position of the methiodide spots. 1-*n*-Butylpiperidine methiodide had R_F 0·51 and 1-*n*-pentylpyrrolidine methiodide had R_F 0·60. The reduced methiodide mixture from the degradation gave a chromatogram similar to that obtained from the 1 : 1 " synthetic " mixture and different from either of the other two. Only partial separation of the *p*-azobenzenebenzylobromides of the saturated amines could be achieved by paper chromatography using *cyclo*hexane–propan-2-ol–acetic acid for development.

Fission of the Base $C_{18}H_{36}ON_2$.—The base (154 mg.) was refluxed with concentrated hydrobromic acid (10 c.c.) for 2 hr., the acid was removed *in vacuo*, and the residue was washed with ether and crystallised from acetone–ether, yielding leaflets of 1-4′-bromobutylpiperidine hydrobromide [21] (207 mg.), m. p. 162° (Found: C, 35·4; H, 6·1; N, 4·6. Calc. for $C_9H_{19}NBr_2$: C, 35·9; H, 6·4; N, 4·7%).

Hofmann Degradation of 2 : 2′-*Dimethylpiperidinium*-1-spiro-1′-*pyrrolidinium Hydroxide*.—1 : 4-Dibromopentane (6·9 g.), 2-methylpiperidine (3 g.), sodium hydroxide (1·2 g.), and water (45 c.c.) were heated together on a steam-bath for 2 hr. with frequent shaking. The mixture was cooled, and the quaternary bromide was precipitated by addition of 10N-sodium hydroxide (60 c.c.) and extracted with chloroform, from which it was precipitated by ether as a hygroscopic solid, m. p. 74°. Addition of ethanolic picric acid to an aqueous solution of the quaternary hydroxide, prepared in the usual way (Ag_2O), gave 2 : 2′-*dimethylpiperidinium*-1-spiro-1′-*pyrrolidinium picrate*, yellow needles (from ethanol), m. p. 249—251° (Found: C, 51·9; H, 6·3; N, 14·3. $C_{17}H_{24}O_7N_4$ requires C, 51·5; H, 6·1; N, 14·1%). An aqueous solution of quaternary hydroxide derived from quaternary bromide (6·9 g.) was evaporated, the residue was decomposed in a bath maintained at 140°, and the volatile products were distilled. Extraction of the distillate and still-residue with ether gave 2-*methyl*-1-*pent*-4′-*enylpiperidine* (3·65 g.), b. p. 200° (bath) (Found: N, 8·2. $C_{11}H_{21}N$ requires N, 8·4%), characterised as the *picrate*, yellow needles (from ethanol), m. p. 72—73° (Found: C, 51·6; H, 6·2; N, 14·4. $C_{17}H_{24}O_7N_4$ requires C, 51·5; H, 6·1; N, 14·1%). Extraction of the still-residue with ethanol gave a little of the original quaternary hydroxide characterised as the picrate, m. p. 249—251°. No quaternary salt was isolated when the unsaturated base (110 mg.) was refluxed in glacial acetic acid (5 c.c.) for 4 hr.; the recovered base (107 mg.) was identified by conversion into the picrate. Hydrogenation of the unsaturated base (525 mg.) in ethanol (10 c.c.) in presence of 10% palladium–charcoal (278 mg.) was complete in 1 hr.; the resulting 2-*methyl*-1-*pentylpiperidine* had b. p. 200° (bath) (Found: C, 78·2; H, 13·9; N, 8·2. $C_{11}H_{23}N$ requires C, 78·0; H, 13·6; N, 8·3%) and yielded a *methiodide*, prismatic needles (from acetone), m. p. 196—198° (Found: C, 46·2; H, 8·2; N, 4·5. $C_{12}H_{26}NI$ requires C, 46·3; H, 8·4; N, 4·5%) undepressed with a specimen prepared as described below.

2-*Methyl*-1-*pentylpiperidine*.—2-Methylpiperidine (5 g.), *n*-pentyl bromide (9 g.), and potassium hydroxide (5 g.) were heated together in a sealed tube at 125° for 24 hr. After being cooled, the mixture was acidified, and excess of pentyl bromide was extracted with ether. The base, recovered from the acid solution, had b. p. 206° (Found: C, 78·5; H, 13·7; N, 8·2. Calc. for $C_{11}H_{23}N$: C, 78·0; H, 13·6; N, 8·3%); the methiodide (Found: C, 46·2; H, 8·3; N, 4·5. Calc. for $C_{12}H_{26}NI$: C, 46·3; H, 8·4; N, 4·5%) had m. p. 196—198°. The tertiary base, b. p. 92—93°/16 mm., has been prepared previously by a different method.[24]

1-n-*Hexyl*-2-*methylpyrrolidine*.—A mixture of 1 : 4-dibromopentane (6 g.), *n*-hexylamine (7·8 g.), and ethanol (50 c.c.) was refluxed for 5 hr., acidified with hydrochloric acid, and evaporated to dryness. The residue was treated with benzoyl chloride and excess of sodium hydroxide solution to remove primary or secondary amines; the residual 1-n-*hexyl*-2-*methylpyrrolidine* had b. p. 202—204° (Found: C, 77·6; H, 13·8; N, 8·0. $C_{11}H_{23}N$ requires C, 78·0; H, 13·6; N, 8·3%) and yielded a *methiodide*, plates (from acetone–ether), m. p. 130—131° (Found: C, 46·7; H, 8·4; N, 4·6; I, 40·3. $C_{12}H_{26}NI$ requires C, 46·3; H, 8·4; N, 4·5; I, 40·8%).

Preparation of cyclo*Hexyldimethyl*cyclo*pentylammonium Iodide*.—*cyclo*Pentanone (50 g.) and *cyclo*hexylamine (59 g.) were refluxed in dry benzene (100 c.c.) in an apparatus with a phase-separation head until, after 24 hr., water (11 c.c.) had separated. The resulting ketimine (65·6 g.), b. p. 110—115°/15 mm., was freed from unchanged more volatile reactants and hydrogenated at 150°/50 atm. in presence of Raney nickel (5 g.). The product was fractionally distilled to separate traces of hydrogenolysis products, and the cyclo*hexyl*cyclo*pentylamine*

[24] Paden and Adkins, *J. Amer. Chem. Soc.*, 1936, **58**, 2487.

(52 g.), b. p. 118—120°/17 mm. (Found: N, 8·1. $C_{11}H_{21}N$ requires N, 8·4%), was methylated on the steam-bath for 4 hr. with 90% formic acid (87 g.) and 40% aqueous formaldehyde (30 g.). The resulting tertiary base (47 g.) was converted with methyl iodide into cyclo*hexyldimethyl*cyclo*pentylammonium iodide*, which was obtained as needles, m. p. 221—222°, from acetone (Found: C, 47·7; H, 8·1; N, 4·4; I, 39·4. $C_{13}H_{26}NI$ requires C, 48·3; H, 8·1; N, 4·3; I, 39·3%).

Hofmann Degradation of cyclo*Hexyldimethyl*cyclo*pentylammonium Hydroxide*.—The aqueous quaternary hydroxide solution from the above iodide (6 g.) was concentrated to small volume and kept at 140° in a distillation apparatus fitted with a cold trap (solid carbon dioxide) for 0·5 hr., during which decomposition took place. The temperature was then slowly increased until all volatile products had distilled, and the distillate was separated into a neutral (0·75 g.) and a basic (2·02 g.) fraction. The latter had b. p. 164—165° and yielded a picrate, m. p. 176°, and a methiodide, m. p. 260—262°, identified (mixed m. p.) as salts of *cyclo*hexyldimethylamine. Vapour-phase chromatography of the basic fraction on a Celite–silicone column at 107° with a nitrogen flow of 52 c.c. per min. showed (by comparison of the potentiometer record from the katharometer with those derived from control mixtures of the components) that the fraction consisted of *cyclo*hexyldimethylamine (95%; retention time 27·5 min.) and dimethyl*cyclo*pentylamine (5%; retention time 10·0 min.).

The very volatile neutral fraction, after being dried with sodium, had n_D^{25} 1·4230 (lit.:[25] *cyclo*hexene n_D^{25} 1·4438; *cyclo*pentene n_D^{25} 1·4194). Circumstances prevented examination by vapour-phase chromatography, but oxidation of the neutral fraction (0·35 g.) in acetone (50 c.c.) at 20° with finely powdered potassium permanganate (3·5 g.) which was gradually added, with continuous stirring, during 4 hr. gave glutaric acid (384 mg.), m. p. (from benzene) and mixed m. p. 95° (Found: C, 45·4; H, 6·3. Calc. for $C_5H_8O_4$: C, 45·5; H, 6·1%).

(cyclo*Pentylmethyl*)*amine*.—*cyclo*Pentylacetic acid (14·5 g.) was converted with thionyl chloride into the acid chloride (14·8 g.), b. p. 176—178°, which was added to a suspension of sodium azide (7 g.) in dry benzene (150 c.c.), the mixture was refluxed for 20 hr., cooled, and filtered, and the filtrate was refluxed with concentrated hydrochloric acid (60 c.c.) for 2·5 hr. The base (5·5 g.) obtained from the resulting hydrochloride had b. p. 140°, and with ethyl oxalate gave the *oxamide*, needles [from benzene–petroleum (b. p. 60—80°)], m. p. 191° (Found: C, 66·5; H, 9·8; N, 11·5. $C_{14}H_{24}O_2N_2$ requires C, 66·6; H, 9·6; N, 11·1%).

Dimethyl(cyclo*pentylmethyl*)*amine*.—The above primary amine (1·5 g.) was heated on a water-bath for 4 hr. with 90% formic acid (4 g.) and 40% formaldehyde (2·5 g.). The resulting dimethyl(*cyclo*pentylmethyl)amine, b. p. 146°, was characterised as the picrate, m. p. 142° (Found: C, 47·0; H, 5·8; N, 16·0. Calc. for $C_{14}H_{20}O_7N_4$: C, 47·2; H, 5·7; N, 15·7%), and the methiodide, m. p. 200—202° (Found: C, 40·0; H, 7·3; N, 5·3. Calc. for $C_9H_{20}NI$: C, 40·2; H, 7·2; N, 5·2%). Methylation of the primary amine with formaldehyde and dilute formic acid gave a tertiary base with the same properties. Treatment of the tertiary base with benzoyl chloride and alkali did not affect the properties of its derivatives. The methiodide, m. p. 200—202°, was obtained directly from (*cyclo*pentylmethyl)amine by refluxing it (407 mg.) in acetone (50 c.c.) with methyl iodide (3 c.c.) and potassium carbonate (5·6 g.) for 12 hr. This methiodide (0·5 g.) in dry tetrahydrofuran [26] (50 c.c.) was refluxed with lithium aluminium hydride (0·5 g.) for 72 hr. with stirring. The resulting tertiary base (96 mg.) yielded a picrate and a methiodide identical with those described above. This detailed characterisation of dimethyl(*cyclo*pentylmethyl)amine and its derivatives was effected partly because Mousseron and his collaborators have recorded [27] m. p. 168—169° for the picrate of the tertiary base (prepared from *cyclo*pentanealdehyde). After our work had been completed, however, Cope and his collaborators described the preparation of the amine by a different method [15] and gave m. p. 142·8—143·8° for the picrate.

(cyclo*Hexylmethyl*)*methyl*(cyclo*pentylmethyl*)*amine*.—*cyclo*Pentylmethyl)amine (4 g.), *cyclo*hexanecarbonyl chloride (7 g.), and excess of 2N-sodium hydroxide were shaken together for 20 min., and the N-cyclo*hexanecarbonyl*(cyclo*pentylmethyl*)*amine* (8·5 g.) recrystallised from light petroleum (b. p. 40—60°) as needles, m. p. 108—110° (Found: C, 74·3; H, 10·9; N, 6·5. $C_{13}H_{23}ON$ requires C, 74·6; H, 11·1; N, 6·7%). The amide (9·5 g.) was reduced (Soxhlet method) with lithium aluminium hydride (2·8 g.) in ether (500 c.c.) during 10 hr., and the

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[25] Rossini, Mair, and Streiff, "Hydrocarbons from Petroleum," Reinhold, New York, 1953, p. 234.
[26] Cf. Cope and Bumgardner, *J. Amer. Chem. Soc.*, 1957, **79**, 960.
[27] Mousseron, Jacquier, and Zagdoun, *Bull. Soc. chim. France*, 1952, 197.

(*cyclo*hexylmethyl)(*cyclo*pentylmethyl)amine (4·2 g.), b. p. 264—266°, was characterised as the *hydrochloride*, plates (from acetone), m. p. 234—236° (Found: N, 5·8; Cl, 15·0. $C_{13}H_{26}NCl$ requires N, 6·0; Cl, 15·3%), and the *hydrobromide*, plates (from acetone), m. p. 280° (Found: C, 56·5; H, 9·5; N, 4·8. $C_{13}H_{26}NBr$ requires C, 56·5; H, 9·5; N, 5·1%). The secondary base (9·8 g.) on methylation with 40% formaldehyde (9 g.) and 85% formic acid (13·8 g.) for 3 hr. at 100° gave (*cyclo*hexylmethyl)methyl(*cyclo*pentylmethyl)amine (8 g.), b. p. 265—270°, characterised as the *picrate*, yellow needles (from ethanol), m. p. 110—112° (Found: C, 54·6; H, 7·0; N, 12·9. $C_{20}H_{30}O_7N_4$ requires C, 54·8; H, 6·9; N, 12·8%), and the *methiodide*, prismatic needles (from acetone), m. p. 167—168° (Found: C, 51·0; H, 8·5. $C_{15}H_{30}NI$ requires C, 51·3; H, 8·6%).

Hofmann Degradation of (cyclo*Hexylmethyl*)*dimethyl*(cyclo*pentylmethyl*)*ammonium Hydroxide*.—An aqueous solution of methohydroxide derived from methiodide (5·4 g.) was concentrated and decomposed at 140°, and the products were distilled into a receiver fitted with a cold trap. The distillate was separated into a neutral (394 mg.) and a basic (2·17 g.) fraction. The neutral fraction had n_D^{22} 1·4440 (lit.: methylene*cyclo*pentane [28] n_D^{20} 1·4354; methylene*cyclo*hexane [29] n_D^{20} 1·4502). Vapour-phase chromatography of the neutral fraction on a Celite–silicone column at 87°, with a nitrogen flow of 45 c.c. per min., showed two peaks corresponding to retention times of 5 min. 56 sec. and 12 min. 34 sec. respectively; the area of the second peak was approximately twice that of the first. Ozonolysis of the neutral fraction in *n*-hexane at −70°, and decomposition of the ozonide by boiling water, gave a ketone which yielded a dinitrophenylhydrazone, m. p. 136—146°. From this on fractional crystallisation was obtained only *cyclo*hexanone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 156—157°.

The basic product (2 g.) from the Hofmann degradation was separated into fractions, b. p. 160° (bath) (0·6 g.) and b. p. 260° (0·75 g.). The first fraction yielded a crude picrate, m. p. 130—137°, and a crude methiodide, m. p. 180—190°, from which were obtained by fractional crystallisation the picrate, m. p. 141—142° (Found: C, 47·5; H, 6·1; N, 15·6. Calc. for $C_{14}H_{20}O_7N_4$: C, 47·2; H, 5·7; N, 15·7%), and the methiodide, m. p. 200°, of dimethyl(*cyclo*pentylmethyl)amine, identified by m. p. and mixed m. p. The second fraction yielded (*cyclo*hexylmethyl)dimethyl(*cyclo*pentylmethyl)amine picrate, m. p. and mixed m. p. 110°.

A vapour-phase chromatogram of a sample (13·0 mg.) of the total base fraction from the Hofmann degradation, in benzene (0·2 c.c.), run on a Celite–silicone column at 131° (with a nitrogen flow of 37 c.c. per min.) showed two bands with retention times 13 min. 45 sec. and 20 min. 38 sec.; these were shown to correspond to dimethyl(*cyclo*pentylmethyl)amine and (*cyclo*hexylmethyl)dimethylamine [30] respectively by experiments with mixtures of these bases, and band-area comparisons indicated that the 13 mg. specimen contained 3·9 mg. of dimethyl(*cyclo*pentylmethyl)amine and 2·0 mg. of (*cyclo*hexylmethyl)dimethylamine. At the column temperature chosen (for satisfactory analysis of the more volatile amines) the third component of the Hofmann mixture was eluted too slowly for analysis, but, by difference, its weight in the sample was 7·1 mg.

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[28] Arnold, Amidon, and Dodson, *J. Amer. Chem. Soc.*, 1950, **72**, 2871.
[29] Egloff in "Physical Constants of Hydrocarbons," Vol. II, Reinhold, New York, 1940, p. 160.
[30] Jaquier, Mousseron, Mousseron-Canet, and Zagdoun, *Bull. Soc. chim. France*, 1952, 1042.